MEDIZINISCHE UNIVERSITÄT WIEN

CeMSIIS MedUni Wien
ZENTRUM FÜR MEDIZINISCHE STATISTIK, INFORMATIK UND INTELLIGENTE SYSTEME

Publikationsworkshop:

Strategie und Vorgangsweise bei der Erstellung wissenschaftlicher Publikationen

Auszug aus dem Präsentationsmaterial

Univ.-Prof. Dr. Wolfgang Schreiner
Ao.Univ.-Prof.Dr. Walter Gall
Dr. Bernhard Knapp
Skriptumassistenz: Judith Ladenstein

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Unit 01:

Publication Types, Features, Quality

Publications: What for?

- Wissensspeicherung und Weitergabe
- Personal presentation
- Personal qualification
- Evaluation of institutions
- Fund raising
  - Proposals
  - Reports
- Education

Types & Quality of Publications

	Quality assured by:
• Populärwissenschaftliche Darstellung	High quality magazines (Scient.Am, Bild der Wissenschaft, etc.) Editorial board of magazine, personal reputation of (peer) author Medium level magazines: no actual quality assurance
•Textbook	.gov-institutes, market, publishing companies ? Rezensionen

Types & Quality of Publications (ctd.)

	Quality assured by:
• Monographie	Market, Publisher
• Buchbeitrag (book chapter)	Editor, personal reputation of author
• Review article (usually invited)	Editor of journal, Personal reputation of author
• Scientific article („full paper“, meta-analysis)	Editorial board, reviewers

Types & Quality of Publications (ctd.)

	Quality assured by:
• Brief report, short communication, rapid communication, medical case report	Editorial board
• Letter to the editor	Reflects personal opinion, quality not guaranteed

Types & Quality of Publications (ctd.)

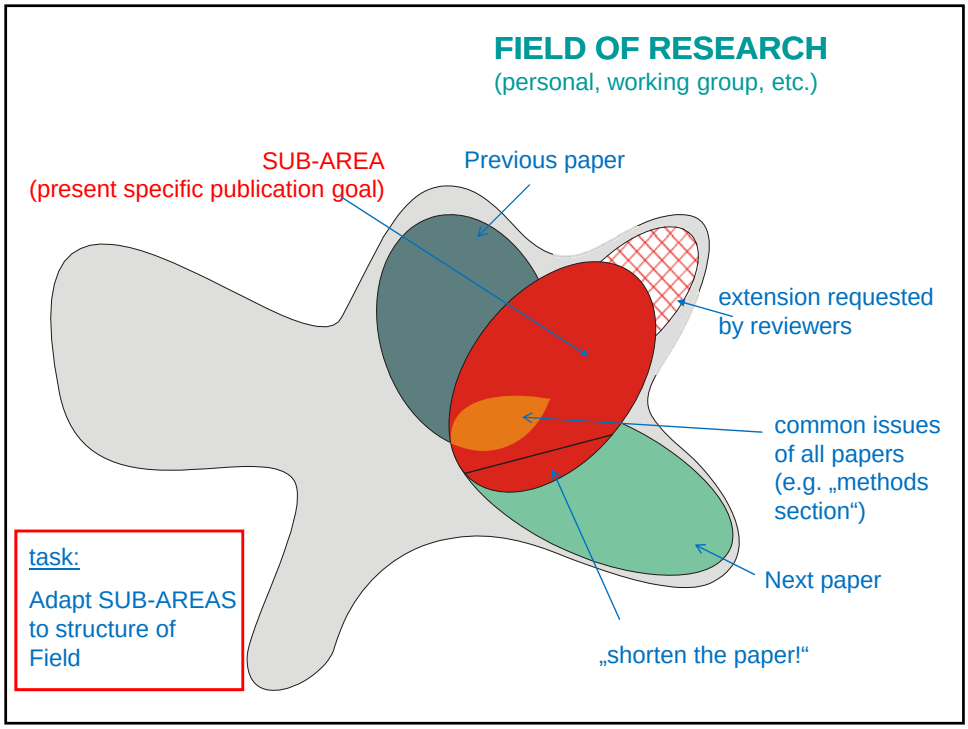
	Quality assured by:
• Poster, abstract, proceedings: – in a (supplement to a) scientific journal – as a separate volume published by organisation hosting the meeting	In some cases mild, in other cases rigorous reviewing process: Publication may severely depend on booking-status of congress, in many cases no throurough quality assessment

Types & Quality of Publications (ctd.)

	Quality assured by:
• Thesis	Institution / staff acting as mentor PhD at MUW: reviewed project mandatory!
• Diplomarbeit	Institution / staff acting as mentor some even published as papers!
• Progress-, technical-, project-report	Institution acting as project host, investigators‘ personal responsibility
• Project application Project report	International review (FWF, EU, etc.) - arbitrary grants, e.g. Pharma-Comp.

Unit 02:

Field of Research, Scope, Title



Projekte & Publikationen: Generelles Procedere

1) *Divide et impera!*
Field of Research in „sub-areas“ gliedern, die Teilziele repräsentieren
(Weltformel: Animation Graphik
wissenschaftliches Land: Animation Graphik)

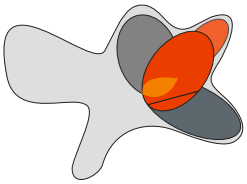
2) Jedes Teilziel als Publikationsthema formulieren („publication schedule“)
   - Allgemeine Aspekte + Kriterien
   - Bezug nehmen zum Rest des Arbeitsgebietes (‚einbetten‘)
   - ‚potenten‘ Titel formulieren: *„…the title of our next paper will be….“*

3) effiziente Realisierung: Research & Publication

The Researcher‘s Bible:
http://www.meduniwien.ac.at/msi/biosim/publiwos/researchers_bible.pdf

Thematische Überlappungen

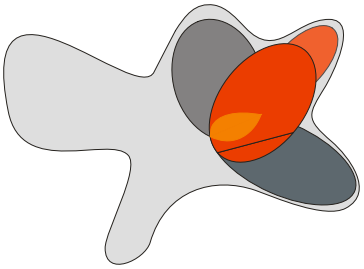
zwischen Papers derselben Gruppe?



- bei { Introduction, Methods, [parts of discussion], [parts of references] } unvermeidlich
- bei { Results, Discussion } (eher) unseriös, wenn sie kommentarlos erfolgen; o.k., wenn korrekt & vollständig zitiert wird

Good Scientific Practice:
http://www.meduniwien.ac.at/files/7/8/goodscientificpractice.pdf

Publikation – Schedule,
weitere Aspekte



- Thematische Überlappungen ✓
- Teilziele aufeinander aufbauend
- sukzessive realisierbar (Arbeitsplan)
- verteilt auf geeignete Zeitschriften
- „gerechte“ Verteilung auf
  - Erstautor
  - Zweitautor
  - sonstige Autoren
  - Letzt (Senior)autor
- Muss die Ethik – Kommission mit diesem Thema befasst werden?

Publikation Schedule,ctd.

„Potente“ (aber nicht präpotente) Titel formulieren!

- Obtain hints & examples from Literature („discussions“, „prospects“)
- „*A strong title is a good starting point*“:
  - kurz, prägnant
  - aktive , inhaltliche Aussage, wenn möglich
  - specific rather than general statements
  - Interesse wecken
    - reviewer
    - scient. community
- Assistenz durch einen erfahrenen Forscher unbedingt ratsam!

Beispiel: 1 Paper, 3 Titles

What do you think of these?

The stochastic relation between the deposition of aerosols during smoking and the formation of malignant cells in the trachea.

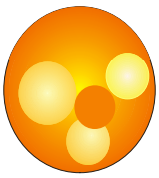
Smokers found at increased risk for small cell carcinoma.

Allocate your title somewhere in between!

Smoking causes cancer.

Der Impact (Factor)

Zielgerichtete, forcierte Vorgangsweise laut Plan



- Milestones: zeitlich, inhaltlich
- „Seitenäste“ nur bearbeiten, wenn „lebenswichtig“
- interessante Seitenäste lediglich notieren, [→ publication schedule]
- laufendes Update von To-Do-Lists

Unit 03:

Selecting a Journal

Welche Journale kommen in die engere Auswahl?

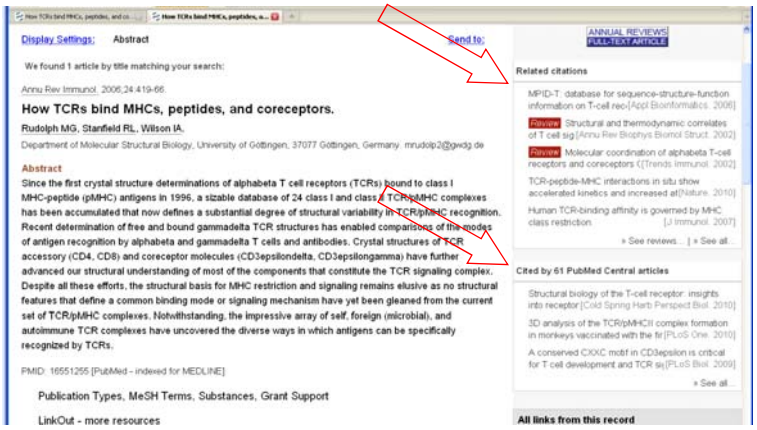
- Literatursammlung der Arbeitsgruppe
- persönliche Literatursammlung (des Mentors)
- Passt die beabsichtigte Arbeit in den Rahmen eines bestimmten Journals?
  → Inhaltsverzeichnisse von 2-3 Bänden betrachten, oder
- Kann die eigene Arbeit gut an den Rahmen eines bestimmten Journals angepasst werden?
- Kann ich (zwanglos) wichtige Arbeiten aus einem Journal zitieren? Wenn ja, dann versuchen, dort zu publizieren (Journals sehen es gerne, wenn sie selbst zitiert werden, da sich dadurch ihr eigener IF erhöht).
- Habilitationsrichtlinien der MUW

Falls Sie von MUW-extern Zugang zu kostenpflichtigen Datenbanken benötigen: Informationen unter:
Homepage / Organisation / Dienstleistungseinrichtungen und Stabstellen / ITSC - IT Systems & Communications / Services & Dienste / Zeitschriftenproxy

Welche Journale in engere Auswahl, ctd?

Keynote-Paper als Ausgangspunkt

- Zitate aus einem keynote - paper (e.g. review-article)
- In welchen Journalen wurde keynote-paper zitiert ?
  (= sekundäre Literatursuche) → PubMed „cyted by…“
- „related citations“ bei PubMed ☝ ☝



Selecting a Journal ctd.

Erforderliche Materialien für das angepeilte Journal:

- Instructions for the Authors (Beispiel: J.Gen.Phys.HTML http://www.jgp.org/misc/ifora.shtml, PDF)
- Inhaltsverzeichnisse (ev. + Abstracts wichtiger Artikel)
- einige gute Basis- & Referenzartikel für die geplante Publikation

Passen Sie sich den formalen Erfordernissen an!
– „Individualität“ ist hier kontraproduktiv!

Selecting a Journal ctd.

Auswahlkriterien ctd.

- medizinische Journale

klinisch orientiert
–klinische Studien
–tierexperimentelle Studien

biowissenschaftlich-, Grundlagenforschungs-orientiert
–neue experimentelle Methoden
–Ergebnisse der Grundlagenforschung

- technische Journale

–Labortechnik
–EDV
–Biomedizinische Technik

Selecting a Journal ctd.

in welcher „catagory“ publizieren?

- medizinische Journale

klinisch orientiert
–klinische Studien
–tierexperimentelle Studien

biowissenschaftlich-, Grundlagenforschungs-orientiert
–neue experimentelle Methoden
–Ergebnisse der Grundlagenforschung

Phase 2

- technische Journale

☝ oft günstig:

Phase 1

–Labortechnik
–EDV
–Biomedizinische Technik

Selecting a Journal ctd.

- Welche Journals bieten passenden Type of Publication (e.g. brief reports)?
- Paßt die Länge der geplanten Arbeit in das Journal? Oder: Kann ich die Länge an das Journal anpassen ?
- Welche turn-around-Zeit (submission, review, revision, proofs, publication) ist zu erwarten ?
  (0.5 - 2 Jahre)
- handling- & page charges
- eigene Erfahrungen mit einem Journal bei früheren Artikeln
- Fakultätsinterne Journal-Reihung und Bewertung
- Impact Factor (per se)?
- fachinternes „Ansehen“ von Journals
- Mitglieder des Editorial boards sind bekannt betreffend ihrer Lieblingsthemen, ein Editor kann als Autor zitiert werden.

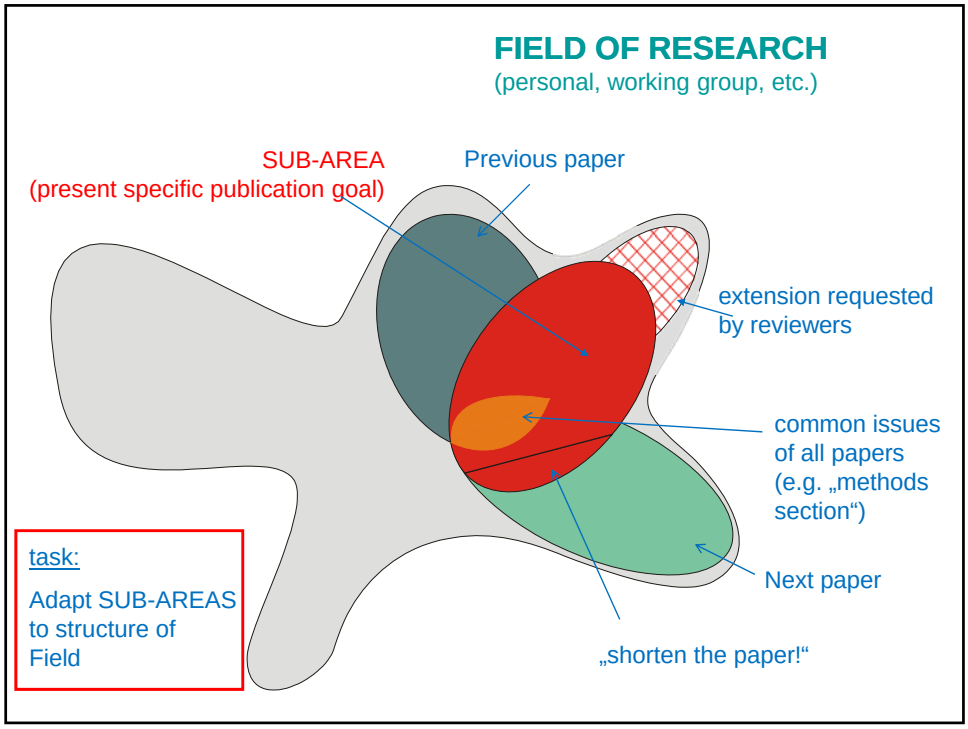
Selecting a Journal ctd.

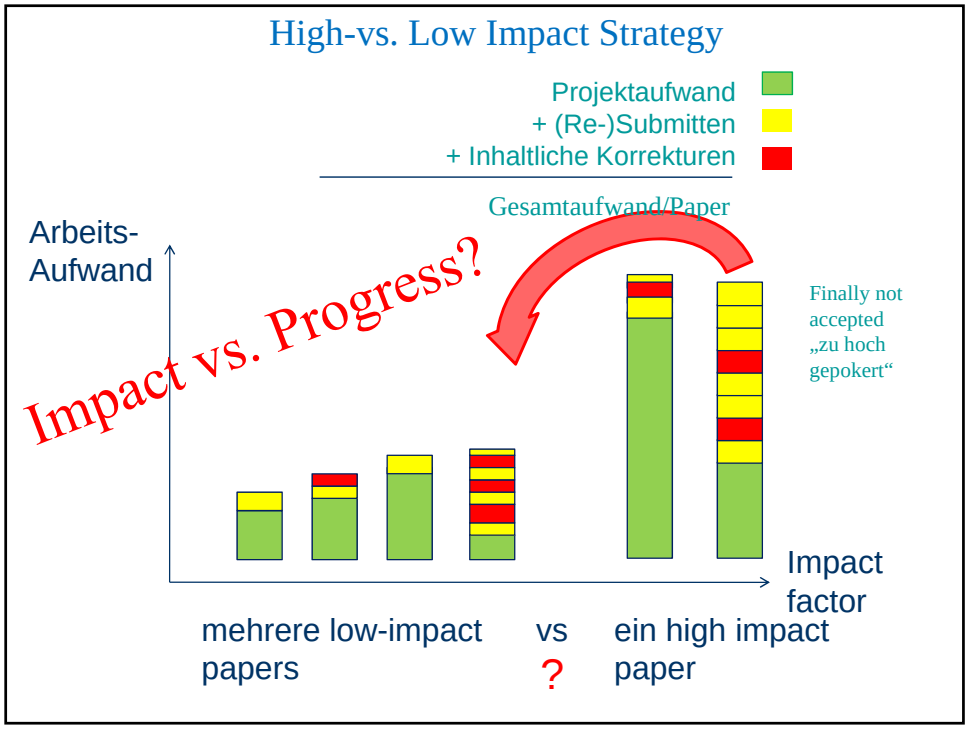
Auswahlkriterien: „halb-seiden“ („semi-satinös“)

- taktische Ziele? z.B. „Selbstdarstellung im Lokalblatt vor einer Bewerbung“
- Ist „fremdgehen“ sinnvoll ?

  z.B. technischer oder IT-Artikel wird in medizinischem Journal publiziert:

  - hoher Impact
  - „Nischen-Nutzung“
  - möglicherweise inkompetente Reviewer
  - banaler technischer Inhalt komplex dargestellt
  - einfache klinische Sachverhalte mit komplexer theoretischer Expertise verbrämt


FIELD OF RESEARCH
(personal, working group, etc.)
SUB-AREA
(present specific publication goal)
Previous paper
extension requested by reviewers
common issues of all papers (e.g. „methods section“)
Next paper
„shorten the paper!“
task:
Adapt SUB-AREAS to structure of Field


High-vs. Low Impact Strategy
Projektaufwand
+ (Re-)Submitten
+ Inhaltliche Korrekturen
Gesamtaufwand/Paper
Arbeits-Aufwand
Impact vs. Progress?
Finally not accepted „zu hoch gepokert“
Impact factor
mehrere low-impact papers
vs
?
ein high impact paper

Selecting a Journal, Résumé

- Selecting a journal is a fuzzy process !
- Rest-Risiko > 0 !
- Trotz aller Kriterien & Argumente: *sehr persönliche Entscheidung !*

→ Empfehlung:

- Nach eingehender Beratung (mit den Mitautoren bzw. dem Mentor) soll jener Autor, der die Arbeit schreibt (= Erstautor meist) letztlich entscheiden, denn er muss gegebenenfalls auch den Aufwand des Scheiterns tragen (Arbeit umschreiben).
- Ausnahme: der Mentor hat eine „totsichere Landemöglichkeit“, ist z.B. Mitglied des Editorial Board einer Zeitschrift.

NCBI PubMed

PubMed Nucleotide Protein Genome Structure PopSet

Computation of Related Articles

The neighbors of a document are those documents in the database that are the most similar to it. The similarity between documents is measured by the words they have in common with some adjustment for document lengths. In order to carry out such a program one must first define what a word is. For us a word is basically an unbroken string of letters and numerals with at least one letter of the alphabet in it. Words end at hyphens, spaces, newlines, and punctuation. A list of 310 common, but uninformative, words (also known as stop words) are eliminated from processing at this stage. Next a limited amount of stemming of words is done but no thesaurus is used in processing. Words from the abstract of a document are classified as text words. Words from titles are also classified as text words, but words from titles also appear a second time with a special added marker designating them as title words. MeSH terms are placed in a third category and a MeSH term with a subheading qualifier is entered twice, once without the qualifier and once with it. Likewise a MeSH term that is starred (indicating a major concept in a document) is entered once without the star and once with it. These three categories of words (or phrases in the case of MeSH) comprise the representation of a document. No other fields such as author or journal enter into the calculations.

Having obtained the set of terms that represent each document, the next step is to recognize that not all words are of equal value. Each time a word is used it is assigned a numerical weight. This numerical weight is based on information that the computer can obtain by automatic processing. Automatic processing is important because the number of different terms that have to be assigned weights is close to two million for this system. The weight or value of a term is dependent on three types of information: 1) the number of different documents in the database that contain the term; 2) an estimate of the importance of the term in producing relationships in the database; 3) the number of times the term occurs in a particular document. The first two of these pieces of information are combined to produce a number called the global weight of the term. The global weight is used in weighting the term throughout the database. The third piece of information pertains only to a particular document and is used to produce a number called the local weight of the term in that specific document. When a word occurs in two documents its weight is computed as the product of the global weight times the local weight in each of the documents.

The global weight of a term is greater for the less frequent terms. This is reasonable because the presence of a term that occurred in most of the documents would really tell one very little about a document. On the other hand a term that occurred in only one hundred documents out of one million would be very helpful in limiting the set of documents of interest. A word that occurred in only ten documents is likely to be even more informative and will receive an even higher weight. The second factor that enters into the computation of the global weight of a term is what we call the strength of the term. It is defined as the probability that a term that occurs in one document will also occur in any other document that is closely related to the first document. For a term of a given frequency the higher the strength the greater the global weight. For details of how the global weight is computed for a term we refer the interested reader to Wilbur and Yang where section 3 is of particular relevance. The local weight of a term within a document is greater the more frequent the term is in that document.

The similarity between two documents is computed in two steps. The first step is to add up the weights (local wt1 * local wt2 *global wt) of all the terms the two documents have in common. This provides an indication of how related two documents are. However, this preliminary score suffers from the problem that when a document is scored against a long document and a short document the long document will usually win out just because of its length. To correct for this problem we divide this preliminary score by the product of the lengths of the two documents. The resultant score is an example of a vector cosine score. Cosine scoring was originated by Gerard Salton and has a long history in text retrieval. The

interested reader is referred to Salton, Automatic Text Processing, Reading, MA: Addison-Wesley, 1989 for further information on this topic. Our approach differs from other approaches in the way we calculate the local and global weights for the individual terms.

Once the similarity score of a document in relation to each of the other documents in the database has been computed, that document's neighbors are identified as the most similar (highest scoring) documents found. These closely related documents are precomputed for each document in MEDLINE so that when you push the button "See Related Articles" the system has only to retrieve this list. This enables a fast response time for such queries.

INSTRUCTIONS TO AUTHORS

These instructions, together with the *Editorial Policies* of *The Journal of General Physiology* included elsewhere in this issue, should be read by all authors who plan to submit a manuscript to *The Journal of General Physiology*. A copy of the most current version of these Instructions and the Editorial Policies are available for retrieval at:www.jgp.org/misc/policies.shtml

Scope of Articles

The Journal of General Physiology publishes original articles that elucidate basic biological, chemical, or physical mechanisms of broad physiological significance. Two types of articles will be considered: *Regular Articles* that should be as concise as possible, but with no lower or upper page limit; and brief *Letters to the Editor* that comment upon, criticize, or interpret findings published in *The Journal*. *The Journal* publishes articles that strive to understand integrative function through innovative model simulations; conventional theoretical articles will be published only if they deal with subjects about which *The Journal* has often published experimental studies or if they are submitted as a companion to an experimental article that depends upon the theoretical article in some significant way. *The Journal* does not publish articles that deal only with methods, but may consider articles that deal largely with a new method, if they report significant new findings obtained by using that method. No substantial part of an article may have been, or may be, published elsewhere.

Submission Address

By mail or courier:

Olaf S. Andersen
Editor
The Journal of General Physiology
The Rockefeller University Press
1114 First Avenue
New York, NY 10021-8325

By e-mail:

jgp@rockvax.rockefeller.edu

Manuscript Submission

Manuscripts can be submitted either in hard copy form, with an accompanying 3.5" floppy disk, or electronically.

Hard copy submission. A *Manuscript Submission Form* and the *Manuscript Content Verification and Provisional Copyright Assignment and Publication Agreement* (published in every issue of *The Journal* and online at www.jgp.org/misc/ifora.shtml) should be submitted together with four high quality copies of the typescript and figures. Authors should identify possible reviewers, and reviewers they deem inappropriate, in a separate letter of submission (see below). Glossy prints should be submitted only if they are essential for the review. All four copies of the manuscript should be unstapled. See *Manuscript Organization and Preparation* below for further details. Authors should retain a copy of any manuscript they submit to *The Journal*, as copies normally will not be returned. Glossy prints will be returned only if requested in the letter of submission. *The Journal* is not responsible for lost or damaged figures.

If a manuscript has more than one author, each author must sign a letter of submission, or in some other way notify the Editor in writing that he/she wishes his/her name to appear as one of the authors of the article. The receipt of each manuscript is acknowledged, and authors should be sure that they receive this acknowledgment.

Electronic submission. Short manuscripts without figures can be submitted electronically by sending a letter of submission and the text file via E-mail (jgp@rockvax. rockefeller.edu). Authors who plan to submit electronically should contact the Editorial Office before doing so. The *Manuscript Submission Form* and the *Publication Agreement* should be faxed to (212) 327-8996. The submitting author should make sure that each author notifies the Editor that he/she wishes his/her name to appear as author of the article. The receipt of the manuscript is acknowledged electronically.

The text file should be a formatted text file, preferably Microsoft Word or WordPerfect (LaTeX files are not acceptable). The text file will be printed as soon as it is received in the Editorial Office, and the authors will be notified immediately of any problems that might necessitate the submission of a paper copy.

Prior publication. When submitting a manuscript, the authors should confirm on the *Manuscript Submission Form* and the *Publication Agreement* that the material has neither been published nor submitted for publication elsewhere—other than as an abstract that is less than 400 words in length and contains no figures. If any other form of publication has occurred or is contemplated, three copies of a reprint or typescript of such other publication should accompany the article submitted to *The Journal* and the authors should explain in a letter of submission how this publication relates to the submitted manuscript. This material will be sent with the manuscript to the reviewers, who will be asked to advise the editors whether there is overlap between the submitted articles and the other material.

Authors should note that provisional copyright to the article is transferred to The Rockefeller University Press at the time of submission (see *Publication Agreement*). The work therefore cannot be made available in an electronic format that is accessible via the Internet or a campus server. Any such posting will be considered a prior publication and a violation of the copyright.

Animal protocols. Articles describing the results of experiments on vertebrates can be accepted for publication only if the experiments were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* (1996. National Academy of Sciences, Washington, D.C.), which is available at:www2.nas.edu/ila-home/. The authors should confirm on the *Manuscript Submission and Copyright Transfer Form* that these principles were followed.

Conflict of interest. All authors are required to disclose in a letter of submission any commercial affiliations or other financial interests (consultant income, equity interests, or patent-licensing arrangements) that could create the appearance of a conflict of interest regarding the submitted manuscript. The specifics of such disclosures will remain confidential, but the Editor may recommend that a general statement be made in the Acknowledgments section. All funding

sources, whether institutional, public, private, or corporate, should be listed in the acknowledgments.

Suggestions for reviewers. To expedite the review of manuscripts, the editors appreciate when the author(s) provide the name, address, telephone and fax numbers, and e-mail address (if known) of potential reviewers in a letter of submission. These individuals should not be recent (within the last three years) collaborators or co-authors, nor should they have provided substantial advice to the author(s) in the conduct of the work or the preparation of the manuscript. The editors will seriously consider these suggestions, as well as reasoned requests to exempt possible candidates, when selecting reviewers.

Manuscript Organization and Preparation

Word processing files. Although we can accept most word processing formats, we prefer Microsoft Word files. Please note that typesetting programs such as LaTeX are not compatible with our system, and cannot be used. When preparing your files, please be aware of the following guidelines:

- Do not try to achieve a "typeset" look as most of your formatting will be removed during the production process, and may interfere with file conversion.
- Please do NOT use the "Insert Symbol" palette in Word. Instead, key in Greek or special characters using Symbol font.
- Use your software's built-in superscript and subscript attributes rather than changing a character's font size/position.

Style. Authors should follow the conventions set forth in the Council of Biology Editors Manual for Authors, Editors, and Publishers, *Scientific Style and Format* (1994. 6th edition. Published for the Council of Biology Editors, Inc., by the Press Syndicate for the University of Cambridge, Cambridge, UK).

Equipment, reagents, and methods. List chemicals and scientific instruments used and their manufacturers' (and suppliers') locations. Capitalize trade names. For chemical compounds, after the first use of the trivial name give the formal name, as established by international convention (e.g., by IUB, IUPAB, IUPAC, or IUPS). Identify statistical software used.

Abbreviations and units. Standard abbreviations (see the list published in most issues) may be used without definition. List all other abbreviations used in the manuscript in a footnote (see section on Footnotes). Terms used fewer than three times in the manuscript should not be abbreviated. Abbreviate units of measure only when used with numbers. Numbers and units must be separated by a space, e.g., 5 pA, not 5pA. The use of abbreviations in text, figures, and tables must be consistent. Use the metric system and Systèmes International d'Unités (SI) units.

Any nonstandard symbols should be defined. Unless typed, all mathematical symbols and Greek and script letters should be identified clearly in the manuscript opposite the line in which they first appear. It is particularly important to distinguish between the numeral 1 (one) and the letter l (el), and between the numeral 0 (zero) and the letter O (oh). With san serif typefaces, a distinction must also be made between the capital I and the lowercase l (el).

Format. Four high-quality copies of the manuscript should be submitted. A complete set of photocopied figures should accompany each copy of the article. Original prints should be sent only if they contain detail that would by lost in photocopying, as with color figures, electron micrographs, or electrophoresis gels. The original manuscript should be laser printer output or typed on 8. 5 × 11" (or equivalent) paper of good quality. There should be 1-inch margins on the sides, top, and bottom. Insertions or corrections should be few and typewritten or printed legibly in ink. Poor quality photocopies or draft quality (dot-matrix) computer printouts are not acceptable and will be returned unreviewed.

All material, including abstract, text, footnotes, references, tables, and legends, must be double spaced. All pages (with the possible exception of the figures) should be numbered in sequence starting with the title page. Each section should begin on a new page, and the sections should be organized in the following order: Title Page; Abstract (with key words listed beneath); Introduction; Materials and Methods; Results; Discussion; Appendices, if any; Acknowledgments; Footnotes; References; Figure Legends; Tables with Table Legends; and photocopies of figures or original figures if needed (all figures should be numbered). Schemes should not be included in the text, but attached separately with the figures. Schemes will be numbered, using roman numerals, in the order in which they appear.

Title page. List the title of the article, the name(s) of the author(s), and department(s) and institution(s), city, state, and zip code where the work was performed. Include the institutional affiliation of each author if different from where the work was performed (multiple affiliations at one institution should be listed separately, i.e., "Department of Medicine, Department of Physiology, and Department of Biology," not "Departments of Medicine, Physiology, and Biology"), and footnote symbols (*, ‡, §, ‖, ¶) should be used to indicate the department(s) with which each author is affiliated. Give the name, complete address, telephone number, fax number, and e-mail address of the author to whom communications about the article should be directed. Telephone and fax numbers should be included whether or not the author(s) is (are) in the United States. Acknowledgments of financial support should not appear on the title page but in the acknowledgments section.

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Unless otherwise instructed, the name, address, fax number, and e-mail address of the corresponding author will appear as a footnote on the first page of the published article.

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94th Congress. US Public Law 94-553 enacted October 19, 1976. Title I-General Revision of Copyright Law. Superintendent of Documents. Government Printing Office, Washington, DC 20402.

General guide to the Copyright Act of 1976, September 1977. Copyright Office, Library of Congress, Washington, DC 20559.

A Handbook for Serial Publishers: Procedures for Using the Programs of the Copyright Clearance Center, Inc. August 1977 AAP/TSM. Copyright Clearance Center Task Force. 1 Park Avenue, New York, NY 10016.

Example for a

Reference List of a Clinical – Technical Cooperation

Clinical Preexperience with Technical Support (BioStatistics):

Müller,M.R., A.Wohlfahrt, H.Schima, W.Schreiner, L.Huber, J.Scharbert, U.Losert, and E.Wolner. 1988. Hematological parameters for in vitro testing of bloodpumps - data and analysis of two different principles. *Proceedings of the International Workshop on Rotary Bloodpumps.* 82-88.

Müller,M.R., W.Schreiner, A.Wohlfahrt, Ch.Schlusche, U.Losert, and E.Wolner 1989 Computerunterstützte Vollblutaggregometrie als klinische Routine-Methode. *Acta Chirurgica Austriaca, 21*:9-10.(Abstract)

Müller,M.R., W.Schreiner, A.Wohlfahrt, A.Salat, and E.Wolner. 1990. The influence of sample age on collagen-induced platelet aggregation in whole blood. *Thrombosis Research 60*:477-487.

Generic Technical Support in Informatics (Customized Application):

Schreiner,W., M.R.Müller, W.Premauer, and E.Wolner. 1991. Whole blood aggregometry: a PC-based system for clinical routine application. *Medical Informatics Europa 1991.* 904-907.

Clinical "Fruits":

Mueller,M.R., A.Salat, S.Pulaki, W.Schreiner, E.Ergun, R.Koppensteiner, U.Losert, and E.Wolner. 1993. Platelet function after total artificial heart replacement: clinical application and experiment. *J. Heart Lung Transplant. 12*:450-459.

Muller,M.R., A.Salat, S.Pulaki, P.Stangl, E.Ergun, W.Schreiner, U.Losert, and E.Wolner. 1995. Influence of hematocrit and platelet count on impedance and reactivity of whole blood for electrical aggregometry. *J. Pharmacol. Toxicol. Methods 34*:17-22.

Müller,M.R., A.Salat, P.Stangl, M.Murabito, S.Pulaki, D.Boehm, R.Koppensteiner, E.Ergun, M.Mittlboeck, W.Schreiner, U.Losert, and E.Wolner. 1997. Variable platelet response to low-dose ASA and the risk of limb deterioration in patients submitted to peripheral arterial angioplasty. *Thromb Haemost 78*:1003-1007.

„Impact“ von Forschungsleistung und Journalen

Bernhard Knapp
Center for Medical Statistics, Informatics and Intelligent Systems
Department for Biosimulation and Bioinformatics

B. Knapp

Inhalt

1. Einleitung
2. Institute for Scientific Information (ISI)
   a) Impact Factor
   b) Cited half-life
   c) Immediacy Index
   d) Eigenfactor
   e) *Article Influence* Score
3. Scopus
   a) SJR
   b) SNIP
   c) Percent not cited
4. Usage Factors
5. Scores für Autoren
   a) Mean oder Median Citations per paper
   b) Hirschfaktor
6. Abschließende Bemerkungen

B. Knapp

1) Einleitung

- „Gift Economy“ – wissenschaftlicher Wert wird definiert als unentgeltliches Beitragen zum Stand der Wissenschaft und das dadurch hervorgerufene Beeinflussen anderer Wissenschaftler
- Weil Autoren Zitate verwenden um anzugeben wer ihre Werke beeinflusst hat, ist es legitim wissenschaftlichen Einfluss auf Basis von Zitaten zu errechnen (?)

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2) Institute for Scientific Information (ISI)

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a) Impact Factor

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Science 28.1
Immunity 20.6
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Impact Factor (cont)

- Berechnung

z.B. für 2008

a = Wie oft Artikel aus 2006 und 2007 in 2008 zitiert wurden
b = Anzahl an Artikeln die 2006 und 2007 erschienen sind

IF = a/b

Ein Impact Factor von 3 bedeutet, dass im Durchschnitt, die Artikel der letzten beiden Jahre 3 mal zitiert wurden

- Im Zähler werden die Zitate aus allen Papers, Articles, Editorial, Letters, Conference Proceedings, Errata usw. herangezogen
- Im Nenner werden allerdings nur die Papers gezählt!

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Impact Factor (cont)

Schlussfolgerungen

- Impact Faktoren stehen immer erst 1-2 Jahre nach Einreichung einer Arbeit zur Verfügung (aktuell: im Mai 2010 gab es erst jene von 2008)
- Journale und Kategorien mit vielen Letters usw. haben höheren Impact Faktor.
- Kategorien in denen viel zitiert wird und viele Forscher arbeiten haben höheren Impact Faktor
- Zitate können auch aus eigener Zeitschrift/Forschungsgruppe kommen

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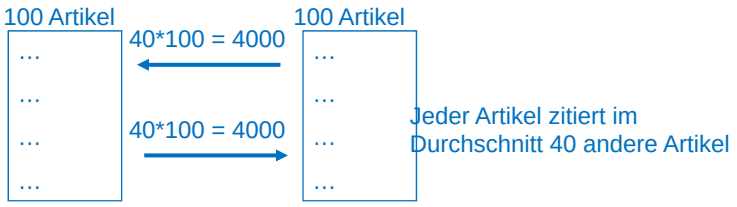

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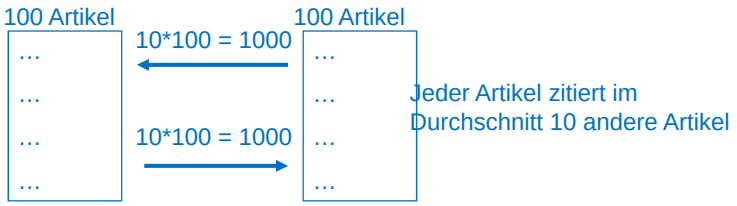

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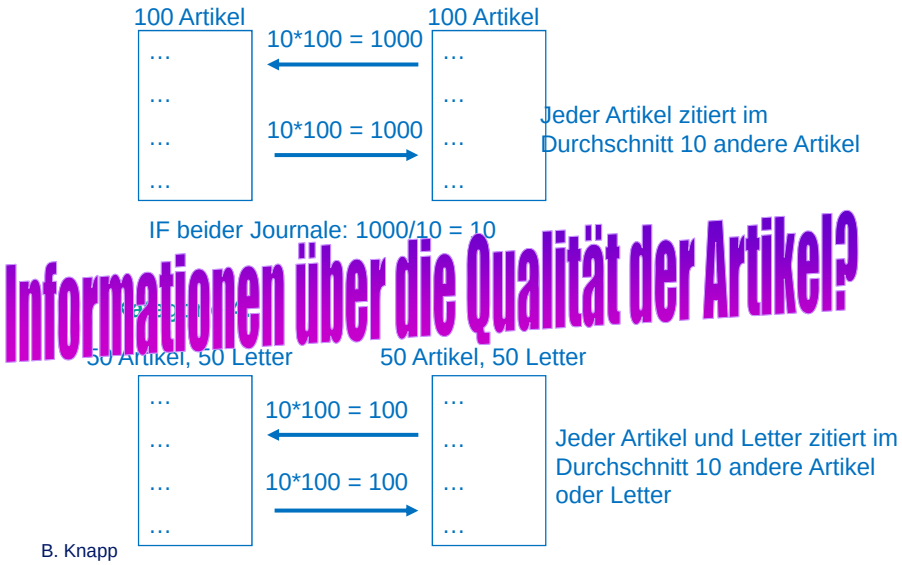

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… daraus resultieren …

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- Endocrinology
- Immunology
- Oncology
- Biochemistry
- Neurosciences
- Behavioral Sciences
- Virology
- Genetics

Medical Informatics (median IF 1.66, Platz 63 von 173)

Kategorien mit niedrigem IF

- Engineering und Material Sciences (median IF 0.359, Platz 163)
- History
- Mathematics

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Der Impact Factor ist fächerübergreifend
NICHT
vergleichbar

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Top Impact Factor?

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Impact Factor (cont)

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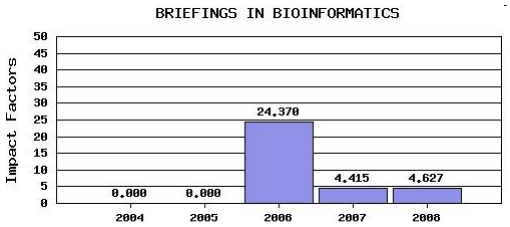
- Kursspekulationen (wie Aktien) auf steigende und oder sinkende IF - Kurse. „Ich publiziere mein Paper in Journal X weil ich erst in 3 Jahren habilitieren will und bis dahin ist das sicher ein Topjournal“
- Arbeit wird eingeschickt und akzeptiert => Impact Factor steht erst 2 Jahre später fest! z.B. gibt aktuell es erst jene für 2008.
- Es gelten nur die Zitate aus den letzten 2 Jahren. Problem bei Kategorien die nicht so schnelllebig sind. z.B. Radontransformation: entwickelt von J. Radon im Jahre 1917: „Über die Bestimmung von Funktionen durch ihre Integralwerte längs gewisser Mannigfaltigkeiten“, Anwendung seit Computertomographie (erste Ansätze 1963). Erst ein halbes Jahrhundert später (!)
- Hohe Kosten ein Journal für den IF indexieren zu lassen

B. Knapp

Impact Factor (cont)

Weitere Probleme mit dem IF

- Wenige „gewichtige“ Artikel



Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor™ Metrics	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor™ Score	Article Influence™ Score
☐	1	CA-CANCER J CLIN	0007-9235	7522	74.575	50.766	24.684	19	3.3	0.03650	17.518
☐	2	NEW ENGL J MED	0028-4793	205750	50.017	49.911	12.225	356	7.3	0.68029	18.763
☐	3	ANNU REV IMMUNOL	0732-0582	15519	41.059	46.200	7.625	24	7.1	0.07382	24.671

B. Knapp

Warum ist der IF trotzdem so erfolgreich?

- Er wird als Teil einer sehr bekannten Zitierdatenbank (Thomson Scientific‘s Journal Citation Report) veröffentlicht
- Der IF ist einfach definiert und jeder versteht ihn

B. Knapp

Der Fall „Folia Phoniatrica et Logopaedica“

- Kleines Spezialjournal mit IF=0.66 (in 2007)
- Veröffentlichung eines Editorials [1], das alle Artikel des Journals in den Jahren 2005 und 2006 zitiert um zu zeigen wie absurd der IF ist
- Resultat: IF stieg auf 1.44 und das Journal wurde 2008 von ISI ausgeschlossen

[1] Harm K. Schuttea, Jan G. Svec (2007). "Reaction of *Folia Phoniatrica et Logopaedica* on the Current Trend of Impact Factor Measures". *Folia Phoniatrica et Logopaedica* **59** (6): 281–285.

B. Knapp

Impact Factor (cont)

Der „Reihenfolgeversuch“ innerhalb von Kategorien

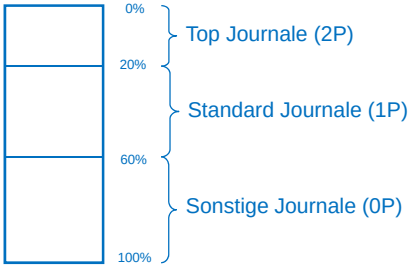
- Es werden alle Journale einer Kategorie nach deren impact factor sortiert und es wird eine Reihung hergestellt

3	NAT IMMUNOL	1529-2908	25245	25.113
4	IMMUNITY	1074-7613	25824	20.579
5	J EXP MED	0022-1007	67322	15.463
9	J ALLERGY CLIN IMMUN	0091-6749	29564	9.773
12	CLIN INFECT DIS	1058-4838	37895	8.266
13	J AUTOIMMUN	0896-8411	3322	7.881
14	EMERG INFECT DIS	1080-6040	15259	6.449
15	ALLERGY	0105-4538	9947	6.204
16	J IMMUNOL	0022-1767	123910	6.000
17	AIDS	0269-9370	20159	5.460
18	AUTOIMMUN REV	1568-9972	2114	5.371

B. Knapp

Einschub: Situation an der MUW - Habilitationsrichtlinien

- Es zählt die Reihenfolge der IF der Journale in der Kategorie



- Nötig sind 9 Punkte als Erst-Autor
- Details: http://www.meduniwien.ac.at/index.php?id=229

B. Knapp

Impact Factor (cont)

Der „Reihenfolgeversuch“ innerhalb von Kategorien - Probleme:

- Journal of Computational Chemistry
  - IF 3.4
  - Kategorie: CHEMISTRY, MULTIDISCIPLINARY
  - Journal Nummer 26 von 127 Journalen in Kategorie (top 20,5%)

- Journal of Chemical Information Modeling
  - IF 3.6
  - Kategorie: COMPUTER SCIENCE, INTERDISCIPLINARY APPLICATIONS
  - Journal Nummer 2 von 94 Journalen in Kategorie (top 2,1%)

Beide Journale haben selben Scope!

B. Knapp

b) Cited half-life
By ISI

- Langfristige Bedeutung eines Artikels (siehe Radon)
- Median des Alters der zitierten Artikel einer Zeitschrift. z.B. Cited half-life = 5 im Jahr 2008 => Die Hälfte aller Zitate stammt aus letzten 5 Jahren (2004-2008)
- Molekurbiologie meist < 5. In Kategorien mit „längerem wissenschaftlichen Anspruch“ meist >10
- Möglichkeit: IF_new = IF x Cited_half_life

B. Knapp

Kategorie Immunology:

Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor™ Metrics	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor™ Score	Article Influence™ Score
☐	1	CAN J MICROBIOL	0008-4166	5081	1.102	1.391	0.123	130	>10.0	0.00624	0.422
☐	1	CELL IMMUNOL	0008-8749	3661	1.893	1.917	0.643	56	>10.0	0.00662	0.651
☐	1	HYBRIDOMA	1554-0014	471	0.321	0.357	0.103	97	>10.0	0.00059	0.094
☐	1	J ANTIBIOT	0021-8820	5341	1.272	1.354	0.354	96	>10.0	0.00489	0.409
☐	1	J IMMUNOL METHODS	0022-1759	10714	2.120	2.337	0.389	211	>10.0	0.01968	0.827
☐	6	LYMPHOLOGY	0024-7766	424	0.939	1.157	0.130	23	9.9	0.00061	0.255
☐	7	ADV IMMUNOL	0065-2776	2245	8.625	7.078	0.227	22	9.7	0.00945	4.182
☐	8	INFLAMMATION	0360-3997	825	2.034	1.550	0.192	52	9.6	0.00139	0.478
☐	9	FOOD AGR IMMUNOL	0954-0105	207	0.350	0.478	0.036	28	8.9	0.00023	0.115
☐	10	IMMUNOL INVEST	0882-0139	527	1.754	1.535	0.113	53	8.2	0.00134	0.427
☐	10	J EXP MED	0022-1007	67322	15.463	15.504	3.078	245	8.2	0.27208	7.785
☐	12	IMMUNOLOGY	0019-2805	8179	3.432	3.373	1.055	183	8.0	0.02329	1.170
☐	13	CLIN EXP IMMUNOL	0009-9104	10655	2.853	2.855	0.668	250	7.9	0.02819	0.898
☐	13	INFECT IMMUN	0019-9567	48776	3.987	3.944	0.759	630	7.9	0.12132	1.253
☐	13	MICROB PATHOGENESIS	0882-4010	2028	2.289	2.443	0.405	121	7.9	0.00300	0.817

B. Knapp

c) Immediacy Index

By ISI

- „Gegenteil“ des „Cited half-life“ und ähnlich zum Impact Factor
- Berechnung wie Impact Factor
- Es zählen aber nur Zitate aus dem selben Jahr

Berechnung

a = wie oft wurden Artikel die in 2009 erschienen im selben Jahr 2009 zitiert

b = Anzahl der Artikel im Jahr 2009

II = a/b

B. Knapp

Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor™ Metrics	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor™ Score	Article Influence™ Score
☐	1	ANNU REV IMMUNOL	0732-0582	15519	41.059	46.200	7.625	24	7.1	0.07382	24.671
☐	2	NAT IMMUNOL	1529-2908	25245	25.113	26.247	5.797	133	4.3	0.20719	14.058
☐	3	NAT REV IMMUNOL	1474-1733	15775	30.006	31.246	5.361	83	4.0	0.13447	15.244
☐	4	IMMUNITY	1074-7613	25824	20.579	17.916	5.007	147	6.0	0.15292	10.117
☐	5	J AUTOIMMUN	0896-8411	3322	7.881	4.616	3.409	93	3.8	0.00971	1.115
☐	6	J EXP MED	0022-1007	67322	15.463	15.504	3.078	245	8.2	0.27208	7.785
☐	7	CLIN INFECT DIS	1058-4838	37895	8.266	7.422	2.379	517	5.4	0.13718	2.343
☐	8	J ALLERGY CLIN IMMUN	0091-6749	29564	9.773	8.744	2.023	347	5.6	0.09546	2.486
☐	9	IMMUNOL REV	0105-2896	10029	11.761	10.932	1.868	114	4.7	0.06307	5.250
☐	10	EMERG INFECT DIS	1080-6040	15259	6.449	6.004	1.390	326	4.3	0.07673	2.066
☐	11	TRENDS IMMUNOL	1471-4906	6542	9.910	9.592	1.380	79	4.4	0.04672	4.191
☐	12	ALLERGY	0105-4538	9947	6.204	5.553	1.362	188	5.1	0.02889	1.354
☐	13	AIDS	0269-9370	20159	5.460	5.561	1.309	353	5.7	0.07834	1.921
☐	14	CURR OPIN IMMUNOL	0952-7915	7852	10.455	8.609	1.274	95	5.3	0.04293	3.905
☐	15	MED MICROBIOL IMMUN	0300-8584	1048	2.222	2.345	1.159	44	7.7	0.00271	0.827

B. Knapp

Page Rank

Developed by Google (U.S. Patent 6,285,999)

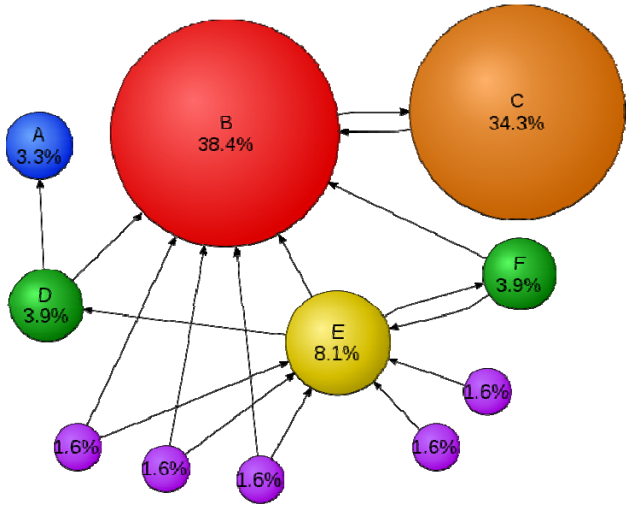


Abbildung aus Wikimedia Commons

B. Knapp

d) Eigenfactor Score

By ISI

- Ähnlich zum Impact Factor
- Mit folgenden Änderungen:

  - wird über 5 Jahre (statt 2) berechnet

  - eliminiert „self-citations“

  - gewichtet jede Referenz abhängig von der Zeit die Forscher verwenden um das Journal zu lesen (Markov-model, PageRank)

B. Knapp

Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor™ Metrics	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor™ Score	Article Influence™ Score
☐	1	ANNU REV IMMUNOL	0732-0582	15519	41.059	46.200	7.625	24	7.1	0.07382	24.671
☐	2	NAT REV IMMUNOL	1474-1733	15775	30.006	31.246	5.361	83	4.0	0.13447	15.244
☐	3	NAT IMMUNOL	1529-2908	25245	25.113	26.247	5.797	133	4.3	0.20719	14.058
☐	4	IMMUNITY	1074-7613	25824	20.579	17.916	5.007	147	6.0	0.15292	10.117
☐	5	J EXP MED	0022-1007	67322	15.463	15.504	3.078	245	8.2	0.27208	7.785
☐	6	IMMUNOL REV	0105-2896	10029	11.761	10.932	1.868	114	4.7	0.06307	5.250
☐	7	CURR OPIN IMMUNOL	0952-7915	7852	10.455	8.609	1.274	95	5.3	0.04293	3.905
☐	8	TRENDS IMMUNOL	1471-4906	6542	9.910	9.592	1.380	79	4.4	0.04672	4.191
☐	9	J ALLERGY CLIN IMMUN	0091-6749	29564	9.773	8.744	2.023	347	5.6	0.09546	2.486
☐	10	SEMIN IMMUNOL	1044-5323	2780	9.114	8.236	0.634	41	4.6	0.01775	3.850

Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor™ Metrics	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor™ Score	Article Influence™ Score
☐	1	J IMMUNOL	0022-1767	123910	6.000	6.165	0.955	1860	6.5	0.47534	2.385
☐	2	J EXP MED	0022-1007	67322	15.463	15.504	3.078	245	8.2	0.27208	7.785
☐	3	NAT IMMUNOL	1529-2908	25245	25.113	26.247	5.797	133	4.3	0.20719	14.058
☐	4	IMMUNITY	1074-7613	25824	20.579	17.916	5.007	147	6.0	0.15292	10.117
☐	5	CLIN INFECT DIS	1058-4838	37895	8.266	7.422	2.379	517	5.4	0.13718	2.343
☐	6	NAT REV IMMUNOL	1474-1733	15775	30.006	31.246	5.361	83	4.0	0.13447	15.244
☐	7	INFECT IMMUN	0019-9567	48776	3.987	3.944	0.759	630	7.9	0.12132	1.253
☐	8	J ALLERGY CLIN IMMUN	0091-6749	29564	9.773	8.744	2.023	347	5.6	0.09546	2.486
☐	9	AIDS	0269-9370	20159	5.460	5.561	1.309	353	5.7	0.07834	1.921
☐	10	EMERG INFECT DIS	1080-6040	15259	6.449	6.004	1.390	326	4.3	0.07673	2.066

B. Knapp

e) Article Influence Score

By ISI

- Eigenfactor misst den totalen Einfluss eines Journals. IF misst den „per article influence“. Um den Eigenfactor mit dem IF vergleichbar zu machen wurde der Article Influence Score entwickelt
- Auf Basis des Eigenfactor Scores erstellt, allerdings ermittelt er die relative Wichtigkeit auf „per article“ Basis
- Details zu Eigenfactor und Article Influence Score unter [1]

[1] Eigenfactor™ Score and Article Influence™ Score: Detailed methods. www.eigenfactor.org/methods.pdf

B. Knapp

Kategorie: Immunology

Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor™ Metrics	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor™ Score	Article Influence™ Score
☐	1	ANNU REV IMMUNOL	0732-0582	15519	41.059	46.200	7.625	24	7.1	0.07382	24.671
☐	2	NAT REV IMMUNOL	1474-1733	15775	30.006	31.246	5.361	83	4.0	0.13447	15.244
☐	3	NAT IMMUNOL	1529-2908	25245	25.113	26.247	5.797	133	4.3	0.20719	14.058
☐	4	IMMUNITY	1074-7613	25824	20.579	17.916	5.007	147	6.0	0.15292	10.117
☐	5	J EXP MED	0022-1007	67322	15.463	15.504	3.078	245	8.2	0.27208	7.785
☐	6	IMMUNOL REV	0105-2896	10029	11.761	10.932	1.868	114	4.7	0.06307	5.250
☐	7	TRENDS IMMUNOL	1471-4906	6542	9.910	9.592	1.380	79	4.4	0.04672	4.191
☐	8	ADV IMMUNOL	0065-2776	2245	8.625	7.078	0.227	22	9.7	0.00945	4.182
☐	9	CURR OPIN IMMUNOL	0952-7915	7852	10.455	8.609	1.274	95	5.3	0.04293	3.905
☐	10	SEMIN IMMUNOL	1044-5323	2780	9.114	8.236	0.634	41	4.6	0.01775	3.850

Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor™ Metrics	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor™ Score	Article Influence™ Score
☐	1	ANNU REV IMMUNOL	0732-0582	15519	41.059	46.200	7.625	24	7.1	0.07382	24.671
☐	2	NAT REV IMMUNOL	1474-1733	15775	30.006	31.246	5.361	83	4.0	0.13447	15.244
☐	3	NAT IMMUNOL	1529-2908	25245	25.113	26.247	5.797	133	4.3	0.20719	14.058
☐	4	IMMUNITY	1074-7613	25824	20.579	17.916	5.007	147	6.0	0.15292	10.117
☐	5	J EXP MED	0022-1007	67322	15.463	15.504	3.078	245	8.2	0.27208	7.785
☐	6	IMMUNOL REV	0105-2896	10029	11.761	10.932	1.868	114	4.7	0.06307	5.250
☐	7	CURR OPIN IMMUNOL	0952-7915	7852	10.455	8.609	1.274	95	5.3	0.04293	3.905
☐	8	TRENDS IMMUNOL	1471-4906	6542	9.910	9.592	1.380	79	4.4	0.04672	4.191
☐	9	J ALLERGY CLIN IMMUN	0091-6749	29564	9.773	8.744	2.023	347	5.6	0.09546	2.486
☐	10	SEMIN IMMUNOL	1044-5323	2780	9.114	8.236	0.634	41	4.6	0.01775	3.850

B. Knapp

Alle Journale

Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor™ Metrics	
		Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor™ Score	Article Influence™ Score
REV MOD PHYS	0034-6861	24577	33.985	40.395	7.028	36	>10.0	0.08932	24.877
ANNU REV IMMUNOL	0732-0582	15519	41.059	46.200	7.625	24	7.1	0.07382	24.671
ANNU REV BIOCHEM	0066-4154	16889	30.016	34.372	3.677	31	9.7	0.06852	20.891
NAT REV MOL CELL BIO	1471-0072	19628	35.423	34.221	7.238	84	4.0	0.17836	19.970
ANNU REV NEUROSCI	0147-006X	10132	26.405	31.209	3.348	23	7.7	0.04611	18.915
CELL	0092-8674	142064	31.253	30.149	6.126	348	8.8	0.67169	18.871
NEW ENGL J MED	0028-4793	205750	50.017	49.911	12.225	356	7.3	0.68029	18.763
CA-CANCER J CLIN	0007-9235	7522	74.575	50.766	24.684	19	3.3	0.03650	17.518
NATURE	0028-0836	443967	31.434	31.210	8.194	899	8.5	1.76345	17.279
SCIENCE	0036-8075	409290	28.103	30.268	6.261	862	8.4	1.58309	16.286
ANNU REV CELL DEV BI	1081-0706	8063	22.731	26.058	1.167	24	7.1	0.04961	16.220
PHYSIOL REV	0031-9333	17865	35.000	35.855	4.300	40	7.8	0.05614	15.259
NAT REV CANCER	1474-175X	18908	30.762	35.007	4.900	80	4.5	0.13525	15.256
NAT REV IMMUNOL	1474-1733	15775	30.006	31.246	5.361	83	4.0	0.13447	15.244
NAT GENET	1061-4036	61812	30.259	26.446	8.549	215	6.6	0.32178	14.505
ANNU REV ASTRON ASTR	0066-4146	6280	25.826	24.370	0.692	13	>10.0	0.02337	14.444

Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor™ Metrics	
		Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor™ Score	Article Influence™ Score
CA-CANCER J CLIN	0007-9235	7522	74.575	50.766	24.684	19	3.3	0.03650	17.518
NEW ENGL J MED	0028-4793	205750	50.017	49.911	12.225	356	7.3	0.68029	18.763
ANNU REV IMMUNOL	0732-0582	15519	41.059	46.200	7.625	24	7.1	0.07382	24.671
NAT REV MOL CELL BIO	1471-0072	19628	35.423	34.221	7.238	84	4.0	0.17836	19.970
PHYSIOL REV	0031-9333	17865	35.000	35.855	4.300	40	7.8	0.05614	15.259
REV MOD PHYS	0034-6861	24577	33.985	40.395	7.028	36	>10.0	0.08932	24.877
JAMA-J AM MED ASSOC	0098-7484	114250	31.718	27.957	7.556	225	7.2	0.38098	11.148
NATURE	0028-0836	443967	31.434	31.210	8.194	899	8.5	1.76345	17.279
CELL	0092-8674	142064	31.253	30.149	6.126	348	8.8	0.67169	18.871
NAT REV CANCER	1474-175X	18908	30.762	35.007	4.900	80	4.5	0.13525	15.256
NAT GENET	1061-4036	61812	30.259	26.446	8.549	215	6.6	0.32178	14.505
ANNU REV BIOCHEM	0066-4154	16889	30.016	34.372	3.677	31	9.7	0.06852	20.891
NAT REV IMMUNOL	1474-1733	15775	30.006	31.246	5.361	83	4.0	0.13447	15.244
NAT REV DRUG DISCOV	1474-1776	10062	28.690	24.856	4.726	62	3.7	0.06812	9.203
LANCET	0140-6736	148106	28.409	27.264	8.505	289	8.1	0.41177	9.946
SCIENCE	0036-8075	409290	28.103	30.268	6.261	862	8.4	1.58309	16.286

B. Knapp

3) Die Konkurrenz via Scopus

B. Knapp

a) SJR and SNIP
by SCOPUS

How to calculate of SJR & SNIP?

Basic calculation for both metrics '2009 Impact' = Citations received by journal J in 2009 from A,R,CP to A,R,CP published in 2006-2008 / A,R,CP published in J 2006-2008

http://www.scopus.com/source/eval.url

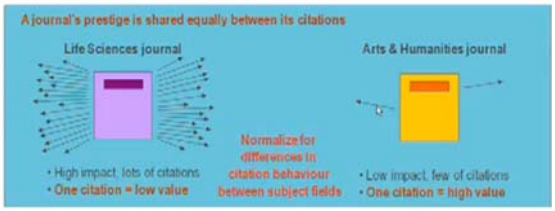
B. Knapp

Declan Butler (2 January 2008). "Free journal-ranking tool enters citation market". Nature 451 (6). doi:10.1038/451006a. http://www.nature.com/news/2008/080102/full/451006a.html.
Matthew E, Falagas et al (2008). "Comparison of SCImago journal rank indicator with journal impact factor". The FASEB Journal (22): 2623–2628. doi:10.1096/fj.08-107938. http://www.fasebj.org/cgi/content/short/22/8/2623.

SCImago Journal Rank (SJR)

By Felix de Moya via SCOPUS

- SJR weist jedem Journal einen Wert zu und adaptiert diese ähnlich dem PageRank-Verfahren iterativ
- Jedes Journal hat fixes Prestige das gleichmäßig durch alle Zitierungen verteilt wird:
  - Wird in einer Kategorie viel zitiert sind die einzelnen Zitierungen weniger wert
  - Wird in einer Kategorie wenig zitiert sind die einzelnen Zitierungen mehr wert



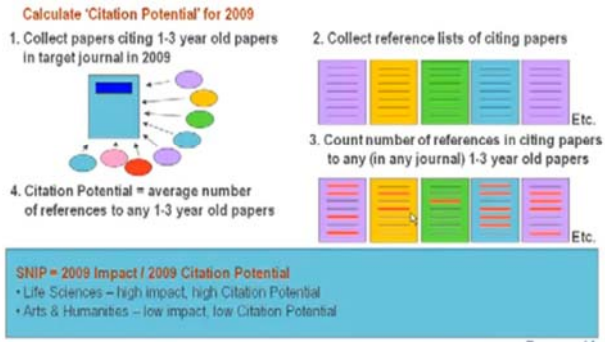
- SJR setzt den Fokus eher auf schon stark publizierende Gebiet

B. Knapp

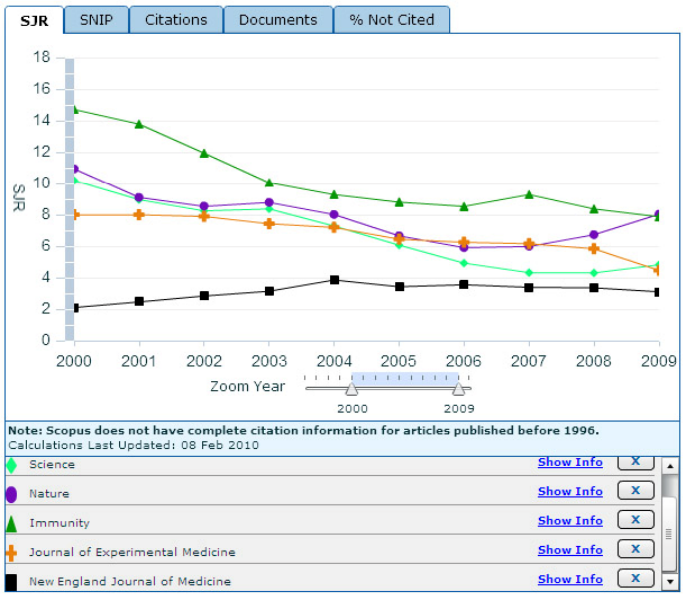
b) Source Normalized Impact per Paper (SNIP)

by Henk Moed via SCOPUS

- Es werden die Referenzlisten der zitierenden Journale untersucht und nach Anzahl der Zitate gewichtet
- Durch den SNIP werden vor allem Publikationen in Fachgebieten, die weniger oder langsamer publizieren, durch eine Normalisierung vergleichbarer gemacht



B. Knapp



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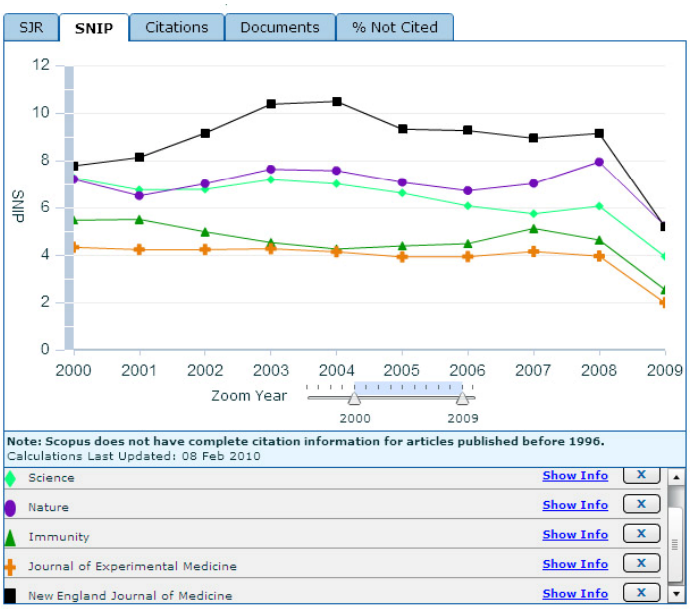

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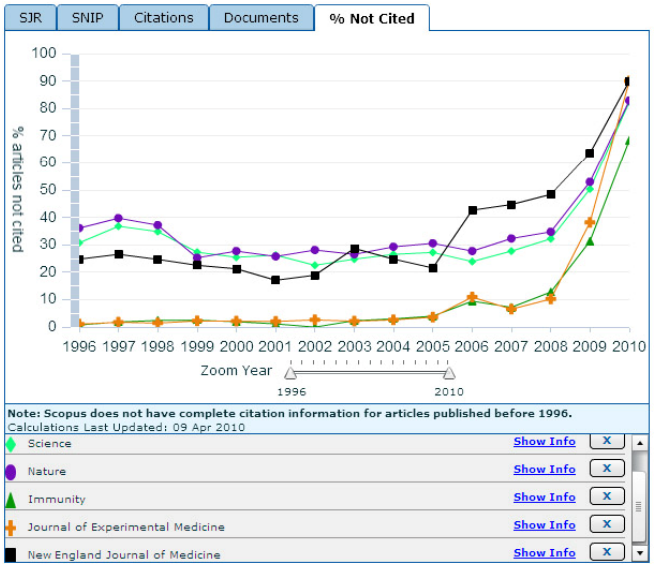
c) Überhaupt nie zitierte Artikel



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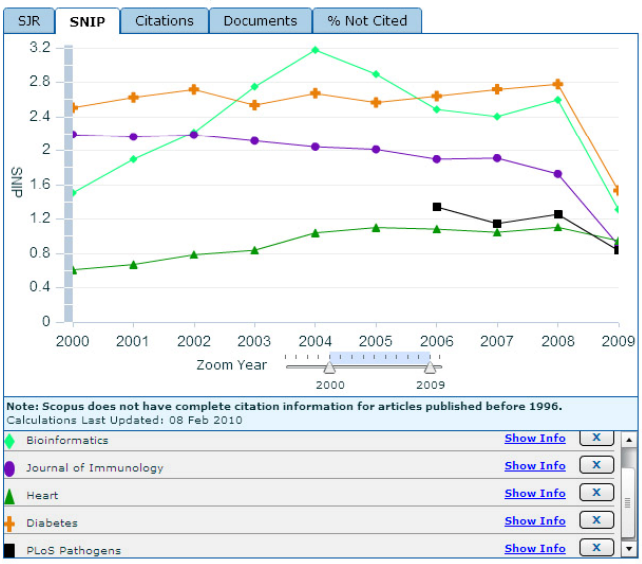
Fächerübergreifend



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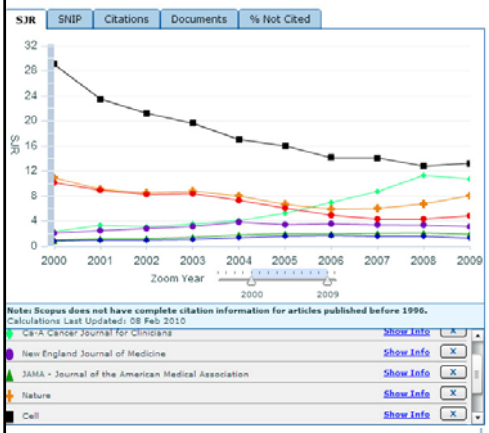
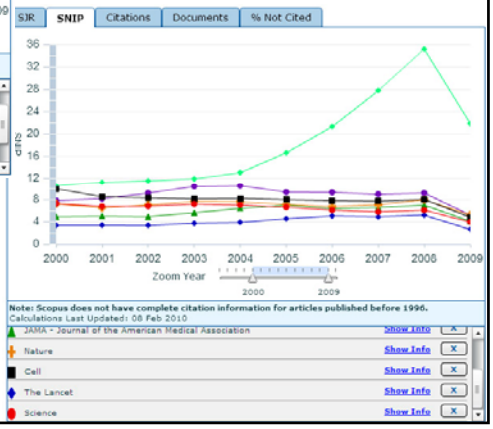
Die Topjournale des Impact Factors (ohne Reviewjournale)



IF-Reihung:
1. CA
2. New England
3. JAMA
4. Nature
5. Cell
…
Lancet
Science



SJR-Reihung
- Cell
- CA
- Nature
- Science
- New England
- JAMA
- Lancet

SNIP
- CA
- New England
- Nature
- Cell
- Science
- JAMA
- Lancet

B. Knapp

4) Usage Factors

- Wie oft werden Artikel von Journalen gelesen (nicht zitiert) „visibility of articles“
- z.B. „A quick update on the status of your paper, [..], which was published 28 weeks ago. Since publication your paper has been viewed 1152 times.“
- Open Access
- PLoS
  e.g. PLoS ONE: [..] making it the fourth most frequently evaluated multi-disciplinary journal after Nature (journal), Science (journal), and PNAS.

PLoS PUBLIC LIBRARY of SCIENCE

B. Knapp

5) Scores für Autoren

a) Mean oder Median Citations per paper

- Im Prinzip ähnlich wie Scores für Journale (Es sind also die meisten der zuvor angeführten Scores auch für einzelne Autoren berechenbar). Es werden allerdings nicht alle Artikel eines Journals bewertet sondern alle Artikel eines Authors, z.B. Mean or median citations per paper

Beispiel: Ein Autor habe 5 Publikationen. Diese wurden 4, 4, 4, 4 und 40 mal zitiert.

Mean citations: 11.2

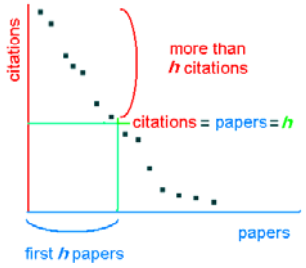
Median citations: 4

B. Knapp

b) Hirschfaktor (Hirschindex, h-index, h-number)

by Jorge Hirsch

- „Ein Wissenschaftler hat einen Index h, wenn h von seinen insgesamt N Veröffentlichungen mindestens jeweils h Zitierungen haben und die anderen (N-h) Publikationen weniger als h Zitierungen."
- Es werden die Publikationen nach der Anzahl der Zitierungen sortiert, gesucht ist jener Punkt an dem die Anzahl der Papers mit der Anzahl der Zitierungen übereinstimmt
- Beispiel: Ein Hirschfaktor von 4 bedeutet mindestens 4 Paper die jeweils mindestens 4 mal zitiert wurden.



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Vorteile:

- Einzelne sehr viel zitierte Arbeiten haben kaum Einfluss
- Geht persönlich auf den Wissenschaftler und nicht auf das Journal
- Viele „verbesserte“ Varianten (Egghe's g-index, Zhang's e-index, Contemporary h-index, AW-index, h-index PoP variation, Multi-authored h-index)

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Nachteile:

- Ähnliche Probleme wie IF (Kategorien der Journale)
- Einzelne sehr viel zitierte Arbeiten haben kaum Einfluss
- Anzahl der Ko-Autoren nicht berücksichtigt
- Kein Unterschied zwischen Review und Paper
- Anzahl der Zitierungen ist Popularität aber nicht Relevanz
- Höhere Anzahl an Paper nötig (z.B. Évariste Galois der den mathematischen Begriff der „Gruppe“ definiert hat hätte einen H-index von nur 2!)
- Abgrenzung zwischen Autoren mit selbem Namen (!)
- Berücksichtigt nicht den Kontext von Zitaten

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Abschließende Bemerkungen

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Allgemeine Probleme **aller** Faktoren

- Basieren auf Zitierungen (Methodik prinzipiell sinnvoll?)
- Popularität aber nicht zwangsläufig wissenschaftlicher Wert wird durch Zitate erhoben
- Zitierkartelle
- Matthäus-Effekt („success breeds success“)
- Zitierungen ohne Kontext (negativ/positiv, Massenzitate in Einleitung, …)
  „Results show a significant improvement over Loser et al.“
  „We used the brilliant technique of Winner et al.“
- Langzeiteffekte einer Arbeit manchmal erst lange nach Tod des Autors
- Nicht alle Journale werden erfasst (Englische Sprache usw.)

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Mögliche Erweiterungen

- Normalisierung eines beliebigen Scores zu den eingesetzten Finanzmitteln
- Normalisierung eines Scores zu Anzahl der Co-Autoren
- Kreative Köpfe nötig für neue und bessere Beurteilungen.

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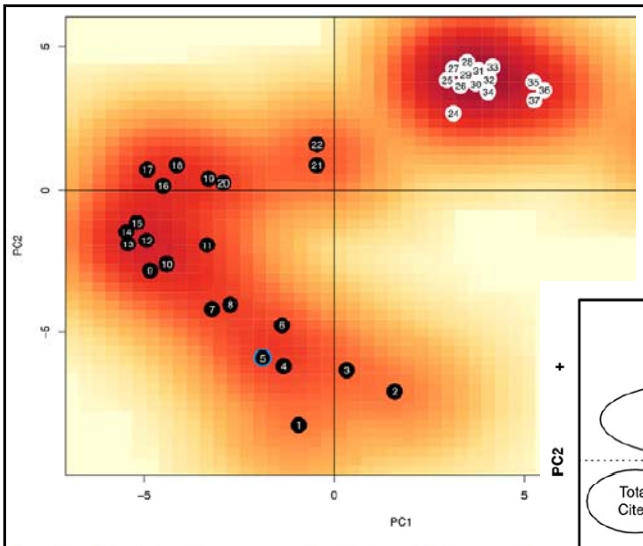

Figure 2. Correlations between 37 measures mapped onto first two principal components (c
Black dots indicate citation-based measures. White dots indicate usage-based measures. The Journal Impact
and 39 excluded.

Bollen et al. 2009

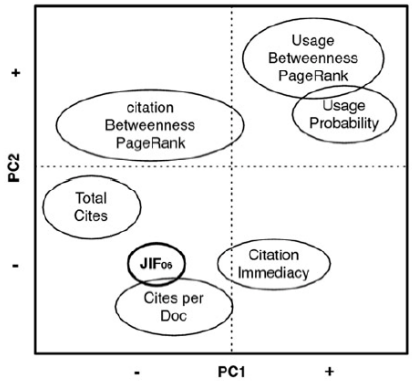

Figure 4. Schematic representation of PCA analysis shown in Fig. 2.

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Weitere Literatur

- Opthof T (1997) Sense and nonsense about the impact factor. Cardiovascular Research 33: 1–7.
- Seglen PO (1997) Why the impact factor of journals should not be used for evaluating research. British Medical Journal 314–497.
- Harter SP, Nisonger TE (1997) ISI's impact factor as misnomer: a proposed new measure to assess journal impact. Journal of the American Society for Information Science 48: 1146–1148.
- Bordons M, Fernandez MT, Gomez I (2002) Advantages and limitations in the use of impact factor measures for the assessment of research performance. Scientometrics 53: 195–206.
- PLoS Medicine (eds) (2006) The impact factor game. PLoS Med 3: doi:10.1371/journal.pmed.003029.
- Egghe L (1998) Mathematical relations between impact factors and average number of citations. Information Processing and Management 24: 567–576.
- Garfield E (1999) Journal impact factor: a brief review. Canadian Medical Association Journal 161: 979–980.

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Hands on Training: Journalbewertung

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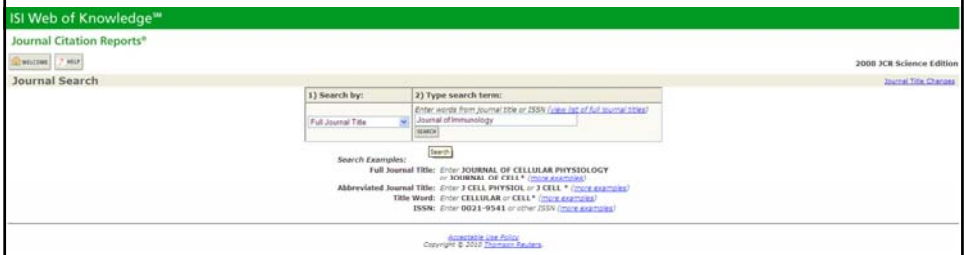
http://isiknowledge.com/

⇒Additional Resources - Journal Citation Reports - Search for a specific journal



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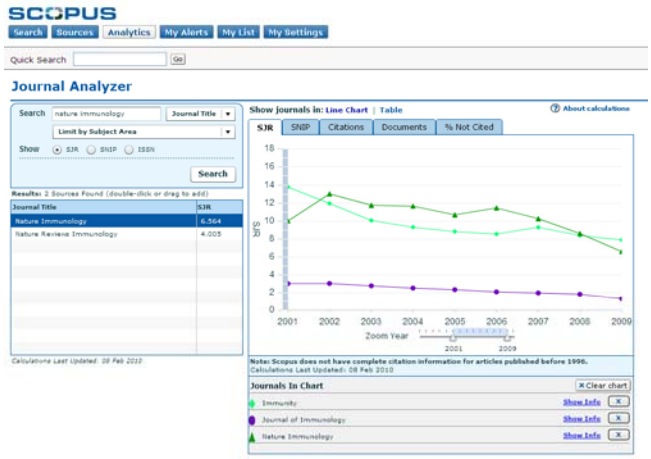
http://www.scopus.com/source/eval.url



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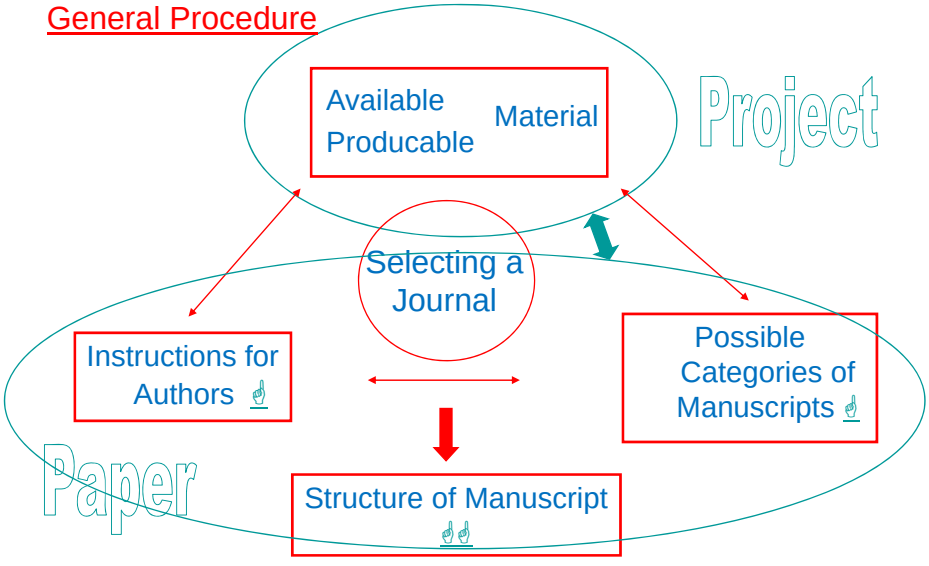
Unit 04:

Structure and Sections of a Paper

Structure & Sections of a Paper ctd.

General Procedure



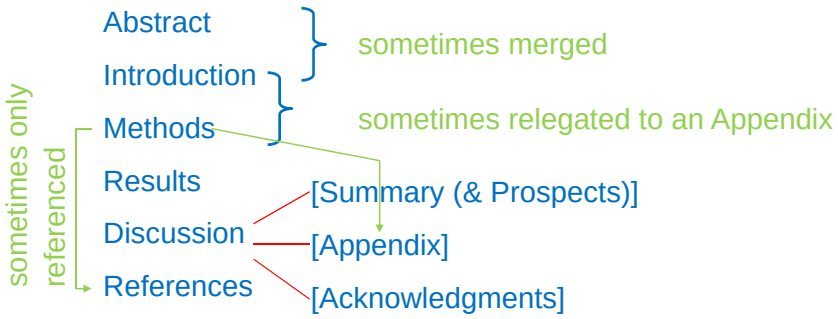
Structure & Sections of a Paper ctd.

General Procedure, Comments

- Jedes Journal gibt sehr bestimmt detaillierte und scheinbar gut begründete Regeln und Strukturen vor (deren Formulierung mitunter sogar als „Bevormundung“ bzw. „Zumutung“ erscheinen können).
- Diese Vorgaben sind jedoch bei verschiedenen Journals oft total unterschiedlich!

Structure & Sections of a Paper ctd.

„Canonical Structure“ of a full research paper:



Reproducing Results Published in the Literature

Special Trail:

Special Trail: Reproducing Results Published in the Literature

(a) Als Test (Eichung) der eigenen Methodik ☝

- Meßtechnik
- Präparationen
- Auswertemethoden
- Computerprogramme
- Statistik-Prozeduren

Ergebnis der Reproduktion wird Teil der Methods/Results/Discussion

- Reproduktion ok
- *„We were able to reproduce the results of author XXX, except for a typing error in eq. YY of ref. ZZZ“*
- *„we were not able to reproduce the results / a specific detail reported by author XXX. Instead we adopted the following procedure“*
- *„the method reported by XXX can be improved in several items: (i), (ii), (iii), etc.“*

Special Trail: Reproducing Results Published in the Literature ctd.

(a) Als Test (Eichung) der eigenen Methodik

- Meßtechnik
- Präparationen
- Auswertemethoden
- Computerprogramme
- Statistik-Prozeduren

(b) Als Inhalt der ganzen Arbeit

- Vergleich der österr. Ergebnisse mit anderen Ländern
- Performance einer neu entwickelten Methode im Vergleich zum „golden Standard“. (Often motivated by „methods“ of other paper.)

Special Trail: Reproducing Results Published in the Literature ctd.

(a) Als Test (Eichung) der eigenen Methodik

- Meßtechnik
- Präparationen
- Auswertemethoden
- Computerprogramme
- Statistik-Prozeduren

b) Als Inhalt der ganzen Arbeit

- Vergleich der österr. Ergebnisse mit anderen Ländern
- Performance einer neu entwickelten Methode im Vergleich zum „golden Standard“

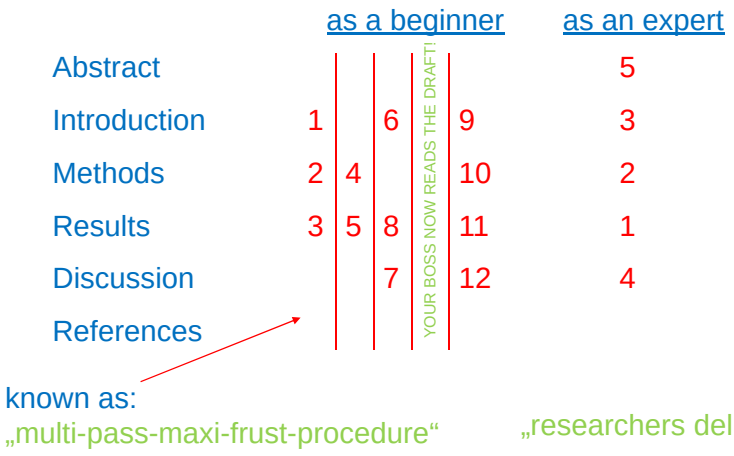
Reproducing results known from literature increases the credibility of new results contained in the article

End of Special Trail:

Reproducing Results Published in the Literature

Structure & Sections of a Paper ctd.

Typical WRITING SEQUENCES for a canonical structure



Instructions for the authors: circulation

Circulation

Circulation publishes articles related to research in and the practice of cardiovascular diseases, including observational studies, clinical trials, epidemiology, health services and outcomes studies, and advances in applied (translational) and basic research.

Manuscripts are examined by the editorial staff and usually evaluated by expert reviewers assigned by the editors. Both clinical and basic articles will also be subject to statistical review, when appropriate. Provisional or final acceptance is based on originality, scientific content, and topical balance of the journal. Decisions are communicated by email, generally within six weeks. The editors will not discuss a decision about a manuscript over the phone. All rebuttals must be submitted in writing to the editorial office.

How to Contact the Journal
How to Prepare a Manuscript
How to Submit a Manuscript
Revised Manuscripts
Accepted Manuscripts
Copyright Transfer Agreement
Key Word List
Subject Codes
Artwork Guidelines

How to Contact the Journal:

Joseph Loscalzo M.D., Ph.D.
Editor, Circulation
Boston University School of Medicine
560 Harrison Ave
Suite 502
Boston MA 02118
Phone: 617-414-8780
Fax: 617-414-8781
E-mail: circ@bu.edu

Online Submission: http://submit-circ.ahajour nals.org

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How to Prepare a Manuscript:

Circulation publishes several types of manuscripts under the umbrella of full-length articles. A brief description of each type follows:

Original Research Articles

Circulation considers all types of original research articles, including experiments conducted in human subjects, laboratory animals, and in vitro. Specific content areas of interest are as follows: arrhythmia, cardiovascular surgery, congenital heart disease, coronary heart disease, epidemiology, exercise physiology, genetics, health services and outcomes research, heart failure, hypertension, imaging, molecular cardiology, preventive cardiology, stroke, transplant, valvular heart disease, and vascular medicine.

Please note that we no longer have the Brief Rapid Communication and Rapid Track options available. All manuscripts are considered for expedited publication; however, if you feel that your work merits special consideration, please indicate this in your cover letter. If the editors agree with your assessment, every effort will be made to review the

manuscript within one week's time, publish the paper online within 10 days, and publish it in print within 5 weeks.

Review Series

Please note that the editors invite most review articles. However, unsolicited material will be considered for publication.

- Contemporary Reviews in Cardiovascular Medicine: Reviews will focus on topics of contemporary interest to the clinician. Overviews of natural history, diagnostic strategies, and treatment approaches will be included in this series.
- Basic Science for Clinicians: Articles will include cutting edge reviews of the scientific basis of cardiovascular disease mechanisms and treatments, and will include molecular cardiology, genetics, genomics, physiology, and pharmacology. Emphasis will be placed on the practical application – or translation – of a contemporary understanding of basic mechanisms of disease and treatment to clinical practice.
- Controversies in Cardiovascular Medicine: Controversial topics in the practice of cardiovascular medicine will be presented in this series. Opposite viewpoints will be presented in tandem, with rebuttal responses by both authors included.
- New Drugs and Technologies: Reviews published in this series will focus on drug therapies, technologies, and therapeutic strategies relevant to the practice of contemporary cardiovascular medicine. Newly approved therapies will be highlighted, in particular, in this series.

Special Sections

- Images in Cardiovascular Medicine: Clinical or basic science images or motion studies that illustrate important findings, provide insight into basic mechanisms responsible for cardiovascular disease, emphasize an abnormality, or elucidate a new therapy will be considered for publication either in print or online. The written portion of the submission should include a title page, descriptive text of no more than one paragraph and a figure legend.

- Book Reviews: Reviews of selected books in cardiovascular medicine and surgery, including books that present innovative concepts, books that describe state-of-the-art diagnostic and therapeutic methods or important advances, and textbooks will be reviewed in this section. Unsolicited book reviews will be considered for publication either in print or online. In addition, authors or publishers may submit books, as well as a list of suggested reviewers, to the editorial office at the address noted above.

- Correspondence: Letters to the Editor, which pertain directly to an article published in the journal within the preceding 12 weeks, will be considered for publication either in print or online. A letter must not exceed 400 words in length and must be limited to three authors and five references. They should not have tables or figures. Authors of the original article cited in the letter will be invited to reply. Editorials: the editors will solicit all editorials. Instructions pertaining to the writing of an editorial will be included with the request from the editorial office.

General Preparation Instructions:

- Maximum Word Length: 6000 words
  - Including title page, abstract, text, references, tables, and figure legends
- Maximum Number of References: 50
- Maximum Number of Figures and Figure Legends: 8
- Manuscript should be typed double-spaced, including title page, abstract, text, references, figure legends, and tables. Text should only appear on one side of the page. Acceptable formats are Word 95, 98, 2000 or WordPerfect.
- Leave a 1-inch margin on all sides. Do not use justified margins.
- Cite references, figures, and tables in numeric order. For review, acceptable figure formats are GIF, TIFF, EPS, JPEG, and single slides of Power Point.

Formats NOT supported are as follows: Object Linking and Embedding (OLE), Bitmap (.bmp), PICT (.pict), Excel (.xls), Photoshop (.psd), Canvas (.cnv), CorelDRAW (.cdr), and locked or encrypted PDFs. For publication, see

acceptable figure requirements under "Accepted Manuscripts" below.

- Use SI units of measure. A more conventionally used measurement may follow in parentheses. Make all conversions before manuscript submission.

- Please provide sex-specific data, when appropriate, in describing the outcomes of epidemiologic analyses or clinical trials; or specifically state that no sex-based differences were present.

- Consult the American Medical Association Manual of Style, 9th ed, Baltimore, Md, Williams & Wilkins, 1998, for style.

- Manuscripts must conform to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" http://www.icmje.org/.

- Assemble the manuscript in this order: Title page, abstract, text, acknowledgments, references, figure legends, tables, and figures.

Title Page

The title page (page 1, do not number) should contain these elements:

- Full title

- First author's surname and short title (not to exceed 50 characters, including spaces)

- Authors' names, academic degrees, and affiliations

- Name and complete address for correspondence (include street name and address as well as post office box, and address for reprints if different from correspondence)

- Fax number, telephone number and email address

- The total word count of the manuscript, including the title page, abstracts, text, references, tables and figures legends

- The Journal Subject Heads pertaining to the article. Please refer to the subject head list.

Abstract and Key Words

- Do not cite references in the abstract

- Limit use of acronyms and abbreviations. Define at first use acronym or abbreviation in parenthesis

- Be concise (250 words maximum)

- Use the following headings:

    - Background – rationale for study

    - Methods and Results – brief presentation of methods and presentation of significant results

    - Conclusions – succinct statement of data interpretation

- Insert three to five Key Words after abstract. Please refer to the key word list.

Text

- Typical main headings include Methods, Results, and Discussion

- Number pages

- Abbreviations must be defined at first mention

- Methods

    - Experimental animals: State the species, strain, number used, and pertinent descriptive characteristics. When describing surgical procedures, identify the preanesthetic and anesthetic agents used and the amounts,

concentrations, routes, and frequency of administration of each. Paralytic agents are not considered acceptable substitutes for anesthetics. For other invasive procedures on animals, report the analgesic or tranquilizing drug used. If none were used, provide justification for exclusion.

- Human studies: Indicate that the study was approved by an institutional review committee and that the subjects gave informed consent.
- Drugs: Give generic rather than trademark names of drugs.
- The generic chemical identification of all investigational drugs must be provided.
- The complete name and location of the manufacturer must be supplied for all reagents, equipment, and devices used in the Methods.

Acknowledgments

The Acknowledgments section recognizes all sources of support for research, plus substantive contributions of individuals. The Editorial Office must receive written, signed consent from each person recognized in the Acknowledgments, since the statement can imply endorsement of data and conclusions.

- Written consent is not required for personal staff; however, the role of each person named must be identified either in the Acknowledgments section or in a separate letter or email to the Editorial Office.
- Authors must completely spell out all grant funding agency abbreviations, with the exception of the NIH.

Conflict of Interest Disclosures

-

All potential conflicts of interest must be stated. This pertains to relationships with pharmaceutical companies, biomedical device manufacturers, or other corporations whose products or services are related to the subject matter of the article. Such relationships include, but are not limited to, employment by an industrial concern, ownership of stock, membership on a standing advisory council or committee, being on the board of directors, or being publicly associated with the company or its products. Other areas of real or perceived conflict of interest could include receiving honoraria or consulting fees or receiving grants or funds from such corporations or individuals representing such corporations.

References

-

Accuracy of reference data is the responsibility of the author

-

Verify all references against original sources

-

List all authors for each reference; do not use “et al.”

-

Cite references in numeric order according to first mention in the text. In the text, ensure accuracy of spelling and details of publication, i.e., the text citation should match the reference information.

-

Personal communications, unpublished observations, and submitted manuscripts are not legitimate references. They must be cited in the text only (not in the reference list) as follows: author name, degree(s) held, unpublished data, year.

-

Abstracts may be cited only if they are the sole source and must be identified in the reference as “Abstract.”

-

References must be from a full length publication in a peer reviewed journal

-

"In press" citations must have been accepted for publication and the name of the journal or book publisher must be included

Figures

-

Figure parts should be clearly labeled. Letters and locants must be uniform in size and style within each figure, and when possible, between figures. (The font size must be 10 point or higher.)

-

Avoid headings on the figure. Heading information should appear in the figure legend.

-

Line art should not contain hair lines, which are hard to reproduce

-

Supply a scale bar with photomicrographs

-

Provide double-spaced copy for figure legends on a separate page

-

Symbols and abbreviations must be defined in the figure or its legend

-

Limit white space between the panel and panel label

Tables

-

Begin each table on a separate page, double-spaced. Please remember that tables prepared with Excel are not accepted unless embedded within your text document.

-

The table number should be Arabic, followed by a period and brief title

-

Use same size type as in text

-

Supply a brief heading for each column

-

Indicate footnotes in this order: *, †, ‡, §, ||, , #, **

-

Do not use vertical lines between columns. Use horizontal lines above and below the column headings and at the bottom of the table only. Use extra space to delineate sections within the table.

-

Abbreviations used in the table must be defined in a footnote to the table.

Online Data Supplements

This optional section provides an opportunity for authors to present supporting materials to the manuscript. The manuscript appears both in the print version and online, but the Online Data Supplement appears only online. Please note that all supplements undergo peer review and must be submitted with the original submission of the manuscript.

Online Data Supplements can consist of the following:

- Expanded Methods and Results
- Additional Figures
- Additional Tables
- Video Files

If citations are made in an Online Data Supplement, the supplement must contain its own Reference Section, with references numbered sequentially beginning with the number 1.

Supplemental Materials Required for Review

- A copy of all submitted manuscripts mentioned in the article must be submitted as part of the review process
- A copy of all in press articles cited in the Reference section must be supplied for review by the editors and the reviewers

Ethical Policy

Manuscripts are considered on the understanding that they contain original material, that the manuscript and material within the manuscript have not been published and are not being considered for publications elsewhere in whole or in part in any language, including publicly accessible web sites or e-print servers, except as an abstract. The authors also certify that any and all other work in preparation, submitted, in press, or published that is potentially overlapping either in the actual data presented or in the conceptual approach is enclosed along with the original submission. Any material within the manuscript that has appeared elsewhere must be cross-referenced and permission to use or adapt the material must be received, in writing from the copyright holder.

Abstracts and Webcasts

If some or all of the work in the manuscript has been published or submitted in abstract form, and/or overlapping data exists, the following rules apply:

- The published or submitted abstract must accompany the submitted manuscript.
- The abstract cannot itself have been referenced in MEDLINE or PubMed.
- The potentially overlapping work and a separate explanation of the nature of any possible overlap with the submitted manuscript must accompany the submitted manuscript.

These restrictions generally do not apply to presentations or press reports published in connection with scientific meetings, or to poster presentations at scientific meetings that are videotaped, provided that the material has not been widely circulated, copyrighted or sold. Posting an audio recording, video recording, or short summary of a presentation

made at a professional meeting on the Internet would be considered as a meeting presentation by the American Heart Association and would compromise consideration of a submission. Direct release of information through press releases or media briefings may preclude publication.

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How to Submit a Manuscript:

All manuscripts must be submitted electronically. Before proceeding to the online submission site, please prepare your manuscript according to the instructions listed above under the heading, "How to Prepare a Manuscript." When your manuscript is ready for submission, please follow the instructions below.

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The Fourth Dimension of Life: Fractal Geometry and Allometric Scaling of Organisms

Geoffrey B. West,[1,2]* James H. Brown,[2,3] Brian J. Enquist[2,3]

Fractal-like networks effectively endow life with an additional fourth spatial dimension. This is the origin of quarter-power scaling that is so pervasive in biology. Organisms have evolved hierarchical branching networks that terminate in size-invariant units, such as capillaries, leaves, mitochondria, and oxidase molecules. Natural selection has tended to maximize both metabolic capacity, by maximizing the scaling of exchange surface areas, and internal efficiency, by minimizing the scaling of transport distances and times. These design principles are independent of detailed dynamics and explicit models and should apply to virtually all organisms.

Evolution by natural selection is one of the few universal principles in biology. It has shaped the structural and functional design of organisms in two important ways. First, it has tended to maximize metabolic capacity, because metabolism produces the energy and materials required to sustain and reproduce life; this has been achieved by increasing surface areas where resources are exchanged with the environment. Second, it has tended to maximize internal efficiency by reducing distances over which materials are transported and hence the time required for transport. A further consequence of evolution is the incredible diversity of body sizes, which range over 21 orders of magnitude, from 10^{-13} g (microbes) to 10^{8} g (whales). A fundamental problem, therefore, is how exchange surfaces and transport distances change, or scale, with body size. In particular, a longstanding question has been why metabolic rate scales as the 3/4-power of body mass, M (*1*).

Biological scaling can be described by the allometric equation $Y = Y_0 M^b$, where Y is a variable such as metabolic rate or life span, Y_0 is a normalization constant, and b is a scaling exponent (*1*). Whereas Y_0 varies with the trait and type of organism, b characteristically takes on a limited number of values, all of which are simple multiples of 1/4. For example, diameters of tree trunks and aortas scale as $M^{3/8}$ rates of cellular metabolism and heartbeat as $M^{-1/4}$, blood circulation time and life span as $M^{1/4}$, and whole-organism metabolic rate as $M^{3/4}$. The question has been why these exponents are multiples of 1/4 rather than 1/3 as expected on the basis of conventional Euclidean geometric scaling.

Recently, we presented a model which suggested that the explanation could be found in the fractal-like architecture of the hierarchical branching vascular networks that distribute resources within organisms (*2*). The model accurately predicts scaling exponents that have been measured for many structural and functional features of mammalian and plant vascular systems. It is not clear, however, how this model can account for the ubiquitous 3/4-power scaling of metabolic rate in diverse kinds of organisms with their wide variety of network designs, and especially in unicellular algae and protists, which have no obvious branched anatomy. Here we present a more general model, based on the geometry rather than hydrodynamics of hierarchical networks, that does not require the existence of such explicit structures and that can account for the pervasive quarter-power scaling in biology.

We conjecture that organisms have been selected to maximize fitness by maximizing metabolic capacity, namely, the rate at which energy and material resources are taken up from the environment and allocated to some combination of survival and reproduction. This is equivalent to maximizing the scaling of whole-organism metabolic rate, B. It follows that B is limited by the geometry and scaling behavior of the total effective surface area, a, across which nutrients and energy are exchanged with the external or internal environment. Examples include the total leaf area of plants, the area of absorptive gut or capillary surface area of animals, and the total area of mitochondrial inner membranes within cells. In general, therefore, $B \propto a$. It is important to distinguish a from the relatively smooth external surface, or "skin," enclosing many organisms. We further conjecture that natural selection has acted to maximize a subject to various constraints while maintaining a compact shape. This is equivalent to minimizing the time and resistance for delivery of resources by minimizing some characteristic length or internal linear distance of the hierarchical network.

Broadly speaking, two sets of variables can be used to describe the size and shape of an organism: a conventional Euclidean set describing the external surface, A, enclosing the total volume, V; and a "biological" set describing the internal structure, which includes the effective exchange area, a, and the

Table 1. Examples of the biological network variables l, a, and v in plant, mammalian, and unicellular systems.

Variable	Plant	Mammal	Unicellular
l	Mean path length from root to leaf, or between leaves	Mean circulation distance from heart to capillary, or between capillaries	Mean distance from cell surface to mitochondria and between mitochondria
a	Total area of leaves; area of absorptive root surface	Total area of capillaries; gut surface area	Actual cell surface area; total surface area of mitochondrial inner membranes
v	Total wood volume; total cell volume	Total blood volume; total tissue, or cell, volume	Volume of cytoplasm

[1]Theoretical Division, MS B285, Los Alamos National Laboratory, Los Alamos, NM 87545, USA. [2]The Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, NM 87501, USA. [3]Department of Biology, University of New Mexico, Albuquerque, NM 87131, USA.

*To whom correspondence should be addressed. E-mail: gbw@lanl.gov

Table 2. The scaling of length, area, and volume associated with biological networks compared to the conventional Euclidean case. Allometric relations with M assume that tissue density is constant.

Variable	Conventional Euclidean	Fractal biological
Length	$L \propto A^{1/2} \propto V^{1/3} \propto M^{1/3}$	$l \propto a^{1/3} \propto v^{1/4} \propto M^{1/4}$
Area	$A \propto L^2 \propto V^{2/3} \propto M^{2/3}$	$a \propto l^3 \propto V^{3/4} \propto M^{3/4}$
Volume	$V \propto L^3 \propto M$	$v \propto l^4 \propto M$

total volume of biologically active material, v (Table 1). Although it is clearly a very difficult technical problem to calculate a, there are some general scaling properties that it must obey regardless of the detailed dynamics. Before examining these, it is instructive to consider the simpler case of how the area of skin, or external physical surface, of an organism or any Euclidean object, scales.

We first show how, and under what conditions, the classic 2/3-power Euclidean scaling law for A arises (*3*). In general, A is some complicated function of the various length scales, L_1, L_2, L_3, . . ., which parameterize size and shape: $A = A(L_1, L_2, L_3, \ldots)$. On purely dimensional grounds this can be expressed as $A(L_1, L_2, L_3, \ldots) = L_1^2\Phi(L_2/L_1, L_3/L_1, \ldots)$, where Φ is a dimensionless function of the dimensionless ratios L_2/L_1, and so on. Suppose that we change the overall size by making a uniform scale transformation on all the lengths, L_i: $L_i \rightarrow L_i' = \Lambda L_i$ (i = 1, 2, 3, . . .), where Λ is some arbitrary number. This similarity transformation preserves the shape of the object as its size varies. In this case Φ clearly does not change, so A responds in the following manner:

$$A \rightarrow A' \equiv A(\Lambda L_1, \Lambda L_2, \Lambda L_3, \ldots) = \Lambda^2 A(L_1, L_2, L_3, \ldots) \quad (1)$$

The Euclidean volume of the object, $V = V(L_1, L_2, L_3, \ldots)$, can be treated similarly; on dimensional grounds, $V = L_1^3\Psi(L_2/L_1, L_3/L_1, \ldots)$, where Ψ is a dimensionless function of the dimensionless ratios L_2/L_1, and so on. After the scale transformation, which leaves Ψ unchanged,

$$V \rightarrow V' \equiv V(\Lambda L_1, \Lambda L_2, \Lambda L_3, \ldots) = \Lambda^3 V(L_1, L_2, L_3, \ldots) \quad (2)$$

From Eqs. 1 and 2, it is clear that $A'/V'^{2/3} = A/V^{2/3}$, that is, $A \propto V^{2/3}$; similarly, $L_i \propto V^{1/3}$. Notice that these are consistent with writing $V = AL$, where L is some length that is a function of the L_i and scales as $L \rightarrow L' = \Lambda L$. Assuming a size-invariant uniform density, these then give the conventional Euclidean geometric scaling results $L \propto L_i \propto M^{1/3}$ and $A \propto M^{2/3}$. These should apply, for example, to the body length and skin area of vertebrates.

The above argument ignores two basic facts of biology. First, the metabolic process relies on the hierarchical fractal-like nature of resource distribution networks. Examples include the macroscopic branching vascular networks of plants and animals and the complicated ultrastructure within cells. We emphasize that the network can be "virtual"; it need not be a physical system of branching tubes, so long as it exhibits hierarchical pathways of material flow. Second, although organisms vary widely in size, these networks terminate at invariant units of fixed size that can be characterized by a biological length scale, l_0. At the whole-organism level they include capillaries of mammals and leaves of plants. At the cellular and molecular levels, they include mitochondria and chloroplasts, and the metabolic rate-limiting cytochrome oxidase and RuBisCo (ribulose-1,5-bisphosphate carboxylase-oxygenase) molecules within these organelles. We now modify the above scaling argument by incorporating these two important biological features.

For a given type of organism the effective surface area is a function of the invariant length, l_0, together with various independent length scales, l_i, that parameterize its fractal-like structure. It is important to distinguish biological length scales, l_i, which characterize the interior networks of the organism, from Euclidean ones, L_i, which characterize its exterior shape. For example, in a mammal one of the l_i is the length of the aorta, whereas one of the L_i is the overall body length; similarly, in unicellular organisms one of the l_i is the distance between mitochondria, whereas one of the L_i is the cell radius. Working as before, the effective exchange area, a, can be expressed as

$$a(l_0, l_1, l_2, \ldots) = l_1^2\phi\left(\frac{l_0}{l_1}, \frac{l_2}{l_1}, \ldots\right) \quad (3)$$

where ϕ is a dimensionless function of the dimensionless ratios l_2/l_1, and so on. Now, as the size of the organism changes, l_0 remains fixed. Consider, then, an arbitrary scale transformation on the network: $l_i \rightarrow l_i' = \lambda l_i$ (i = 1, 2, 3, . . .) keeping l_0 fixed. The analog of Eq. 1 reads

$$a \rightarrow a' \equiv a(l_0, \lambda l_1, \lambda l_2, \lambda l_3, \ldots) = \lambda^2 l_1^2\phi\left(\frac{l_0}{\lambda l_1}, \frac{l_2}{l_1}, \frac{l_3}{l_1}, \ldots\right) \quad (4)$$

Because l_0 is fixed, the right-hand side is no longer simply proportional to λ^2 as in Eq. 1. Although we do not know the λ-dependence of ϕ, we can parameterize it as a power law reflecting the hierarchical fractal-like organization:

$$\phi\left(\frac{l_0}{\lambda l_1}, \frac{l_2}{l_1}, \frac{l_3}{l_1}, \ldots\right) = \lambda^{\epsilon_a}\phi\left(\frac{l_0}{l_1}, \frac{l_2}{l_1}, \frac{l_3}{l_1}, \ldots\right) \quad (5)$$

where ϵ_a is an "arbitrary" exponent. In this case

$$a \rightarrow a' \equiv a(l_0, \lambda l_1, \lambda l_2, \lambda l_3, \ldots) = \lambda^{2+\epsilon_a} a(l_0, l_1, l_2, l_3, \ldots) \quad (6)$$

The crucial point here is that, because of the presence of l_0, a does not scale simply as λ^2. The assumption of a power law does not require the existence of an idealized mathematical self-similar fractal, which has no "fundamental" length scale such as l_0. Even though the actual physical network is not a pure fractal because it has terminal units of fixed size and can be asymmetric, it is still natural to use the fractal language. We can therefore interpret the exponent in Eq. 6, $(2 + \epsilon_a) \equiv d_a$, as the fractal dimension of a (*4*). As such, it satisfies $0 \leq \epsilon_a \leq 1$. The lower limit, $\epsilon_a = 0$, is the conventional Euclidean case discussed above; the upper limit, $\epsilon_a = 1$, represents the "maximum fractality" of a volume-filling structure in which the effective area scales like a conventional volume.

Similarly, the biological volume, v, associated with a, can be expressed as $v(l_0, l_1, l_2, l_3, \ldots) = l_1^3\psi(l_0/l_1, l_2/l_1, l_3/l_1, \ldots)$, where ψ is a dimensionless function of the dimensionless ratios l_2/l_1, and so on. This represents the volume of protoplasm or biologically active material in the organism. It is not necessarily identical to V, because most organisms contain empty spaces enclosed by the skin; however, $v \propto V$. By analogy with ϕ, we assume that, under a scale transformation, ψ transforms as a power with an exponent ϵ_v: $\psi(l_0/\lambda l_1, l_2/l_1, l_3/l_1, \ldots) = \lambda^{\epsilon_v}\psi(l_0/l_1, l_2/l_1, l_3/l_1, \ldots)$. Consequently, v scales as

$$v \rightarrow v' \equiv v(l_0, \lambda l_1, \lambda l_2, \lambda l_3, \ldots) = \lambda^{3+\epsilon_v} v(l_1, l_2, l_3, \ldots) \quad (7)$$

with $0 \leq \epsilon_v \leq 1$. Combining Eqs. 6 and 7 straightforwardly leads to $a \propto v^{(2+\epsilon_a)/(3+\epsilon_v)}$.

Now v can always be expressed as $v = al$, where l is some length characteristic of the internal structure of the organism. We can therefore relate the scaling behaviour of v to that of a and l, with l expected to be proportional to one of the l_i. It is instructive, however, to consider the more general case and write $l = l(l_0, l_1, l_2, \ldots) = l_1\sigma(l_0/l_1, l_2/l_1, \ldots)$, as was done with a and v; σ is a dimensionless function, analogous to ϕ and ψ. This scales as $l \rightarrow l' = \lambda^{1+\epsilon_l} l$, where $d_l \equiv 1 + \epsilon_l$ is the fractal dimension of l, with $0 \leq \epsilon_l \leq 1$. Consequently, $v \rightarrow v' = \lambda^{3+\epsilon_a+\epsilon_l} v$ which, when compared to Eq. 7, gives $\epsilon_v = \epsilon_a + \epsilon_l$ (*4*). Assuming a uniform constant density, so that $v \propto M$, then gives

$$a \propto v^{\frac{2+\epsilon_a}{3+\epsilon_a+\epsilon_l}} \propto M^{\frac{2+\epsilon_a}{3+\epsilon_a+\epsilon_l}} \quad (8)$$

Our conjecture that organisms have evolved so as to maximize the scaling of a implies that the exponent, $b \equiv (2 + \epsilon_a)/(3 + \epsilon_a + \epsilon_l)$, must be maximized. It is straightforward to verify that this occurs when $\epsilon_a = 1$ and $\epsilon_l = 0$, thereby giving $b = 3/4$. Metabolic rate should therefore scale as $B \propto M^{3/4}$, regardless of the details of the branching architecture (*5*) and dynamics governing the metabolic process and distribution of resources.

This has several important consequences. First, because $a \propto M^{3/4}$, the number of invariant units in the network also scales as $M^{3/4}$. Second, the result $\epsilon_l = 0$, which gives $d_l = 1$, implies that internal distances associated with the network are not themselves fractal. This is consistent with the constraint that times for supply of resources, and therefore path lengths, should be minimized. Third, and perhaps most significant, is that $\epsilon_a = 1$, which implies that the fractal dimension of a is $d_a = 3$ rather than the canonical Euclidean value of 2. Thus, the effective surface area is "maximally fractal" and the network structure is volume-filling. It is in this sense that organisms have exploited a fourth spatial dimension (*6*) by evolving hierarchical fractal-like structures to maximize resource acquisition and allocation. More specifically, the area of the effective exchange surface scales as if it were a volume: $a \rightarrow a' = \lambda^3 a$, (rather than $\lambda^2 a$), whereas characteristic internal lengths associated with the fractal-like structure scale as $l \rightarrow l' = \lambda l$. Consequently, the biological volume scales as $v \rightarrow v' = \lambda^4 v$, so that in addition to $a \propto M^{3/4}$, we also have $l \propto l_i \propto M^{1/4}$.

These relationships should apply to all organisms that have been selected to maximize metabolic power under the constraint of minimizing internal transport distances and thereby having a maximally compact three-dimensional body shape (Table 2). For organisms such as roundworms and flatworms, which may be functionally one- or two-dimensional, these geometric relationships can be appropriately modified. In D dimensions, for example, our argument straightforwardly generalizes to give $a \propto B \propto M^{D/(D+1)}$ as in (*2*) and $l \propto M^{1/(D+1)}$ for the biological variables, and $A \propto M^{(D-1)/D}$ and $L \propto M^{1/D}$ for the Euclidean ones. These relationships are not expected to apply to a few organisms, such as filamentous algae and fungi, that have been selected to maximize linear dimensions so as to sparsely occupy a maximal volume.

The present derivation is more general than our original model in which it was assumed that resource distribution networks were volume-filling and that energy dissipated was minimized. Incorporating dynamics led to a complete description of the physics and geometry of the networks that were shown to be fractal-like with 1/4-power scaling (*2*, *7*). Versions of this physically explicit model show how the universal geometric derivation given here is realized in a variety of systems in different kinds of organisms. It is no accident, therefore, that many biological networks exhibit area-preserving branching, even though different anatomical designs exploit different hydrodynamic principles (*2*, *7*). Unlike the genetic code, which has evolved only once in the history of life, fractal-like distribution networks that confer an additional effective fourth dimension have originated many times. Examples include extensive surface areas of leaves, gills, lungs, guts, kidneys, chloroplasts, and mitochondria, the whole-organism branching architectures of trees, sponges, hydrozoans, and crinoids, and the treelike networks of diverse respiratory and circulatory systems. It is not surprising, therefore, that even unicellular organisms exhibit quarter-power scaling, including the 3/4-power scaling law for metabolic rate. Although living things occupy a three-dimensional space, their internal physiology and anatomy operate as if they were four-dimensional.

Quarter-power scaling laws are perhaps as universal and as uniquely biological as the biochemical pathways of metabolism, the structure and function of the genetic code, and the process of natural selection. The vast majority of organisms exhibit scaling exponents very close to 3/4 for metabolic rate and to 1/4 for internal times and distances. These are the maximal and minimal values, respectively, for the effective surface area and linear dimensions for a volume-filling fractal-like network. On the one hand, this is testimony to the power of natural selection, which has exploited variations on this fractal theme to produce the incredible variety of biological form and function. On the other hand, it is testimony to the severe geometric and physical constraints on metabolic processes, which have dictated that all of these organisms obey a common set of quarter-power scaling laws. Fractal geometry has literally given life an added dimension.

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In vivo location and mechanism of EDHF-mediated vasodilation in canine coronary microcirculation

YASUHIRO NISHIKAWA, DAVID W. STEPP, AND WILLIAM M. CHILIAN
Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226

Nishikawa, Yasuhiro, David W. Stepp, and William M. Chilian. In vivo location and mechanism of EDHF-mediated vasodilation in canine coronary microcirculation. *Am. J. Physiol.* 277 (*Heart Circ. Physiol.* 46): H1252–H1259, 1999.—Responses of epicardial coronary arterioles to ACh were measured using stroboscopic fluorescence microangiography in dogs (n = 38). ACh (0.1 and 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ic) dilated small (<100 μm, 11 ± 2 and 19 ± 2%, respectively) and large (>100 μm, 6 ± 3 and 13 ± 3%, respectively) arterioles at baseline. Combined administration of N^{ω}-monomethyl-L-arginine (L-NMMA; 1.0 μmol/min ic) and indomethacin (10 mg/kg iv) eliminated ACh-induced dilation in large coronary arterioles but only partially attenuated that in small arterioles. Suffusion of a buffer containing 60 mM KCl (high KCl) completely abolished cromakalim-induced dilation in arterioles and in combination with L-NMMA plus indomethacin completely blocked ACh-induced dilation in small arterioles. This indicated that the vasodilation to ACh that persists in small arterioles after administration of L-NMMA and indomethacin is mediated via a hyperpolarizing factor. The ACh-induced vasodilation remaining after L-NMMA and indomethacin was completely blocked by the large-conductance potassium-channel antagonist iberiotoxin or by epicardial suffusion of miconazole or metyrapone, inhibitors of cytochrome *P*-450 enzymes. These observations are consistent with the view that endothelium-derived hyperpolarizing factor (EDHF) is a product of cytochrome *P*-450 enzymes and produces vasodilation by the opening of large-conductance potassium channels. We conclude that ACh-induced dilation in large coronary arterioles is mediated mainly by nitric oxide (NO), whereas, in small arterioles both NO and EDHF mediate dilation to ACh. These data provide the first direct evidence for an in vivo role of EDHF in small coronary arterioles.

coronary circulation; endothelium-dependent dilation; hyperpolarization; endothelium-derived hyperpolarizing factor

THE ENDOTHELIUM releases a variety of vasodilators, including nitric oxide (NO), prostacyclin (PGI_2), and the yet unidentified endothelium-derived hyperpolarizing factor (EDHF) (32). The existence of EDHF was initially based on observations that ACh caused hyperpolarization and relaxation of isolated vascular preparations occurred in the presence of NO synthase/cyclooxygenase blockade, including coronary (13, 16, 30, 34), mesenteric (5), and cerebral arteries (32).

Inhibitors of endothelial NO synthase completely abolished in vivo ACh-induced dilation of the human (19) and canine epicardial coronary arteries (23), suggesting that EDHF has no role in in vivo ACh-induced dilation in epicardial conductance vessels. In contrast, in vitro studies of isolated epicardial coronary arteries report relaxation to ACh after inhibition of NO and PGI_2 production (13, 29, 34). In the coronary microcirculation, most studies have reported that inhibition of NO synthase did not block completely ACh-induced vasodilation in dogs (15, 17, 36) or humans (19). Interestingly, inhibition of NO synthase produced different effects on ACh-induced dilation in large and small arterioles (15, 17). Specifically, inhibition of NO synthase completely blocked ACh-induced dilation in large but not in small arterioles (17). Because a component of microvascular dilation to ACh seems to be resistant to NO synthase inhibition, it is not unreasonable to suggest that ACh-induced dilation may have different mediators at different sites within the coronary microcirculation (22).

Conventionally, the "residual" dilation to ACh that remains after inhibition of NO synthase and cyclooxygenase has been attributed to EDHF. However, more recently, some investigators have found that in arterial endothelial cells ACh-induced production of an endothelium-derived factor that produced hyperpolarization could be blocked by antagonists to the cytochrome *P*-450 enzyme family (7, 14). A recent report concluded that coronary arteriolar EDHF-induced dilation occurred in vivo, because the dilation was inhibited by antagonists of cytochrome *P*-450 (37). Importantly, the role of EDHF in the coronary microvascular dilation to ACh has not been unequivocally verified, because results consistent with hyperpolarization were not presented. We state this with conviction, because given the many differences in regulation between macrovascular arteries and resistance microvessels, the assumption that a class of inhibitors (cytochrome *P*-450 enzyme antagonists) block the same vasodilator (EDHF) in the two classes of vessels should not be accepted without question. Moreover, a role for EDHF in the residual dilation to ACh appeared improbable, because Komaru et al. (17) found that tetraethylammonium (TEA), the large-conductance potassium-channel antagonist, did not block this dilation in vivo.

Thus a physiological in vivo role of EDHF in coronary microvascular adjustments remains unclear. Unequivocal information of EDHF-mediated responses is best accomplished by measurement of membrane potentials, or potassium channel conductance, which is impossible to accomplish in the beating heart. However, we designed experiments to examine the role of EDHF in ACh-induced dilation by using interventions designed to "clamp" membrane potential in a depolarized state to block the effects of a hyperpolarizing factor (elevated KCl) or to block the opening of large-conductance potassium channels (iberiotoxin). Therefore, the purpose of this study was to test the hypotheses that *1*)

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EDHF produces vasodilation of coronary microcirculation in vivo; *2*) EDHF-mediated vasodilation occurs via activation of large-conductance calcium-activated potassium (K_{Ca}) channels; and *3*) EDHF is a metabolite of *P*-450 enzymes. Our study has provided unequivocal evidence for the existence of EDHF in the coronary microcirculation and the mechanism by which it produces vasodilation.

METHODS

General Preparation

Surgical preparation. Adult mongrel dogs of either sex (7–12 kg) were anesthetized with pentobarbital sodium (35 mg/kg iv), intubated, and ventilated with room air. A femoral artery and a femoral vein were catheterized for measurement of arterial pressure, arterial blood gases, and pH and drug administration. A catheter was inserted into the carotid artery and advanced into the left ventricle (LV) for measurement of LV pressure and LV d*P*/d*t*. The heart was exposed via a left thoracotomy, and the pericardium was incised. The proximal left circumflex or anterior descending coronary artery was isolated, and a 24-gauge Teflon catheter was placed for measurements of coronary arterial pressure and intracoronary administration of drugs.

High-frequency jet ventilation. After these procedures, the animal was ventilated on a high-frequency jet ventilator (supplemented with 100% O_2 at a pressure of 9–12 pounds/square in.) synchronized to the cardiac cycle. A pressure regulator connected to a solenoid valve was triggered from the LV d*P*/d*t* and remained open for 30–40 ms each cardiac cycle. The advantage of this procedure is that respiratory influences on cardiac motion are eliminated because the jet ventilation system produces almost no pulmonary movement. Arterial blood gases and pH were monitored throughout the study and were maintained within normal limits (pH 7.35–7.45, P_{CO_2} 25–40 mmHg, P_{O_2} 100–220 mmHg). All experimental procedures were performed to conform with the "Guiding Principles for Research Involving Animals and Human Beings". The protocol of this study was approved by the Animal Care and Research Committee in the Medical College of Wisconsin.

Microvascular Preparation

Intravital microscopy. The intravital microscope system consisted of a Leitz Ploemopak (Wild Leitz, Rockleigh, NJ) mounted on a vertical support over an X-Y adjustable table. The use of the X-Y adjustable table allowed for fine movements of the position of the heart within the field of view. The Ploem system was used with either a polarizing filter to minimize reflected light from the surface of the heart or filters for fluorescence microscopy. A total magnification of the video image of approximately ×200 was achieved by the microscope objective (Leitz L10 × 10, numerical aperture 0.22) in conjunction with a ×10 magnification eyepiece and video display. The resolution of this configuration is 2 μm.

Illumination of the epicardial surface of the LV was accomplished with a xenon stroboscopic light source (Chadwick-Helmuth; 100-W Xenon Arc, El Monte, CA) synchronized with the cardiac cycle (1 pulse/cycle). A computer (Quadra 950; Macintosh) received input from the LV d*P*/d*t* and subsequently triggered the strobe at the same point in time (late diastole) per cardiac cycle. With this system, the heart and microvasculature appear to be "fixed," because the epicardium is in view for a short instant (15–25 ms) at the same time of cardiac cycle.

Cardiac motion was partially restrained by inserting two 22-gauge needles attached to a rod. By this method, the horizontal movement of the microvascular field was restricted, and vertical movements were nearly abolished. Without pinning, the majority of studies would be impossible because the vessels would move in and out of the field of view and therefore in and out of focus. It has been determined that both resting and maximal myocardial blood flow are the same in normal and "restrained" areas of the myocardium (10), indicating that resting vasomotor tone and vasodilator reserve are not compromised by this procedure.

Diameter measurements. Video images of blood vessels were made with a Cohu intensified charge-coupled device video camera (Cohu, San Diego, CA) and were recorded with a frame digitizer. Control of video acquisition was achieved with LabView software (National Instruments, Austin, TX). A series of camera frames were digitized and stored on the hard disk of a Macintosh Quadra 950. Images were later replayed on a high-resolution black and white video monitor for diameter analysis with a Power Mac computer utilizing image-processing software (Image 1.28c; NIH Research Services Branch, Bethesda, MD). The microvasculature was visualized using fluorescence video microscopy. Small bolus injections (50–100 ml) of fluorescein isothiocyanate-labeled dextran were made via the coronary catheter. The existence of a well-defined anatomic landmark (branching point, etc.) was the major criterion used in the selection of a blood vessel.

Experimental Protocol

Protocol 1: Verification that KCl suffusion blocks dilation by hyperpolarization (cromakalim-induced vasodilation). Five nanomoles of cromakalim in 2 ml saline solution were injected manually within 2 s into the coronary artery ($n = 6$). Microvascular measurements were performed within 2 min after the cromakalim injection. After 10 min, 10 nmol of cromakalim were injected. A 60 mM KCl solution (high KCl) was suffused continuously onto the microvascular field of interest. This dose of KCl should depolarize cells by lowering the equilibrium potential for the outward diffusion of potassium from cells. Fifteen minutes later, administration of cromakalim was repeated. This protocol was performed to ensure that the protocol for suffusion of the KCl solution could completely inhibit dilation induced by hyperpolarization. Microvascular responses to papaverine (2 mg ic), an agonist that signals independently of potassium channels, in the presence of the KCl suffusion were measured to verify that the microvasculature was still capable of dilation.

Protocol 2: Contribution of NO, PGI_2, and EDHF to ACh-induced vasodilation. Measurements were made during the following conditions ($n = 9$): *1*) baseline; *2*) ACh (0.1 and 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ic for 5 min each); *3*) baseline; *4*) N^{ω}-monomethyl-L-arginine (L-NMMA; 1 μmol/min ic for 10 min) and indomethacin (10 mg/kg iv) to block the production of NO and prostanoids, respectively; *5*) ACh during L-NMMA plus indomethacin; *6*) baseline; *7*) suffusion of the high-KCl buffer onto the epicardium; *8*) ACh (during L-NMMA + indomethacin + high KCl); *9*) baseline; and *10*) papaverine (2 mg ic). Papaverine was administered to verify that the vessels were responsive to agonists during the high-KCl suffusion. At least 5 min was placed between each ACh infusion. In another three animals, the same protocols were repeated with higher doses of L-NMMA (3 μmol/min ic) and indomethacin (30 mg/kg iv) to demonstrate that higher doses of these antagonists would not completely antagonize ACh-induced dilation of coronary arterioles.

Protocol 3: Role of ATP-sensitive and calcium-activated potassium channels to EDHF-induced vasodilation. Measurements were made during the following conditions ($n = 9$): *1*) baseline; *2*) ACh (0.1 and 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ic for 5 min each); *3*) baseline; *4*) L-NMMA (1 μmol/min ic for 10 min) and indomethacin (10 mg/kg iv); *5*) ACh (during L-NMMA + indomethacin); *6*) baseline; *7*) iberiotoxin [IBTX, selective inhibitor of high-conductance K_{Ca} channels, 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 20 min]; *8*) ACh (during L-NMMA + indomethacin + IBTX); *9*) baseline; and *10*) papaverine (2 mg ic). The dose of IBTX was shown to block bradykinin-induced increases in coronary blood flow during NO synthase antagonism (nitro-L-arginine methyl ester) without any effects on the cardiac contractile function (29). In six dogs, the same protocol was repeated with the substitution of glibenclamide (1 mg /kg iv) for IBTX.

Protocol 4: Role of P-450 metabolite pathway in EDHF-induced vasodilation. Measurements were made during the following conditions ($n = 5$): *1*) baseline; *2*) ACh (0.1 and 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ic for 5 min each); *3*) baseline; *4*) L-NMMA (1 μmol/min ic for 10 min) and indomethacin (10 mg/kg iv); *5*) ACh during L-NMMA plus indomethacin; *6*) baseline; *7*) miconazole suffusion (*P*-450 enzyme inhibitor, 30 mM, 20 min); *8*) ACh during L-NMMA plus indomethacin plus miconazole; *9*) baseline; and *10*) papaverine (2 mg ic). In addition to its inhibitory action on cytochrome *P*-450 enzymes, miconazole can potentially inhibit other enzymes containing heme moieties that synthesize vasoactive substances, e.g., lipoxygenase-induced production of leukotrienes. Thus, in two dogs, the same protocol was repeated using metyrapone (10 mM, 2-methy-1,2-di-3-pyridyl-1-propanone), which inhibits cytochrome *P*-450 enzymes. Metyrapone shows greater specificity for cytochrome *P*-450 enzymes than miconazole and does not bind to heme groups (18, 24).

Drugs

ACh was prepared as a 10 μg/ml solution in 0.9% saline. Indomethacin was dissolved in 95% ethanol and made up to a 10 mg/ml solution in 0.9% saline. L-NMMA was prepared as a 0.27 mg/ml solution in 0.9% saline brought to a physiological pH (between 7.3 and 7.5) by addition of small aliquots of 1 mol/l NaOH immediately before use. Krebs solution (in mM: 142 NaCl, 5.4 KCl, 2.0 $CaCl_2$, 1.2 $MgCl_2$, 11.0 dextrose, and 18 bicarbonate) and high-KCl solution (in mM: 102 NaCl, 45.4 KCl, 2.0 $CaCl_2$, 1.2 $MgCl_2$, 11.0 dextrose, and 18 bicarbonate) were bubbled with 20% O_2-5% CO_2-75% N_2. Miconazole (metyrapone) was initially dissolved in 100% ethanol and was subsequently dissolved in the Krebs perfusate to provide a final concentration of 30 (10) μM. All drugs were obtained from Sigma Chemical.

Statistical Analysis

Microvascular diameters in response to ACh infusion in the presence of inhibitors for NO, prostaglandins, K_{Ca} channel, and/or *P*-450 enzymes were calculated as a percent change from the data before ACh infusion at each state. Thus +% and −% indicate dilation and constriction, respectively. Data were analyzed separately in view of the well-recognized differences in physiological behavior between vessels of these size classes (large arterioles >100 μm, small arterioles <100 μm). Two-way repeated measures of ANOVA were used to assess the effects of ACh infusion on the diameters and hemodynamics in each condition. If ANOVA showed significant difference, then a paired *t*-test was used. To show significant vasodilation to ACh, the percent changes in diameter were compared with zero using a paired *t*-test. The data are presented as means ± SE. *P* value <0.05 was considered significant.

RESULTS

Systemic and Microvascular Hemodynamics

Mean aortic blood pressure and heart rate did not change significantly during any of the interventions. All vessels studied were 38–258 μm in diameter. The average baseline diameters of large (>100 μm) and small (<100 μm) arterioles under control conditions were similar among the various protocols.

Protocol 1: Verification that KCl Suffusion Blocks Dilation by Hyperpolarization (Cromakalim-Induced Vasodilation)

Figure 1 shows the scatter plot of relation of diameter and the percent changes in diameter in response to cromakalim (5 and 10 nmol ic), which was used as a challenge to verify block of hyperpolarization-induced dilation by KCl suffusion. Five and ten nanomoles of cromakalim caused 4 ± 2 and 9 ± 2% increases in diameter in large arterioles and 8 ± 4 and 17 ± 6% increases in small arterioles ($P < 0.05$), respectively. The average percent change of diameter to high-KCl suffusion was −7 ± 2% (−24 ± 3%, $P < 0.05$ vs. 0) for small arterioles and 6 ± 1% (−17 ± 0.6%, $P < 0.05$ vs. 0) for large arterioles. Cromakalim-induced dilation was completely blocked by KCl suffusion. This suggested that the suffusion was effective in blocking hyperpolarization-mediated dilation by the ATP-sensitive potassium (K_{ATP}) channel opener cromakalim.

Protocol 2: Contribution of NO, PGI_2, and EDHF to ACh-Induced Vasodilation

Figure 2 illustrates a scatter plot of the relation of baseline diameters to the percent changes in diameter during administration of low (*A*) and high (*B*) doses of ACh during *1*) control conditions, *2*) L-NMMA plus indomethacin, and *3*) L-NMMA plus indomethacin plus high KCl. Figure 3 shows the average data of the percent changes in diameter to ACh at each condition in

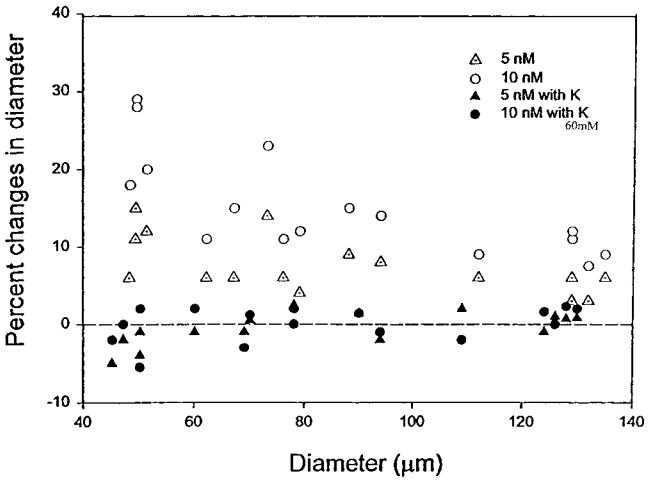

Fig. 1. Scatter plots showing the percent changes in diameter to 5 and 10 nM of ic cromakalim injection before and during high-potassium suffusion. Potassium suffusion abolished completely cromakalim-induced vasodilation in large and small arterioles.

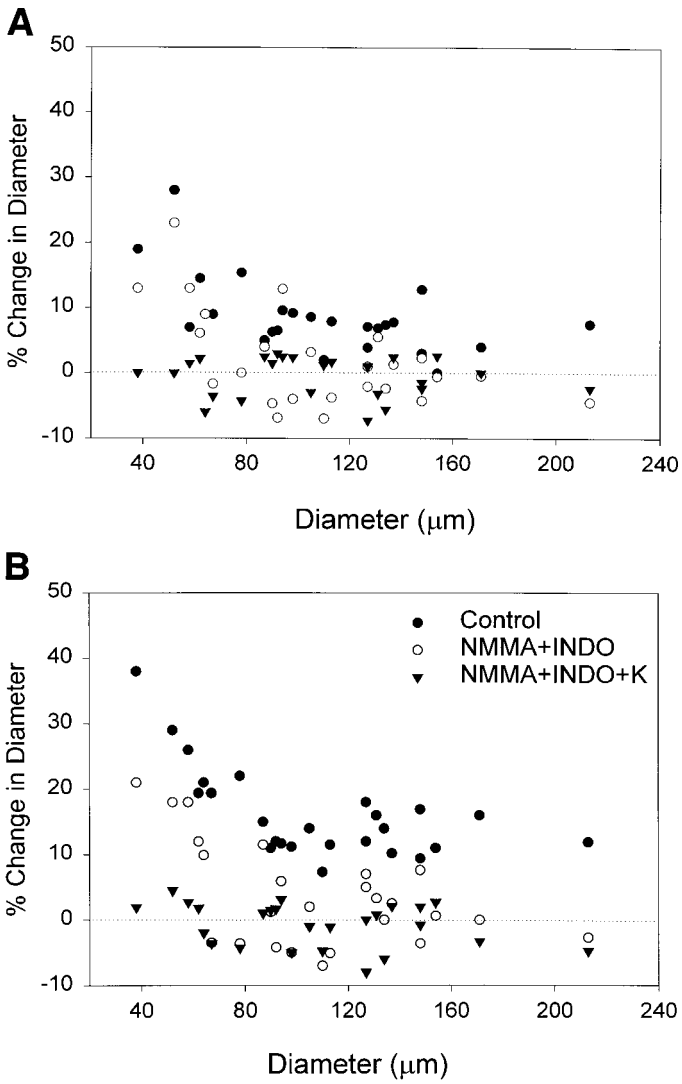

Fig. 2. Scatter plots showing the percent changes in diameter to 0.1 (*A*) and 0.5 (*B*) $\mu g \cdot kg^{-1} \cdot min^{-1}$ ic ACh. In large arterioles, N^{ω}-monomethyl-L-arginine (L-NMMA) with indomethacin (Indo) causes almost complete blockade on ACh-induced vasodilation (○) compared with control conditions (●). In contrast, small arteries still dilate to ACh in the presence of L-NMMA and indomethacin, although to a lesser degree. Additional administration of potassium suffusion with L-NMMA and indomethacin causes complete blockage on ACh-induced vasodilation (▼).

large (*A*) and small (*B*) arterioles. Small arterioles dilated by 11 ± 6 and 19 ± 8% at 0.1 and 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively, and large arterioles dilated by 6 ± 3 and 13 ± 3% ($P < 0.05$ vs. small arterioles). L-NMMA and indomethacin caused small but significant constriction of the large (−6 ± 5%, $P < 0.05$) and small arterioles (−7 ± 7%, $P < 0.05$). In small arterioles, ACh-induced dilation was only partially attenuated by the combination blockade with L-NMMA and indomethacin, but additional suffusion of KCl abolished the vasodilatory response. In contrast, L-NMMA and indomethacin completely blocked the dilation of large arterioles to ACh. Although the vessels did not dilate to ACh during L-NMMA plus indomethacin plus high KCl, they were still capable of dilation to papaverine (15 ± 3 and 21 ± 2%, large and small arterioles, respectively, $P <$ 0.05 vs. baseline).

Protocol 3: Role of K_{ATP} and K_{Ca} Channels to EDHF-Induced Vasodilation

Figure 4 shows a scatter plot of the relation between the baseline diameter and the percent changes in diameter in response to ACh (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during *1*) control conditions, *2*) L-NMMA plus indomethacin, and *3*) L-NMMA plus indomethacin plus IBTX. Figure 5 shows averaged percent changes in diameter to ACh in each condition in large (*A*) and small (*B*) arterioles. L-NMMA and indomethacin caused small, but significant, constriction of the large (−5 ± 2%) and small arterioles (−9 ± 5%). Baseline diameters did not change in response to IBTX (−1 ± 2%), but the L-NMMA- and indomethacin-resistant vasodilation to ACh in small arterioles was blocked by administration of IBTX.

Baseline diameter did not change in response to glibenclamide (−3 ± 3%). In small coronary arterioles, glibenclamide did not affect vasodilation to ACh (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) after L-NMMA and indomethacin (17 ± 2 vs. 16 ± 2% before and after glibenclamide, respectively). Papaverine caused 16 ± 4 and 14 ± 5% in-

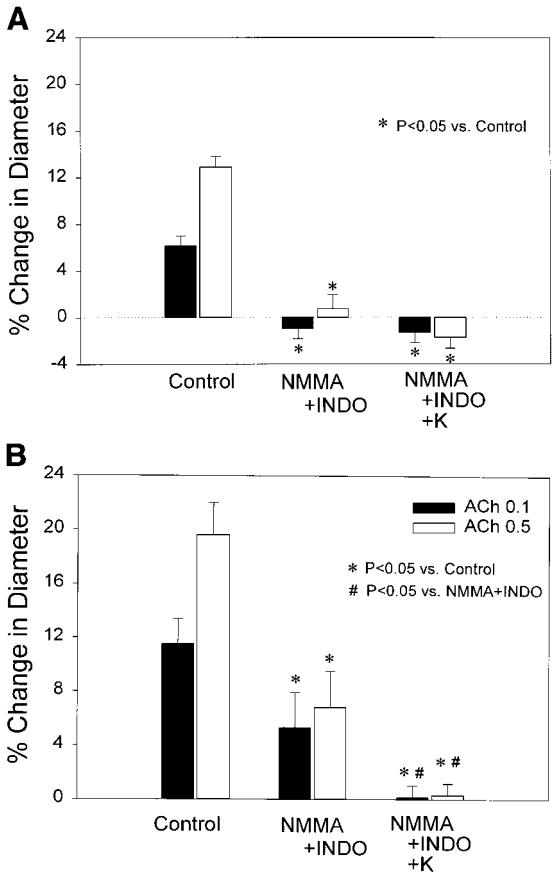

Fig. 3. Bar graphs showing averaged data of the percent changes in diameter in control, L-NMMA + indomethacin (Indo), and L-NMMA + indomethacin + potassium suffusion (K) in large arterioles (*A*) and small arterioles (*B*).

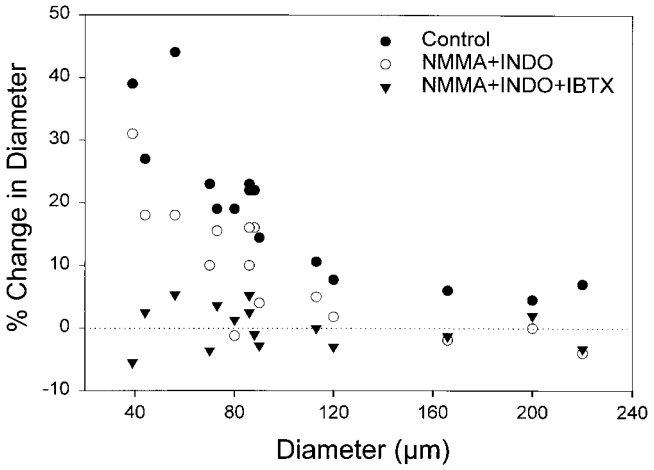

Fig. 4. Scatter plots showing the percent changes in diameter to 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of ACh in control (●), L-NMMA + indomethacin (○), and L-NMMA + indomethacin + iberiotoxin (IBTX) (▼). ACh-induced dilation in small arterioles is partially blocked by L-NMMA and indomethacin and completely blocked by additional administration of IBTX.

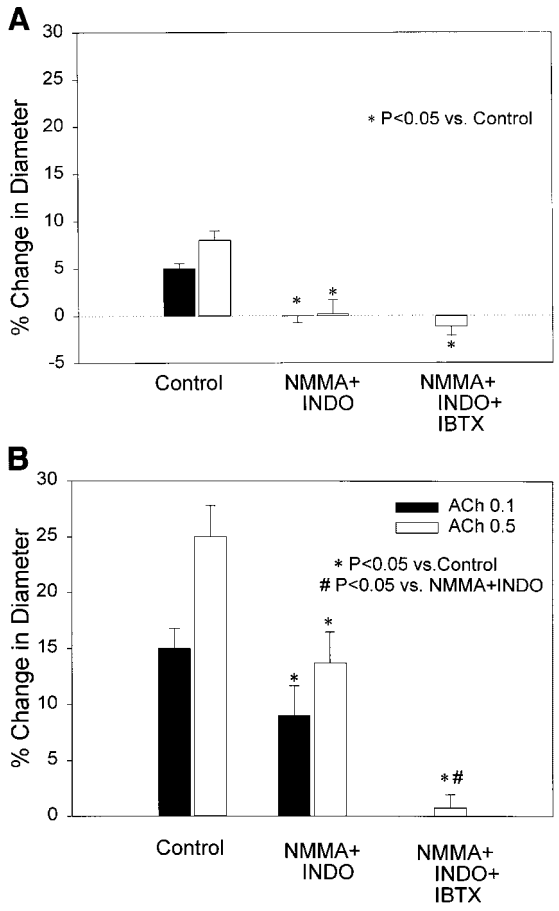

Fig. 5. Bar graphs showing averaged data of the percent changes in diameter to 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of ACh in control, L-NMMA + indomethacin, and L-NMMA + indomethacin + IBTX in large arterioles (*A*) and small arterioles (*B*).

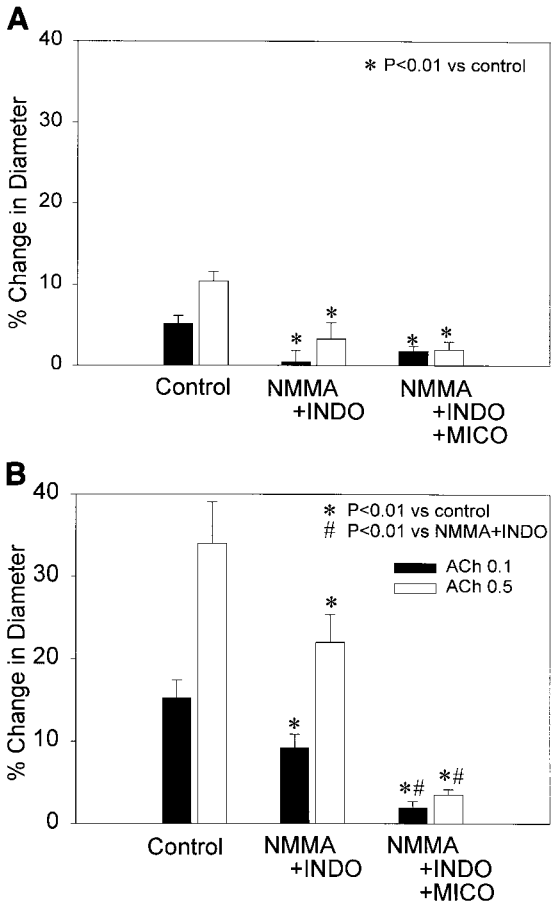

Fig. 6. Bar graphs showing averaged data of the percent changes in diameter in baseline, with L-NMMA and indomethacin and with L-NMMA, indomethacin, and miconazole (Mico) in large (*A*) and small (*B*) arterioles.

creases in diameter of large and small arterioles, respectively ($P < 0.01$).

Protocol 4: Role of P-450 Metabolite Pathway in EDHF-Induced Vasodilation

Miconazole suffusion after L-NMMA and indomethacin increased the baseline diameter by 6%. Figure 6 shows the averaged data of percent changes in diameter to ACh at each condition in large (*B*) and small (*A*) coronary arterioles. In small arterioles, L-NMMA and indomethacin partially blocked the ACh-induced vasodilation, and additional administration of miconazole with L-NMMA and indomethacin caused complete blockade of vasodilation in small arterioles. In five vessels (76 ± 5 μm) with metyrapone, ACh-induced L-NMMA/indomethacin-resistant vasodilation was significantly inhibited by metyrapone (14 ± 2 vs. 3 ± 1% before and after metyrapone, respectively, at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of ACh; 22 ± 6 vs. 6 ± 2% before and after metyrapone, respectively, at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of ACh).

DISCUSSION

The major new findings we have made are that the in vivo ACh-induced dilation of coronary microvessels is unequivocally mediated by a hyperpolarizing factor,

independent of NO and prostanoids. This factor appears to signal through large-conductance K_{Ca} but not via K_{ATP} channels. We also found that an inhibition of cytochrome *P*-450 blocks the EDHF response, which confirms a previous report (37). We conclude that EDHF, in the canine coronary microcirculation, is a product of cytochrome *P*-450 enzymes. Relevant to these conclusions are several issues concerning the limitations of the methodology, the role, mechanisms of action, and identity of EDHF, and physiological implications.

Limitations of Methodology

Because of technical problems of measuring membrane potentials in coronary microvessels in the beating heart preparation, which would unequivocally verify hyperpolarization, we suffused a buffer of 60 mM KCl onto the epicardium to clamp membrane potential in a depolarized state and thus prevent membrane hyperpolarization. This dose of KCl would depolarize many cell types on the epicardial surface, e.g., cardiac myocytes and nerve cells, in addition to smooth muscle cells. The relatively mild contraction that we observed (<10% decrease in diameter) could be due to the release of neurotransmitter or vasoconstrictor paracrine factors. However, we do not believe this possibility complicates our findings, because to our knowledge such factors do not prevent the actions of hyperpolarizing factors. In addition, suffusion of KCl did not cause any alterations in hemodynamics, which means that the effects of the suffusion were likely confined to the superficial subepicardium. Cromakalim-induced vasodilation was completely blocked by topical suffusion of the high-KCl buffer, indicating that the suffusate prevents vasodilation mediated by hyperpolarization, i.e., potassium channel opening. Thus this in vivo observation strongly supports that L-NMMA/indomethacin-resistant but KCl-sensitive vasodilation to ACh is mediated by a hyperpolarizing factor.

The specificity of miconazole and IBTX as antagonists of *P*-450 enzymes and K_{Ca} channels, respectively, is an important assumption in our experiment. Miconazole inhibits all cytochrome *P*-450 enzymes and can affect smooth muscle contraction (38). However, it caused only small changes in baseline diameter and completely inhibited L-NMMA/indomethacin-resistant dilation to ACh. Likewise, IBTX caused only minor changes in vessel tone but blocked the L-NMMA- and indomethacin-resistant ACh-induced dilation. Moreover, papaverine dilated the coronary microvessels in the presence of miconazole or IBTX. These results further suggest that data obtained using miconazole, metyrapone, and IBTX can be interpreted on the basis of inhibition of cytochrome *P*-450 enzyme activity and large-conductance potassium channels, respectively. Taken together, these observations indicate that miconazole and IBTX have negligible nonspecific effects on the reactivity of smooth muscle.

Role of EDHF in Vasodilation

Nagao et al. (25) showed that nitro-L-arginine abolished relaxation to ACh in the aorta, pulmonary artery, and common iliac arteries in rats, whereas as much as 80% of the maximal relaxation persisted in the mesenteric and femoral arteries and the majority of the renal arteries studies. Chen et al. (9) showed that membrane hyperpolarization may account for 20–25% of the relaxation by ACh in large vessels such as pulmonary artery and aorta of the rat. Thus contribution of EDHF in the ACh-induced vasodilation varies in different parts of the circulation. It appears that a larger component of the relaxation is mediated by EDHF in the more peripheral and slightly smaller vessels. Our data, in the presence of EDHF-dependent vasodilation in small arterioles but not in large arterioles, support the concept that the small arterioles are more exquisitely controlled by K_{Ca} channels than the upstream vessels.

We presume that the hyperpolarizing factor is produced by the endothelium, and the factor is EDHF. Although we did not verify endothelial production, previously our laboratory found that in vivo ablation of coronary microvascular endothelium with CO_2 gas completely abolished dilation to ACh (12). Thus we believe the hyperpolarizing factor is endothelium derived. This view is also consistent with a plethora of reports demonstrating that ACh-induced dilation is endothelium dependent.

Mechanisms of Action of EDHF

Although EDHF-mediated vasodilation has been suggested to occur by activation of potassium channels, the subtype of potassium channels involved in endothelium-dependent hyperpolarization remains uncertain in vivo in coronary microcirculation. We observed that glibenclamide, an antagonist of K_{ATP} channels, had no significant effect on EDHF-induced vasodilation, which is consistent with a previous observation in epicardial coronary arteries of the guinea pig (8). IBTX completely blocked L-NMMA/indomethacin-resistant vasodilation to ACh in small coronary arterioles, which was similar to the blockade produced by high-KCl suffusion. This strongly indicated that EDHF-mediated vasodilation was mediated through activation of K_{Ca} channels in the coronary microcirculation in vivo. One previous study (17) showed that TEA (topical administration, large-conductance K_{Ca} channel) failed to block ACh-induced vasodilation in canine small coronary arterioles in the presence of L-NMMA. However, the investigators did not ascertain the efficacy of blockade of potassium channels by epicardial suffusion of TEA. Our study is notably different from this previous work, because we found a role for hyperpolarization via opening of K_{Ca} channels in ACh-induced vasodilation. Specifically, we established that KCl suffusion inhibited the vasodilatory action of a hyperpolarizing factor by showing that this intervention prevented dilation via the K_{ATP}-channel agonist cromakalim. We also observed that the component of ACh-induced dilation remaining after combined blockade with L-NMMA plus indomethacin

was dependent on K_{Ca} channel activation. This was concluded from experiments using intracoronary infusion of IBTX, a specific antagonist of large-conductance K_{Ca} channels. This dose of IBTX was shown to block bradykinin-induced coronary vasodilation after inhibition of NO production (29). Finally, the ACh-induced dilation remaining after blockade with L-NMMA plus indomethacin was inhibited by suffusion with the high-KCl solution. Our data are compatible with previous in vitro data showing the importance of K_{Ca} channels in EDHF-induced relaxation in isolated coronary arteries (2, 8, 20) and suggest a role for EDHF in ACh-induced dilation of coronary microvessels.

In contrast to NO, a role of EDHF in the regulation of resting vasomotor tone in vivo has not been clearly demonstrated. Depolarization of vascular smooth muscle after removal of endothelium (4, 26, 35) suggested that there might be tonic release of EDHF at the resting state, whereas others (9, 26) do not show that removal of endothelium does not affect the resting membrane potential in isolated blood vessels. These contradictory results may be explained by the possibility of damage of the smooth muscle cells during the removal procedure. Recently, one study in an open-chest anesthetized canine model showed that IBTX did not change resting myocardial blood flow in nonischemic myocardium (29). In our study, the microvascular diameter did not change after administration of IBTX with L-NMMA. This indicates that, unlike NO, EDHF probably is not released in a tonic manner in the coronary circulation of a beating heart. This may be explained by the results of Bauersachs et al. (3), who reported that NO exerts a feedback inhibition on EDHF; thus vasodilation due to EDHF is most prevalent only after NO production has been blocked.

Identity of EDHF

A recent study has shown that EDHF activity may be attributed to the action of epoxyeicosatrienoic acids (EETs) formed from arachidonic acid by the action of cytochrome *P*-450 (7). The chemical nature of EDHF remains obscure, and patch-clamp studies have demonstrated that EETs increase the activity of the K_{Ca} channels in coronary arterial smooth muscle cells (14), suggesting that activation of K_{Ca} channels plays a role in EDHF-mediated vascular dilatation. Because we found that EDHF production was blocked after inhibiting cytochrome *P*-450 and that its dilation was antagonized by IBTX, we suggest that EDHF is an EET or a metabolite of this pathway.

Physiological Significance and Conclusions

The endothelial production of NO is impaired in a variety of pathological conditions, such as hypertension, diabetes, heart failure, and hyperlipidemia (11). Endothelial vasomotion controlled by NO will be lost with progression of the disease process. In contrast, it remains unclear whether these diseases cause similar impairments in EDHF-mediated vasodilation. Endothelium-dependent hyperpolarization is present in coronary arteries form patients with different cardiac diseases (28). Carotid arteries in rabbits with a high-cholesterol diet suggest an increased EDHF-mediated vasodilation in the presence of reduced production of NO (27). Recent several studies have shown that hypertension results in a compensatory increase in the activity of potassium channels (21, 31), and possibly, increased synthesis/release of the putative hyperpolarizing factors (1, 6). These data suggest that the EDHF-mediated response is spared or even augmented in the presence of endothelial dysfunction of NO production.

In conclusion, we have demonstrated that ACh produces dilation of small coronary arterioles via activation of K_{Ca} channels and that EDHF appears to be a cytochrome *P*-450 metabolite. Because at rest 55% of total coronary resistance is distal to the 100-μm arterioles (10) and EDHF appears to have its major action confined to these small resistance vessels, it has the potential to greatly modify total coronary resistance and flow. An improved understanding of the physiological mechanisms for EDHF-mediated vasomotor adjustment will help in clinical evaluation and therapy for patients with coronary heart disease.

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Address for reprint requests and other correspondence: Y. Nishikawa, Dept. of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226 (E-mail: yasu@mcw.edu).

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Unit 05:

Structure and Sections of a Paper

Structure & Sections of a Paper ctd.

(See example: AJP-article for reference!)

Abstract

- Das Abstract ist der richtige Ort um „mit der Tür ins Haus zu fallen“:

  „Mice (N=25) were premedicated with Y2β (2ml/g) and randomized for treatment (0.1 ml Biopolit i.m.) vs. control according to the investigator‘s shoe size. Treated mice showed significantly ($p<0.05$) lower reflexes than controls. We conclude that BioPolit is effective in decreasing reflexive responses.

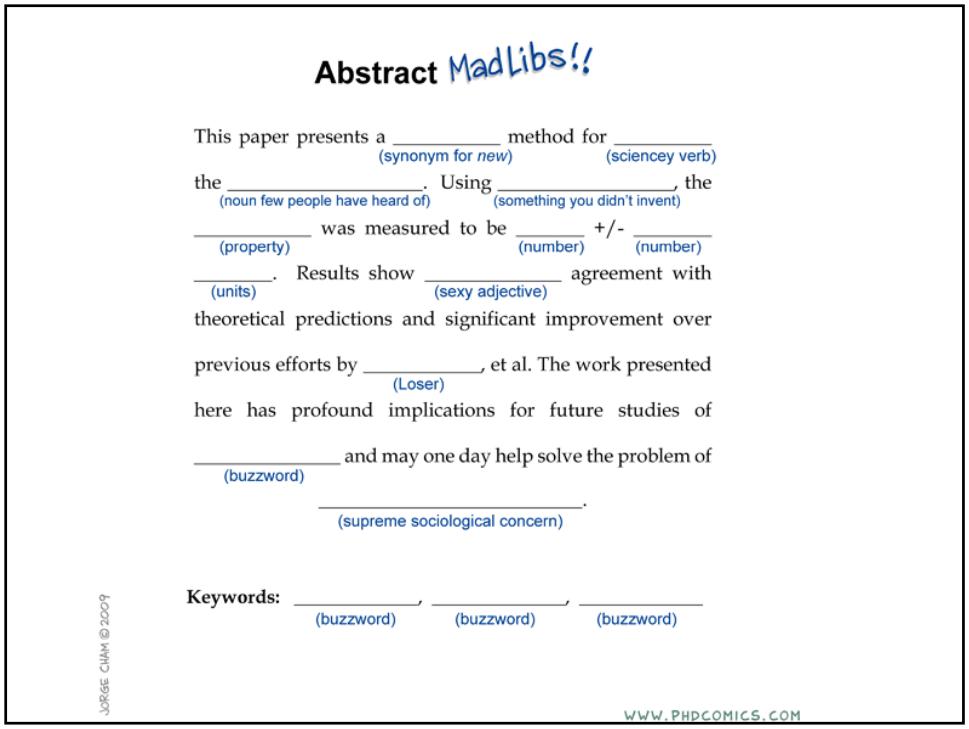
- [Erst mit Beginn der Introduction kehren Sie zurück zu Ihren guten Manieren und bieten dem Leser glatten Text !]

Structure & Sections of a Paper ctd.

Abstract, ctd.

- strikte Längenbegrenzung einhalten
- Nüchterne, „schmucklose“ Aufzählung dessen, was in der Arbeit „geleistet“ wurde (keine Motivation, keine Bewertung etc.).
- Quantitative Ergebnisse nennen, z.B. „Enzyme activity increased by 25 ± 2% in the treated versus the placebo group ($p < 0.05$).
- Verweis auf „Explanations & Relations“, die geleistet wurden: *„Our findings explain/confirm/contradict the results reported by...“*

- Abstract zuletzt verfassen (oder x-mal umschreiben)
- Abstract ist „wichtigster“ Teil der Arbeit (wegen Literaturdatenbanken!)



Structure & Sections of a Paper ctd.

Introduction

- Historie der wissenschaftlichen Entwicklung und Begriffsbildung
  „Over the last decade.....". „Many approaches have been made...."
- Give survey over important, related concepts
- Provide references to own previous work
- Report compatible and conflicting results previously published in the literature, see appendix at end of section
- As Final part of the introduction:
  Motivate the present work !
  „Despite numerous efforts on this subject (references 1-87) up to now no concept has been presented to comprehensivly solve the puzzle 007. In this work not only previous results will be explained on the basis of a new theory but we also provide a systhesis for the previously unknown substance XYαZ, which crucially.....

Structure & Sections of a Paper ctd.

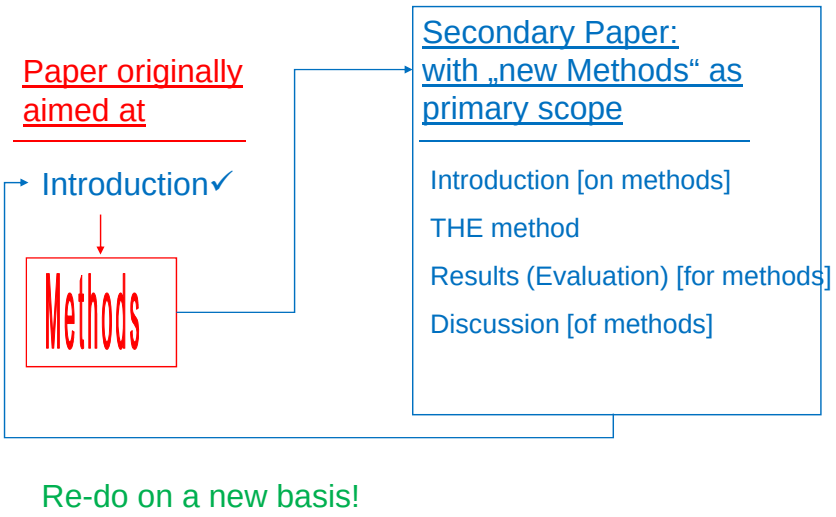
Methods (example: AJP-article)

- Methods what for ?
  - Technical information for the reader, basis for critical judgement, see appendix at end of section
  - documentation („proof") that the work was carried out according to current technical standards & expertise
  - $\Rightarrow$*„Clean methods yield trustable results....."*.
- Topics described in Methods:
  - Nomenclature, abbreviations, formulae (math., chem.)
  - details of preparation
  - study protocols
  - fulfilment of guidlines (regarding patients, animals)
  - statistical analysis (description, justification)
  - bio-technical-, bio-engineering, informatics - support
- Don't anticipate results !

Special Trail

on Side Steps induced by „Methods“

Special Trail on Side Steps induced by „Methods“



Re-do on a new basis!

Special Trail on Side Steps induced by „Methods“

Paper originally aimed at

- Introduction ✓
- Methods ✓
- Results ✓
- Discussion ✓

Secondary Paper: with „new Methods“ as primary scope

- Introduction [on methods]
- THE method
- Results (Evaluation) [for methods]
- Discussion [of methods]

Re-do on a new basis!

Special Trail on Side Steps induced by „Methods“

What happens to the Publication Schedule?

a)
- Interrupt original work
- establish (& publish) new methods
- resume original work

→ 2 high quality papers

b)
- Finish original work, disregarding the need/possibility for advanced methods.
  Risk of Rejection, have to aim at rather low quality journal!
- establish & publish advanced methods
- Re-Do original work with new methods

→ 2 high quality papers, 1 run of the mill paper

c)
- Bounce back and forth between original work, new methods and a Re-Do. Spend a year or two in these activities and finally get lost.

→ no papers

Special Trail on Side Steps induced by „Methods“

BEWARE:

- Finding „advanced methods“ may disintegrate a publication schedule
- Finding „advanced methods“ calls for clear decisions to stay on track!

End of Special Trail

on Side Steps induced by „Methods“

Special Trail:

Reproducing Results Published in the Literature

Special Trail: Reproducing Results Published in the Literature

a) Als Test (Eichung) der eigenen Methodik

- Meßtechnik
- Präparationen
- Auswertemethoden
- Computerprogramme
- Statistik-Prozeduren

Ergebnis der Reproduktion wird Teil der Methods/Results/Discussion

- Reproduktion ok
- *„We were able to reproduce the results of author XXX, except for a typing error in eq. YY of ref. ZZZ“*
- *„we were not able to reproduce the results / a specific detail reported by author XXX. Instead we adopted the following procedure“*
- *„the method reported by XXX can be improved in several items: (i), (ii), (iii), etc.“*

Special Trail: Reproducing Results Published in the Literature ctd.

(a) Als Test (Eichung) der eigenen Methodik

- Meßtechnik
- Präparationen
- Auswertemethoden
- Computerprogramme
- Statistik-Prozeduren

b) Als Inhalt der ganzen Arbeit

- Vergleich der österr. Ergebnisse mit anderen Ländern
- Performance einer neu entwickelten Methode im Vergleich zum „golden Standard“

Reproducing results known from literature increases the credibility of new results contained in the article

End of Special Trail:

Reproducing Results Published in the Literature

Unit 06:

Structure and Sections of a Paper

Structure & Sections of a Paper ctd.

Results (example: AJP-article)

- are the Key Part of the Work !
- Create sub-sections with meaningful sub-headings
  ✍ check: Would sub-headings outline the main results and conclusions (if they would appear in a table of contents) ?
  See annotated example: immunity-article
- Facts only, no beliefs, no feelings, no perspective, no future...
- Usable display elements:
  - Text with embedded numbers
  - tables
  - figures

  } which one to use?
  - [additional material (e.g. on WEB)]

Have Elements of Results Ready?

Figures (+ legends, captions)	⇔	Which results are worthy for figures ? • key issues • surprising results • results requiring halve-tone display • schematic drawings (cycles, procedures...) Text explaning the figures
Tables (headings, legends)	⇔	should supplement, not duplicate figures findings aiming at a numerical (quantitative) rather than an intuitive understanding
Citable results (references)	⇔	which part of the work is confirmed in the literature ? Can I risk to contradict established results ? Should I address or leave out tricky problems ?

Structure & Sections of a Paper ctd.

Discussion(example: AJP-article)

- Summarize your own work and relate it to previous work
- Make transparent, which assumptions underly the present work
- Address limitations to methods and results
- range (scope) for the validity of results
- sensitivity of results to changes in preconditions & assumptions
- Explain the significance of your work (clear cut words)

[Summary (& Prospects), may be implicit or as a last paragraph]

- Which problems are still unsolved ? Make conjectures !
- Which results are still lacking ?
  Propose coming studies? (May be dangerous.)
  „... much more work is to be done to finally scrutinize the relation between blood flow and the gravity particle $\Omega_2 W$....."

Special Trail:

More Results, motivated by discussion

Special Trail: More Results, motivated by discussion

If new questions are raised by results of present work:

What to do if:

- preconditions have to be changed due to results of present work ?
- the methods should be modified due to results of present work ?
- ..... And
- Supplementary measurements/results would allow to explain/remove contradictions between present work and the literature

Only for didactical reasons or to increase readability:
Exceptionally one may include supplementary results in the discussion!

This style violates format requirements but possibly increases acceptance of paper by reviewer

End of Special Trail:

More Results, motivated by discussion

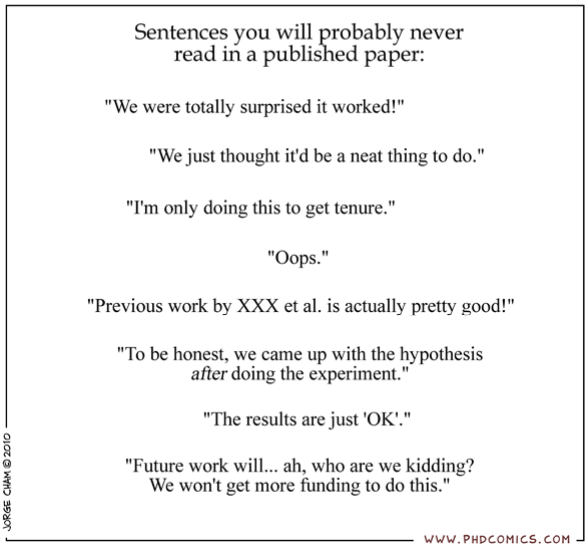
Structure & Sections of a Paper ctd.

References

- Use the reference-data-base of your working group (see section „Handling the Tools“)
- cite correctly whenever using results of other people
- cite specifically, embedding citations immediately after the respective statements in the text
- act distinctly but sparsely with self citations
- try to cite all (most) relevant research groups in the field
- cite those people extensively, whom you wish to provoke as reviewers
- [cite permission for reproduction when re-using material (e.g. figures) from other papers]

…trotz aller Planung entstehen oft auch über Abwege gute Publikationen….

[….und man muß nicht alles transparent machen….]



Immunity
Article

Title expressing main results of paper

Full Activation of the T Cell Receptor Requires Both Clustering and Conformational Changes at CD3

Susana Minguet,[1] Mahima Swamy,[1] Balbino Alarcón,[2] Immanuel F. Luescher,[3] and Wolfgang W.A. Schamel[1,*]
[1] Max Planck-Institut für Immunbiologie and Faculty of Biology, University of Freiburg, Stübeweg 51, 79108 Freiburg, Germany
[2] Centro de Biología Molecular "Severo Ochoa," CSIC, Universidad Autónoma de Madrid, 28049 Madrid, Spain
[3] Ludwig Institute for Cancer Research, Lausanne Branch, 1066 Epalinges, Switzerland
*Correspondence: schamel@immunbio.mpg.de
DOI 10.1016/j.immuni.2006.10.019

SUMMARY

T cell receptor (TCR-CD3) triggering involves both receptor clustering and conformational changes at the cytoplasmic tails of the CD3 subunits. The mechanism by which TCRαβ ligand binding confers conformational changes to CD3 is unknown. By using well-defined ligands, we showed that induction of the conformational change requires both multivalent engagement and the mobility restriction of the TCR-CD3 imposed by the plasma membrane. The conformational change is elicited by cooperative rearrangements of two TCR-CD3 complexes and does not require accompanying changes in the structure of the TCRαβ ectodomains. This conformational change at CD3 reverts upon ligand dissociation and is required for T cell activation. Thus, our permissive geometry model provides a molecular mechanism that rationalizes how the information of ligand binding to TCRαβ is transmitted to the CD3 subunits and to the intracellular signaling machinery.

INTRODUCTION

Ligand binding and signal transmission functions of the T cell receptor (TCR-CD3) complex are located on different subunits. The TCR-CD3 is composed of the ligand-binding TCRαβ (or TCRγδ) heterodimer and the signal-transducing dimers of CD3εγ, CD3εδ, and ζζ. The variable immunoglobulin (Ig) domains of TCRα and TCRβ form the binding surface for its ligand, the major histocompatibility complex-peptide (MHCp). The TCRα and TCRβ constant Ig and transmembrane regions couple TCRαβ to the CD3 dimers (Call et al., 2002). The CD3 subunits contain an extracellular Ig domain, a transmembrane region, and a cytoplasmic tail including several signal-transduction motifs (Alarcon et al., 2003; Malissen, 2003). The stoichiometry of the TCR-CD3 complex is controversial, and several distinct stoichiometries might coexist on the cell surface (Schamel et al., 2005).

A central issue in T cell activation is to understand how the information of MHCp binding to TCRαβ is transmitted into the cell via the CD3-signaling units. Two main models have been put forward, involving TCR-CD3 clustering and conformational changes (Alarcon et al., 2003; Choudhuri et al., 2005; Cochran et al., 2001; Germain, 2001; Malissen, 2003; Sigalov, 2005). One model stipulates that TCR-CD3 clustering by multimeric MHCp brings individual TCR-CD3 complexes into close proximity, thereby enabling transphosphorylation of the receptors by associated tyrosine kinases. In support of this view, soluble monomeric MHCp, unlike dimeric or oligomeric MHCp, is unable to elicit TCR-CD3 activation (Abastado et al., 1995; Boniface et al., 1998; Cochran et al., 2000; Stone and Stern, 2006). Similarly, T cells can be stimulated by intact anti-CD3 or anti-TCRαβ, but not by the corresponding Fab fragments (Kaye and Janeway, 1984).

Alternatively, conformational changes in the TCR-CD3 complex upon antibody binding have been proposed to explain T cell-signaling studies because differences in receptor clustering or in antibody affinities were insufficient to explain distinct activation potentials of TCR-CD3 antibodies (Janeway, 1995). However, with one exception (Kjer-Nielsen et al., 2003), crystallographic studies argue against large conformational changes within the TCRαβ Ig ectodomains. Structures from MHCp-bound and free soluble TCRαβ revealed ligand-induced structural changes in the complementarity-determining regions of the variable Ig domains of TCRαβ that were not transmitted to TCRαβ-constant regions (Bankovich and Garcia, 2003; Ding et al., 1999; Reiser et al., 2002; Rudolph et al., 2006). It is therefore difficult to envisage how ligand-induced conformational changes could be transmitted from the TCRαβ heterodimer to the CD3 tails.

Despite these conceptual problems, the TCR-CD3 complex undergoes a ligand-induced conformational change that allows a conserved proline-rich sequence (PRS) in the cytoplasmic tail of CD3ε to bind to the first SH3 (src homology 3) domain of Nck (SH3.1(Nck)), a ubiquitously expressed adaptor protein (Gil et al., 2002). This structural change can be induced by anti-CD3 and anti-TCRαβ as well as by MHCp (Gil et al., 2002, 2005; Risueno et al., 2005). To date, it is unclear whether Nck recruitment to TCR-CD3 is a crucial step in T cell activation (Gil et al.,

2002; Szymczak et al., 2005) and whether conformational changes are required for TCR-CD3 triggering. However, the conformational change is probably a more global event that also affects the other signaling subunits of the TCR-CD3 and additional signaling molecules besides Nck. Indeed, the cytoplasmic tail of the ζ chain might convert from a lipid-bound helical structure to an unfolded structure upon TCR-CD3 triggering (Aivazian and Stern, 2000).

By using TCR-CD3 ligands of defined valencies and geometries, we demonstrated that induction of the conformational change required both multivalent engagement and the mobility restriction imposed by the membrane. So far, TCR-CD3 clustering and the conformational change were discussed as two independent mechanisms to activate T cells and were not integrated into a unique model of TCR-CD3 triggering. We showed that TCR-CD3 clustering was a prerequisite for inducing the conformational change, and it further required the reorientation of two TCRαβ heterodimers with respect to each other. This reorientation resulted in rearrangements within the TCR-CD3 complex promoting the conformational change. We also demonstrated that the conformational change of CD3 was necessary, but not sufficient, for optimal T cell activation and was reversible upon dissociation of TCR-CD3-ligand complexes.

RESULTS

Subsection title gives results

Multivalent Engagement of TCRαβ Is Required to Induce the Conformational Change

The conformational change leading to exposure of the PRS of CD3ε is induced upon binding of both bivalent and monovalent antibodies to CD3ε (Gil et al., 2002). To determine whether stimulation with monomeric and multimeric MHCp changes the conformation of CD3ε, we took advantage of T cells expressing the T1 TCR. This TCR recognizes the PbCS252-260 peptide (SYIPSAEKI) containing a photoreactive 4-azidobenzoic acid on K259 (pepABA) (Gregoire et al., 1996) in the context of K^d. After binding to the T1 TCR, photoactivation of ABA results in covalent crosslinking of TCRαβ with MHCp (Doucey et al., 2003; Gregoire et al., 1996), thereby "freezing" the interaction between MHCp and TCR-CD3.

Monomeric and tetrameric versions of the K^dpepABA were used to stimulate CD8-negative T1 hybridoma cells. Both could bind to the T1 TCR, as seen by flow cytometry (data not shown). After photocrosslinking, the conformational change in CD3ε was detected by the pull-down assay with the immobilized SH3.1(Nck) domain. The MHCp tetramer and CD3 antibody were equally potent in inducing the conformational change (Figure 1A, lanes 3 and 4). In contrast, monomeric MHCp was not able to induce any conformational change (lane 2), although it bound to the T1 TCR as shown by the presence of β2-microglobulin in the anti-CD3 immunoprecipitates (lowest panel). A comparison of MHCp dimer and tetramer indicated that both have the same capacity to induce the conformational change (Figure 1B). In contrast, not all TCR-CD3 antibodies had equal capability to induce the conformational change in CD3ε (see Figure S1 in the Supplemental Data available online). Likewise, complete TCRαβ antibodies but not their monovalent Fab fragments induced the conformational change (Figure S1). These data showed that monovalent MHCp binding to TCRαβ did not induce the conformational change in TCR-CD3 and that bivalent or multivalent MHCp engagement was required. Hence, induction of the conformational change in CD3ε via TCRαβ requires TCR-CD3 clustering.

In the absence of photocrosslinking, the K^dpepABA is not covalently fixed to the T1 TCR (Gregoire et al., 1996). To test whether the conformational change is dependent on continuous engagement, T1 hybridomas were incubated with MHCp tetramers or CD3 antibodies and subsequently UV irradiated or left unexposed. The CD3ε conformational change was preserved only when the MHCp-TCR-CD3 interaction was covalently fixed. When MHCp was not photocrosslinked to TCRαβ, the conformational change was not detected (Figure 1C, lane 2). Nevertheless, in both cases MHCp was bound to TCR-CD3 (Figure 1D). Upon detergent lysis, MHCp rapidly dissociates from TCRαβ (Arcaro et al., 2001), probably because of the low MHCp-TCRαβ affinity. Indeed, the MHCp tetramer was not detected in an anti-TCR-CD3 immunoprecipitation when UV irradiation was omitted (Figure 1C, lowest panel), whereas the induction of the conformational change by CD3 antibodies was independent of UV irradiation. The experiment was repeated with a T1 CTL clone (Doucey et al., 2003) with similar results (Figure S2). Thus, disruption of MHCp binding most likely results in reversion of the conformational change.

Next, we tested whether MHCp expressed by antigen-presenting cells (APCs) can induce the conformational change. K^d-expressing APCs were loaded with pepABA and used to stimulate CD8-negative (Figure 1E) and CD8-positive (Figure 1F) T1 hybridoma cells. Indeed, stimulation with APCs induces the conformational change, and this induction is independent of CD8 expression. Thus, induction of the conformational change via TCRαβ by MHCp requires multivalent engagement in absence of any additional interaction.

Subsection title gives results

Close Proximity of Two TCR-CD3 Is Necessary to Induce the Conformational Change

To exclude that ligand binding was directly altering the conformation of the TCRαβ heterodimer, we designed a system in which the ligand did not directly bind to TCRαβ, but only to an appended immunoglobulin single-chain (sc) construct. The V_H and V_L regions of an anti-hapten (nitro-iodo-phenol, NIP)-specific antibody were made as one single-chain molecule and fused to the N terminus of a mature TCRβ chain through a flexible linker (Figure 2A). The resulting NIP-specific single-chain TCRβ protein (scTCRβ) was stably expressed in a TCRβ-deficient Jurkat mutant (31-13), yielding the cell line 31-13.scTCRβ. The scTCRβ was expressed within the TCR-CD3 complex on the cell surface (Figure S3). Because hapten binding to antibodies does not lead to a change in the structure

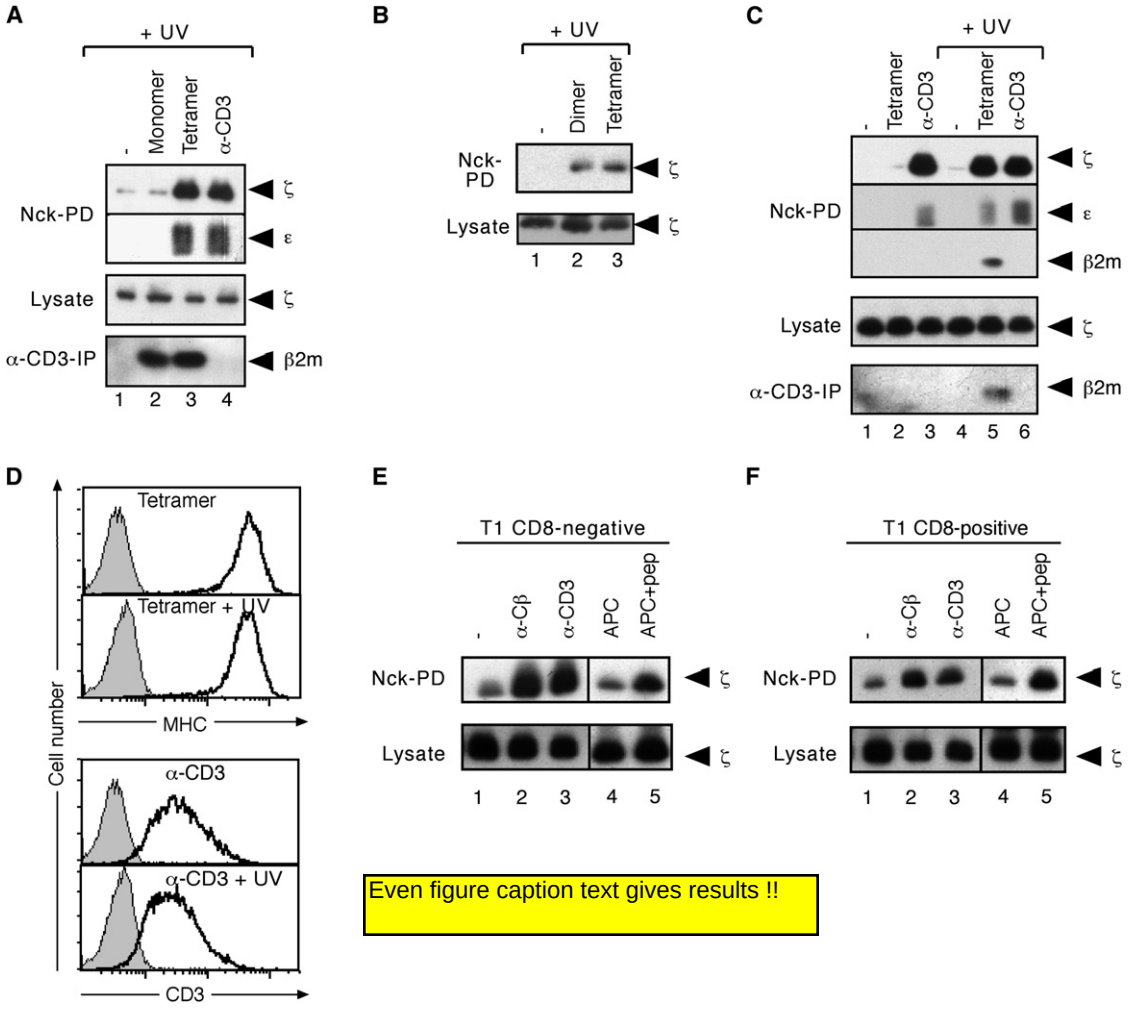


Figure 1. Only Multimerized MHCp Induce the Conformational Change in CD3

(A) T1 hybridoma T cells were incubated with 500 nM of K^dpepABA monomer, 5 nM of K^dpepABA tetramer, or 5 μg/ml of CD3 antibody (145-2C11) corresponding to maximal TCR-CD3 binding. Cells were UV irradiated to covalently crosslink the MHCp to the TCR-CD3. Upon lysis, the Nck pull-down assay was performed and TCR-CD3 detected by anti-ζ and anti-CD3ε immunoblotting (top). As control, an aliquot of each lysate was subjected to anti-ζ immunoblotting to confirm equal amount of TCR-CD3 (middle). Alternatively, an anti-CD3 immunoprecipitation was done and presence of MHC detected with a β2-microglobulin antibody (bottom).

(B) T1 hybridoma cells were incubated with 50 nM K^dpepABA dimer or 5 nM tetramer that resulted in maximal TCR-CD3 binding and subjected to UV irradiation. Nck pull-down was performed as in (A).

(C) T1 hybridoma was incubated with 5 nM K^dpepABA tetramer or 5 μg/ml anti-CD3. Cells were UV irradiated or left untreated and processed as in (A).

(D) Aliquots of the samples from (C) were used to confirm stimuli binding. The tetramer already included streptavidin-PE (middle), and bound anti-CD3 was detected with anti-IgG-PE (bottom). Untreated cells are shown in gray.

(E) T1 hybridoma T cells lacking CD8 expression were stimulated with pepABA-pulsed A20 cells 10 min at 37°C. Upon UV irradiation and paraformaldehyde fixation, cells were lysed and processed as above. As a control, T1 cells were stimulated with the indicated antibodies or left untreated.

(F) T1 hybridoma T cells expressing CD8 were stimulated with pepABA-pulsed A20 cells, and induction of the conformational change was probed as in (E).

The results are representative of at least three independent experiments.

outside the hapten-binding pockets (Wedemayer et al., 1997) and because the sc molecule was fused to the TCR-CD3 via a flexible linker, it is highly unlikely that NIP binding could transmit a structural change to TCRαβ.

To test whether monovalent or multivalent engagement of the scTCRβ could induce the conformational change, we generated a series of peptides in which the number of NIP molecules coupled to each peptide was increased from one to four (Figure 2B). For comparison, NIP-coupled bovine serum albumin (BSA) was used in which one BSA molecule was conjugated on average to 15 NIP molecules (NIP15-BSA). Stimulations were performed maintaining equimolar amounts of the NIP moiety (Figure S3). The monovalent NIP1 peptide did not induce the conformational change (Figure 2C, lane 2), nor did monomeric free hapten (data not shown). However, as the number

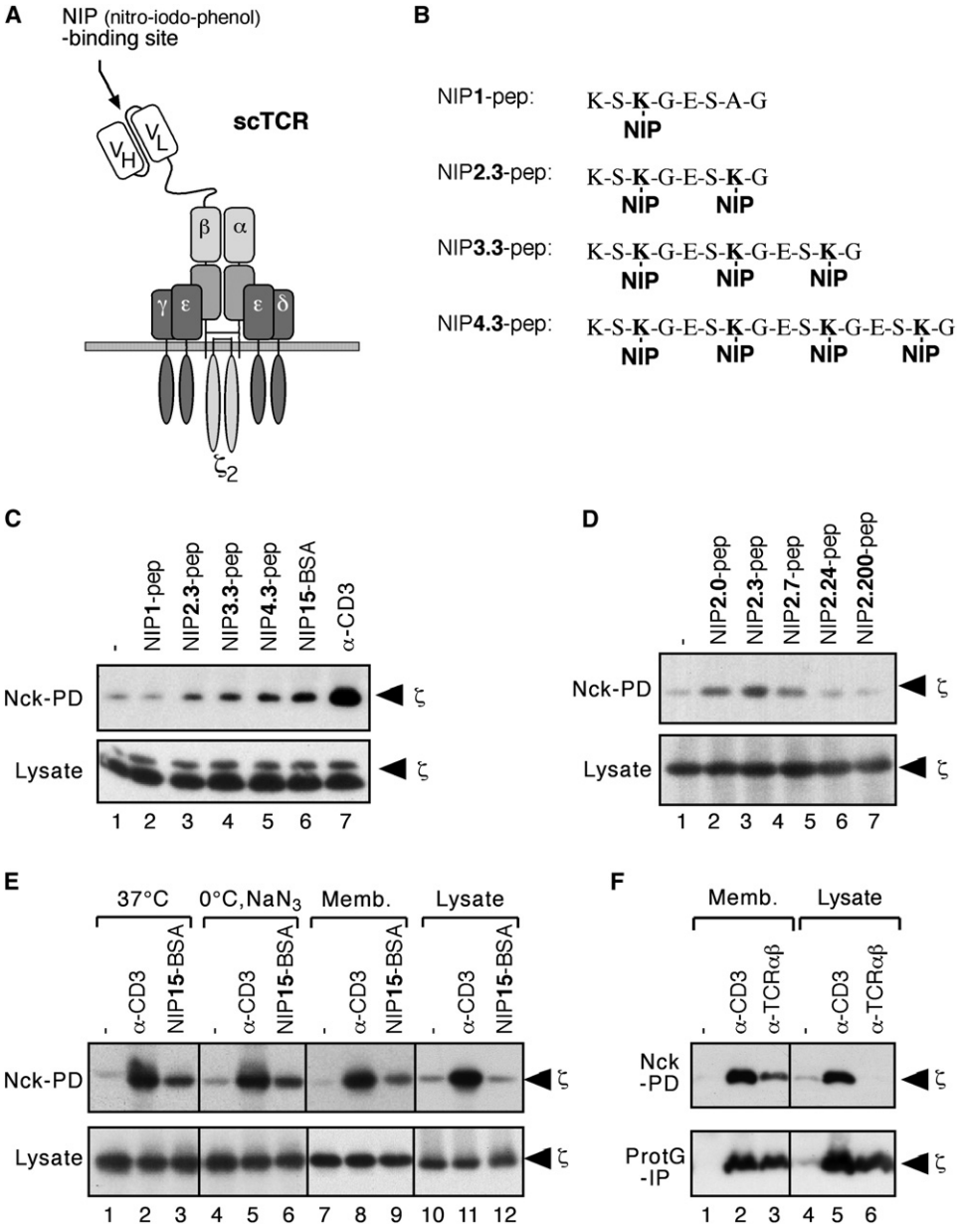


Figure 2. Simultaneous Engagement of Several TCRαβ Is Sufficient to Induce the Conformational Change

(A) scTCRβ is composed of the NIP binding variable immunoglobulin domains of a NIP antibody connected by a flexible linker of 8 amino acids to the N terminus of wild-type TCRβ.

(B) The sequence of the peptides that contain the NIP-conjugated lysine are shown. The one letter code for amino acids is used. The first number in the name of the peptide indicates the number of NIP-conjugated lysines and the second number indicates the number of amino acids between two adjacent NIP-conjugated lysines.

(C) 31-13.scTCRβ cells were stimulated with the indicated NIP-coupled peptides (lanes 2–5), NIP15-BSA, anti-CD3ε (UCHT1), or left untreated. Concentrations of the NIP-coupled reagents were chosen in order that the number of NIP molecules per stimulation was constant. After lysis, the Nck pull-down assay was performed as in Figure 1.

(D) 31-13.scTCRβ cells were either stimulated with equal molarities of the indicated peptides or left untreated. Upon lysis, the Nck pull-down was assayed as in (C).

(E) 31-13.scTCRβ cells were stimulated at 37°C or on ice in the presence of azide. Alternatively, a membrane fraction of 31-13.scTCRβ cells was incubated with the stimuli on ice, or stimuli were added to the detergent lysates. The stimuli were NIP15-BSA and CD3 antibody. The Nck pull-down assay was done as in (C).

(F) A membrane fraction of SRD10 cells was incubated on ice with anti-CD3 (145-2C11) or anti-TCRαβ (3D3). Alternatively, the antibodies were added to the lysates. After lysis of the membranes, the Nck pull-down assay was done as above. As control for antibody binding, protein G-coupled sepharose was incubated with the corresponding lysates and the presence of the antibody-TCR-CD3 complex was assayed (bottom).

The results are representative of at least three independent experiments.

of NIP molecules per peptide increased, the PRS of CD3ε became increasingly accessible (Figure 2C). Thus, simultaneous engagement of several TCR-CD3 complexes, but not a change in the TCRαβ structure, is necessary and sufficient to induce the conformational change.

We then examined how the distance between two NIP ligands influences the ability to induce the conformational change. To this end, we synthesized peptides with varying numbers of amino acids between two NIP-conjugated lysines. The NIP2.0 peptide contained no spacer between the two NIP lysines, the NIP2.3 peptide has a three amino acid spacer, etc. (Figure S3). An increase in the distance between the two haptens within a peptide resulted in decreased induction of the conformational change (Figure 2D). With a spacer of 24 amino acids or more, the peptide ligands did not induce the conformational change. We excluded the possibility that the bivalent NIP peptides bound to two TCR-CD3s on two different T cells (Figure S4). Hence, our data indicate that two TCRαβ have to be brought into close proximity and/or in a specific orientation in order to transduce the conformational change.

The Mobility Restriction Imposed by an Intact Membrane Is Necessary to Induce the Conformational Change via TCRαβ

The above results argue that two or more TCR-CD3s have to be contacted in order to change their conformation. This does not depend on metabolic processes because the PRS was also exposed when T cells were stimulated in the presence of azide at 0°C (Figure 2E, lanes 4–6). The conformational change also occurred on isolated membrane patches prepared in the absence of detergent, indicating that cytosolic proteins were not involved in the process (lanes 7–9). However, when detergent-solubilized TCR-CD3s were incubated with NIP15-BSA, the conformational change was not induced (lane 12). We could not demonstrate that NIP15-BSA bound to TCR-CD3 in the lysate. Therefore, we repeated the experiment with SRD10 cells stimulated with an idiotypic antibody. The TCRαβ antibody induced the conformational change on membrane preparations but not in detergent lysates (Figure 2F, lanes 3 and 6). Here we demonstrated that the antibody was bound to the TCR-CD3 in the lysates by immunoprecipitation with ProteinG-Sepharose beads (Figure 2F, bottom). In both experiments, anti-CD3ε induced the conformational change in detergent lysates by binding directly to CD3ε (Figures 2E and 2F). These results indicate that induction of the conformational change via TCRαβ clustering requires an intact membrane.

The Conformational Change in CD3 Reverts upon TCRαβ-Ligand Dissociation

As we showed in Figure 1, covalent fixation of the T1 TCR-CD3 to its cognate MHCp was necessary to detect the conformational change in CD3ε. This could be explained if the conformational change was reverted upon ligand detachment during cell lysis. To directly test this hypothesis, we used our scTCR system, in which the ligand can be removed under controlled conditions (Figure 3A). Binding of

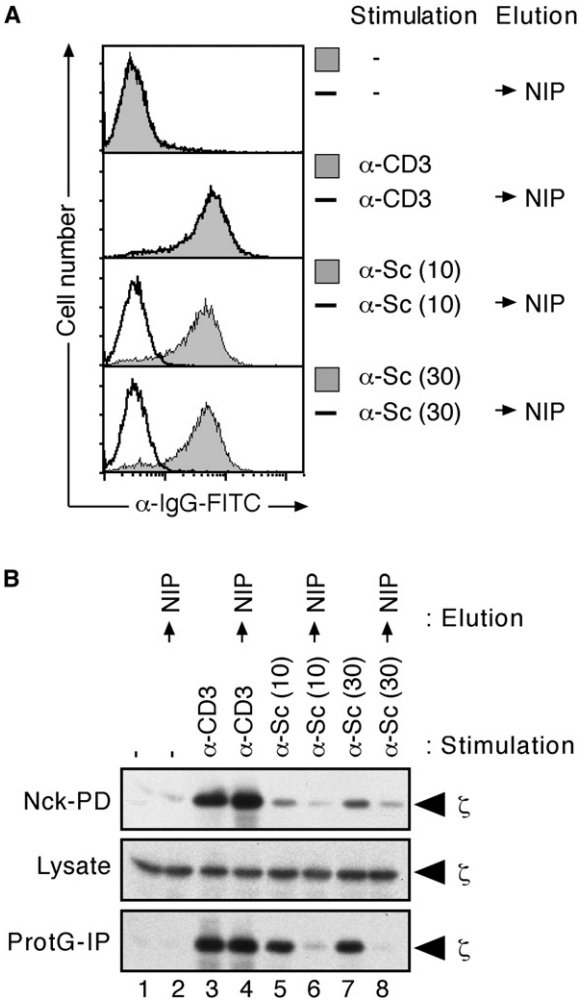


Figure 3. The Conformational Change Is Reversible

(A) 31-13.scTCRβ cells were left unstimulated and either subsequently treated with 1 mM free monomeric NIP (top, solid line) or left untreated (gray graph). Alternatively, the cells were stimulated with anti-CD3ε and either treated with free NIP (second panel, solid line) or left untreated (gray graph). Lastly, sc antibody (10 μg/ml, third panel or 30 μg/ml, last panel) was used, in combination with or without subsequent elution with NIP (solid line or gray graph, respectively). Cells were stained with anti-IgG and analyzed by flow cytometry.

(B) Anti-CD3ε (10 μg/ml) and anti-sc (10 μg/ml or 30 μg/ml)-stimulated 31-13.scTCRβ cells were left untreated (lanes 3, 5, 7) or treated with 1 mM NIP (lanes 4, 6, 8). The Nck pull-down assay was performed as in Figure 1. Protein G-coupled sepharose was incubated with an aliquot of the corresponding lysates and the presence of antibody-TCR-CD3 complexes was assayed (bottom). The samples were from the same experiment as in (A).

The results are representative of at least four independent experiments.

the sc antibody Ac146 to the hapten-recognition site of the sc domain was inhibited by incubation with the free hapten NIP (Reth et al., 1979). When 31-13.scTCRβ cells were incubated with the sc antibody, the conformational change was detected (Figure 3B, lanes 5 and 7). However, the conformational change was reverted when the sc antibody was removed by adding an excess of monovalent NIP to the living cells (lanes 6 and 8). Note that similar to

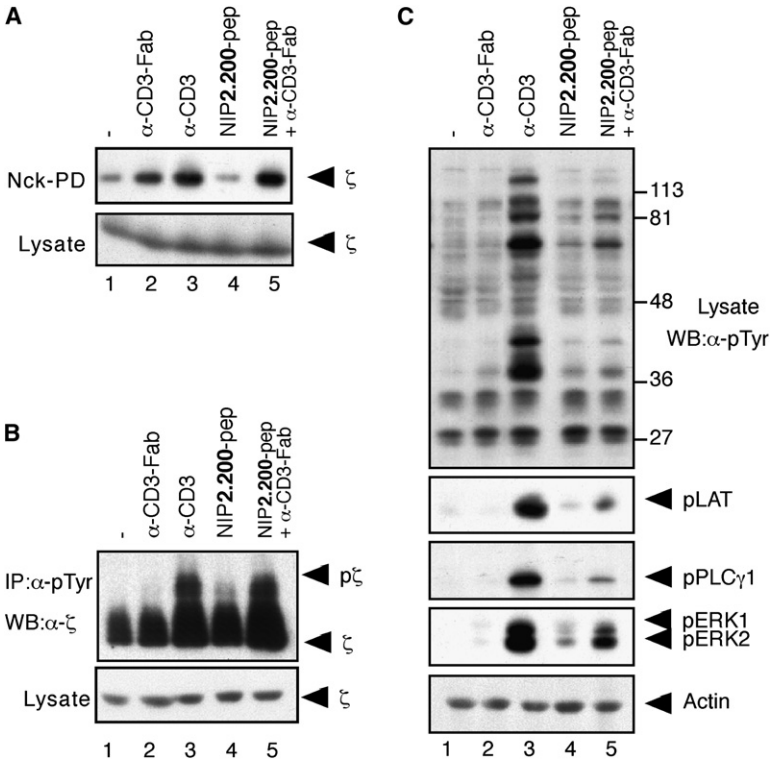


Figure 4. The Conformational Change Is Required for TCR-CD3 Signaling

(A) 31-13.scTCRβ cells were incubated with the indicated stimuli 3 min at 37°C. The stimuli were: 5 μg/ml of the anti-CD3-Fab fragment or the CD3 antibody (OKT3) as well as 2.8×10^4 NIP molecules/ml of the NIP2.200 peptide. Upon lysis, the Nck pull-down assay was performed as before.

(B) Stimulation of 31-13.scTCRβ cells was done as in (A). After lysis, an anti-phosphotyrosine immunoprecipitation was carried out and the purified proteins were detected by anti-ζ immunoblot (top). Anti-ζ immunoblotting of an aliquot of the lysate verifies equal loading.

(C) 31-13.scTCRβ cells were stimulated as in (A). The lysate was separated by SDS-PAGE and the indicated proteins were detected by immunoblotting with anti-phospho-tyrosine (4G10) or anti-phospho-specific antibodies as indicated. Anti-actin immunoblotting serves as control.

The results are representative of at least three independent experiments.

the bivalent NIP2 peptides (Figure 2C), the anti-sc antibody is a weak inducer of the conformational change. As a control, incubation of 31-13.scTCRβ cells with monomeric NIP had no effect on the conformational change induced by anti-CD3 (Figure 3B, lanes 3 and 4). Taken together, these results as well as those observed for the MHCp and the T1 TCR-CD3 (Figure 1) show that the TCR-CD3 reverts to its basal conformation when the stimulus dissociates.

The Conformational Change Is Necessary for T Cell Activation

Whereas overexpression of the CD3ε binding SH3 domain of Nck (SH3.1) inhibited T cell activation (Gil et al., 2002), mutation of the PRS in CD3ε did not affect T cell development or antibody stimulation of T cells (Szymczak et al., 2005). Therefore, it is controversial whether Nck recruitment is important for T cell activation. We should stress that the Nck pull-down, and therefore the exposure of the PRS, is used in this study as a marker for the presence of the conformational change. However, because in addition to Nck the conformational change possibly has other effectors, we addressed whether lack of conformational change impairs T cell activation. 31-13.scTCRβ cells were stimulated with NIP-coupled peptides containing two NIP moieties separated by spacers of different length. Induction of the conformational change (Figure 2D) correlated with the ability of the NIP-modified peptides to stimulate Ca^{2+} influx and to upregulate the activation marker CD69 (Figure S5). Hence, poor inducers of the conformational change were also inefficient T cell activators.

To directly assess whether the conformational change is required for T cell activation, we used two different reagents. First was the NIP2.200 peptide, which does not induce the conformational change (Figure 2D) but simultaneously binds to two TCR-CD3s, and second was a Fab fragment of the CD3 antibody OKT3, which induces the conformational change (Figure 4A; Gil et al., 2002) but does not cluster the TCR-CD3. Simultaneous incubation with both reagents induced the conformational change (Figure 4A). When ζ phosphorylation was measured, we found that either stimulus alone was hardly active (Figure 4B), whereas both together induced strong phosphorylation, similar to that evoked by stimulation with bivalent anti-CD3 (Figure 4B). Thus, induction of the conformational change is required, but not sufficient, for optimal ζ phosphorylation.

Phosphorylation of TCR-CD3 leads to the recruitment of ZAP-70, which in turn phosphorylates several substrates including the adaptor proteins LAT and SLP-76. These proteins serve as docking sites to organize multiprotein complexes resulting in phosphorylation of phospholipase Cγ1, the MAP kinases ERK1 and ERK2, and activation of gene transcription factors such as NF-AT and NF-κB. To study the contribution of the conformational change to these events, we analyzed phosphorylation of several substrates with phospho-specific antibodies (Figure 4C). Only the simultaneous stimulation with anti-CD3-Fab fragments and NIP2.200 peptide caused substantial phosphorylation of LAT, PLCγ1, and ERK.

An important early event upon TCR-CD3 triggering is Ca^{2+} flux into the cytoplasm. Stimulation with

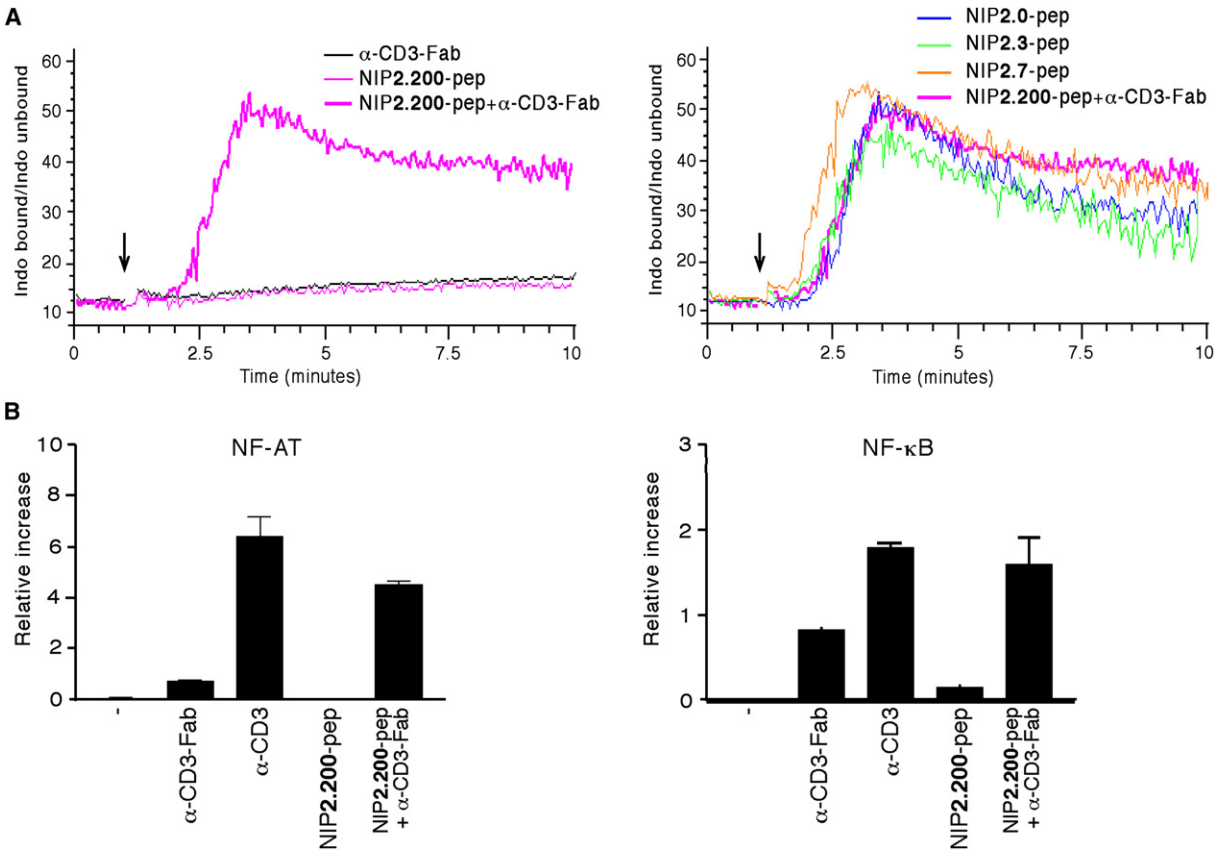


Figure 5. The Exposure of the PRS Is Crucial for T Cell Activation

(A) 31-13.scTCRβ cells were loaded with Indo-1 and stimulated with the indicated reagents (concentrations as in Figure 4) to induce Ca^{2+} responses. Equal molarities of the NIP-coupled peptides were used. The Indo-1 ratio was integrated over 10 min and measured by flow cytometry. The stimuli were added after 1 min (arrow).

(B) Upon transfection with an NF-AT (left) or an NF-kB (right) reporter plasmid, 31-13.scTCRβ cells were incubated 6 hr with the described stimuli and lysed, and luciferase activity was assayed relative to unstimulated cells. The mean of three independent, simultaneously performed stimulations is shown. Error bars indicate standard deviation.

The results are representative of at least five independent experiments.

anti-CD3-Fab or NIP2.200 peptide alone was not sufficient to induce a Ca^{2+} response. However, combination of both stimuli induced a strong Ca^{2+} flux indistinguishable from the one elicited by the other NIP2 peptides (Figure 5A). This indicates that it was the inability of the NIP2.200 peptide to induce the conformational change that accounted for its poor activity. These data also show that the distance of the two NIP moieties on the peptides did not play a substantial role in activation, as long as the conformational change is induced. The need for TCR-CD3 clustering was also demonstrated in this system, because a combination of the monovalent NIP1 peptide with the Fab fragment did not give any Ca^{2+} response, whereas clustering the Fab fragment with light chain antibodies did result in Ca^{2+} flux (Figure S5). In agreement with these results, optimal activation of NF-AT and NF-κB (Figure 5B) was detected only in the presence of both TCR-CD3 clustering and conformational change in the 31-13.scTCRβ cell line. Stimulation with the Fab fragment alone resulted in some activity, probably resulting from Fab multimerization by the tissue culture plate.

To confirm our data with primary T cells, we transiently transfected human peripheral blood mononuclear cells (PBMCs) with an expression vector encoding for the scTCRβ chain together with a GFP marker for transfected cells. Only stimulation with the anti-CD3-Fab and the NIP2.200 peptide resulted in a marked CD69 upregulation in the transfected, GFP-positive cells. As a control, no effect of the NIP2.200 peptide was seen in nontransfected, GFP-negative cells (Figure 6).

These results argue that it is possible to separate the conformational change from TCR-CD3 clustering by increasing the distance between binding groups in a bivalent ligand. With this approach we demonstrate that the conformational change in the TCR-CD3 complex is necessary for full T cell activation.

DISCUSSION

A key finding of the present study is that the relationship between the two models of TCR-CD3 triggering, namely

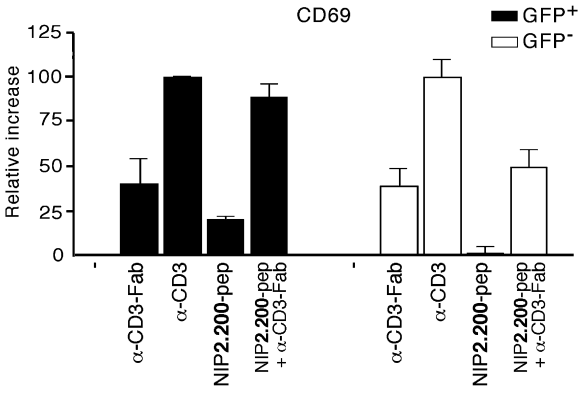


Figure 6. The Conformational Change Is Required for T Cell Activation in Human PBMCs

Human PBMCs were transiently cotransfected with vectors encoding for scTCRβ and GFP. The cells were stimulated (concentrations as in Figure 4) 24 hr or left untreated. After staining with a CD69 antibody, cells were analyzed by flow cytometry gating on GFP-positive (left) and GFP-negative (right) cells. The relative increase was calculated considering the percent of CD69-positive cells upon anti-CD3 stimulation as 100%. The mean of triplicates and the standard deviation are indicated. The results are representative of at least two independent experiments.

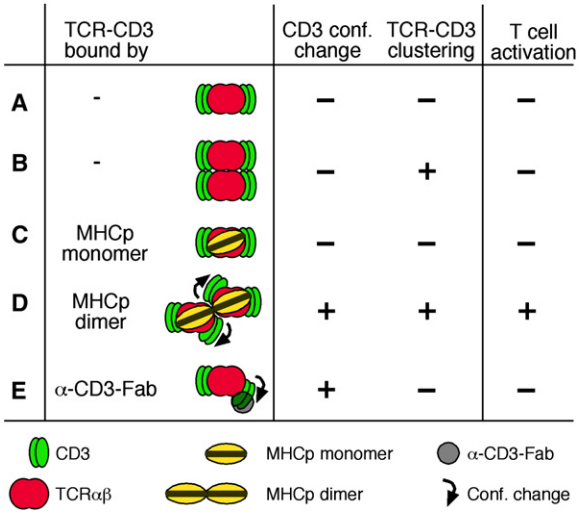


Figure 7. The Permissive Geometry Model of TCR-CD3 Triggering

(A) In absence of ligand binding, the TCR-CD3 complex is in a resting state.

(B) Clustering of two (or more) TCR-CD3 in a nonpermissive geometry that does not induce the conformational change is not sufficient for TCR-CD3 triggering. Inactive clustering is achieved by the NIP2.200 peptide. The TCR-CD3 might also be preclustered in the nonpermissive geometry before ligand binding (Schamel et al., 2005).

(C) Monovalent MHCp binding does not lead to a structural change of the TCRαβ heterodimer, thus not rearranging the cytoplasmic tails of CD3. Consequently, TCR-CD3 is not triggered.

(D) Bivalent (and multivalent) MHCp binding does not change the structure of one TCRαβ outside the direct contact region. Since two TCR-CD3 are engaged simultaneously, they have to adjust to the geometry of the preformed MHCp dimer. This results in a reorientation of two TCRαβ into a permissive geometry, thereby "pushing and squeezing" the extracellular and transmembrane regions of the CD3 and ζ subunits (arrows). The rearrangement is transmitted through the membrane and affects the conformation of the cytoplasmic regions of CD3.

(E) Fab fragments of CD3ε antibodies alter the conformation of CD3 by the monovalent direct binding event. The conformational change alone is not sufficient for TCR-CD3 triggering and T cell activation.

clustering and conformational change, is closer than anticipated because clustering is required to induce the conformational change (summarized in Figure 7). Remarkably, we found that monovalent engagement of TCRαβ by MHCp or anti-TCRαβ Fab fragments did not transmit a conformational change to the cytoplasmic region of CD3ε, whereas bivalent and multivalent engagement did. This implies that TCRαβ ligation per se is not sufficient to transmit structural alterations through the TCRαβ heterodimer to the CD3 subunits. Indeed, ligand binding generates induced-fit type changes only in the variable TCRαβ regions at the ligand-binding interface (Bankovich and Garcia, 2003; Reiser et al., 2002; Rudolph et al., 2006; Wu et al., 2002), but no alterations at the distal portions of the heterodimer, which are connected to the CD3 units. Note that unlike Fab fragments of antibodies against TCRαβ, Fab fragments of the CD3 antibodies OKT3 and UCHT1 induce the conformational change by binding directly to CD3ε (Figure S6).

To combine the rigidity of TCRαβ with the presence of conformational changes in CD3, a piston-like model, in which TCRαβ are displaced perpendicular to the membrane, and a rotational model, where TCRαβ rotate with respect to CD3, have been proposed (Choudhuri et al., 2005; Gil et al., 2005; Sun et al., 2001). These models imply that the ligand exerts a mechanical force on TCRαβ, which is possible only if a second fixed interaction is present. The coreceptors CD8 and CD4 could theoretically provide this interaction. We show that soluble bivalent MHCp or peptide-pulsed APCs induce the conformational change in the CD8-negative T1 hybridoma, indicating that CD8 is not involved in inducing the conformational change. Furthermore, anti-TCRαβ can induce the conformational change in the absence of any additional interaction. However, CD8 and CD4 can strengthen the MHCp-TCR-CD3 interaction, and therefore could aid in stabilizing the conformational change. Our data thus argue that the second fixed interaction is the second TCRαβ. Bivalent ligand binding could change the relative orientation of two TCRαβ dimers toward each other, enforcing cooperative interactions. After bi- or multivalent binding, the two TCRαβ might "pinch" the CD3 subunits so that the extracellular parts of CD3 are pushed away from their original positions. Because the short stalks connecting the extracellular domains and the transmembrane regions of CD3 appear to be rigid (Arnett et al., 2004; Sun et al., 2001), such displacement could be transmitted to the transmembrane domains, resulting in rearrangements of the cytoplasmic tails (Figure 7).

When TCRαβ were clustered in detergent lysates, the conformational change in CD3ε was not induced. This indicates that two TCRαβ need to be brought not only into close proximity (because increased distance led to

a reduced change), but also into a defined orientation within the constraints of the membrane. If the TCR-CD3 dimer does not have the right orientation, the conformational change is not induced. Thus, inducing proximity of two TCRαβ is necessary, but not sufficient, to generate the conformational change. Likewise, not all TCR-CD3 antibodies have the same capability to induce the conformational change, even when they bind to the same number of TCR-CD3s. Because these antibodies bind to distinct regions of TCR-CD3, they should lead to different geometries of the clustered complex. We therefore suggest that the exact geometry determines whether a conformational change takes place or not. A permissive geometry would lead to structural reorganization to expose the PRS of CD3ε, whereas a different inert geometry would not (permissive geometry model).

Further support for the permissive geometry model comes from our experiments with the scTCRβ chimera, in which the hapten binding domain (sc) is connected via a flexible linker to TCRβ. Engagement by a bivalent hapten or a bivalent anti-sc antibody probably brings two TCRαβ together in a random geometry. Therefore, only a few TCR-CD3 form the correctly oriented clustered αβ-αβ complex capable of communicating the conformational change to CD3. Increasing the valence of the haptenated peptides augments the probability of creating permissive geometries, which explains the increase in conformationally changed TCR-CD3s. Even NIP15-BSA was less efficient than anti-CD3 to induce the conformational change. In contrast, MHCp dimers, tetramers, and anti-CD3 were equally potent in inducing the conformational change, suggesting that because of conserved interactions between two MHCp molecules (Krishna et al., 1992; Schafer et al., 1995), the binding of dimeric MHCp already places all TCR-CD3s in the permissive geometry. Thus, TCR-CD3 dimers in the permissive geometry are necessary and sufficient to induce the conformational change of the TCR-CD3 complex.

In the present study, we address for the first time the importance of the ligand-induced conformational change in CD3, in contrast to previous reports that have studied only the role of the PRS of CD3ε (Szymczak et al., 2005) or the recruitment of Nck to this PRS (Gil et al., 2002). One of the consequences of the conformational change is the exposure of the PRS of CD3ε (Gil et al., 2002). By the use of a mutant TCR-CD3 complex lacking the PRS of CD3ε (Szymczak et al., 2005), only the importance of the PRS can be studied and not the role of the conformational change itself. To directly study the contribution of TCR-CD3 clustering and conformational changes to TCR activation, we used the Fab fragment of the CD3 antibody OKT3, which by direct binding induces the conformational change (Gil et al., 2002) but does not cluster TCR-CD3. In addition, the NIP2.200 peptide does not induce the conformational change, but does bind simultaneously to two TCR-CD3s. By combining the NIP2.200 peptide and anti-CD3 Fab, we show that both TCR-CD3 clustering and conformational changes are needed for optimal T cell activation.

The necessity of the conformational change for effective TCR-CD3 signaling in combination with the permissive geometry model might also explain the fact that all TCRαβ adopt a diagonal orientation on MHCp (Rudolph et al., 2006). Conserved MHCp-TCR-CD3 interactions that dictate this orientation are not apparent. We suggest that initially other orientations exist, but that the MHC self-peptide-TCR-CD3 interaction in the thymus selects those TCR-CD3s that bind to multivalent MHCp in the permissive geometry, i.e., the conformational change might be necessary for thymic selection to guarantee optimal T cell activation in the periphery. In addition, the diagonal orientation might ensure that MHCp-bound CD8 or CD4 will contact the TCR-CD3 complex at the correct position (Bankovich and Garcia, 2003; Buslepp et al., 2003; Garboczi et al., 1996).

Recently, a pseudodimer model of TCR activation was proposed, providing a theoretical background of how soluble MHC agonist-MHC self-peptide heterodimers can activate T cells (Krogsgaard et al., 2005). Our permissive geometry model provides an alternative explanation. Preformed TCR-CD3 oligomers (Schamel et al., 2005), which bind dimeric MHCp with higher avidity than TCR-CD3 monomers, are in a nonpermissive geometry (Figure 7B). Binding of the MHCp heterodimers to the oligomeric TCR-CD3 would induce the permissive geometry and therefore T cell triggering (Figure 7D). The role of CD4 would be to stabilize the interaction between MHCp and TCR-CD3 and to recruit additional kinases.

Lastly, we show that removal of MHCp tetramers or stimulating antibody reverts the conformational change in the TCR-CD3. Thus, the conformational change is not the molecular event that marks activated TCR-CD3s after MHCp dissociation, which could lead to TCR-CD3 internalization (Coombs et al., 2002), or accumulation during serial triggering (Valitutti et al., 1995). It might be, however, one of the events that directly communicate MHCp binding to the cytoplasmic signaling machinery. Consequently, the duration of TCR-CD3 ligand engagement can be measured intracellularly as proposed by the kinetic proofreading model (McKeithan, 1995). In fact, the combination of an avidity proofreading model with the requirement of conformational changes for T cell activation allowed us to propose recently a thermodynamic model that accounts for the paradox of the high sensitivity and low affinity of the MHCp-TCR-CD3 interaction (Schamel et al., 2006).

In summary, we propose a permissive geometry model that might explain how ligand binding to the rigid TCRαβ subunits is communicated into a conformational change at the cytoplasmic tail of CD3ε, which is necessary, but not sufficient, for full TCR-CD3 triggering and T cell activation.

EXPERIMENTAL PROCEDURES

Cells

We generated the expression vector pSRscTCRβ that encodes a leader peptide, a signal peptidase cleavage site, the NIP-specific

single chain Fv fragment (sc), a linker with the LDGSGGDV sequence, and the mature human Vβ3 HA1.7 chain. The sc was taken from the plasmid pL(-I)VHVL-XhRSI-B (Schamel et al., 2003) and the TCRβ sequence from pJ6β (Hewitt et al., 1992). pSRscTCRβ was transfected into the human Jurkat-derived TCRβ-negative line 31-13 to yield 31-13.scTCRβ (Figure 2A).

The murine T cell line SRD10 and the T1 hybridoma (T1.4 $CD8^-$ and T1 $CD8^+$) have been described (Luescher et al., 1995; Rojo and Janeway, 1988). Murine A20 cells were used as antigen-presenting cells. All cells were maintained in complete RPMI-1640 with 5% serum. T cell clones from T1 transgenic mice were culture as described (Doucey et al., 2003). Human peripheral blood mononuclear cells were isolated from healthy donors according to the local ethics committees on human experimentations via a Ficoll gradient and cotransfected with the pSRscTCRβ and pCMV-GFP plasmids with the Human T Cell Nucleofector Kit (Amaxa GmbH).

Antibodies and Reagents

The rabbit anti-ζ antiserum 448 has been described (San Jose et al., 1998). The following antibodies were used: UCHT1 (anti-human CD3, P. Beverly, UK), 145-2C11 (anti-mouse CD3, J. Bluestone, USA), anti-sc (Ac146, M. Reth, Germany), 3D3 (anti-mouse Vα/β, J.M. Rojo, Spain), and anti-β2microglobulin (T. Dick, Germany). Other antibodies were purchased as follows: OKT3 (anti-human CD3) from Ortho, anti-mouse IgG-PE or IgG-FITC, anti-mouse kappa from Southern Biotech, anti-phospho-LAT (Y191) from Cell Signaling, anti-activated MAPK (12D4) from Nanotools, and anti-phopho-PLCγ (Y383), anti-actin (I-19), and anti-CD3ε (M20) from Southern Biotech. OKT3-Fab fragments were prepared with the Immunopure IgG1-Fab Preparation kit and confirmed by SDS-PAGE and immunoblotting. Secondary antibodies for western blot were obtained from Southern Biotech. NIP (nitro-iodo-phenol)-conjugated BSA (15 haptens per BSA molecule) and free NIP were purchased from Biosearch Technologies (Novato, CA). All NIP peptides were synthesized by IRIS Biotech. Streptavidin-PE was purchased from Molecular Probes. PbCS(ABA) peptide (pepABA) was synthesized as described (Luescher et al., 1991). Soluble monomeric, dimeric, and tetrameric K^dpepABA complexes were prepared as described (Cebecauer et al., 2005; Gregoire et al., 1996; Kalergis et al., 2000).

Cell Stimulations and Lysis

Cells were harvested, resuspended in medium without serum, and incubated 1 hr at 37°C prior to stimulation with the indicated stimulus at 37°C. Alternatively, cells were resuspended in PBS with 2% serum and 0.01% NaN_3 and stimulated at 0°C. The different NIP-coupled reagents were used at the same concentration of the NIP hapten per stimulation. The optimal concentration to stimulate 31-13.scTCRβ cells was determined empirically based on the induced tyrosine-phosphorylation in cellular lysates (data not shown). This concentration (2.8×10^4 NIP molecules/ml) was used in all experiments. T1.4 cells were incubated with the K^dpepABA complexes in medium without serum for 1 hr at 0°C. After UV irradiation, cells were harvested and lysed. A20 cells were loaded overnight with 1 μM of PbCS(ABA) peptide by incubation in complete medium with 1% serum. After PBS washing, A20 and T1 hybridoma cells were brought into close contact by centrifugation and incubated 10 min at 37°C. A ratio of four APCs per T cell was used. Upon UV irradiation and 1% formaldehyde fixation in PBS, cells were lysed. Membrane fractions were prepared by disrupting 3×10^7 cells in hypotonic buffer (10 mM HEPES [pH 7.4], 42 mM KCl, 5 mM $MgCl_2$, and protease inhibitors) with a Dounce homogenizer and pelleting the membranes in an ultracentrifuge at 150,000 × g. NIP elution was performed by incubation with 1 mM of free NIP 1 hr at 4°C. All lyses were done in 1 ml lysis buffer containing 20 mM TrisHCl (pH 8), 137 mM NaCl, 2 mM EDTA, 10% glycerol, 10 μg/ml leupeptin, 10 μg/ml aprotinin, 1 mM PMSF, 500 μM sodium orthovanadate, 1 mM NaF, and 0.5% Brij96.

SH3.1(Nck) Pull-Down Assay, Immunoprecipitation, and Immunoblotting

Postnuclear fractions were subjected to the SH3.1(Nck) pull-down assay as described (Gil et al., 2002). TCR-CD3 immunoprecipitations were performed with 5 μg of anti-CD3 antibodies overnight at 4°C. Phosphotyrosine immunoprecipitations were performed with PT-66 agarose from Sigma. Samples were subjected to SDS-PAGE separation and transferred to PVDF membranes. Immunoblotting was performed by conventional methods.

T Cell Activation Assays

Ca^{2+} Influx

Cells resuspended in medium with 1% serum were incubated with 5 μg/ml of Indo-1 and 0.5 μg/ml of pluronic F-127 (both Molecular Probes) 45 min at 37°C. After washing, cells were resuspended in medium with 1% serum and kept on ice. Ca^{2+} response was induced by addition of the indicated stimulus 1 min after starting to record the ratio of Ca^{2+}-bound Indo-1 versus unbound Indo-1 with a LSRII fluorescence spectrometer (Becton Dickinson). Data were analyzed with the FloJo 6.1 software.

Luciferase Assay

For the measurement of transcriptional activity, 3×10^7 cells were transiently transfected with 30 μg of NF-AT-luciferase (Hoey et al., 1995) or NF-κB-luciferase (Minguet et al., 2005) reporter plasmids by electroporation. Cells were grown for 24 hr, harvested, resuspended in medium with 0.5% serum, and stimulated 6 hr as indicated. After harvesting, the cells were lysed and luciferase activity measured with the Luciferase assay system from Promega.

Upregulation of CD69

Cells were stimulated for 24 hr with the indicated stimuli. After harvesting, cells were stained with an CD69-PE antibody (Caltag Laboratories) and analyzed by flow cytometry.

Supplemental Data

Six Supplemental Figures can be found with this article online at http://www.immunity.com/cgi/content/full/26/1/43/DC1/.

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Unit 07:

Getting Together

Getting Everything together
... before writing up!

Literature ready?

- Your literature expertise in the field
- several reference articles to „lean upon“

Gute Köche bereiten die Zutaten vor, ehe sie „loslegen“

⇨ special Trail on „Management of References“

Getting Everything together ... before writing up!

(preliminary, working) RESULTS ready?

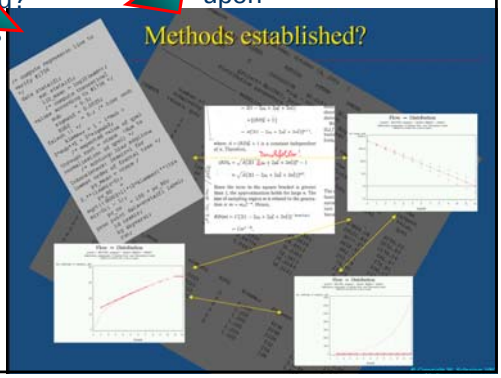
- figures + capt
- tables
- protocols & notes
- preliminary text-passages
- grant-proposal

Methods established?

- methods specific to your field (clinical, lab, etc.)
- statistics
- [illegible]ical
- eng[illegible]g?
- informatics

Literature ready?

- Your literature expertise in the field
- several reference articles to „lean upon“



Getting Everything together ... before writing up!

(preliminary, working) RESULTS ready?

- figures + captions
- tables
- protocols & notes
- preliminary text-passages
- grant-proposal

Methods established?

- methods specific to your field (clinical, lab, etc.)
- statistics
- biomedical engineering?
- informatics support?

Literature ready?

- Your literature expertise in the field
- several reference articles to „lean upon“

have 2-5 hours/day available, continuously over several weeks

Desktop facilities

- text processor (+facility for formulae) + reference manager
- chart program (Sigma Plot)
- illustrator program (Corel Draw)
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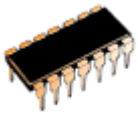

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diese und hunderte andere Online-Datenbanken sind über die IVS-Literaturrecherche zugänglich.

ACHTUNG: Für alle mit * gekennzeichneten Datenbanken benötigen Sie den NetMan WebClient!
Installationsanleitung

alphabetisch geordnet

AMED	Allied and Alternative Medicine; British Libary/GB (ab 1985).	
ARTS & HUMANITIES INDEX	Arts & Humanities Citation Index; ISI/USA (ab 2001).	
AUSTRIA CODEX*	Austria Codex	UBMUW Server
BIOSIS PREVIEWS	Biological Abstracts; BIOSIS/GB (ab 1990).	UBMUW Server
CINAHL	Cumulative Index to Nursing & Allied Health Literature; USA (ab 1982).	UBMUW Server
COCHRANE LIBRARY*	Datenbank zum Bereich EBM-Evidence Based Medicine; Cochrane Collaboration/GB	UBMUW Server
Current Contents connect	ISI/USA (ab 2000)	
EMBASE	Excerpta Medica-Database; Elsevier/NL (ab 1988).	UBMUW Server
EMBASE (OVID Gateway)	Excerpta Medica-Database; Elsevier/NL (ab 1988).	OVID Gateway
ExtraMED*	300 biomedizinische Journale aus den Entwicklungsländern im Volltext, ausgewählt von WHO Index Medicus Projekten	UBMUW Server
INSPEC	INSPEC / INIS	ZB-Physik Wien
ISI HighlyCited	Forschungsevaluierung; ISI/USA (1981-1999)	
ISI Proceedings	Index zu Beiträgen von Konferenzen, Symposien, Seminaren; ISI/USA (1990-2002)	
JOURNAL CITATION REPORT	Impact Factor; ISI/USA (ab 1998)	
Medizinische Kongresse 2004	Kongresskalender; Password für MUW-Angehörige per E-Mail: karin.silberhorn@meduniwien.ac.at	
MEDLINE	Index Medicus-Datenbank; NLM-National Library of Medicine/USA (ab 1966)	UBMUW Server
OTseeker	Occupational Therapy Systematic Evaluation of	

Medizinische Datenbanken erfolgreich nutzen
Medizin, Pharmakologie, Toxikologie, Biologie, Molekularbiologie, Chemie, Psychiatrie, Psychologie und Soziologie
König, J., **Erhart**, G., **Gengler**, M., **Grabner**, M.
2004, Etwa 250 S. 150 Abb. in Farbe., Softcover
ISBN: 3-211-83749-3

Erscheinungstermin: Mai 2004

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JETZT BESTELLEN

Druckversion
Diesen Titel empfehlen

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Erhart, Gabriele
Gengler, Manfred
Grabner, Martin

Verwandte Fachbereiche
Biomedizin
Chemie
Medizin
Pharmakologie & Toxikologie
Psychologie

Über dieses Lehrbuch | Inhaltsverzeichnis

Über dieses Lehrbuch

Elektronische Datenbanken liefern fast jede Information, aber man muss lernen, mit der Fülle der Daten umzugehen. Dabei hilft das Buch. Es stellt die Inhalte der wichtigsten Datenbanken aus Medizin, Genetik und Molekularbiologie, Pharmakologie und Toxikologie, Biologie, Immunologie, Chemie, Psychologie, Psychiatrie und Soziologie vor. Am Beispiel von MEDLINE, einer der größten Datenbanken der Medizin mit rund 11 Millionen Einträgen, wird genau erklärt, wie man in einer Datenbank erfolgreich recherchiert. Schwerpunkt ist die Suche in Faktendatenbanken der Molekularbiologie.

Geschrieben für:

Forscher und Studenten aus allen Fachgebieten der Medizin Psychologie und Life Science

Schlagworte:

- Biologie
- Biomedizin
- Chemie allgemein
- Computer Anwendung in der Medizin
- Medizin allgemein
- Pharmazie
- Psychologie

Unit 08:

Preparing the Manuscript

Preparing the Manuscript ctd.

Formal issues:

- Define all abbreviations in full after 1st usage
- Do not laugh at notations, invent them; they are powerful! (R.P.Feynman). BUT: Keep to notations already introduced (by others, by yourself).
- use consistent units of measurement in text, figure axes, and tables (see instructions for authors)
- carefully choose markers and symbols in figures and address them consistently in the text.

Technical issues:

- ***Start from WORD-template („Dokumentvorlage“) with empty section headings!***
- See our tutorials „Handling the Tools“ (Word, Endnote)

Preparing the Manuscript ctd.

Start with empty Section headings

Introduction

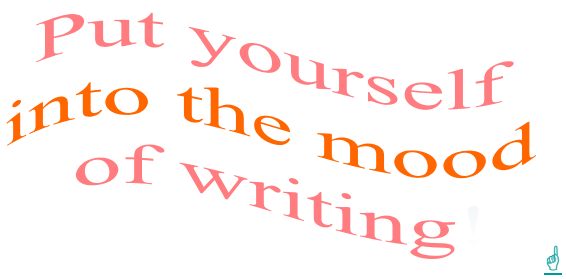
Methods

Results

Discussion

References

Figure Captions



Schreiben: flüssig oder gehemmt?

Schiller:
Ohne den Modergeruch halbfauler Äpfel ging gar nichts. Ohne den Apfelduft gäbe es wahrscheinlich keine "Räuber", keine "Kabale und Liebe", keinen "Don Carlos". Das Obst musste in der Schublade von Schillers Schreibtisch vor sich hingammeln, dann war alles gut: Das Dichten wurde zum Kinderspiel, die Feder flog nur so übers Papier.

Der Geruch von Fäulnis als Schreibstimulanz – das klingt kurios, ist aber ganz normal: Um die Qual des Schreibens zu erleichtern, nutzen Schreibprofis und -laien seit eh und je kühne Ticks und Tricks.

Goethe:
Goethe ließ sich in seine halb fertigen Manuskripte weiße Blätter einheften - zum "Anlocken".

Balzac:
Der französische Schriftsteller Balzac brauchte nächtliche Dunkelheit, viel Kaffee, blaues Papier und eine bestimmte Sorte Federn.

Preparing the Manuscript ctd.

Start with empty Section headings

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Figure Captions

.... And then „flood“ text into sections !

Preparing the Manuscript ctd.

Start with empty Section headings

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Figure Captions

.... And then „flood“ text into sections !

During text generation, correction and revision by your coauthors

line spacing 1

may be more convenient.
[change to appropriate spacing not before final formatting.]

Preparing the Manuscript ctd.

Start with empty Section headings

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.... And then „flood“ text into sections !

Do it in English right away, whenever possible.

If you think you cannot write in English:

- write in German
- employ a professional translator
- have a scientist of your field correct the translator‘s output.

Essentials of Writing Biomedical Research Papers, 2nd Edition

ISBN: 0-07-134544-2
Format: Softcover, 35 illus., 440p.
Pub date: September, 1999
Copyright: 2000
Price: $45.00US
Categories: Life Sciences -- Biological Sciences -- Biology
Publishers: Medical

DESCRIPTION

Provides immediate help for anyone preparing a biomedical paper by giving specific advice on organizing the components of the paper, effective writing techniques, writing an effective results section, documentation issues, sentence structure and much more. The new edition includes new examples from the current literature including many involving molecular biology, expanded exercises at the end of the book, revised explanations on linking key terms, transition clauses, uses of subheads, and emphases. If you plan to do any medical writing, read this book first and get an immediate advantage.

BACK COVER

An engaging and effective nuts-and-bolts approach to scientific writing. "...outstanding for its approach to the logic of presenting scientific work." - British Medical Journal review of first edition.Now revised and updated, this straightforward guide to biomedical writing helps authors understand both what a well-written scientific research paper is and how to create such a work. Essentials of Writing Biomedical Research Papers, Second Edition, provides writers with specific, clear guidelines on word choice, sentence structure, and paragraph structure. In addition, it explains how to construct each section of a research paper, so that, ultimately, the paper as a whole tells a clear story and sends a clear message.New to This Edition!New examples from the current literature, including many involving molecular biology; Expanded exercises at the end of the book; Revised explanations on linking key terms, transition clauses, uses of subheads, and emphases The specific principles of effective biomedical writing are presented and explained, and then summarized in handy chapter checklists. Each section of the prototypical biomedical research paper is then systematically analyzed in terms of its function, content, organization, detail, and length. The section-by-section analysis covers the following: the introduction, materials and methods, results, discussion, figures and tables, references, abstract, and title. Of special note: The book contains a full-length paper for readers to evaluate and revise in accordance with the book book's principles and guidelines. Also from McGraw-Hill. -Gehlbach: Interpreting the Medical Literature; Glantz: Primer of Biostatics Books and Software; Friedman: Primer of Epidemiology.

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Credits.
The Goal: Clear Writing.
Section I: The Building Blocks of Writing.
Chapter 1: Word Choice.
Chapter 2: Sentence Structure.
Chapter 3: Paragraph Structure.
Section II: The Text of the Biomedical Research Paper.
Chapter 4: The Introduction.
Chapter 5: Materials and Methods.
Chapter 6: Results.
Chapter 7: Discussion.
Section III: Supporting Information.
Chapter 8: Figures and Tables.
Chapter 9: References.
Section IV: The Overview.
Chapter 10: The Abstract.
Chapter 11: The Title.
Chapter 12: The Big Picture.

Put the Action in the Verb

Verbs express action in English. If the action of a sentence is expressed by the main verb, the sentence is natural and direct and easy to understand. If, instead, the action is expressed in a noun, the sentence is oblique, tangled, and more difficult to understand.

There common ways of expressing action in a noun instead of in a verb are (1) to put the action in the subject of the sentence, (2) to put the action in the object of the verb, and (3) to put the action in a prepositional phrase.

Action Inappropriately in the Subject

Example 2.2 An increase in heart rate **occurred**.

In this example, the verb (**occurred**) does not express the action of the sentence. Instead, the subject of the sentence (increase) expresses the action. As a result, the grammar does not coordinate with the meaning, and the sentence is complicated and indirect.

To revise a sentence whose action is in the subject, the trick is to

- Omit the subject and the preposition that follows it (here "increase in").
- Replace the vague verb (here "occurred") with the action from the omitted subject (here "increase" becomes "increased").

Revision Heart rate increased.

In the revised sentence, the grammar and the meaning coincide. That is, the subject states the topic (heart rate) and the verb expresses the action (increased). Thus, the sentence is simple and direct.

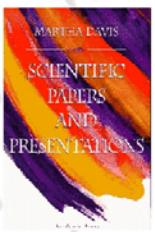
In addition, the revised sentence has fewer words than the original sentence and hence is more efficient.

Action in the Subject: An increase in heart rate occurred. (6 words)

Action in the Verb: Heart rate increased. (3 words)

Note also that the verb of the original sentence, **occurred**, is vague and general. It does not contribute to the meaning of the sentence (the meaning is in the subject) but simply performs the function of a verb. It could be replaced by another general verb, such as "was seen" or "was noted," without appreciably altering the meaning of the sentence.

Scientific Papers and Presentations



Author	Martha Davis
Publisher	Academic Press
Pub Year	1997
Page	296 pp
Cover	Soft cover
ISBN	0122063708
List Price	US$19.95
Our Price	US$18.00
Price	KRÆÜ25,000
Our Price	KRÆÜ20,000

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Preface

Whether it is a chemical structure, the anatomy of a rose, or an odysseansiren hidden in the recesses of a DNA code, something stirs the curiosity andlures people into the realm of science. Most scientists are effective, intelligent,logically thinking individuals who are coordinated enough not to destroy thelaboratory or the field plans and samples, but many become frustrated withcommunication. The siren did not tell them that many hours of their scientificdays would be spent writing reports, preparing for presentations, serving oncommittees to solve problems, or telling the nonscientist about the value of thescience. This book is an attempt to alleviate some of those frustrations withpapers and presentations.

Because it is a single, relatively brief volume, I cannot hope to treat everykind of scientific communication in great detail. Other more definitive booksconcentrate on their respective subjects such as writing skills, jounal articlepublication, writing proposals, group communications, public speaking, and allthe other topics to which I have dedicated single chapters. My purpose here is to introduce fledgling scientists to most of the kinds of professional communicationthat will confront them during graduate studies and as career scientists.
My objectives are (1) to answer the basic questions that might be asked aboutscientific communications and (2) to refer the scientist to more detailedsources of information.

To accomplish these objectives, the first part of the book proposes somepractical ideas relative to preparing for, organizing, and producing a roughdraft of any scientific paper or presentation. From these general concepts, thebook moves to specific written forms that graduate students in science willlikely encounter--the literature review, the research proposal, the graduatethesis, the journal article, and the practices and problems that accompanythese forms. In scientific writing and speaking, it is important to understandpublication styles, abstracts and titles, presenting data, reviewing and revising,and even ethics, copyrights, and patents.

Preparing the Manuscript ctd.

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2 mögliche Vorgangsweisen zur Texterstellung:

1. Gliederung schrittweise verfeinern (Subüberschriften, Schlagworte, Textbrocken).

Vorteil: Gesamtkonzept der Arbeit bleibt im Visier, einzelne Teile stehen hinsichtlich ihrer Tiefe der Darstellung und ihrer Länge im richtigen Verhältnis. „Man wird ständig zum Thema zurückgeholt". Außerdem zeigt sich rechtzeitig, wenn die gewählten Überschriften umstrukturiert werden müssen.

Nachteil: Es ist mitunter schwierig, von vorgefertigten Textbrocken wegzukommen und in eine glatte Darstellung umzuformulieren.

.... And then „flood" text into sections !

Preparing the Manuscript ctd.

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2. Write running text straight ahead.

Advantage: In this way it is easy to compose a fluent text which is easy to follow for the reader. The logical and stepwise development of thought is directly reflected in the manuscript.

Disadvantage: One must be careful not to adhere too extensively to certain details, thereby running astray and loosing the focus and scope of the paper. Several details will be covered (more than) thoroughly, others will be missing and it may be difficult to implant them afterwards.

.... And then „flood" text into sections !

Blend of 1 and 2: Man geht mit der Gliederung noch eine Stufe unter die niedrigste Ebene der tatsächlich vorkommenden Überschriften, z.B. man definiert „virtuelle" Überschriften für jeden Absatz; diese werden nach Verfassen der Absätze eines Kapitels wieder gelöscht.

Preparing the Manuscript ctd.

Start with empty Section headings

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Hinweis zum Verfassen eines flüssigen Textes:

- Nicht nach Worten ringen, sondern auf Schlagworte, mitunter sogar einzelne deutsche Worte zurückgreifen und flüssig fortfahren.
- Literaturzitate als Marken (evtl. mit #-zeichen statt Zitatnummer bzw. mit fliegendem Hinweis (z.B. „#Referenzarbeit von Zamir“) einfügen.
- Generell: Alles vermeiden bzw. sichtbar auslassen, was den Gedankenfluß unterbricht.
- Nach Abschluß einer Sektion Lauftext wird das Fehlende ergänzt.

.... And then „flood“ text into sections !

Preparing the Manuscript ctd.

Start with empty Section headings

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Methods

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Figure Captions

Whenever a formulation seems to become difficult

übergehen Sie sie einfach oder schreiben Sie ein paar Worte auf Deutsch -

to keep your text fluent and not to loose your thread of thought!

Roche-Lexikon: http://www.gesundheit.de/roche
Leo: http://dict.leo.org

.... And then „flood“ text into sections !

Preparing the Manuscript ctd.

Start with empty Section headings

Introduction

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Results

FIGURE A: Temperature affects clothing.

Discussion

References

Figure Captions

It may be handy to place figure captions within the sections text temporarily,

and move them to appropriate location finally.

.... And then „flood“ text into sections !

Preparing the Manuscript ctd.

Start with empty Section headings

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or

Discussion

ad discussion: *e.g. make reference to data of dubiosi-study. argue why we did it differently.“*

References

Figure Captions

While writing a section, thoughts may come to your mind -

- place them as preliminary notes into your manuscript at some convenient place

Later on replace notes by actual text.

.... And then „flood“ text into sections !

Preparing the Manuscript ctd.

Start with empty Section headings

During writing:
Whenever quoting is easy via Endnote, do it right away!

Introduction

Methods

≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈[22]≈≈[537]≈≈≈≈≈≈≈≈≈≈[926]≈≈≈≈≈≈≈≈≈≈≈
≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈[#ref]≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈≈

Results

When quoting may disturb your course of writing, insert just a reminder and continue writing.

Discussion

References

Figure Captions

.... And then „flood" text into sections !

Preparing the Manuscript ctd.

Suggestion I:

Write to raise the reader's interest, understanding & motivation!

Preparing the Manuscript ctd.

Suggestion II: ☝

Submit your manuscript in a form that convinces reviewers and the editor!

MEDIZINISCHE UNIVERSITÄT WIEN

Center for Medical Statistics,
Informatics & Intelligent Systems
A-1090 Wien, Spitalgasse 23

CeMSIIS
MedUni Wien

Publizieren mit Word 2007

Ergänzende Unterlagen zum Publikationsworkshop im Rahmen der postgraduellen Fortbildung an der MUW.

W. Schreiner, J. Ladenstein

22. Mai 2011

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1 Motivation

Viele Benutzer halten es für unnötig, sich näher mit WORD, dem meistgenutzten Textverarbeitungsprogramm zur Erstellung wissenschaftlicher Arbeiten, zu beschäftigen. Es wird einfach darauf los getippt und nicht weiter über die formalen Möglichkeiten nachgedacht.

Microsoft hat diesen direkten und intuitiven Zugang zu seinen Produkten stets ermöglicht, und daraus erklärt sich auch deren weltweite Beliebtheit und Verbreitung. Jedoch, was für den allerersten Einstieg vorteilhaft sein mag, wird bei intensiverer Nutzung rasch unzureichend[1]. Das müsste aber nicht so sein! WORD etwa bietet sehr wohl optional professionelle Layout-Features an, und wir raten Ihnen, die wichtigsten nach der folgenden Anleitung zu erlernen. Sie steigern Ihre Effizienz beim Verfassen von Publikationen, was immerhin einen zentralen Teil Ihrer professionellen Karriere ausmacht.

Bei der Nutzung von Desktop Applikationen (WORD, EXCEL, etc.) gibt es für eine gewünschte Aktion stets zahlreiche Möglichkeiten zur Umsetzung (Drop Down Menüs, Multifunktionsleise, rechter Mausklick auf einzelne Objekte etc.). Wir sehen es nicht als Zielsetzung, alle Möglichkeiten zu beschreiben (wie dies etwa ein Handbuch tut), sondern Ihnen als Studenten und angehenden Wissenschaftlern **einen gangbaren und möglichst effizienten Weg aufzuzeigen.** Wir wollen Sie in die Lage versetzen, in minimaler Zeit ausreichende Kompetenz für einen effizienten Umgang mit den Werkzeugen zu erwerben.

Eine Kurzfassung dieser Anleitung finden Sie auch in einem „Lecture MUWie“ auf

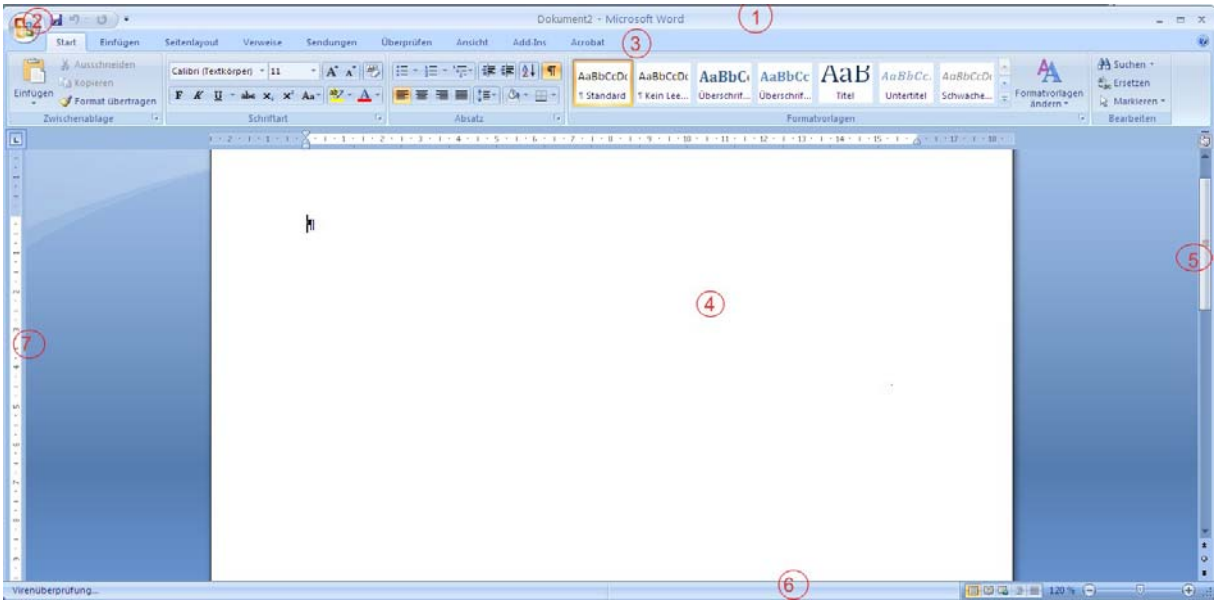
Link: http://www.meduniwien.ac.at/msi/biosim/publiwos/.

[1] **Analogon:**

Sie können die Rechnung 4+4+4 = 12 direkt durch zweimaliges Addieren ausführen, ebenso die Rechnung 7+7+7+7+7+7+7+7+7 =63. Irgendwann jedoch wird es effizient, das kleine Einmaleins zu lernen. Für die meisten von uns ist es jedoch nicht mehr effizient, das große Einmaleins (13 x 7 =?) zu lernen.

Ähnliches gilt für Word. Dabei ist es wichtig, den „optimalen Grad an Professionalität“ für die Erstellung von Publikationen zu wählen. Wir machen Ihnen dazu Vorschläge, abgestimmt auf „scientific writing“.

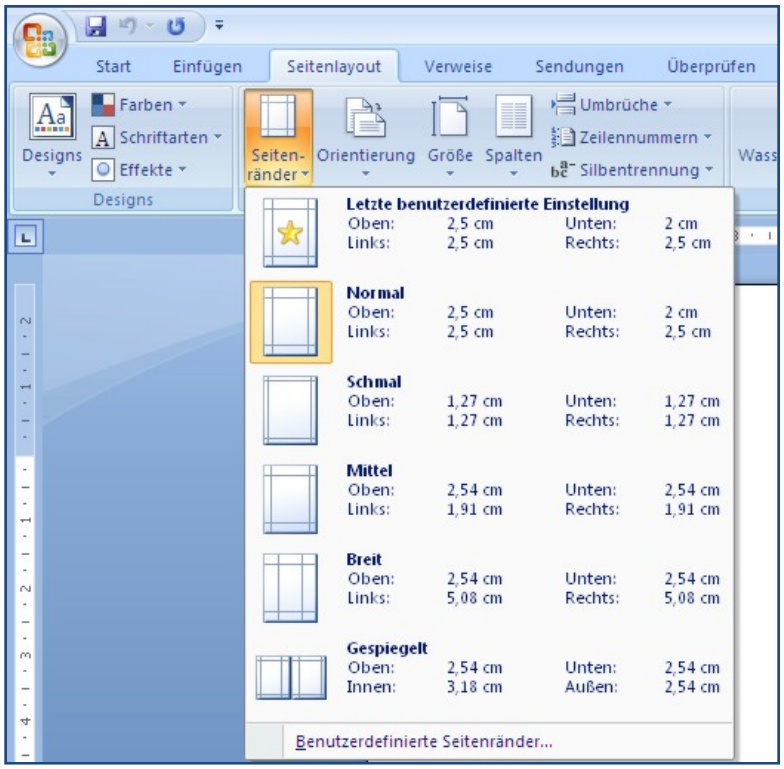
2 Was heißt wie?



1. In der **Titelleiste** stehen der Name des aktuell geöffneten Dokuments und die Symbole für den Schnellzugriff. Ganz rechts in der Leiste finden Sie wie bei Windows-Programmen üblich die Symbole, mit denen Sie die Fenstergröße bestimmen und das Programm schließen können.
2. Die Microsoft Office-Schaltfläche  ersetzt das „Menü Datei“. Sie befindet sich in der Ecke oben links. Wenn Sie auf Microsoft „Office-Schaltfläche“ klicken, werden die gleichen Basisbefehle angezeigt, die in früheren Versionen von Microsoft Office zum Öffnen, Speichern und Drucken von Dateien zur Verfügung standen.
3. Über die **Multifunktionsleiste** haben Sie Zugriff auf alle Funktionen und Befehle.
4. Auf der **Arbeitsfläche** tippen Sie ihre Texte ein.
5. Die **Bildlaufleisten** unterstützen Sie beim Navigieren.
6. In der **Statusleiste** bekommen Sie verschiedene Informationen zu Ihrem Dokument (Gesamtumfang und Seitenzahl). Rechts finden Sie die Möglichkeit auf verschiedene Layouts umzuschalten, zusätzlich zu zoomen.
7. Das horizontale und das vertikale **Lineal** können Ihnen bei der Gestaltung eines Dokuments hilfreich sein. (Das Lineal können Sie unter *Ansicht* aktivieren.)

3 Seite einrichten

Bevor Sie mit der Arbeit an einem Dokument beginnen, sollten Sie die Seite einrichten. Klicken Sie mit der linken Maustaste auf die „Office Schaltfläche“ und gehen Sie auf „Neu“. Damit öffnen Sie ein neues Worddokument.



- Klicken Sie in der Registerkarte „Seitenlayout“ auf „Seitenränder“.
- Hier sehen Sie einige mögliche Varianten von Einstellungen für Seitenränder.
- Durch das Klicken auf den gewünschten Seitenrand wird dieser automatisch auf das gesamte Dokument angewendet.
- Falls Sie die Seitenränder selbst definieren wollen, gehen Sie auf „Benutzerdefinierte Seitenränder“. Hier können Sie in die Felder **Oben, Unten, Links und Rechts** neue Werte eingeben.

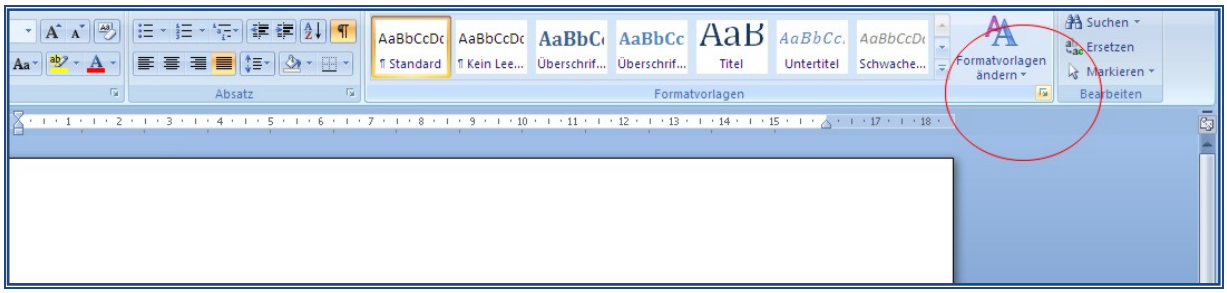
4 Formatvorlagen und Dokumentvorlagen

Mit Formatvorlagen können Sie ein Dokument schnell, professionell und einheitlich gestalten. Formatvorlagen sind die professionelle Alternative zum „Formatieren durch Klicken“ des WORD-Anfängers. Es stehen Ihnen Formatvorlagen für Zeichen und Absätze zur Verfügung. Mehrere Formatvorlagen können in einer Dokumentvorlage (Filename *.dotx) zusammengefasst werden. Wir bieten Ihnen Unterlagen zum Download auf http://www.meduniwien.ac.at/msi/biosim/publiwos/ an. Formatvorlagen und Dokumentvorlagen sollten möglichst zu Beginn definiert werden, das erspart viel Arbeit und Ärger.

4.1 Formatvorlagen auflisten

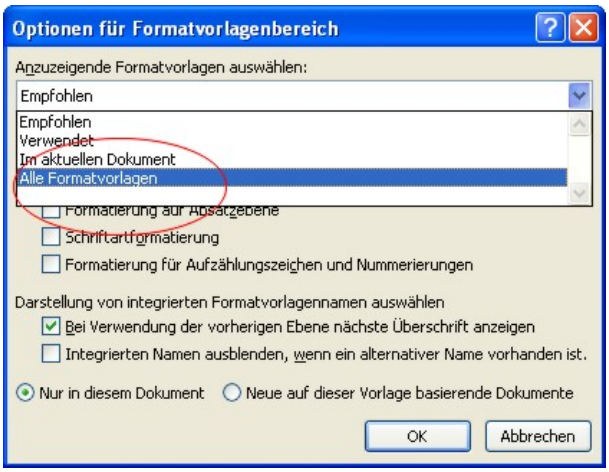
Öffnen Sie „Word“.

Gehen Sie in die Registerkarte „Formatvorlagen“ und klicken Sie dort auf den kleinen Pfeil in der rechten unteren Ecke.



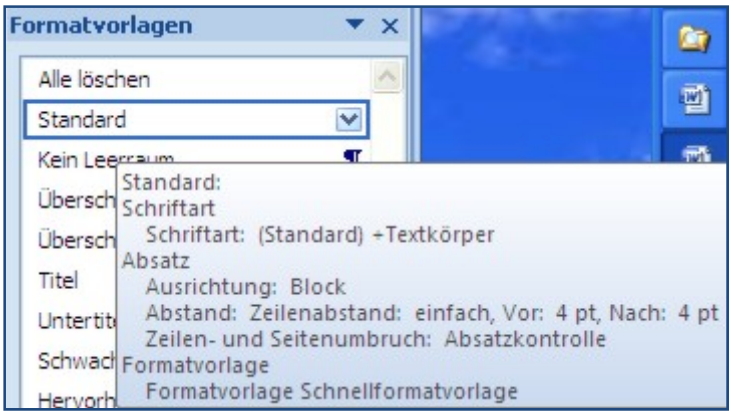
Damit öffnen Sie das Formatvorlagenfenster. Hier sehen Sie eine Auswahl der in Word schon vorgegebenen Formatvorlagen.

Weitere Formatvorlagen werden erst sichtbar, wenn Sie diese benötigen. Sie können sich aber auch (via „Optionen“) alle Formatvorlagen, die „Word“ schon vorab definiert hat, anzeigen lassen.

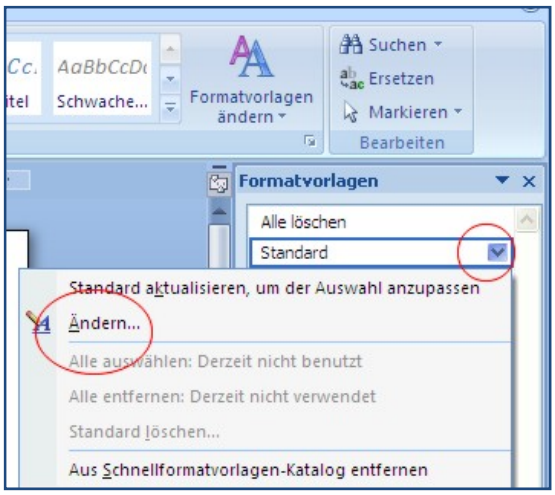


4.2 Formatvorlage Standard ändern

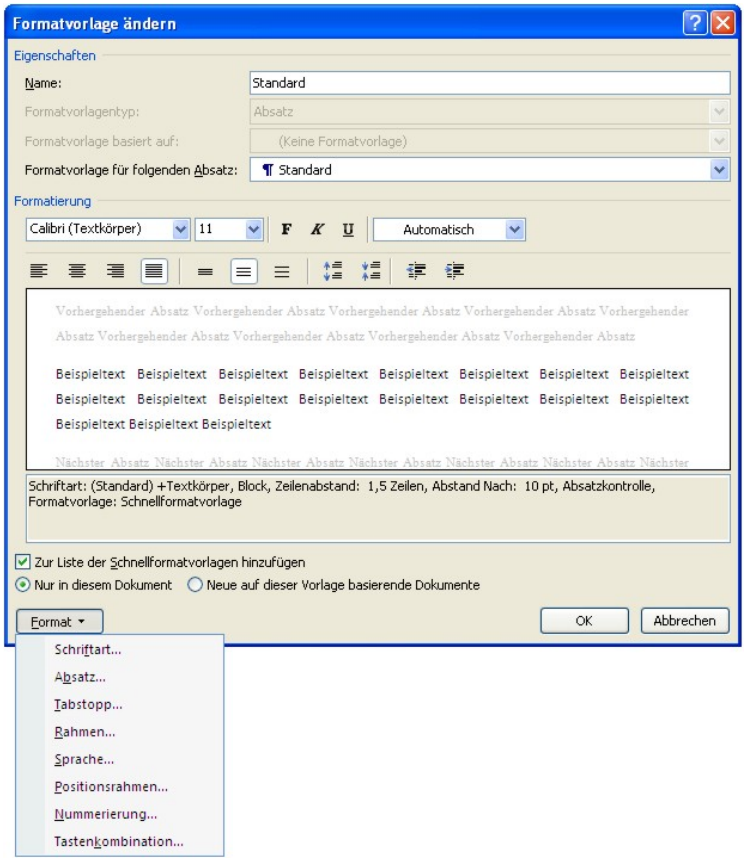
Wenn Sie im Formatvorlagenfenster die Maus über einen Eintrag positionieren (in „Mouse over“), werden die Einstellungen der Formatvorlage sowie ihre Abhängigkeiten („basiert auf“) sichtbar.



Klicken Sie nun im Formatvorlagenfenster auf den kleinen Pfeil, den Sie neben der Formatvorlage Standard sehen. Dadurch öffnet sich ein neues Fenster.

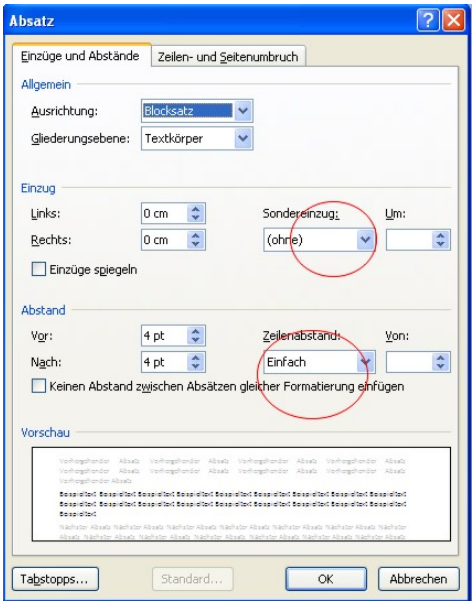


Wählen Sie „Ändern“.



Hier können Sie nun viele Formatierungen in Standard Ihren Wünschen entsprechend anpassen: Schriftart, Größe, Farbe.

Klicken Sie nun im Fenster „Formatvorlagen ändern“ links unten auf „Format“. Dadurch sehen Sie verschiedene Aspekte der Formatierungsmöglichkeiten. Gehen Sie beispielsweise auf „Absatz“. Hier finden Sie zwei Registerkarten: „Einzüge und Abstände“ und „Zeilen- und Seitenumbruch“.

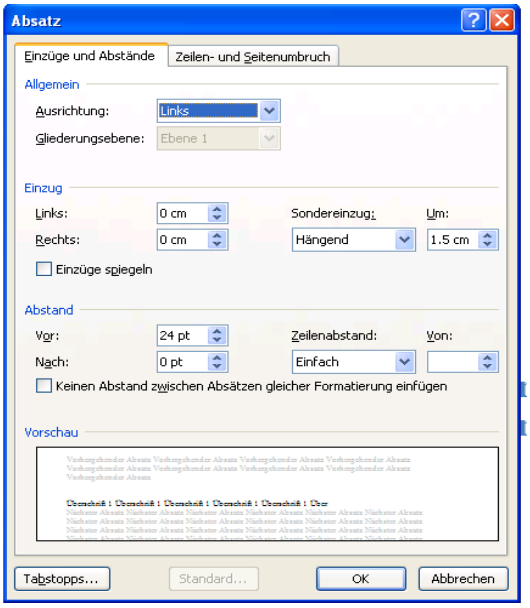


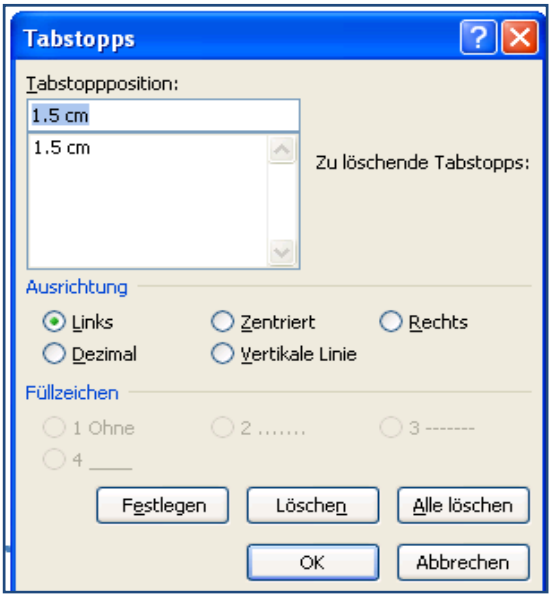
4.2.1 „Einzüge und Abstände“ ändern

- Ausrichtung: Wahlmöglichkeiten sind linksbündig, zentriert, rechtsbündig, Blocksatz. Blocksatz ergibt das optisch ansprechendste Erscheinungsbild, in ganz speziellen Fällen kann es jedoch zu unerwünschten Effekten kommen: Bei großer Schriftgröße und langen Wörtern werden unter Umständen große Abstände eingefügt, um die Zeile bis zum Seitenrand zu erstrecken, dies kann unvorteilhaft aussehen. Deswegen wird bei Überschriften häufig die Einstellung „linksbündig“ verwendet.

- Einzug: Hier können Sie einen zusätzlichen Abstand zum bereits definierten Seitenrand angeben (sowohl rechts wie auch links), der für alle Zeilen eines Absatzes gilt.

- Sondereinzug:
  - Ohne: bedeutet dass alle Zeilen eines Absatzes gleichartig behandelt werden
  - erste Zeile: hier können Sie die erste Zeile eines Absatzes einrücken. Dies wurde früher oft verwendet um Absätze deutlicher von einander zu trennen, ist mittlerweise weitgehend obsolet.
  - Hängend: dies bedeutet, dass die zweite und alle folgenden Zeilen eingerückt sind. Dieses Formatelement findet sehr häufige Anwendung, wie etwa bei Überschriften und Aufzählungen, um für die Nummer oder das Aufzählungszeichen Platz zu lassen. Beachten Sie, dass nach der Nummer bzw. nach dem Aufzählungszeichen stets ein Tabulator einzufügen ist, dessen Position mit dem Ausmaß des hängenden Einzuges abgestimmt sein muss.





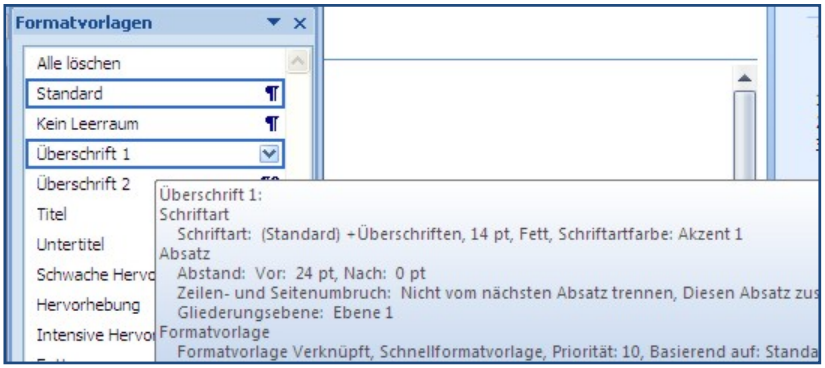
- Abstand
  - Vor/nach: Nach jedem Absatz, den Sie durch ein RETURN beenden, wird ein größerer „Zeilenabstand eingefügt“ (Ohne dass Sie zusätzliche „Returns“ einfügen müssen). Für normalen Text passt üblicherweise eine Einstellung „6pt nach“ bzw. „10pt nach“. Zum „Freistellen von Überschriften“ werden große Abstände vor/nach eingefügt (20pt und mehr).
  - Zeilenabstand: Normalerweise wählen Sie einfach, 1,5 Zeilen bzw. doppelt. Dazwischen liegende Abstände können Sie durch „Mehrfach“ und eine Angabe als Dezimalzahl erreichen.

4.2.2 „Zeilen- und Seitenumbruch“

- Dies wird später behandelt (siehe Seite 33), da Zeilen- und Seitenumbrüche in „Standard“ unverändert belassen werden können.

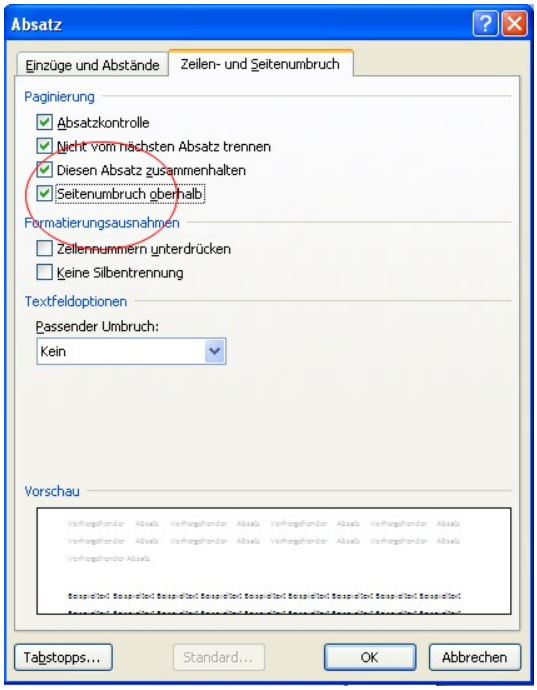
4.3 Formatvorlagen für Überschriften formatieren

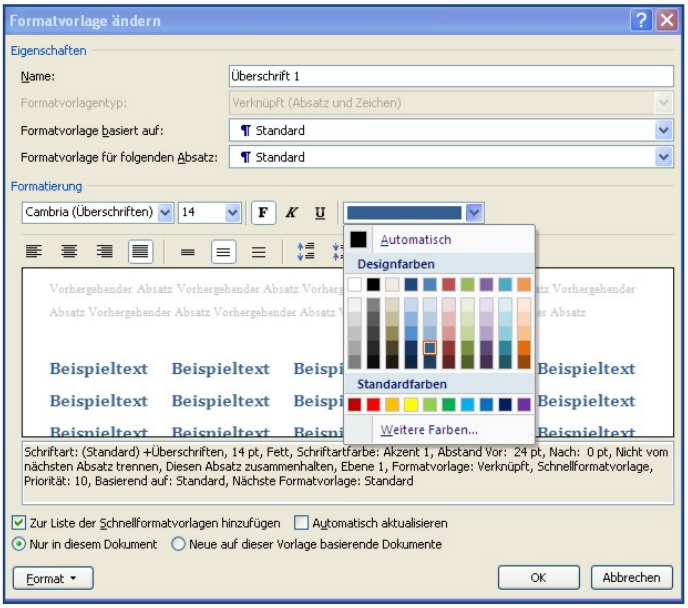
In der gleichen Weise, wie beim Ändern von Standard, gehen Sie nun auch beim Ändern der Überschriften vor.



Beim „mouse over“ sehen Sie die Grundeinstellung von „Word“ für die jeweilige Überschrift.

Formatieren Sie jede Überschrift nach Ihren Wünschen bzw. nach den Vorgaben eines Journals.





In größeren Dokumenten (etwa in Buchbeiträgen) kann es wünschenswert sein, bei Überschriften 1. Ordnung (Formatiert mit „Überschrift 1“) jeweils eine neue Seite zu beginnen. Dies sollte man nicht in „naiver“ Weise dadurch erledigen, indem man jeweils vor den Überschriften händisch Seitenumbrüche einfügt. Professionell ist es, den Seitenumbruch oberhalb einer Überschrift direkt in Ihre Formatvorlage zu integrieren. Gehen Sie folgendermaßen vor:

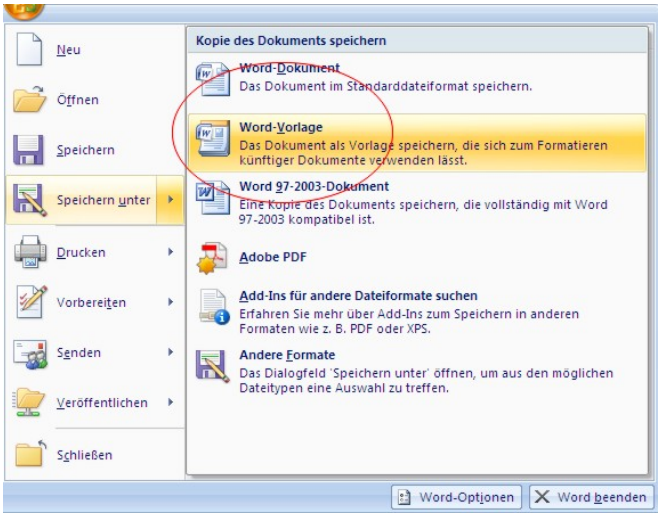
- Klicken Sie nun wieder auf „Format“ und hier auf den Karteireiter „Zeilen- und Seitenumbruch“.
  Hier können Sie festlegen, an welcher Stelle Sie einen Seitenumbruch wollen.
- Aktivieren Sie „Seitenumbruch oberhalb“, dann wird jeweils beim Verwenden der „Überschrift 1“ eine neue Seite begonnen.
- Haben Sie alle gewünschten Änderungen vorgenommen, klicken Sie auf „OK“. Alle Ihre Einstellungen werden sofort übernommen

4.4 Neue Formatvorlagen speichern

Die Formatvorlagen werden immer mit dem Dokument mitgespeichert. Wenn Sie das Dokument wieder öffnen, sind die Formatvorlagen, die Sie für dieses Dokument erstellt haben, wieder vorhanden.

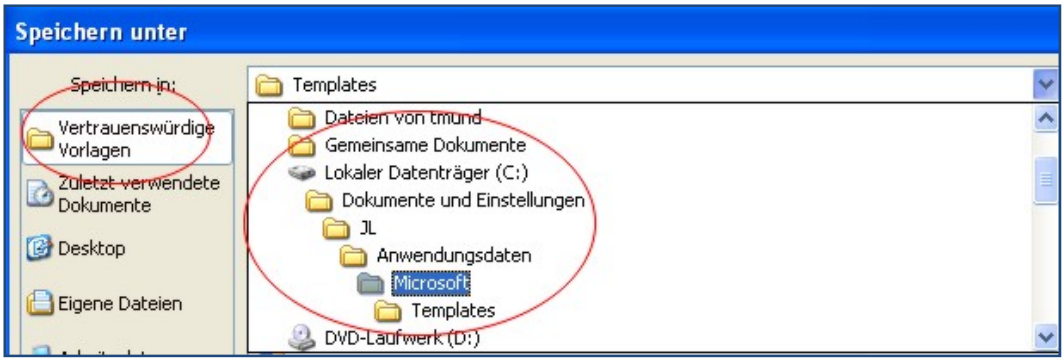
Sie können aber auch nur eine Sammlung von Formatvorlagen, ohne den Text des Dokumentes, speichern. Ein solches File nennt man „WORD Dokument-Vorlage“, und es besitzt stets den Typ „*dotx“. Gehen Sie wie folgt vor:

- Erstellen Sie zuerst eine Kopie Ihres Dokumentes (aus Sicherheitsgründen).
- Löschen Sie den gesamten Inhalt des Dokumentes
- Gehen Sie im Menü auf „Speichern unter“/ Wählen Sie „WordVorlage“ aus und einen passenden, ev. Neuen Namen, z.B. „myPaperFormat.dotx“.
- Sie haben damit eine neue Dokument-Vorlage myPaperFormat.dotx hergestellt, die Sie künftig benützen können!



Auf Ihrem Computer sind bereits Dokument-Vorlagen gespeichert, dies ist im Lieferumfang von Office enthalten. Deshalb sollten Sie Ihre neuen Vorlagen ebendort abspeichern.

Wählen Sie beim Speichern den Dateityp „Dokumentvorlage“ „vertrauenswürdige Vorlagen“, dann schlägt Ihnen Windows sogleich das passende Verzeichnis vor!



Normalerweise heißt es:

C:\Dokumente und Einstellungen\ UserName\ Anwendungsdaten\ Microsoft\ Templates (Suchen Sie eventuell auch danach.[2])

Sie können das Verzeichnis auch durch Unterverzeichnisse gliedern.

Laden Sie die vorbereiteten Dokumentenvorlagen „PapersNoNumLeft.dotx“ und „PapersNumLeft.dotx“ von der Adresse http://www.meduniwien.ac.at/msi/biosim/publiwos/ herunter und speichern Sie die Vorlage im oben angegebenen Verzeichnis.

[2] Analog ppt: Damit dieses Verzeichnis im Explorer angezeigt wird, stellen Sie im Windows-Explorer via „Extras“ die „Ordneroptionen“ auf „alle Ordner und Dateien anzeigen ein.

5 Formatierungszeichen

Wenn Sie heikle Formatierungsarbeiten durchführen, blenden Sie stets die Formatierungszeichen ein! Sie zeigen Ihnen, „wie Ihr Dokument wirklich entstanden ist".

Klicken Sie dazu einfach auf das im folgenden Bild markierte Symbol:

Ohne Formatierungszeichen können Sie nicht sicher erkennen, was „hinter den Kulissen vorgeht".

Im Folgenden ein Beispiel mit Formatierungszeichen.

1.→Die·wichtigsten·Formatvorlagen¶

1.1.→Überschriften¶

Ich·bin·ein·Fülltext.·Der·Fülltext·geht·weiter·und·zeigt·wie·dieses·Dokument·mit·und·ohne·Formatierungszeichen·dargestellt·wird.¶

1.2.→Absätze¶

Fülltext·Fülltext·Fülltext·Fülltext·Fülltext·Fülltext·Fülltext·Fülltext·Fülltext·Fülltext·Fülltext·Fülltext·Fülltext·Fülltext·Fülltext·Fülltext¶

Und ohne Formatierungszeichen:

1. Die wichtigsten Formatvorlagen

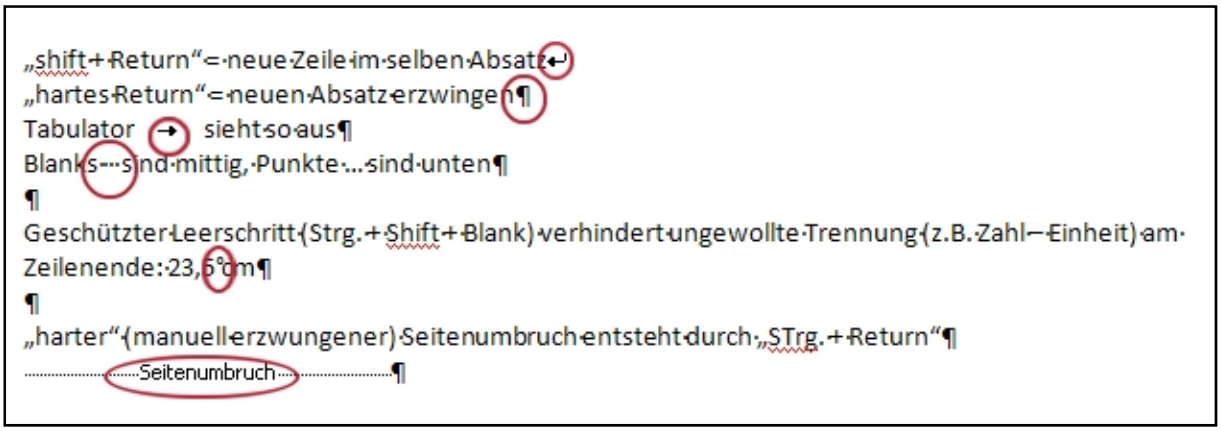
1.1. Überschriften

Ich bin ein Fülltext. Der Fülltext geht weiter und zeigt wie dieses Dokument mit und ohne Formatierungszeichen dargestellt wird.

1.2. Absätze

Fülltext Fülltext Fülltext Fülltext Fülltext Fülltext Fülltext Fülltext Fülltext Fülltext Fülltext Fülltext Fülltext Fülltext Fülltext Fülltext.

Die wichtigsten Formatierungszeichen sind:



Diese Formatierungszeichen werden in jedem Fall mit dem Dokument gespeichert, können aber angezeigt oder nicht angezeigt werden!

6 Beschriftungen (Legenden) für Abbildungen und Tabellen

Nummerieren Sie Ihre Abbildungen nicht „händisch“!

Benutzen Sie die in Word eingebaute Funktion „Beschriftung“!

Die Beschriftung von Abbildungen und Tabellen ist in Word sehr unkompliziert und sollte unbedingt verwendet werden.

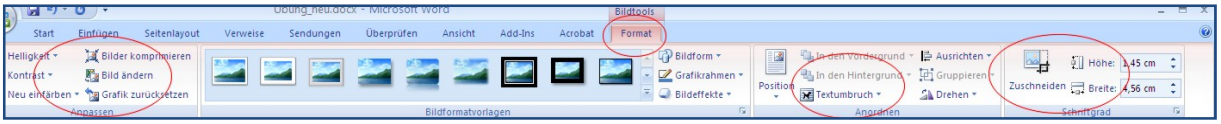
Vorteile:

- Falls Sie im Laufe Ihrer Arbeit eine Abbildung einfügen oder löschen, werden alle danach Folgenden automatisch umnummeriert!
- Alle Querverweise (z.B. Siehe Abb. xx) übernehmen automatisch die geänderten Nummern! (Nachdem Sie “aktualisiert” haben.)
- Analog für Tabellen

Anmerkung: In Manuskripten, die Sie an Journals schicken, wird gewöhnlich verlangt, dass die Abbildungslegenden getrennt vom Text angeführt werden. Dies geschieht häufig in einem separaten Abschnitt „Captions to the Figures“ am Schluss des Manuskriptes. Die Abbildungen selbst werden dem Manuskript häufig gar nicht physisch beigefügt, sondern getrennt davon eingereicht. Um diese Vorgaben zu erfüllen, benötigen Sie einige Handgriffe, die sich geringfügig von jenen unterscheiden mit denen Sie Abbildungen samt Legenden in einen Text einbetten können. Aus didaktischen Gründen beschreiben wir zuerst die Version „Abbildung + Legende in Text einbetten“, wie Sie etwa zum Erstellen von Buchbeiträgen oder eigenständigen längeren Arbeiten erforderlich ist (z.B. Dissertation oder Diplomarbeit). Jene Form, die in Publikationsmanuskripten verlangt wird, lässt sich anschließend davon leicht ableiten.

6.1 Einfügen der Abbildung bzw. Tabelle

1. Gehen Sie auf die Registerkarte „Einfügen“/„Grafik“/ oder „Tabelle“ oder „Diagramm“
2. Falls das Bild noch nicht die richtige Größe hat, schneiden Sie es auf die entsprechende Größe zu
   - Dazu klicken Sie auf das Bild, dadurch geht ein neues Registerblatt auf – „Format“

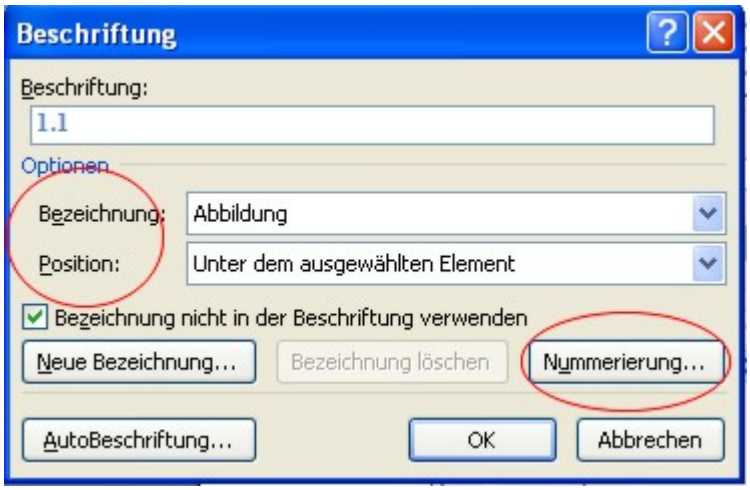


- Klicken Sie auf „Zuschneiden“
- Ziehen Sie mit gedrückter linker Maustaste den schwarzen Rand an die gewünschte Stelle
- Bild ist zugeschnitten

6.2 Einfügen der Beschriftung

Zum Einfügen einer Beschriftung (Legende) für eine Abbildung gehen Sie wie folgt vor:

- Positionieren Sie den Cursor an jene Stelle, wo Sie die Beschriftung haben möchten. Dies kann entweder direkt unter der Abbildung selbst sein (wenn sie die Abbildungen direkt in den Text eingefügt haben, wie etwa bei Dissertationen und Diplomarbeiten), es kann aber auch in einer separaten Sektion „Captions to the Figures“ am Ende Ihres Dokumentes sein (etwa in einer Publikation), siehe auch Kapitel 6.5.
- In der Registerkarte „Verweise“ klicken Sie dann auf die Schaltfläche „Beschriftung einfügen“, dadurch öffnet sich folgendes Fenster:



- Wählen Sie hier nun die Bezeichnung „Abbildung“. Falls die Bezeichnung Abbildung nicht vorhanden ist, oder die von Ihnen bevorzugte Bezeichnung, gehen Sie auf „Neue Bezeichnung“. Hier können Sie jede von Ihnen gewünschte Bezeichnung eingeben, und diese neue Bezeichnung steht dann immer für Sie zur Auswahl bereit.
- Nun wählen Sie noch die Position der Beschriftung: Sie können zwischen „Unter dem ausgewählten Element“ und „Über dem ausgewählten Element“ wählen.

Analog gehen Sie auch für Tabellen vor.

Hinweis: Wenn Sie mit einer deutschen Version von Word einen englischen Text schreiben, wird Ihnen beim Beschriften einer Abbildung natürlich die Kategorie „Abbildung“ angeboten. Verwenden Sie diese nicht! Definieren Sie stattdessen eine neue Kategorie wie „figure“ und verwenden Sie diese weiterhin. Dadurch können Sie erreichen, dass etwa bei Querverweisen anstelle der deutschen Bezeichnung „Abbildung“ sogleich die englische Bezeichnung „figure“ eingefügt wird. In der für Sie vorbereiteten Formatvorlage ist diese Definition schon getroffen.

6.2.1 Beschriftungen samt Kapitelnummer

Manche Verlage (und etwa auch die MUW im Rahmen von Diplomarbeiten) verlangen eine Nummerierung der Abbildungen in der Form „Kapitelnummer. Abbildungsnummer“. Um dies zu erreichen, gehen Sie folgendermaßen vor:

1. Im oben gezeigten Panel für „Beschriftung“ klicken Sie auf „Nummerierung“.

2. Klicken Sie auf „Kapitelnummer einbeziehen“, „Kapitel beginnt mit Formatvorlage Überschrift 1“

3. Nun können Sie noch das gewünschte Trennzeichen wählen.

4. Klicken Sie auf ok. Die Abbildung wird automatisch nummeriert.

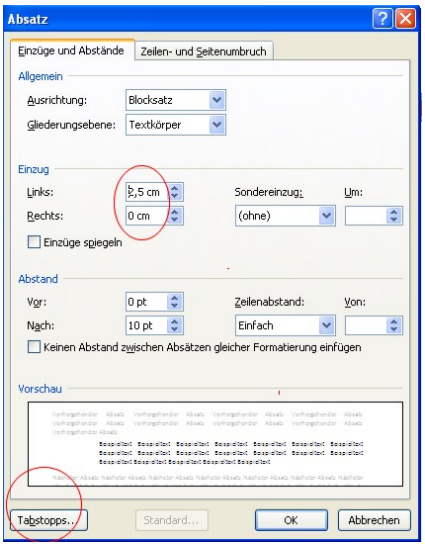
6.2.2 Beschriftungstitel und Beschriftungstext

Fügen Sie nach der Abbildungsnummer immer einen Doppelpunkt und dann einen Tabulator ein. Dadurch werden unterschiedlich lange Nummerierungen ausgeglichen und alle Beschriftungstitel beginnen an derselben Stelle.

Hinweis: Word weist beim Einfügen einer Beschriftung automatisch die vordefinierte Formatvorlage „Beschriftung“ zu. Falls Sie ein anderes Aussehen wünschen, müssen Sie die vordefinierte Formatvorlage ändern (überschreiben), oder eine eigene Formatvorlage (z.B. „BeschriftungTitel“) definieren. Beachten Sie beim Formatieren, dass der Beschriftungstitel länger als eine Zeile sein kann, und daher ein hängender Einzug verwendet werden muss, der mit der Position des Tabulators abgestimmt ist, damit sich ein ansprechendes Layout ergibt.

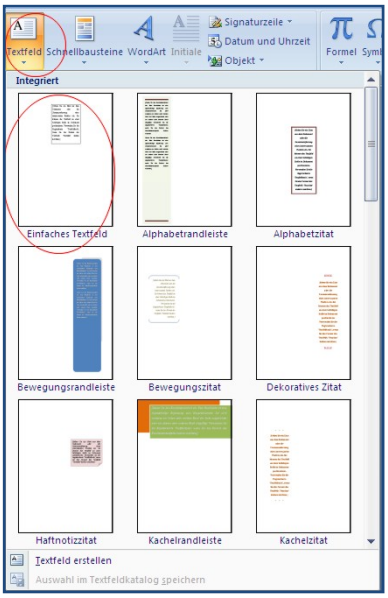
Bei manchen Abbildungen sollen neben dem Titel noch weiterführende Erklärungen hinzugefügt werden (z.B. Hinweise auf spezielle Teile der Abbildung), („Beschriftungs-Text“). Sie können dafür eine Formatvorlage verwenden, deren linker Einzug ebenfalls auf die Tabulatorposition abgestimmt ist, sodass die weiterführende Erklärungen stets bündig mit dem Beginn des Beschriftungstitel zu liegen kommen.

In der für Sie vorbereiteten Dokumentenvorlage ist die entsprechende Formatvorlage „BeschriftungText“ bereits vordefiniert.

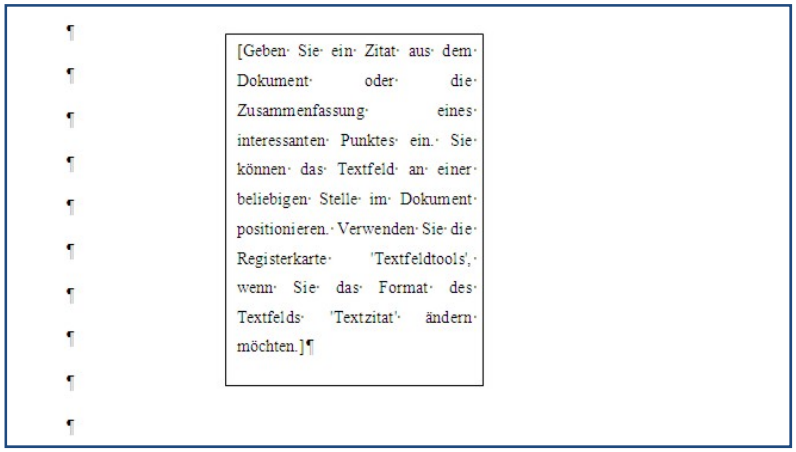


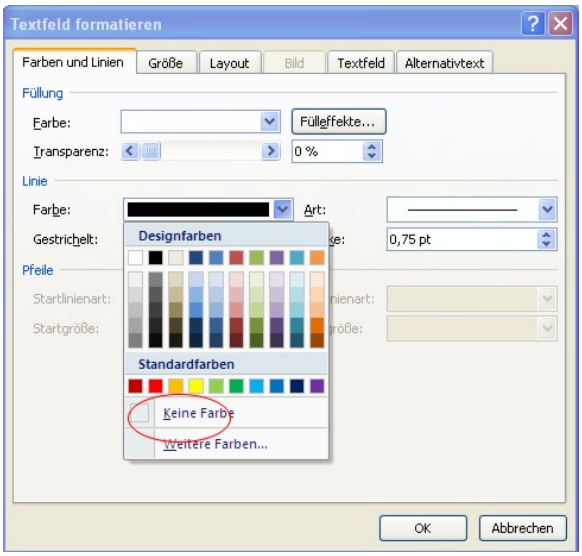
6.3 Abbildung und Beschriftung als gemeinsamen Block im Text positionieren

Falls Sie ein Bild von Text umfließen lassen wollen, müssen Sie das Bild auf eine andere Weise einfügen, da ansonsten auch die Bildbeschriftung das eingefügte Bild umfließt.

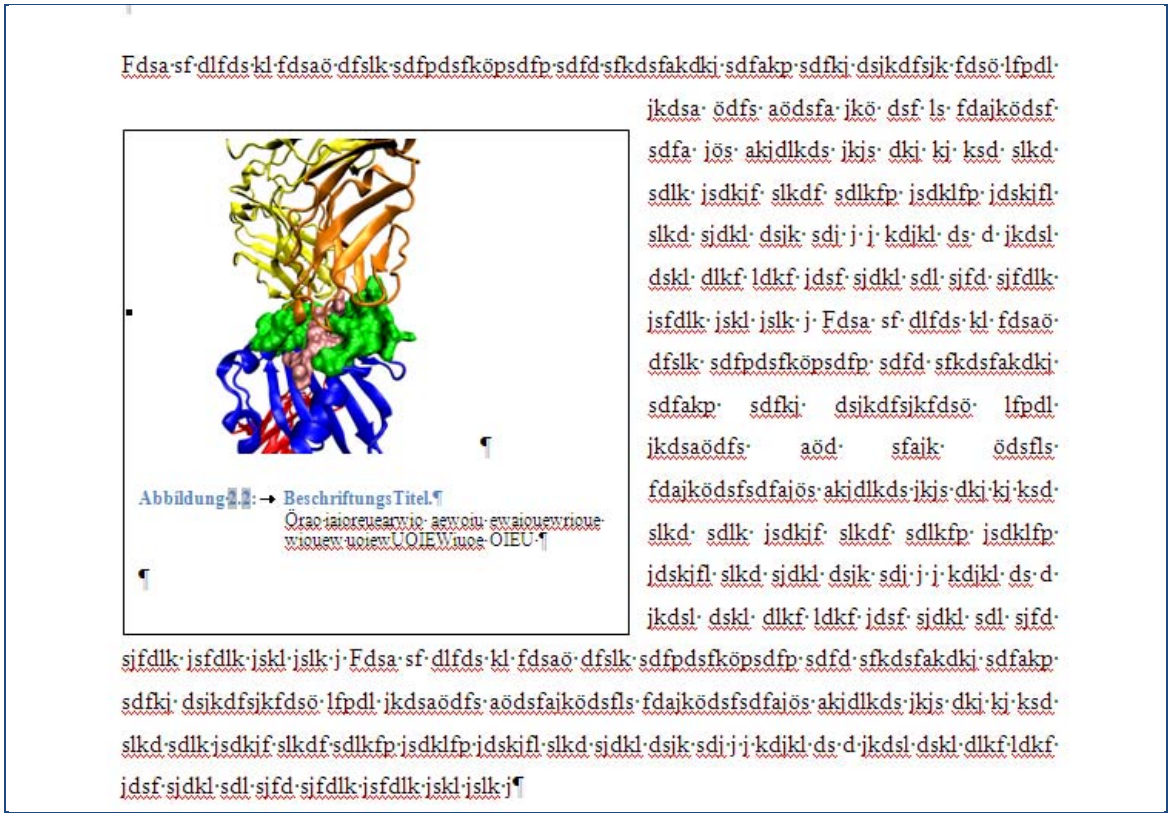


- Gehen Sie auf die Registerkarte „Einfügen“
- Klicken Sie auf den kleinen Pfeil im Icon „Textfeld“
- Wählen Sie „Einfaches Textfeld“





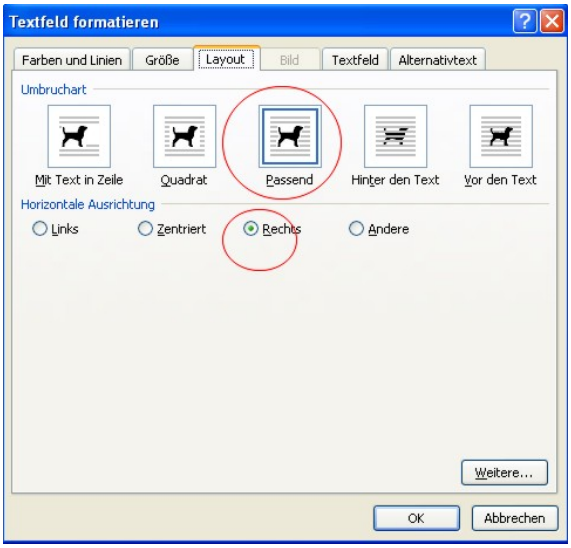
- Fügen Sie nun die gewünschte Grafik im Textfeld ein
- Anschließend beschriften Sie die Grafik wie gewohnt
- Passen Sie nun den Rahmen der Größe des Bildes und der Beschriftung an
- Wenn Sie nun auf den Rahmen klicken, können Sie Bild und Beschriftung gemeinsam verschieben.
- Klicken Sie noch auf den Rahmen, „Textfeld formatieren“, es öffnet sich folgendes Fenster
- Wählen Sie für Linie „keine Farbe“, dann verschwindet der Rahmen.



Wollen Sie, dass der Text auch seitlich vom Bild weiterläuft (das Bild samt Beschriftung umfließt), dann gehen Sie auf die Registerkarte „Seitenlayout“. Hier können Sie nun zwischen

verschiedenen Optionen wählen: „mit Text in Zeile“, „Quadrat“, „Passend“, „Hinter dem Text“, „vor dem Text“. Wählen Sie das von Ihnen Gewünschte aus. Außer bei „mit Text in Zeile“, sind noch die Optionen: „links“, „zentriert“, „rechts“, „andere“ möglich.

Klicken Sie auf das Gewünschte und anschließend auf ok.

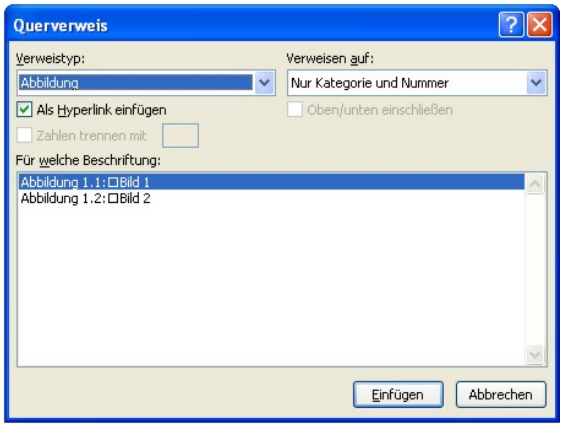


6.4 Verweise auf Abbildungen, Tabellen und Diagramme

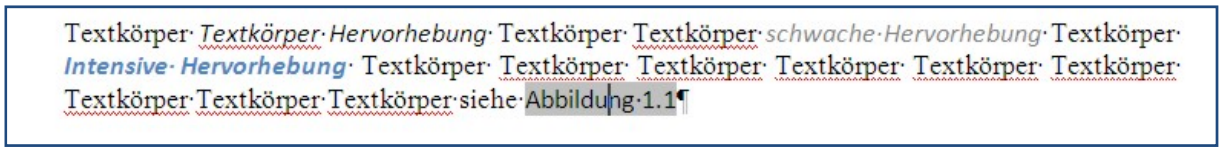
Wollen Sie nun aus dem Text Ihrer Arbeit auf eine Abbildung verweisen, klicken Sie mit dem Cursor dorthin, wo sich der Verweis später befinden soll. Anschließend klicken Sie auf die Registerkarte „Verweise“, anschließend „Querverweis“

Im nun sich öffnenden Fenster wählen Sie den „Verweistyp“ „Abbildung“, oder „Tabelle“, je nachdem worauf Sie verweisen wollen.

Nun sollten Sie eine Auswahl aller erstellten Abbildungen sehen.



„Verweisen auf“: Hier wählen Sie „Nur Kategoerie und Nummer, um folgendes Ergebnis zu bekommen:

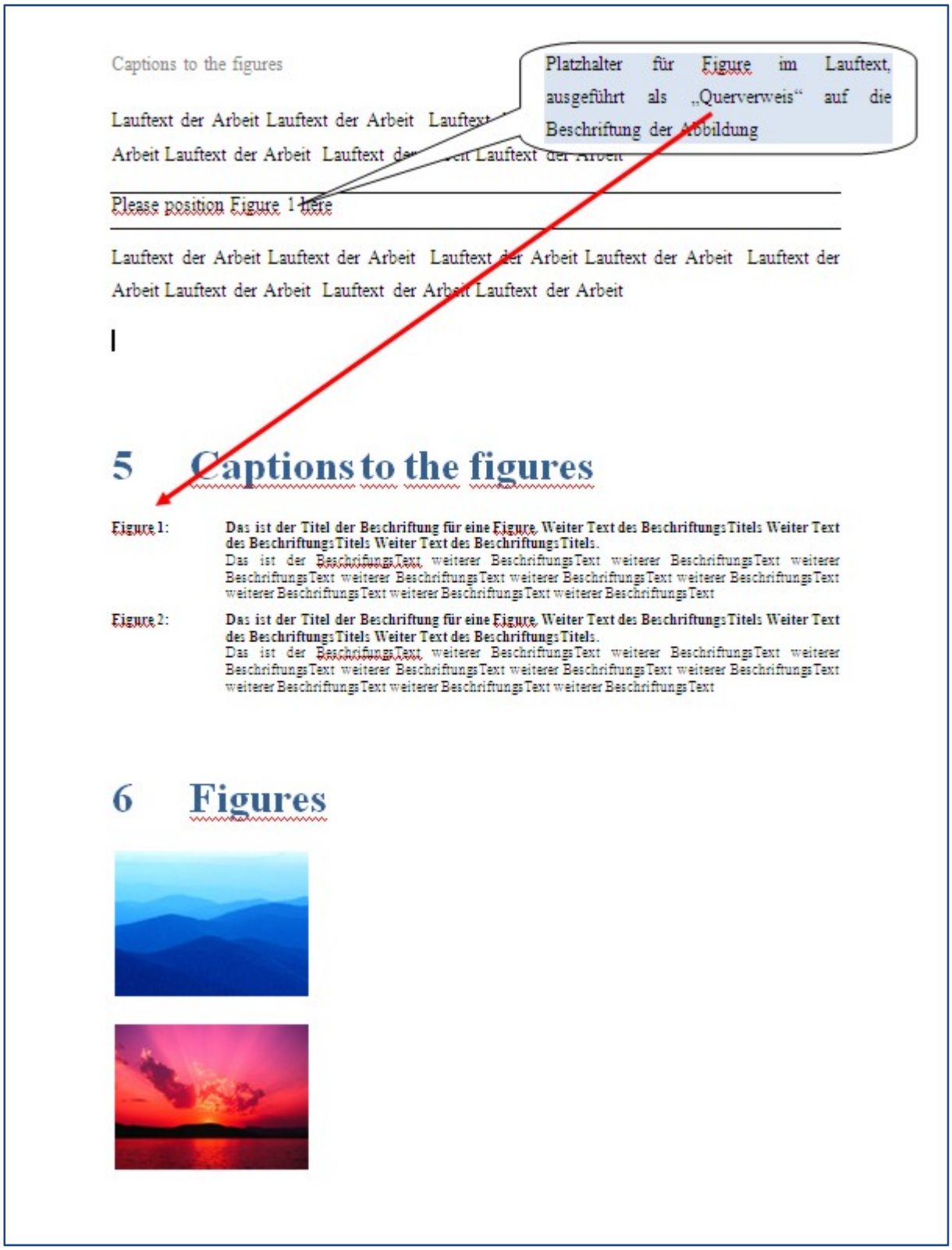


Vorteil: Wenn Sie nun ***vor*** der bestehenden Abbildung weitere Abbildungen einfügen, und sich dadurch alle nachfolgenden Nummern ändern, werden auch die Verweise automatisch umnummeriert. Sie müssen nur mit der rechten Maustaste auf einen Verweis klicken, und im neu geöffneten Fenster „Felder aktualisieren“ wählen.

Manchmal ist es praktisch, in einem Dokument alle Nummerierungen und Querverweise zu aktualisieren. Dazu

- Tippen Sie „STRG-a“ (dadurch wird das gesamte Dokumetn markiert)
- Klicken sie mit der rechten Maus irgendwo in den Text und wählen Sie „Felder aktualisieren“
- Lassen Sie mehrmals hintereinander „Gesamtes Verzeichnis“ aktualisieren.

6.5 „Figures“ and „Captions to the figures“ getrennt vom Text



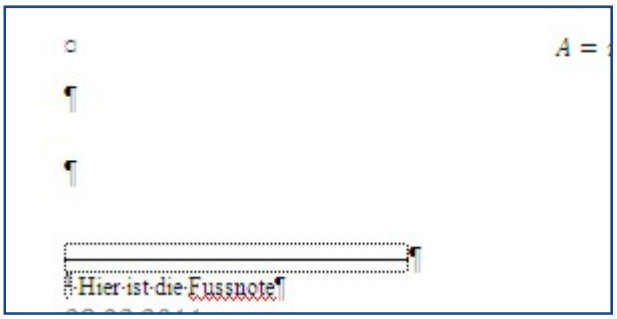
Wie schon erwähnt, verlangen Journals zumeist die „Caption to the Figures“ in einem separaten Kapitel am Ende des Manuskriptes und die Abbildungen überhaupt getrennt vom Manuskriptes. Um die Vorteile der automatischen Nummerierung auch in diesem Zusammenhang vollständig auszuschöpfen, können wir Ihnen folgendes Vorgehen empfehlen:

- Fügen Sie Ihre Abbildungen nicht in den Lauftext ein, sondern öffnen Sie ein eigenes Kapitel „Figures“ am Ende der Arbeit, siehe Abbildung. Fügen Sie dort wie beschrieben Ihre Bilder ein.
- Öffnen Sie davor ein Kapitel „Captions tot he Figures“ ein.
- Fügen Sie dort zu jedem Bild eine Beschriftung ein, wie oben beschrieben, wenn gewünscht auch mit Beschriftungstext.
- Sobald Sie die Beschriftung für eine Abbildung eingefügt haben, können Sie darauf an jeder Stelle des Manuskriptes, d.h. auch vorne inmitten des Lauftextes, einen Querverweis darauf setzen. So können Sie etwa mit einer Marke „place figure 1 hier“ die gewünschte Position einer Abbildung anzeigen.

7 Fußnoten

Klicken Sie an der Stelle, an der Sie die Fußnote einfügen wollen, anschließend in der Registerkarte „Verweise“ auf „Fußnote einfügen“.

Word fügt automatisch die entsprechende Nummer ein und springt in die Fußzeile: Sie können jetzt den Text zur Fußnote eingeben. [3]



[3] Anmerkung: Fußnoten sind eine effiziente Methode, um komplexe Zusatzinformationen anzufügen ohne den Fluss des Haupttextes zu stören. Während Sie in den Geisteswissenschaften geradezu als „Qualitätskriterium“ guter Texte gewertet werden, sind sie in den Naturwissenschaften verpönt und die meisten Zeitschriften verbieten deren Verwendung.

8 Schnellbausteine definieren

Schnellbausteine dienen dazu, komplexe Ausdrücke und Inhalte zu speichern, um sie dann einfach wieder verwenden zu können. Dadurch sparen Sie viel Zeit und Mühe.

Sie können beliebige Inhalte (Texte, Formeln, Tabellen), speichern und entweder einfach durch Kürzel abrufen, oder durch öffnen der Registerkarte „Einfügen“, „Schnellbausteine“ und Klicken auf den entsprechenden Eintrag.

Und so wird es gemacht:

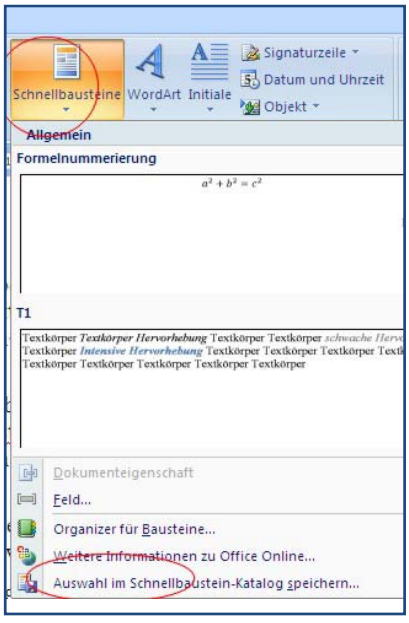
Markieren Sie die Formel, oder den Textteil, den Sie gerne speichern würden:

komplexe Ausdrücke wie z.B. CTLA-4$^{+/-}$

Gehen Sie auf die Registerkarte „Einfügen“/ „Text“/ „Schnellbausteine.

Klicken Sie auf den kleinen Pfeil.

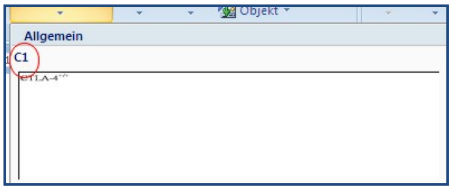
Anschließend klicken Sie auf „Auswahl im Schnellbaustein-Katalog speichern“.



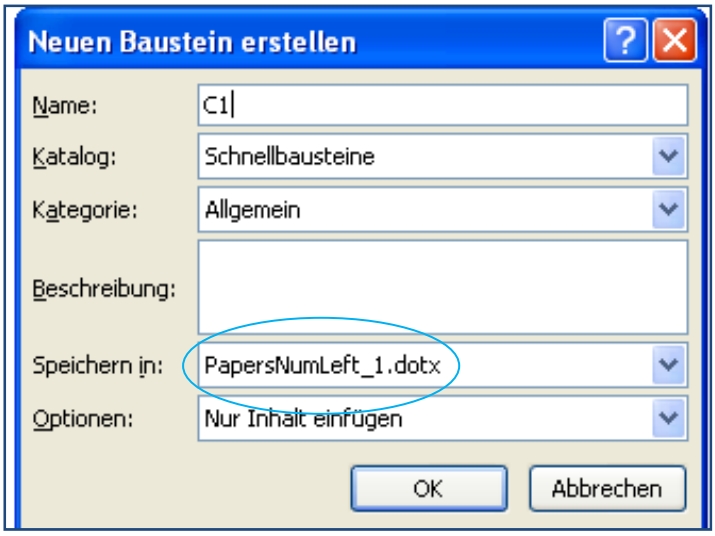
Fügen Sie nun unter „Name“ einen Kürzel, z.B. „C1“, ein.

Wenn Sie nun die Formel wieder benötigen, tippen Sie C1 und anschließend die Funktionstaste F3, und die Formel wird automatisch eingefügt. Oder Sie öffnen die Registerkarte mit dem „Schnellbaustein“ und klicken direkt auf den Gewünschten.

Alle definierten Kürzel können Sie auch jederzeit im Schnellbausteinfenster nachsehen.



Die beschriebene Vorgehensweise speichert den Schnellbaustein auf Ihrem Computer (in der Datei Building Blocks.dotx), sodaß Sie ihn dort auch in allen anderen Dokumenten zur Verfügung haben. Alternativ können Sie den Schnellbaustein auch in einer von Ihnen erstellten Dokumentvorlage speichern:



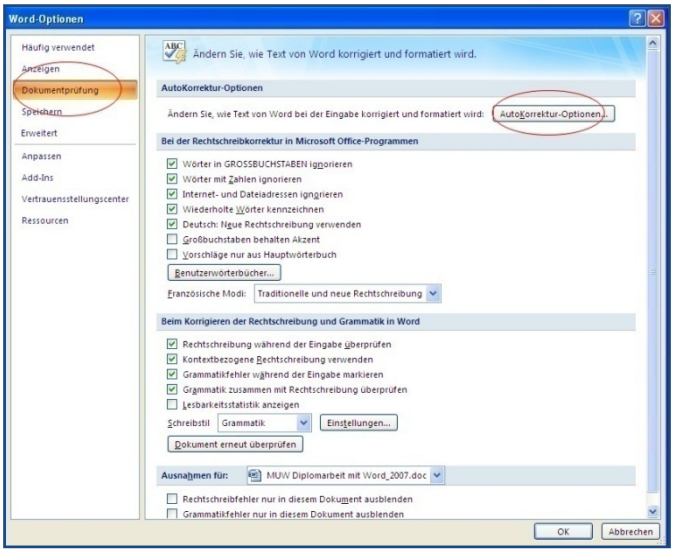
Wenn Sie diese auf den Arbeitsgruppenserver legen, können alle Kollegen diese Dokumentvorlage öffnen und den Schnellbaustein ebenfalls verwenden.

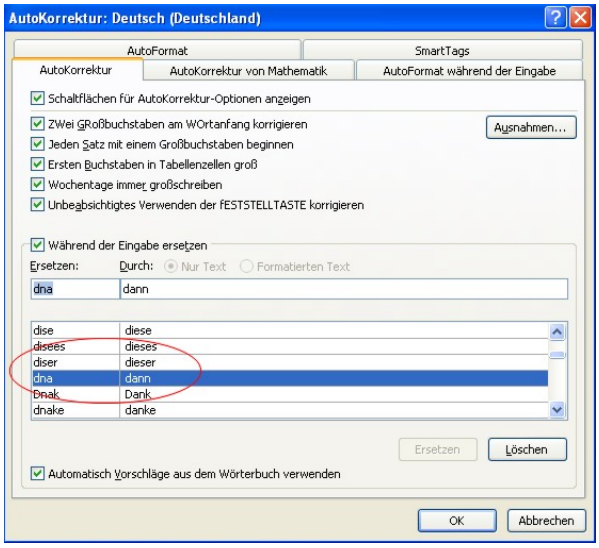
9 Autotexte

Mit Hilfe dieses Features können Sie Tippfehler automatisch korrigieren lassen. Allerdings kommt es auch vor, dass Wörter von Word automatisch geändert werden, obwohl Sie dies nicht wünschen.

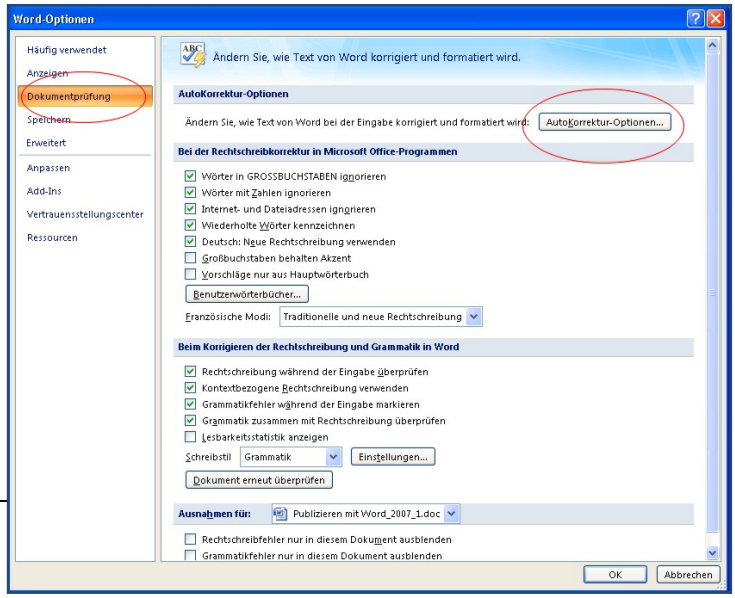
Als Beispiel nehmen wir „DNA“. Wenn Sie dieses Wort im Text schreiben, wird es von Word automatisch in „Dann“ geändert, und dies ist sehr lästig. In solchen Fällen ist folgende Anpassung ratsam:

Gehen Sie auf Die Word-Office Schaltfläche / „Word Optionen“ / „Dokumentenprüfung“/ „Autokorrektur-Optionen“. Hier können Sie nun einfach den Eintrag „dann“ löschen, sodass DNA nicht korrigiert wird, oder Sie können jedes von Ihnen gewünschte Wort eingeben. Das Löschen von Autotexten wirkt jedoch generell und kann in anderen Dokumenten unter Umständen unerwünscht sein.

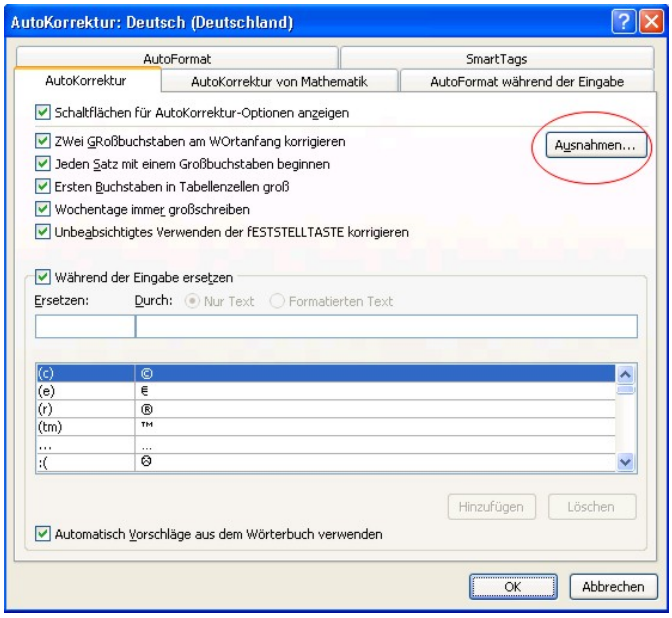


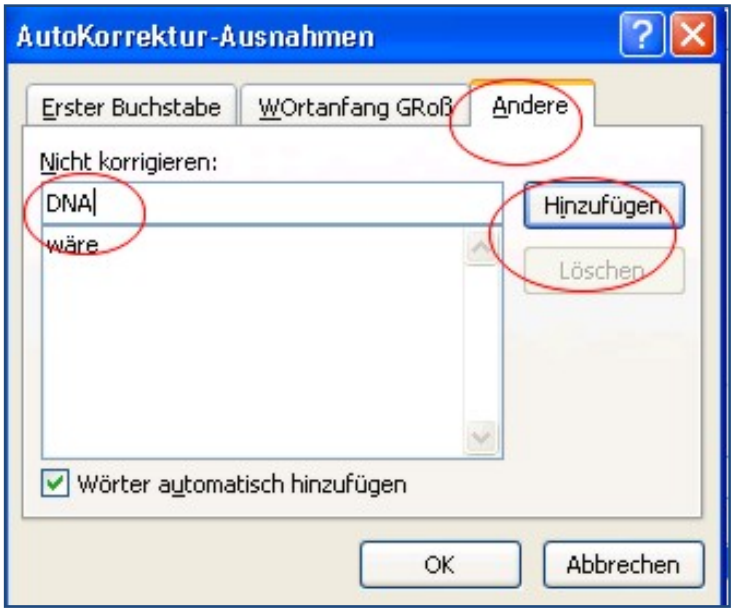


Eine andere Möglichkeit besteht über die Definition von „Ausnahmen von der Autokorrektur“ – dieses Feature ist in der jetzt ausgelieferten WORD –Version 2007 noch nicht ausreichend stabil, sodass wir die Variante via löschen derzeit eher empfehlen.



Wollen Sie jedoch Ausnahmen definieren, gehen Sie wie folgt vor:

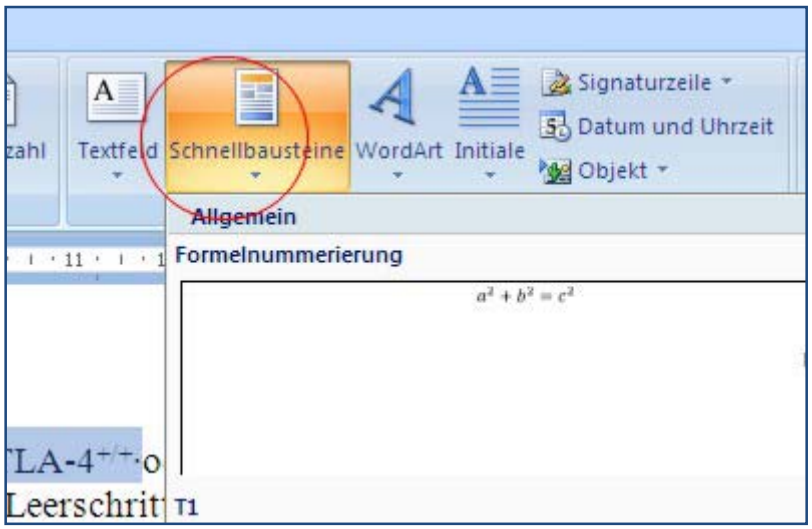




Gehen Sie wieder auf die Office-Schaltfläche , „Word-Optionen“, „Dokumentenprüfung“, „Autokorrektur-Optionen“. Klicken Sie auf „Ausnahmen“.

Geben Sie nun das Wort ein, das Sie nicht korrigiert haben möchten.

10 Mathematische & chemische Formeln via Schnellbaustein einfügen



Um eine mathematische Formel samt Nummerierung einzufügen, gehen Sie auf die Registerkarte „Einfügen“/ „Schnellbaustein“.

Wählen Sie den Schnellbaustein „Formel mit durchlaufender Nummer“

Damit wird eine Dummy-Formel (hier $a^2 + b^2 = c^2$) samt Nummerierung eingefügt.

$$a^2 + b^2 = c^2 \quad (1)$$

Falls Sie die Kapitelnummer in der Formelnummerierung mit einbezogen haben wollen, wählen Sie den Schnellbaustein „Formel nummeriert mit Kapitel“.

$$a^2 + b^2 = c^2 \quad (10.1)$$

Sie ersetzen einfach die Dummy-Formel durch die von Ihnen Gewünschte. Die Nummerierung der Formeln passt sich automatisch an.

Für englische Texte bietet Ihnen die vorbereitete Dokumentvorlage 2 analoge Schnellbausteine „equation with single number“ und „equation with chapter number“ an.

Anstelle der Formel können Sie auch eine chemische Reaktionsgleichung einsetzen.

Chemische Strukturformeln werden unter der Kategorie „Abbildung“ eingefügt.

Freie Software für Strukturformeln: Symyx Draw.

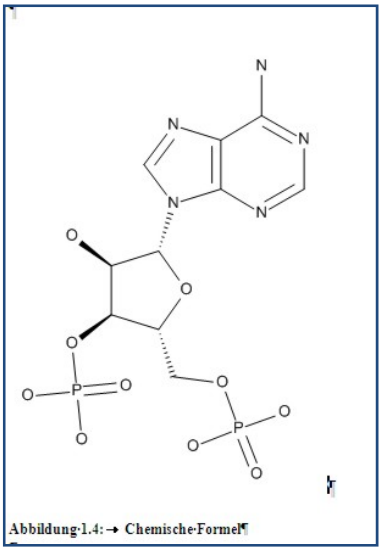
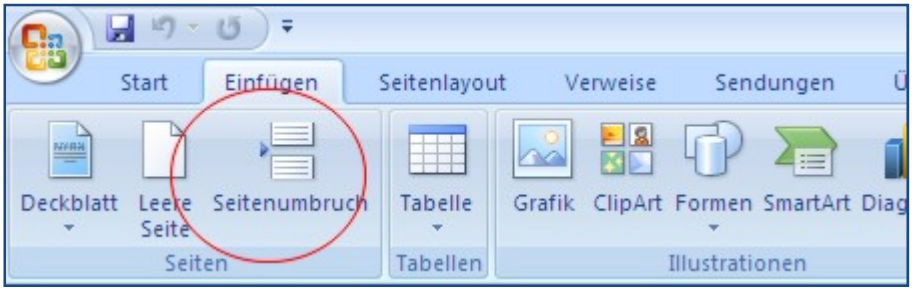


Abbildung 1.4: → Chemische Formel

11 Seitenumbruch

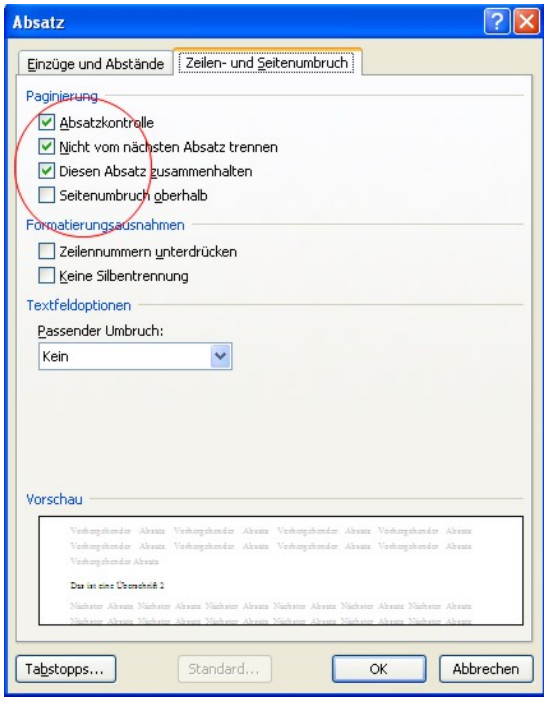
11.1 Seitenumbruch einfügen



Sie können einen Seitenumbruch an einer beliebigen Stelle im Dokument einfügen. Dazu gehen Sie im Registerblatt „Einfügen“ auf „Seitenumbruch“.

Sie können aber auch bestimmten Formatvorlagen einen Seitenumbruch zuweisen. Zum Beispiel, wenn Sie gerne hätten, dass jede Überschrift 1 grundsätzlich auf einer neuen Seite beginnt. (Wie im vorliegenden Skriptum).

Dazu gehen Sie auf die jeweilige Überschrift im Formatvorlagenfenster, klicken auf den kleinen Pfeil, „Ändern“/ „Format“/ „Absatz“/ „Zeilen- und Seitenumbruch“. Auf dieser Registerkarte aktivieren Sie das Kästchen „Seitenumbruch oberhalb“. [4]



Das Kästchen „nicht vom nächsten Absatz trennen“ bewirkt, dass die Überschrift nicht alleine am Schluss einer Seite stehen kann.

Die Option „diesen Absatz zusammenhalten“ bewirkt, dass die Überschrift zur Gänze auf einer Seite zu liegen kommt und nicht etwa nach der ersten Zeile der Überschrift ein Umbruch erfolgt und die restliche Überschrift auf der nächsten Seite stehen könnte.

Seien Sie sparsam mit händisch eingefügten zusätzlichen Seitenumbrüchen!

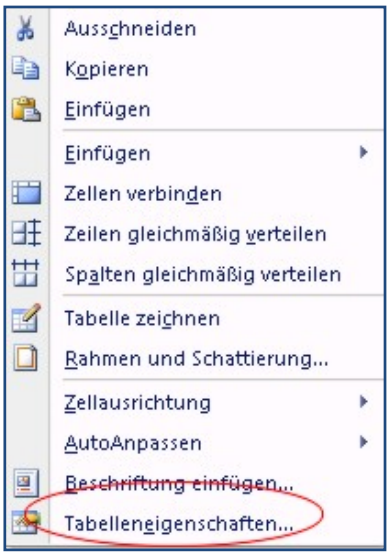
[4] Sollte die Überschrift zufällig ohnehin am Beginn einer neuen Seite zu liegen kommen, wird dann kein zusätzlicher Seitenumbruch eingefügt, wie es der Fall wäre, wenn Sie ihn als „manuellen Seitenumbruch“ zusätzlich eingefügt hätten.

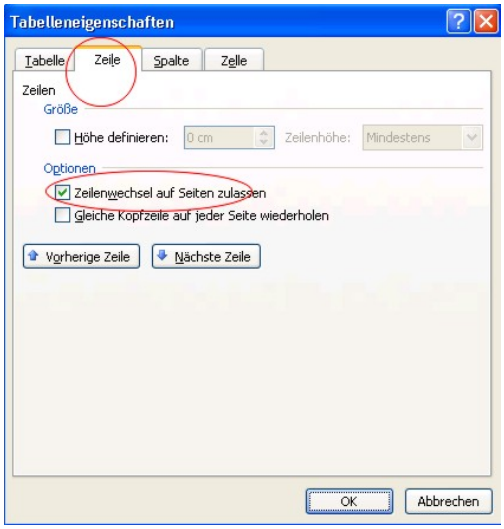
11.2 Verhindern von unpassenden Seitenumbrüchen

Gute Formatvorlagen (z.B. für Überschrift 1) verhindern dies automatisch (via „mit dem nächsten Absatz zusammenhalten)!

Sie können Umbrüche aber auch dezidiert verhindern, z.B. in Tabellen:

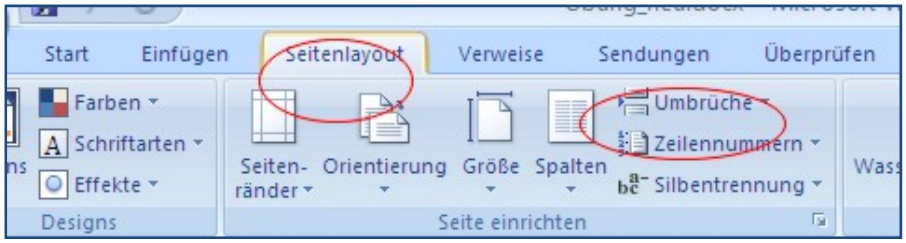
Klicken Sie auf die Tabelle (oder auf die Tabellenzeile), die keinen Seitenumbruch enthalten soll. (Eine Tabelle, die nicht auf die Seite passt, muss natürlich einen Seitenumbruch enthalten!) Rechter Mausklick, „Tabelleneigenschaften“, „Zeile“. Deaktivieren Sie das Kontrollkästchen „Zeilenwechsel auf Seiten zulassen“.





12 Abschnittswechsel

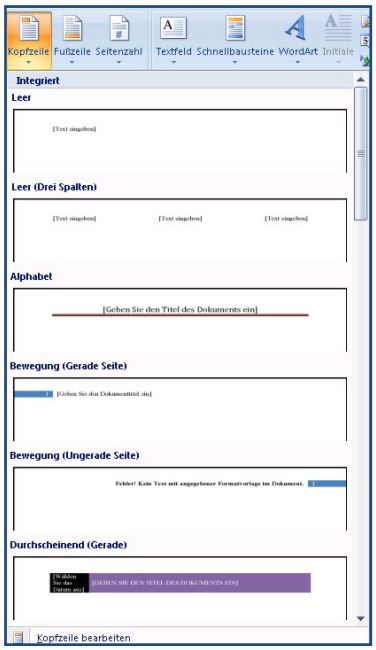
Abschnittswechsel sind unter anderm dann erforderlich, wenn Ihr Dokument einen Teil enthält für den sich die Seiteneinrichtung von jener für das restliche Dokument unterscheidet. Das häufigste Beispiel sind Dokumententeile im Querformat.



Falls Sie Tabellen oder Listen einfügen und dazu auf Querformat wechseln wollen, fügen Sie vorher und nachher einen Abschnittswechsel ein:

- Gehen Sie auf „Seitenlayout“/ „Umbrüche“. Hier können Sie zwischen verschiedenen Möglichkeiten wählen. Falls Sie möchten, dass im neuen Abschnitt die Seitennummerierung fortlaufend ist:
- Gehen Sie dazu auf „Einfügen“/ „Kopf-Fußzeile“/ „Seitenzahl“/ „Seitenzahlen formatieren“
- Wählen Sie „Fortsetzen vom vorherigen Abschnitt“

13 Seitenzahl und Running Title



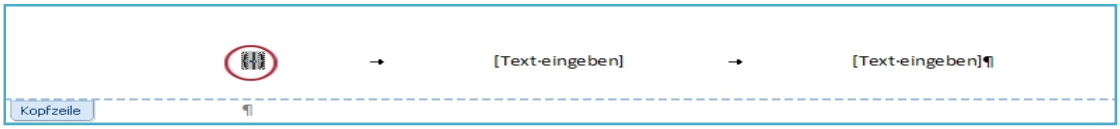
Running Titles und Seitenzahlen fügen Sie in Kopf- bzw. Fußzeilen ein.

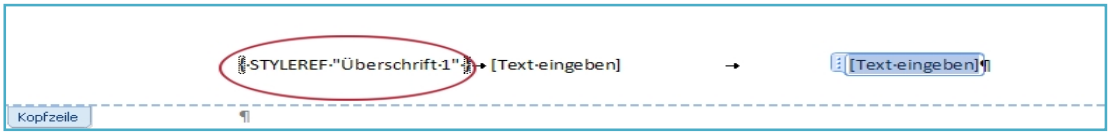
- Gehen Sie auf die Registerkarte „Einfügen“ und klicken Sie auf „Kopf- od. Fußzeile“.
- Sie können nun zwischen verschiedenen Möglichkeiten wählen, klicken Sie auf jenes Format, das Sie gerne hätten.

Es besteht auch die Möglichkeit, in die Kopfzeile einen „Running Title“ einzufügen, in dem stets der Text der „Überschrift 1“ angezeigt wird.

Dies gelingt Ihnen mit Hilfe einer Funktion:

- Gehen Sie auf „Einfügen“ – „Kopfzeile“.
- Klicken Sie nun in die Kopfzeile, drücken Sie [STRG] + [F9], dadurch entsteht eine geschwungene Klammer.
- Klicken Sie in die Klammer und geben Sie folgendes ein: STYLEREF „Überschrift 1“. Anschließend via rechtem Mausklick „Felder aktualisieren“.





Hier sehen Sie das Resultat.

Wichtig: Damit Sie hier keinen Fehler angezeigt bekommen, muss im Dokument schon eine Überschrift 1 enthalten sein!

Falls Sie die Fuß- oder Kopfzeile auf jeder Seite vom darüber liegenden Text durch eine Linie trennen möchten, klicken Sie einfach in der Kopfzeilenansicht im Menü auf *Rahmen*, und *Rahmen unten* bzw. *oben*, so erscheint eine Begrenzungslinie.

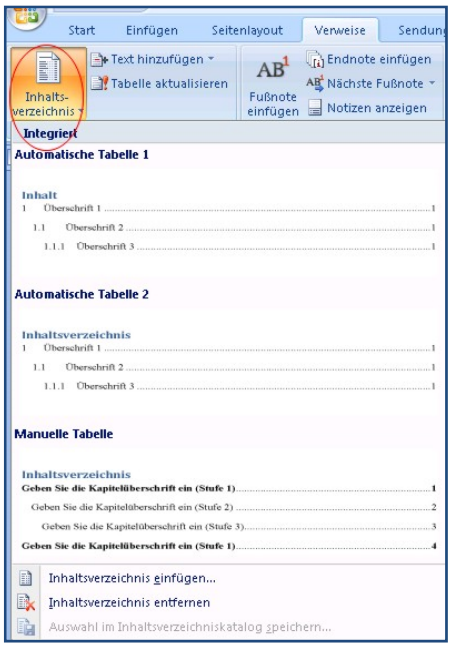
14 Verzeichnisse erstellen

Zur Publikation von Journalartikeln ist es zumeist nicht notwendig Verzeichnisse zu erstellen. Falls Sie jedoch eine Dissertation, einen Reviewartikel, einen Buchbeitrag, einen Jahresbericht oder gar ein Lehrbuch schreiben, ist die Erstellung von Verzeichnissen unbedingt notwendig. Wir geben daher einen kurzen Leitfaden.

Sie können ein Inhaltsverzeichnis, ein Abbildungsverzeichnis und einen Index einfügen. [5]

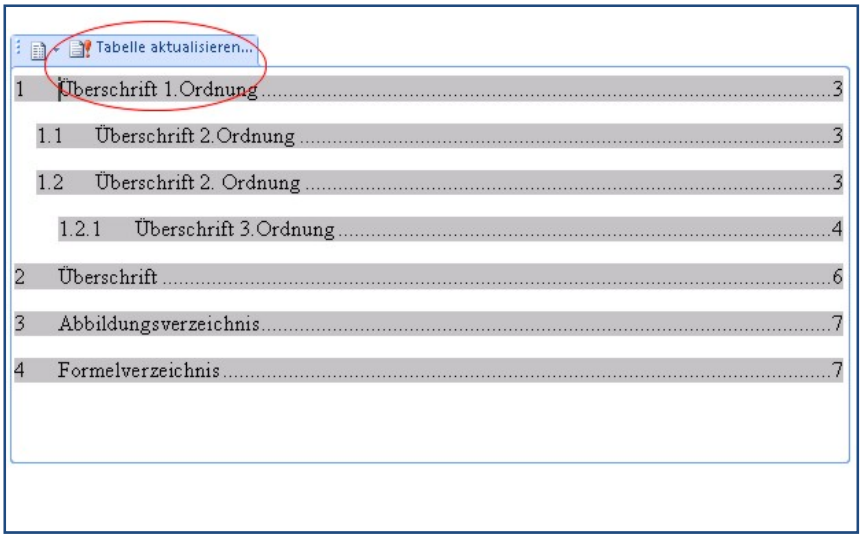
14.1 Inhaltsverzeichnis

- Klicken Sie einfach im Dokument an jene Stelle, wo Sie das Inhaltsverzeichnis positionieren wollen.
- Gehen Sie auf die Registerkarte „Verweise“ und klicken Sie auf den kleinen Pfeil neben „Inhaltsverzeichnis“. Damit öffnet sich ein Fenster, mit verschiedenen Varianten für ein Inhaltsverzeichnis.
- Klicken Sie auf das von Ihnen Gewünschte, es wird automatisch eingefügt.
- Normalerweise fügt man nach dem Inhaltsverzeichnis einen Seitenumbruch ein, damit das eigentliche Dokument auf einer neuen Seite beginnt. Wenn Sie aber, wie von uns empfohlen, bereits in der Formatvorlage für die Überschrift 1 einen „Seitenumbruch oberhalb“ eingefügt haben, ist kein zusätzlicher manueller Seitenumbruch sinnvoll. Dies zeigt wie wichtig die Abstimmung der Formatvorlagen aufeinander ist, um ihr Zusammenwirken sicherzustellen.



Wenn Sie nun auf das Inhaltsverzeichnis klicken, erscheint am oberen Ende des Inhaltsverzeichnisses „Tabelle aktualisieren“. Klicken Sie darauf, passt sich das Inhaltsverzeichnis immer dem neuesten Stand Ihres Dokuments an.

[5] Word bietet auch die Möglichkeit ein Literaturverzeichnis einzufügen. Für Publikationen im Rahmen des Forschungsbetriebes an der MUW empfehlen wir jedoch, die Literatureinträge aus dem Programm End Note nach Word zu übernehmen und nicht das von Word angebotene Literaturverzeichnis zu nutzen.

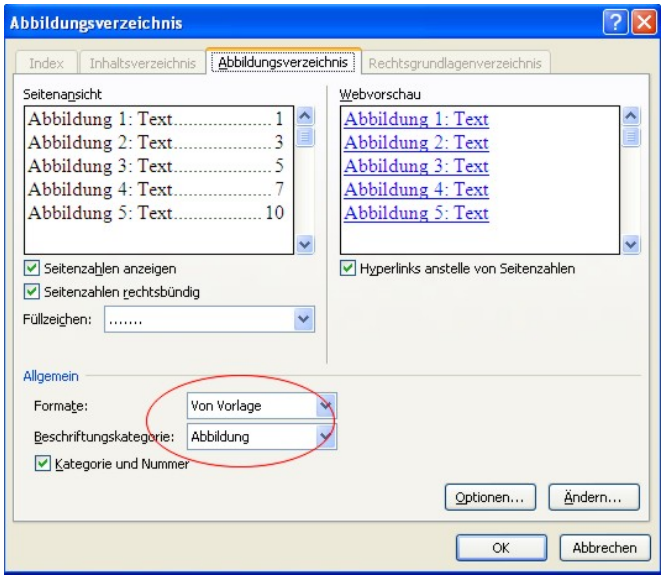


Wenn Sie mit Strg und Mausklick auf eine bestimmte Überschrift im Inhaltsverzeichnis klicken, kommen Sie automatisch auf die gewünschte Seite.

14.2 Abbildungsverzeichnis

- Klicken Sie wieder zuerst an die Stelle im Dokument, an der Sie das Abbildungsverzeichnis positionieren möchten.
- Gehen Sie nun unter „Verweise“/ „Beschriftungen“/ „Abbildungsverzeichnis einfügen“.

- Gehen Sie auf „Beschriftungskategorie“ und wählen Sie „Abbildung“ aus. (Oder entsprechend Tabelle, Formel,…).
- Zusätzlich können Sie wählen, ob Sie die Seitenzahl mit anzeigen wollen, und wo sich die Seitenzahl befinden soll.
- Sobald Sie auf ok drücken, wird das Abbildungsverzeichnis eingefügt. Mit rechtem Mausklick auf das Verzeichnis, und „Felder aktualisieren“, wird es auf den neuesten Stand gebracht.



Anmerkung: Verzeichnisse werden von Word mit Hyperlinks gestaltet, mit Strg + Mausklick können Sie dem gewünschten Link folgen.

14.3 Stichwortverzeichnis (Index)

Für manche Dokumente ist die Erstellung eines Index erforderlich bzw. wünschenswert.

Gehen Sie wie folgt vor:

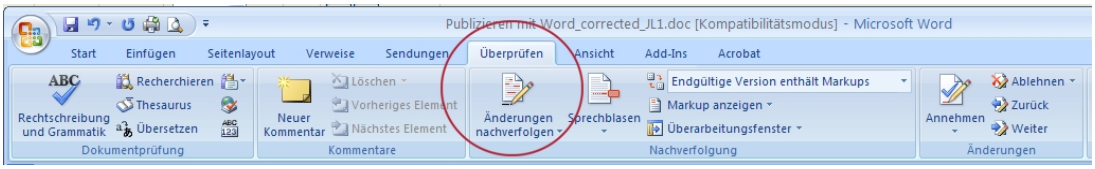
Blättern Sie ihren Text von Anfang an durch, markieren Sie entsprechende Begriffe und definieren Sie diese via Registerkarte „Eintrag festlegen“ als zum Index gehörend.

Bedenken Sie dabei, dass im Text derselbe Begriff oft in unterschiedlichen grammatikalischen Fällen und Schreibweisen auftreten kann und alle Einträge letztlich alphabetisch gelistet werden.

15 Änderungen durch die Autoren verfolgen

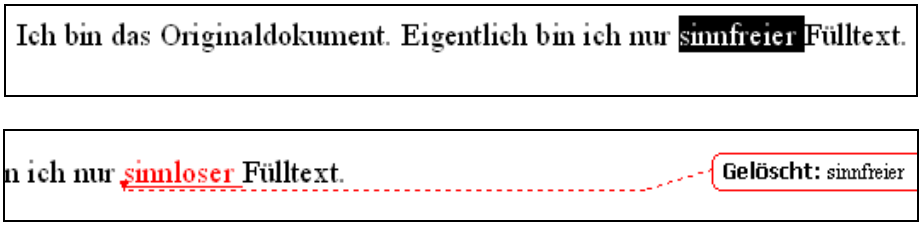
Oft wird die Originalversion einer Publikation verändert oder erweitert, z.B. durch Ihre Co-Autoren. Wenn ein Dokument durch mehrere Hände geht, ist es nahezu unmöglich herauszufinden, wer welche Änderungen vorgenommen hat. WORD bietet hier in der Multifunktionsleiste „Überprüfen“ die Möglichkeit „Änderungen nachverfolgen“.

Gehen Sie also beim Überarbeiten eines Dokuments folgendermaßen vor: Geben Sie Ihrem Dokument zuerst einen neuen Dateinamen.



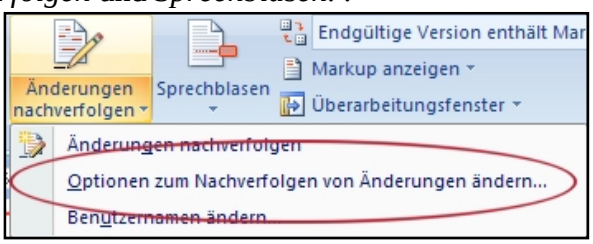
Klicken Sie auf Änderungen nachverfolgen, damit erteilen Sie WORD die Anweisung, die folgenden Änderungen am Dokument als vorläufig zu betrachten.

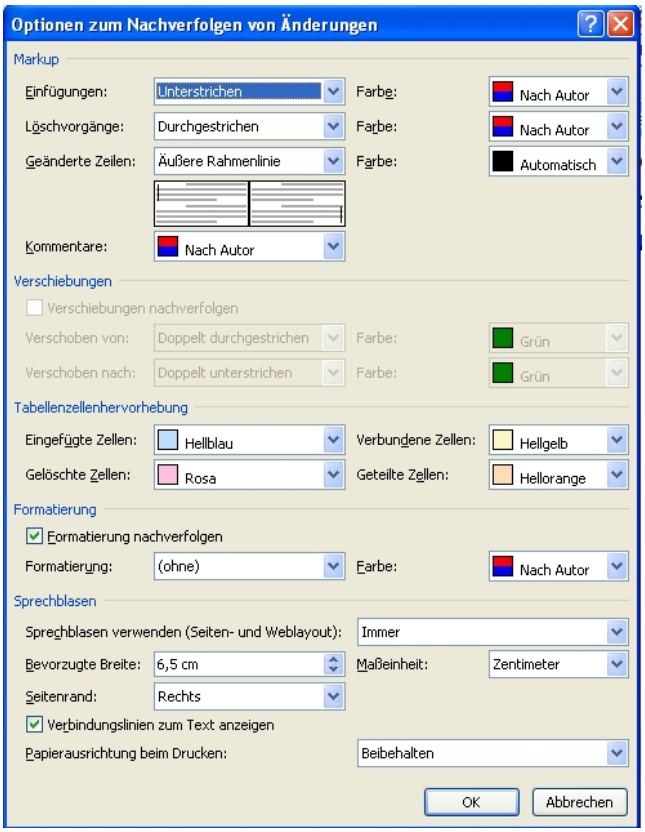
Überschreiben Sie nun beispielsweise ein markiertes Textstück, erscheint am rechten Rand eine Sprechblase, die die Originalformulierung zeigt:



Dasselbe gilt für andere Änderungen, beispielsweise Formatierungen. Auch hier wird die Änderung zwar im Dokument durchgeführt, aber eben auch als solche gekennzeichnet:

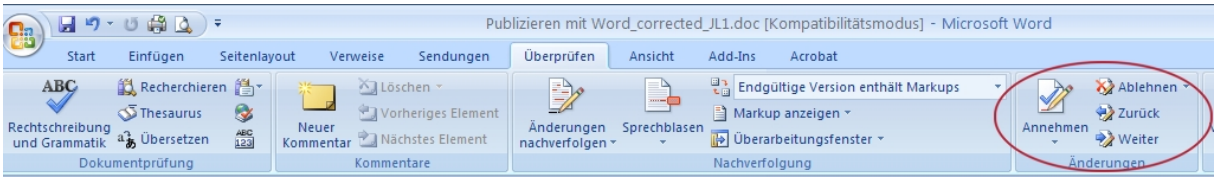
Wenn Sie im Überarbeitungs-Modus eine Textstelle ändern, wird diese Änderung ausgeführt, und in der Sprechblase am Rand ist die ursprüngliche Formulierung zu sehen. Sie haben aber auch die Möglichkeit, die Darstellungsform zu ändern. Klicken Sie dazu auf den Pfeil neben *Änderungen nachverfolgen* und *Sprechblasen*. :



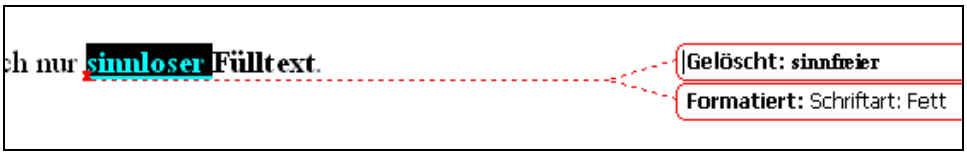


Sie können aus mehreren Möglichkeiten wählen.

Bei der Endbearbeitung des Dokuments müssen Sie nur noch entscheiden, welche Änderungen Sie annehmen und welche Sie verwerfen möchten. Selbst einzugeben brauchen Sie im Allgemeinen nichts mehr.



Durch Klicken auf die Steuersymbole  können Sie sich von einer zur nächsten Änderung bewegen, die dann jeweils hervorgehoben erscheint.

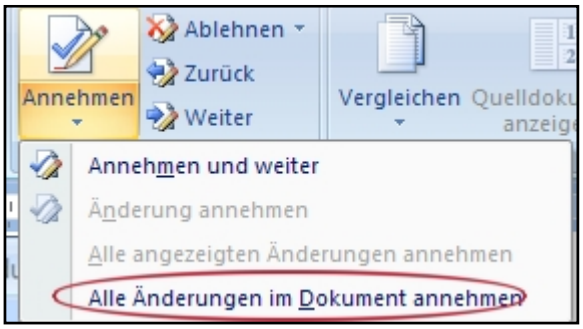


Wenn Sie die vorgeschlagene Änderung übernehmen möchten, klicken Sie einfach auf annehmen. Schon wird die Änderung permanent und die Sprechblase am Rand verschwindet.

Sind Sie dagegen mit der neuen Formulierung nicht glücklich, klicken Sie auf „ablehnen“ um sie zu verwerfen.

Sollten Sie bereits nach der ersten Durchsicht des überarbeitenden Dokuments von der Richtigkeit der Änderungen überzeugt sein, können Sie auch alle Änderungen pauschal akzeptieren:

Klicken Sie dazu in der Schaltfläche „Annehmen“ auf den nach unten weisenden Pfeil und wählen dann „Alle Änderungen im Dokument annehmen“.



Die bisher besprochenen Techniken beziehen sich auf Änderungen durch die Autoren (in der “Arbeitsversion“/Draft) **vor der Submission** des Artikels zu einem Journal.

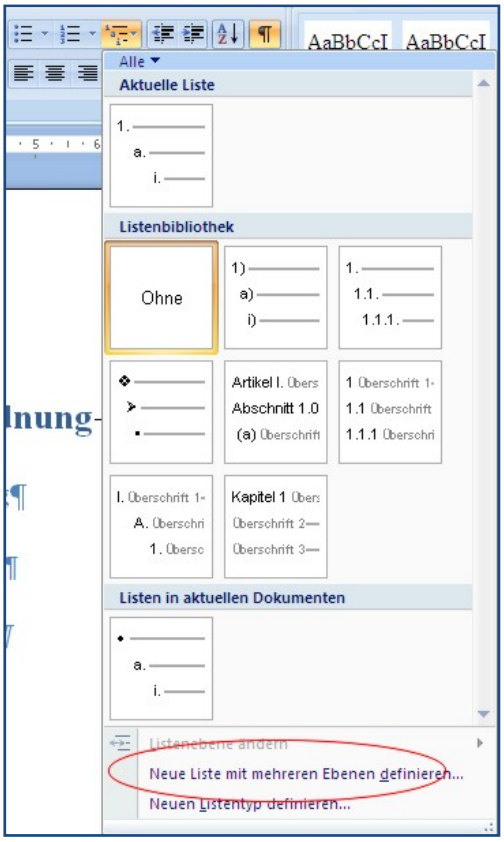
16 Nummerierung für Überschriften

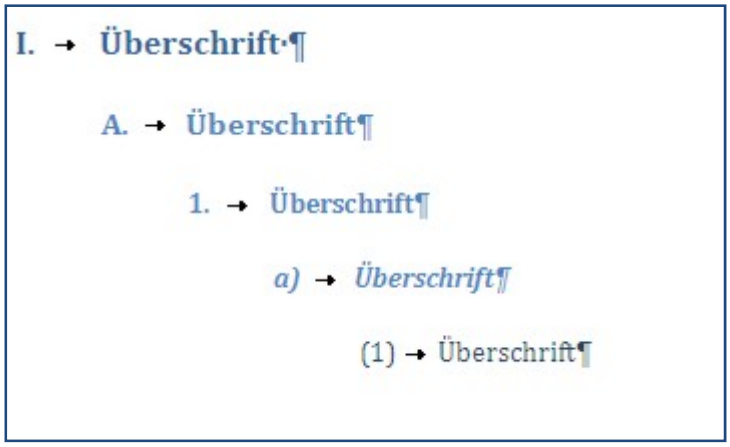
In Publikationen ist der Wortlaut für die Überschriften 1. Ordnung gewöhnlich vorgegeben: „Introduction, Methods, Results,…´“ etc. oder ähnlich. Nummerierungen der Überschriften sind normalerweise nicht vorgesehen.

Falls Sie jedoch ein stärker strukturiertes Dokument erstellen, wie etwa einen Review-Artikel, eine Dissertation, einen Buchbeitrag, einen Jahresbericht oder gar ein Lehrbuch, sind nummerierte Überschriften in unterschiedlichen Gliederungsebenen äußerst vorteilhaft. Deshalb geben wir im Folgenden einen kurzen Leitfaden.

Stellen Sie bereits am Anfang Ihrer Arbeit das Nummerierungsformat für Ihre Überschriften ein, dann wird von Word immer automatisch die richtige Nummerierung eingefügt. Falls Sie die von uns bereitgestellten Dokumentvorlagen für Publikationen benutzen, finden Sie eine Version mit nicht nummerierten Überschriften (PapersNoNumLeft_1.dotx)und eine zweite mit nummerierten Überschriften in unterschiedlichen Gliederungsebenen (PapersNumLeft_1.dotx). Sie können diese zweite Vorlage unmittelbar benutzen, auch ohne den Weg Ihrer Erstellung zu kennen. Falls Sie jedoch das Erscheinungsbild der Überschriften ändern möchten, geben wir dazu die entsprechenden Hintergrundinformationen:

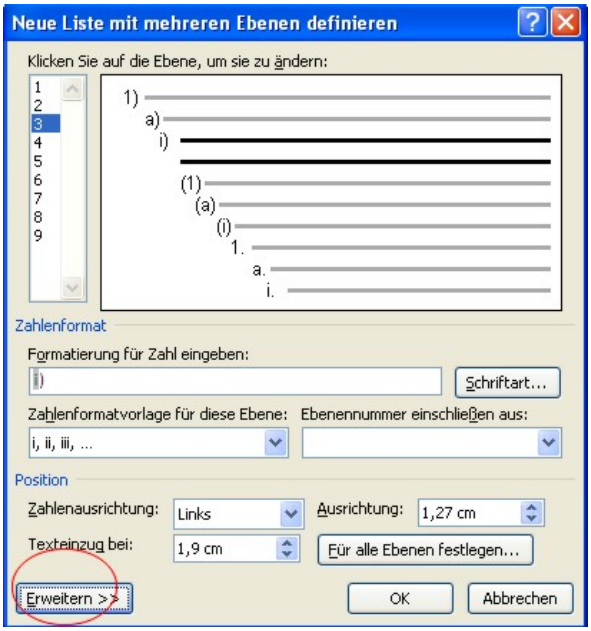
- Gehen Sie auf „Start“ und dann auf „Absatz“. „Liste mit mehreren Ebenen“.
- Klicken Sie nun auf den kleinen Pfeil. Hier können Sie ein von Word vorgegebenes Format verwenden. Klicken Sie einfach darauf.

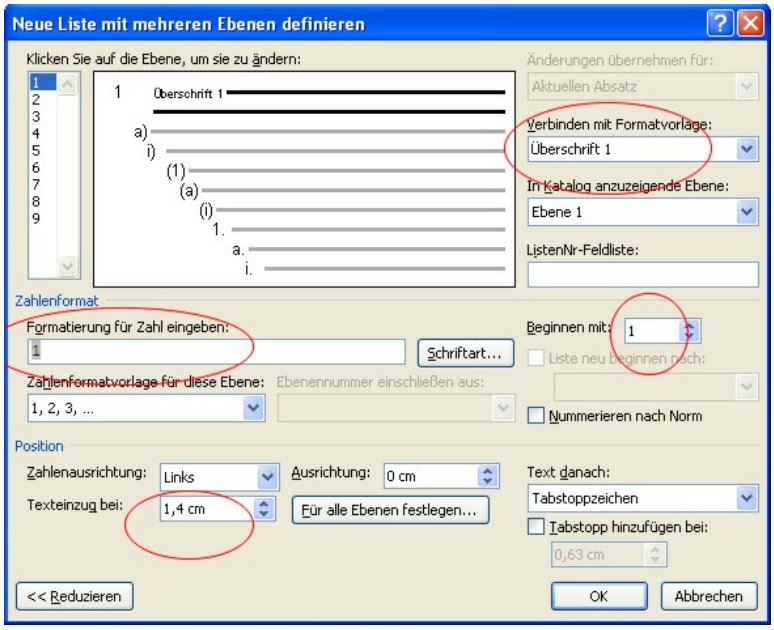




- Wenn Ihnen das Format nicht zusagt, dann definieren Sie ein Neues. Im selben Fenster finden Sie „Neue Liste mit mehreren Ebenen definieren“.

- Nun sehen Sie folgendes Fenster: Klicken Sie auf „Erweitern“. Hier haben Sie nun die Möglichkeit, für jede Überschrift ein für Sie passendes Format einzustellen.

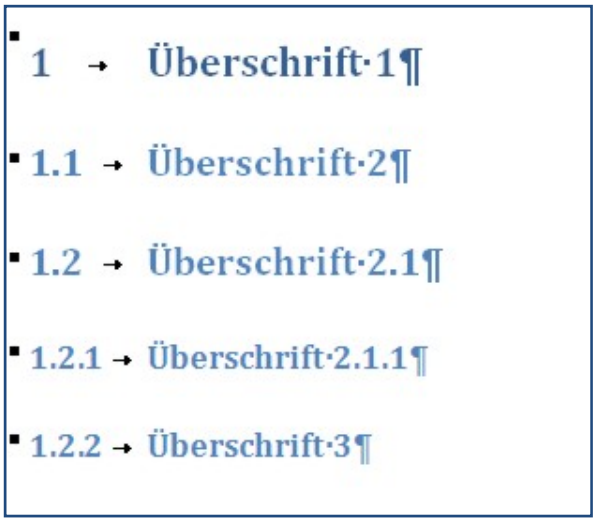




- Klicken Sie auf „Ebene 1“. Anschließend auf „Verbinden mit Formatvorlage: Überschrift 1“.
- Nun wählen Sie „Formatierung für Zahl eingeben“ und geben Ihr gewünschtes Format ein, oder wählen aus der Liste der vorgegebenen Formaten aus. „Beginnen mit“: 1 „Position“: Ausrichtung je nach Wunsch (falls Sie die Überschriften links wollen, dann 0 eingeben).

- Texteinzug: Hier sollten Sie bedenken, dass die Nummerierung der Überschriften unterschiedlich viel Platz einnimmt, Unterüberschriften mehrere Zahlen enthalten, z.B. 2.3.1, daher sollte der Texteinzug für alle gleich sein.

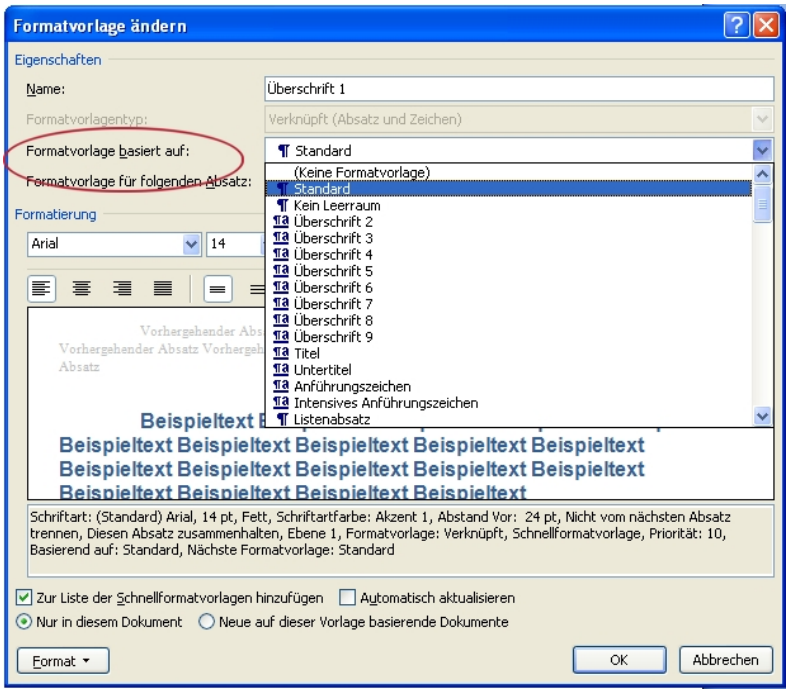
- Nun führen Sie dasselbe mit Ebene 2 und Überschrift 2 durch. Geben Sie als Zahlenformat nun 1.1 ein (oder entsprechend Ihr Format) und wählen Sie wieder den gleichen Texteinzug.
- Führen Sie das auch mit allen weiteren Überschriften durch und gehen Sie dann auf OK.
- Nun klicken Sie auf die Überschrift. Wählen Sie die von Ihnen definierte Liste, und die Überschriften werden entsprechend nummeriert.



Nun haben Sie für alle Überschriften die entsprechende Nummerierung für das ganze Dokument fixiert und die Nummerierung passt sich immer automatisch an. Falls Sie merken, dass der Abstand des Texteinzugs zu gering ist, weil die Nummerierung der Unterüberschriften zu lang wird, einfach ändern. So passen sich alle Überschriften automatisch an.

17 Formatvorlagen erben Eigenschaften (Hintergrundinformation)

Jede Dokumentvorlage (*.dotx) enthält meist zahlreiche Formatvorlagen. Diese sind jedoch nicht unabhängig voneinander: Beim Erstellen einer neuen Formatvorlage spezifizieren Sie im Dialog das Feld „Formatvorlage basiert auf“:



Im entsprechenden Pull Down Menü werden alle bereits vorhandenen Formatvorlagen angeboten, Sie wählen eine davon aus. Dies bewirkt, dass alle Formatierungsmerkmale von dieser „Mutter“ übernommen werden. Dadurch entsteht eine Vernetzung zwischen Formatvorlagen. Wird in der „Mutter“ etwas geändert, ändert sich dies auch automatisch in allen „Töchtern“. Jede „Tochter“ kann jedoch zusätzlich zu den ererbten auch noch eigene Formatelemente definieren. Dadurch entsteht ein Netz von wechselweisen Abhängigkeiten.

Das wichtigste Beispiel ist die Abhängigkeit vieler Formatvorlagen von „Standard“: Sie erben etwa Schriftart und Zeilenabstand, sofern diese Elemente nicht bewusst geändert („überschrieben) werden.

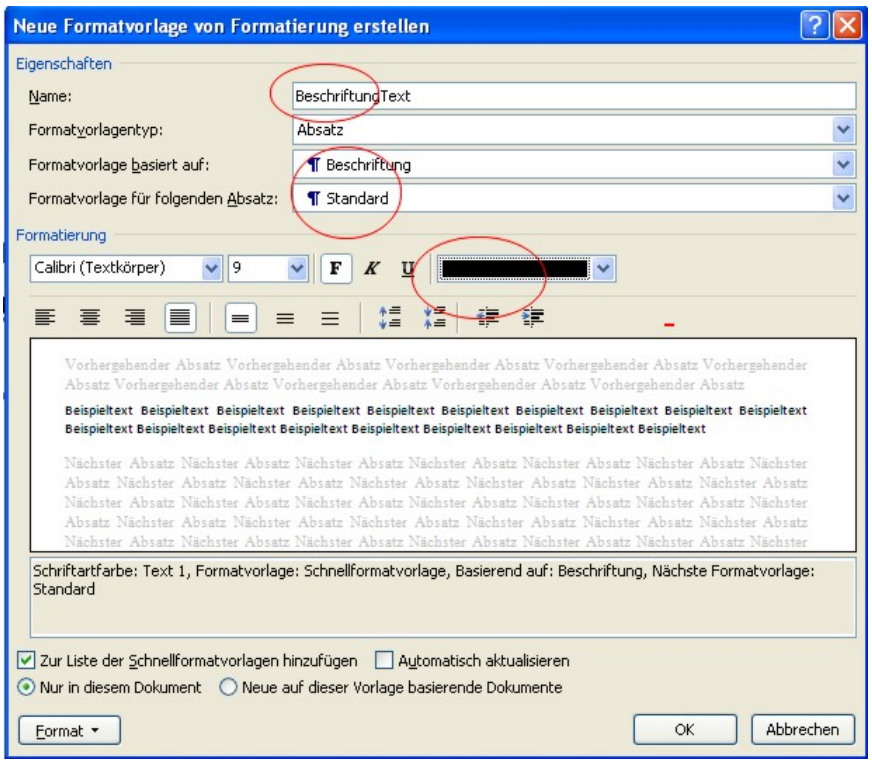
Ein weiteres Beispiel wird im folgenden Kapitel (siehe: Neue Formatvorlage erstellen) erläutert.

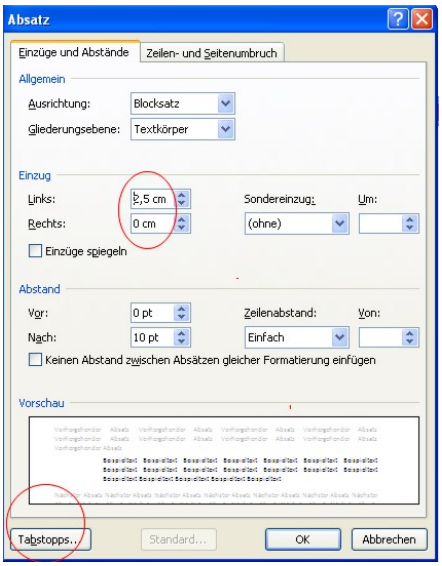
18 Neue Formatvorlage erstellen, bestehende nachjustieren

Falls Sie eine Formatvorlage benötigen, die von „Word“ nicht automatisch bereitgestellt wird, dann können Sie eine neue Vorlage selber definieren. Als Beispiel zeigen wir, wie in der bereitgestellten Dokument-Vorlage die Formatvorlage „BeschriftungText“ definiert wurde (werden kann).

Gehen Sie im Formatvorlagenfenster auf das Zeichen links unten:

Es öffnet sich folgendes Fenster:

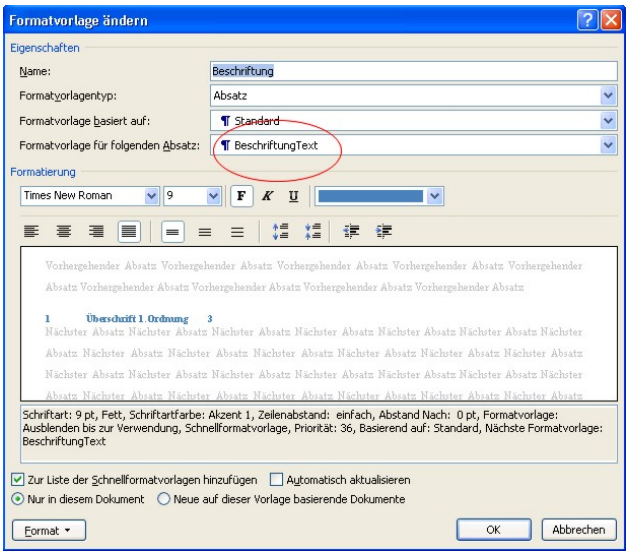




Wir definieren z.B. eine neue Formatvorlage „BeschriftungText“.

Die Formatvorlage soll auf „Beschriftung“ basieren, da wir nach dem Titel zum Bild in der gleichen Schrift und Größe weiterschreiben wollen, aber nicht mehr fett, und nicht blau. Wenn die neue Formatvorlage auf „Beschriftung“ basiert, müssen wir möglichst wenig Parameter ändern.

- Formatvorlage für folgenden Absatz: nach dem Text zur Beschriftung des Bildes soll wieder normaler Lauftext kommen, deshalb wählen wir „Standard“.
- Wir ändern die Farbe auf schwarz und „nicht fett“. Nun klicken Sie noch auf „Absatz“.
- Fixieren Sie den Einzug links auf 2,5. So beginnt der BeschriftungsText exakt unter dem Titel der Beschriftung.[6] Anschließend klicken Sie auf ok.
  Nun justieren Sie noch die Formatvorlage „Beschriftung“ nach.
- Gehen Sie im Formatvorlagenfenster auf „Beschriftung“, „Ändern“.
- Für „Formatvorlage für folgenden Absatz“ wählen Sie nun: „BeschriftungText“.[7]
- Anschließend gehen Sie noch auf „Format“/ „Absatz“. Hier setzen Sie den „Abstand Nach“ auf 0. So beginnt der Text zur Beschriftung direkt unter dem Beschriftungstitel.



[6] Diese hat einen Tabulator samt hängenden Einzug bei 2,5.

[7] Dadurch bietet Word nach dem „Return“ sofort die passende Formatvorlage an.

19 Schnellbaustein für mathematische Formeln und chemische Reaktionsgleichungen definieren

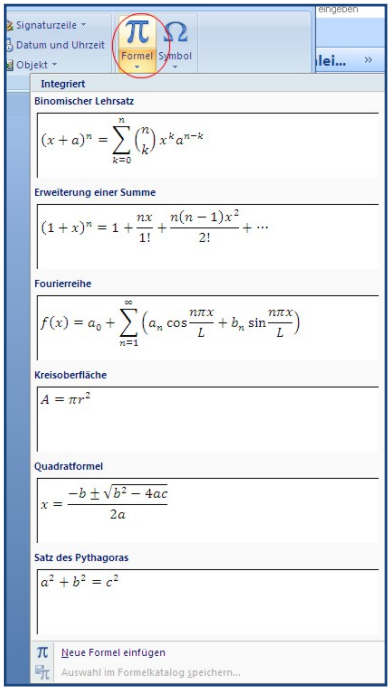
Im vorangehenden Kapitel (siehe: Neue Formatvorlage erstellen,) wurde bereits erklärt, wie man mathematische Formeln und chemische Reaktionsgleichungen unter Benutzung eines Schnellbausteins effizient einfügen und nummerieren kann. Nun erhalten Sie weitergehende Informationen, wie der Schnellbaustein erstellt wurde. Aus dieser beispielhaften Beschreibung können Sie wichtige Arbeitsschritte entnehmen, die zur Definition neuer Schnellbausteine erforderlich sind (falls Sie einen zusätzlichen benötigen sollten).

Zur Definition des Schnellbausteins für Einfügen und Nummerierung von Formeln gehen Sie beispielweise folgendermaßen vor:

Angenommen die Formeln sollten zentral platziert werden, die Nummerierung am rechten Seitenrand in Klammern stehen.

Fügen Sie als erstes eine Tabelle mit einer Zeile und 3 Spalten ein.

In die mittlere Spalte fügen Sie nun eine Formel mit Hilfe des Formeleditors ein. Dazu gehen Sie auf „Einfügen“ und ganz rechts auf „Formel“. Hier finden Sie vordefinierte Formeln, Sie können aber auch selbst eine Formel definieren:



	$A = \pi r^2$	

Anschließend schreiben Sie in die rechte Spalte eine öffnende und eine schließende Klammer:

	$A = \pi r^2$	()

Jetzt fügen Sie innerhalb der Klammer eine Feldfunktion ein. Dazu drücken Sie Strg+F9 und erhalten eine geschwungene Klammer. Nun fügen Sie innerhalb der geschwungenen Klammer folgendes ein:

SEQ Formel * Arabic\s 1

	$A = \pi r^2$	({ SEQ Formel * Arabic\s 1 })

Anschließend klicken Sie mit rechter Maustaste auf die Funktion und gehen auf „Felder aktualisieren.

	$A = \pi r^2$	(2)

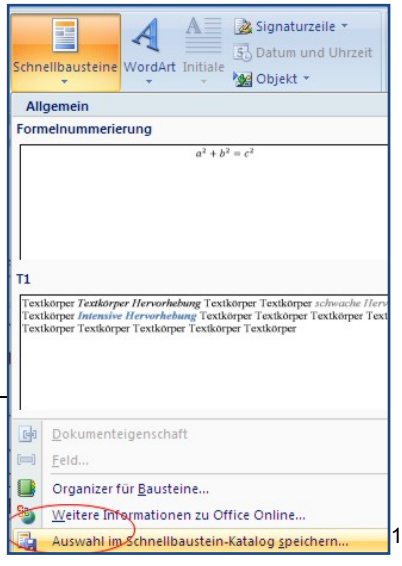
Jetzt formatieren Sie die Tabellenzelle noch rechtsbündig und entfernen den Rahmen der Tabelle.

So erhalten Sie das endgültige Resultat.

$$A = \pi r^2 \qquad (2)$$

Nun markieren Sie die fertige Tabelle (indem Sie auf das Kreuz am linken Rand klicken), und speichern Sie diese als Schnellbaustein ab. Dazu gehen Sie auf die Registerkarte „Einfügen“, „Text“, und klicken Sie auf „Schnellbausteine“

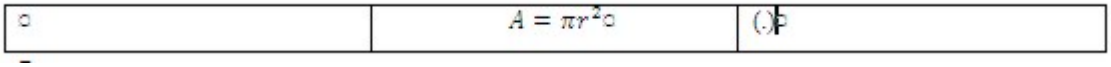
Klicken Sie auf „Auswahl im Schnellbaustein-Katalog speichern“. Beachten Sie bitte, wo der Schnellbaustein gespeichert wird: Wenn Sie die Voreinstellung belassen, ist der Speicherort die Datei „Building Blocks.dotx“ auf Ihrem Computer, siehe auch den Kommentar auf Seite 27 und das Kapitel „Formatvorlagen auf dem Arbeitsgruppenserver“



Auf Wunsch können Sie nun immer aus dem Schnellbausteinkatalog die Tabelle wählen. Sie müssen nur die Formel ändern, die Zahlen passen sich automatisch an.

Falls Sie zur Nummerierung der Formeln auch die Kapitelnummern miteinbeziehen wollen, gehen Sie wie folgt vor:

Fügen Sie eine öffnende und eine schließende Klammer in die rechte Spalte der Tabelle und dazwischen fügen Sie einen Punkt ein. (.)

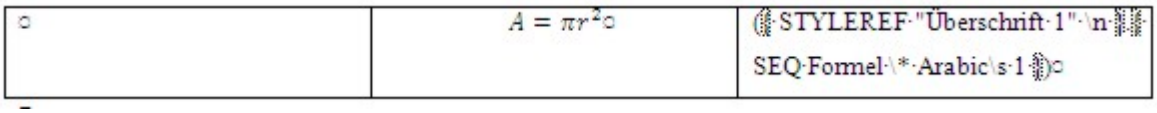


Jetzt fügen Sie eine Feldfunktion ein. Dazu drücken Sie Strg+F9 und Sie bekommen eine geschwungene Klammer. Die erste Feldfunktion vor den Punkt innerhalb der Klammer. Sie bekommen eine geschwungene Klammer. Nun fügen Sie innerhalb der geschwungenen Klammer folgendes ein:

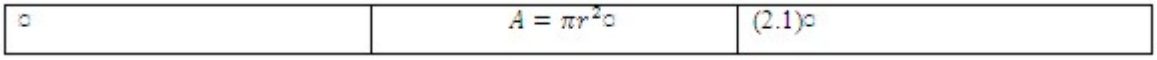
STYLEREF „Überschrift 1“ \n

Hinter dem Punkt wieder eine Feldfunktion und innerhalb der geschwungenen Klammer folgendes:

SEQ Formel * Arabic\s 1



Anschließend klicken Sie zuerst auf die erste geschwungene Klammer mit der rechten Maustaste und gehen auf „Felder aktualisieren“, dann auf die zweite geschwungene Klammer und wieder auf „Felder aktualisieren“.



Nun haben Sie vor dem Punkt die Kapitelnummer und hinter dem Punkt die Nummer der Formel. Jetzt formatieren Sie die Zelle noch rechtsbündig, entfernen den Rahmen und erhalten folgendes Ergebnis:

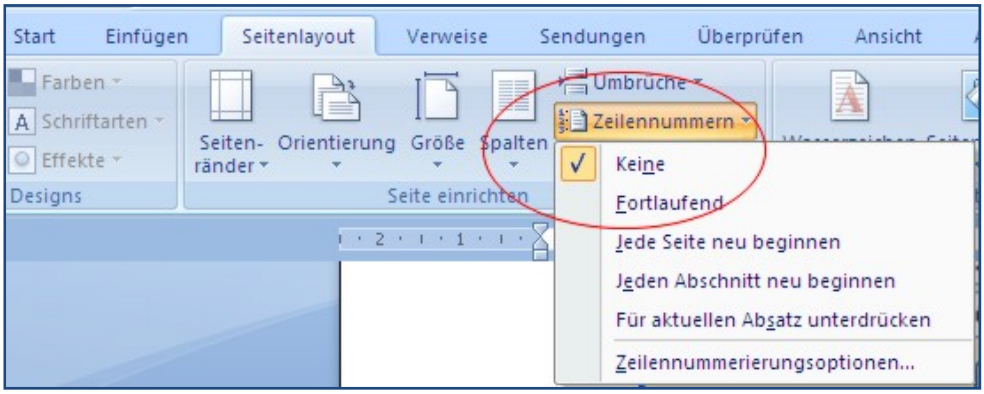
$$A = \pi r^2 \quad (2.1)$$

Speichern Sie die Tabelle als Schnellbaustein ab (wie weiter oben beschrieben).

Aber achten Sie darauf, dass immer eine Überschrift 1 vorhanden ist, andernfalls bekommen Sie eine Fehlermeldung, weil keine Kapitelnummer gefunden werden kann.

20 Laufende Zeilennummern

Manchmal erfordert die Korrespondenz mit dem Editor einen exakten Zeilenbezug. Zu diesem Zweck gehen Sie auf „Seitenlayout“/ „Zeilennummern“.



Wählen Sie nun die von Ihnen günstigste Option.

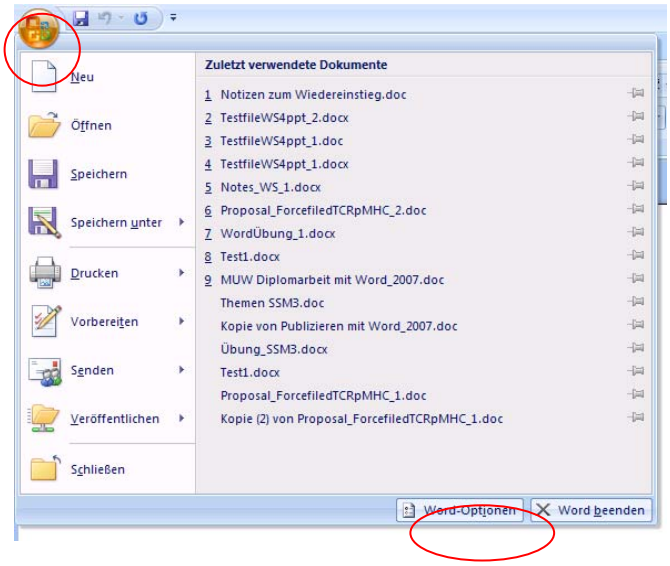
Ausschalten einfach wieder auf „keine“ klicken.

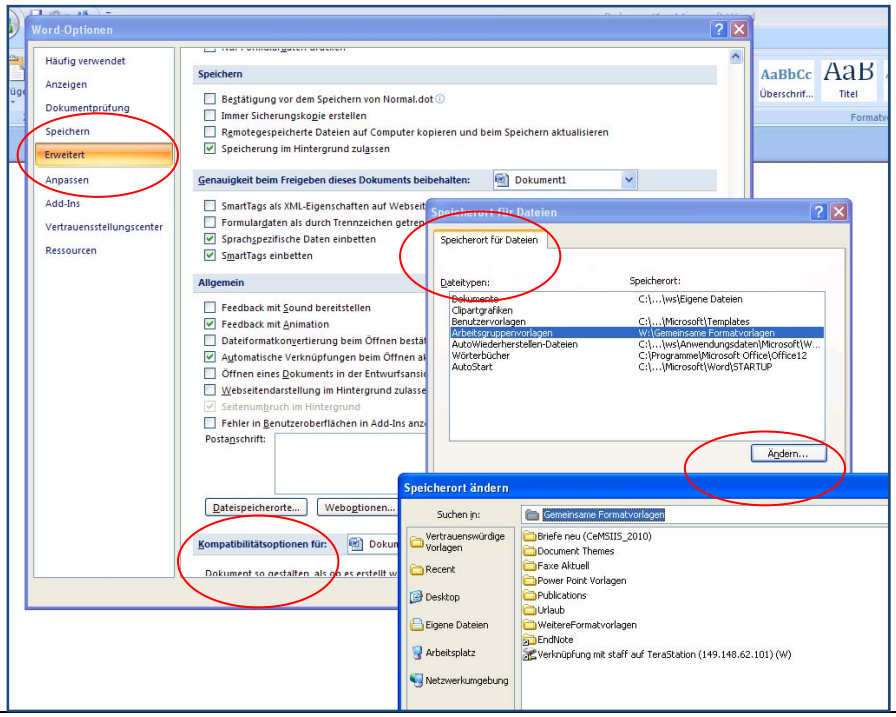
21 Formatvorlagen auf dem Arbeitsgruppenserver

Richten Sie auf Ihrem Server ein entsprechendes Directory ein, z.B. W:\...\GemeinsameFormatvorlagen,… samt Zugriffsrechten für alle beteiligten Mitarbeiter.

Legen Sie dort die Vorlagen mit sprechenden Namen ab und passen Sie die Optionen in WORD so an, dass dieses Directory angezeigt wird, sobald Sie eine neue Datei anlegen.

Die folgenden Screenshots zeigen Ihnen, welche Optionen Sie jeweils wählen müssen.





22 Änderungen in einer „revised version“ für den Reviewer übersichtlich anführen[8]

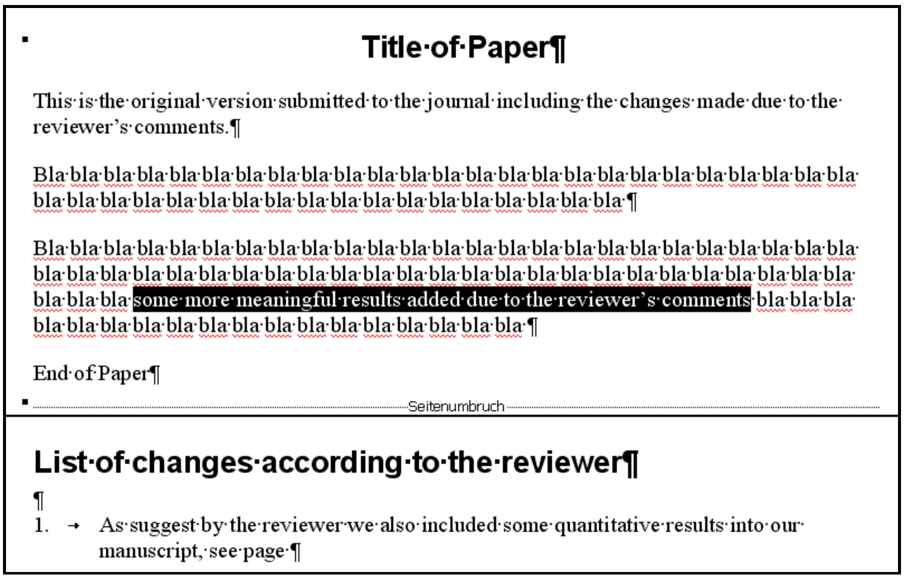
In diesem Abschnitt zeigen wir Ihnen einen möglichen Weg, eine Liste zu erstellen, die Änderungen für den Editor/Reviewer übersichtlich zeigt.

Hilfreich ist grundsätzlich, wenn Sie als Erstautor und alle Koautoren Ihre Änderungen jeweils im Änderungsmodus von WORD durchführen (siehe auch Kapitel Änderungen durch die Autoren verfolgen).Viele Journale erwarten die „revised version“ in genau diesem Änderungsmode. In diesem Falle erzeugen Sie eine entsprechende „List of Changes“ in einem separaten Dokument. Sie beschreiben jede Änderung mit Angabe von Seite und Absatz.

Soll die revised version hingegen nicht im Änderungsmodus sondern mit akzeptierten Änderungen als „glatter Text“ eingesandt werden, können Sie „Textmarken“, wie folgt nutzen:

Fügen Sie zunächst eine Überschrift „List of changes“ (auf eine neue Seite) an das Ende des Dokuments. Diese „List of changes“ wird später zu einem „Beiblatt“ für den Editor/Reviewer, aus dem genau hervorgeht, wo welche Änderungen tatsächlich zu finden sind (Seite, Absatz). Dies erleichtert das Nachvollziehen der Änderungen durch den Reviewer.

Bei jeder wichtigen Änderung im Manuskript, die Sie im Korrekturmodus ja leicht erkennen können, markieren Sie ein kleines Stück Text und erzeugen eine Textmarke:



Title·of·Paper¶

This·is·the·original·version·submitted·to·the·journal·including·the·changes·made·due·to·the·reviewer's·comments.¶

Bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·¶

Bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·some·more·meaningful·results·added·due·to·the·reviewer's·comments·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·bla·¶

End·of·Paper¶

Seitenumbruch

List·of·changes·according·to·the·reviewer¶

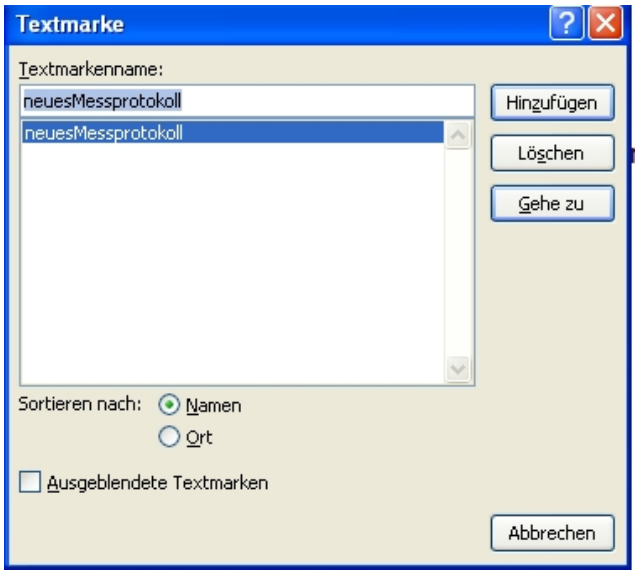
¶

1. → As·suggest·by·the·reviewer·we·also·included·some·quantitative·results·into·our·manuscript,·see·page·¶

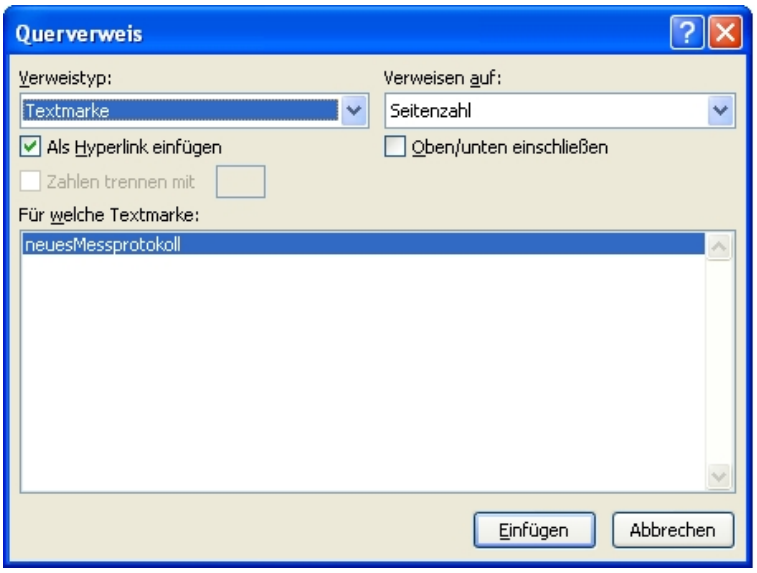
[8] Falls Sie Ihre Änderungen eher nicht besonders transparent für den Editor darstellen wollen – aus welchen Gründen immer – ignorieren Sie dieses Kapitel.

Klicken Sie nun in der Multifunktionsleiste auf „Einfügen“/Textmarke:

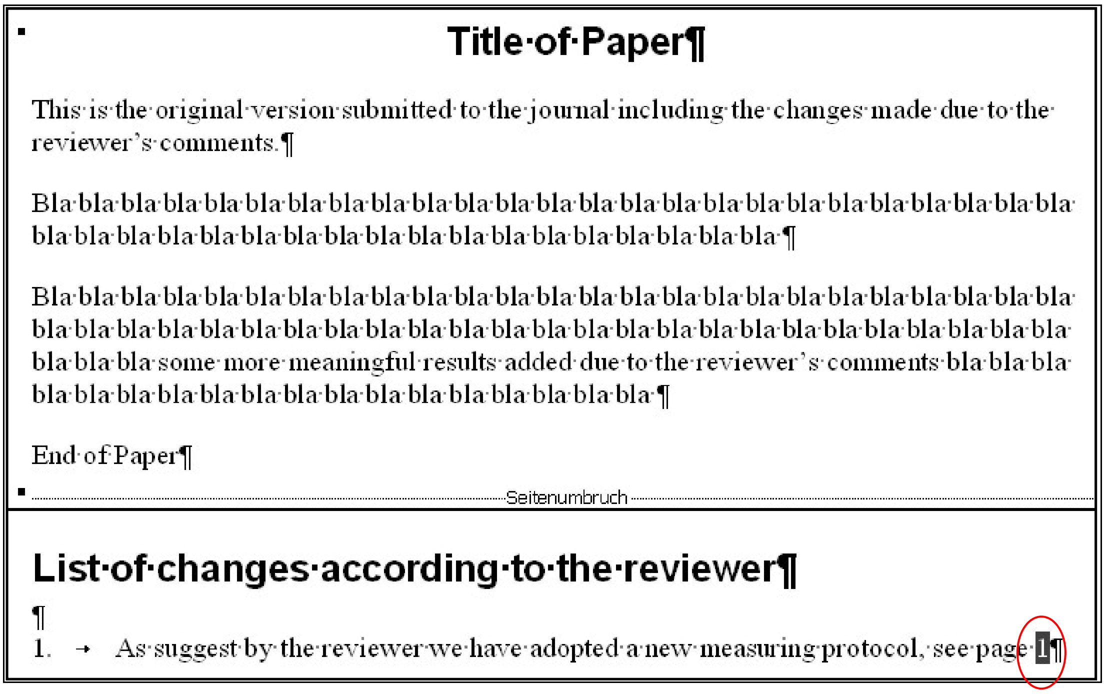
Geben Sie dieser Textmarke einen der Änderung entsprechenden Namen (z.B. “neuesMessprotokoll”) und klicken auf „Hinzufügen“.



Gehen Sie nun in die „List of changes according to the reviewer“ (am Ende des Dokuments) und beschreiben dort inhaltlich die durchgeführte Änderung, siehe Beispiel: „we have adopted a new measuring protocol“. Daran anschließend können Sie nun – zur leichteren Nachvollziehbarkeit – auf jene Stelle (Seite) verweisen, wo die Änderung zu finden ist: Klicken Sie in der Multifunktionsleiste auf „Einfügen/Querverweis“. Sie bekommen dann folgendes Fenster zu sehen:



Wählen Sie nun die entsprechende Textmarke. Wählen Sie unter „Verweisen auf“ „Seitenzahl“ und klicken Sie auf „Einfügen“. Sie haben einen Verweis erstellt, die korrekte Seitennummer wird in der „List of changes according to the reviewer“ angezeigt!



Title of Paper¶

This is the original version submitted to the journal including the changes made due to the reviewer's comments.¶

Bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla¶

Bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla some more meaningful results added due to the reviewer's comments bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla bla¶

End of Paper¶

Seitenumbruch

List of changes according to the reviewer¶

¶

1. As suggest by the reviewer we have adopted a new measuring protocol, see page 1¶

Beachten Sie, dass sich die eingefügte Seitennummer „dynamisch“ ändert: Wenn Sie später auf einer vorangehenden Seite etwa (als weitere Änderung) einen ganzen Absatz einfügen, wird Ihre erste Änderung (z.B. von Seite 5 auf Seite 6) verschoben. Ihr dynamisch erstellter Verweis auf die Textmarke der Änderung „geht mit“. Klicken Sie dazu einfach mit der rechten Maustaste auf Ihren erstellen Verweis und wählen „Felder aktualisieren“.

Und noch ein Vorteil: Klicken Sie mit gehaltener Strg-Taste auf Ihren erstellten Verweis, gelangen Sie automatisch zu Ihrer vorgenommenen Änderung.

Bewertung:

Die hier beschriebene, etwas komplexe Erstellung einer „List of Changes“ steht für Sie am Rande der Effizienz, siehe auch die einleitenden Bemerkungen. Sie ist nur rentabel, wenn Sie in einem sehr langen Manuskript viele Änderungen vornehmen und diese mit maximaler Transparenz vermitteln möchten.

Viel effizienter ist und bleibt die Einsendung im Korrekturmodus mit einer getrennten „List of Changes“.

23 „Draft“ und Submitted Version

Journale verlangen meist ganz bestimmte Formate für eingesandte Artikel: zweizeiliger Ausdruck, Tables und Figure-Captions getrennt von Text auf eigenem Blatt, Figures auf eigenen Blättern,… Letztendlich muss Ihr Manuskript auch in genau diese Form gebracht werden. Während Sie Ihr Manuskript erstellen, von Kollegen lesen lassen und oftmals ändern, ist jedoch eine vollkommen andere Formatierung wesentlich praktischer:

- Sie möchten wahrscheinlich einzeilig arbeiten, um besseren Überblick zu haben
- Sie möchten die Legenden direkt neben den Abbildungen, aus Gründen der Übersichtlichkeit
- Sie möchten Abbildungen samt Legenden direkt im Text, zur besseren Übersichtlichkeit
- Sie möchten Ihre Tabellen direkt im Text, zum leichteren Vergleich der Werte mit jenen Textteilen, die die Tabelle beschreiben.

Nachdem Sie während der Erstellung des Manuskripts über längere Zeit hinweg dieses „bequemere Format“ verwendet haben, ist vor dem Einsenden eine Umformatierung erforderlich. Diese kann wesentlich erleichtert werden, wenn Sie einige effiziente Funktionen von WORD benutzen, wie im Folgenden beschrieben:

- Für die Nummerierung von Abbildungen und Tabellen verwenden Sie stets die oben beschriebene Technik „Legenden für Abbildungen und Tabellen“. Dadurch können Sie die Position und Reihenfolge von Tabellen und Abbildungen mehrfach verändern, wobei die Nummerierung und alle Bezüge auf diese Nummern korrekt bleiben.
- Die Umstellung von einzeilig auf zweizeilig für das gesamte Paper kann mit einem einzigen Mausklick erfolgen, in dem Sie den Zeilenabstand in der Formatvorlage „Standard“ ändern. Dadurch werden alle weiteren Formatvorlagen ebenfalls automatisch umgestellt. Sie erhalten das gewünschte Ergebnis natürlich nur dann, wenn Sie Ihren gesamten Text mit Formatvorlagen formatiert haben, daher auch diese Empfehlung.

Medizinische Universität Wien
Zentrum für
Medizinische Statistik, Informatik und Intelligente Systeme
A-1090 Wien, Spitalgasse 23

Publizieren mit EndNote

Einführung

Anleitung zum Publikationsworkshop
im Rahmen der postgraduellen Fortbildung an der MUW

W. Schreiner, B. Knapp, W. Gall

7. November 2011

1 Einleitung

Mit diesem Programm können Sie eine Literaturdatenbank führen, entweder für Sie persönlich oder im Rahmen Ihrer Arbeitsgruppe. Bevor Sie beginnen, sollten Sie sich für eine der beiden Varianten entscheiden. Bedenken Sie bitte, dass mehrere Mitglieder einer Arbeitsgruppe zahlreiche Artikel gemeinsam zitieren und benutzen, woraus sich möglicherweise Synergieeffekte ergeben. Andererseits erfordert die gemeinsame Nutzung einer Literaturdatenbank einen gewissen Organisationsaufwand. Wir machen Ihnen Vorschläge für eine möglichst einfache Umsetzung. Grundsätzlich ist es immer leicht, von einer gemeinsam genutzten Datenbank auf eine persönliche umzustellen, jedoch nicht umgekehrt. Wir beschreiben daher zuerst eine möglichst einfache Lösung für die gemeinsame Nutzung.

Die wesentlichsten Funktionen einer solchen Literaturdatenbank sind:

- Ein elektronisches Verzeichnis aller von Ihnen bereits gelesenen/bearbeiteten/in Erwägung gezogenen Artikel.
- Die Speicherung Ihrer Kommentare zu diesen Artikeln.
- **Last but not least:**

  Das Erstellen der „List of references“ sowie der “In-text-citations” in allen Ihren Publikationen mit automatischer Formatierung entsprechend den Vorgaben der Journale.

2 Erstellen einer Literaturdatenbank

2.1 Speicherort

Die erste und wichtigste Entscheidung ist der Speicherort:

Wählen Sie eine Platte/Directory auf einem PC, auf dem allen Beteiligten der Zugriff erlaubt wird. Der Systemadministrator muss den Ordner im Netzwerk freigeben. Auf jedem der „Clienten-PCs“ (die die Datenbank nutzen wollen) muss das „Netzlaufwerk“ verbunden werden (im Windows Explorer mit “Extras“ > “Netzlaufwerk verbinden“). Die gemeinsam genutzte Literaturdatenbank sollten Sie unbedingt regelmäßig sichern (ADSM, CD brennen, Kopie auf anderen Computer). Lassen Sie sich diesbezüglich von ITSC beraten. Durch diese einfachen Vorarbeiten ist es möglich, die Literaturdatenbank als Unikat auf einem PC zu halten und Sie von mehreren PCs aus zu nutzen.

2.2 Neue Datenbank erstellen

Sie erstellen Ihre neue Literaturdatenbank in EndNote via “File“ > “New“.

3 Herunterladen von Artikeln

Wann immer möglich, laden Sie Artikel aus dem Netz herunter. Vermeiden Sie die händische Eingabe – sie führt oft zu Fehlern!

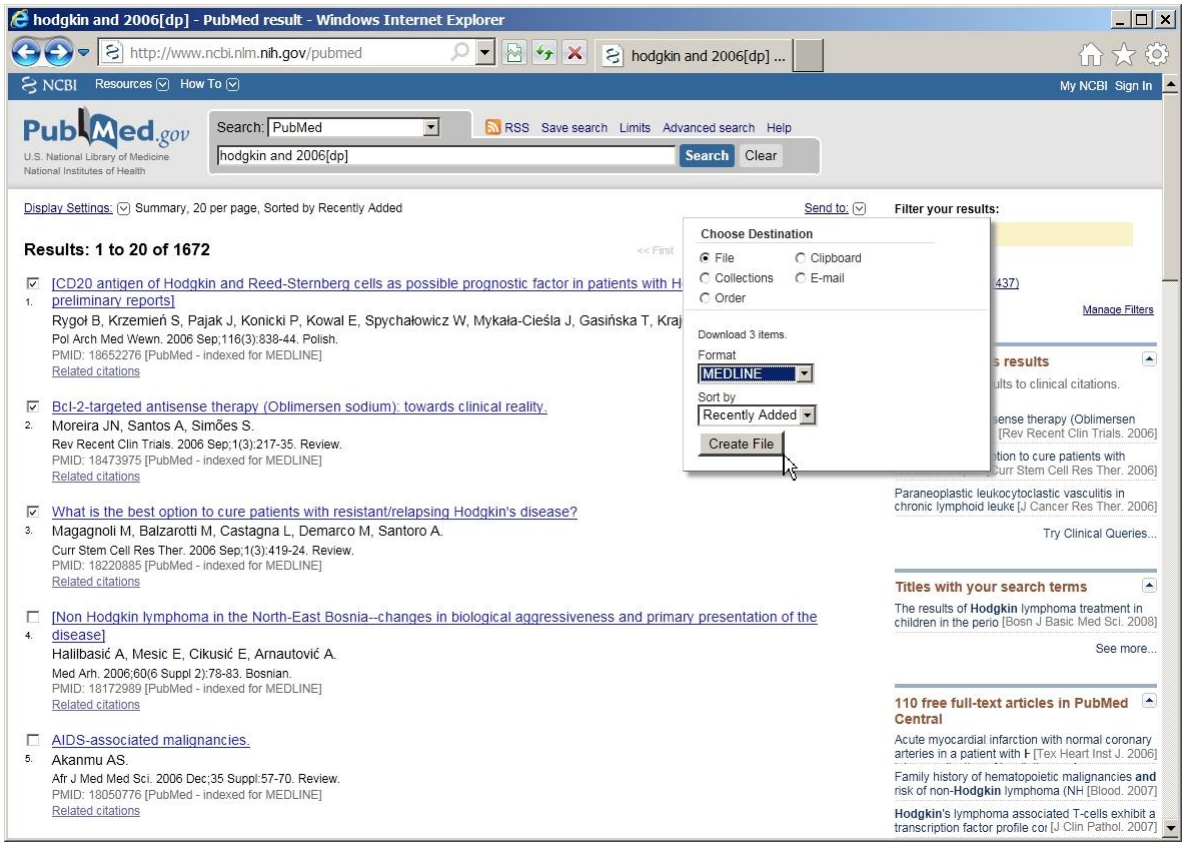
Wichtig ist, dass sie von jeder Quelle (Literaturdatenbank wie Medline) die Referenzen im angebotenen Datenbankformat das ihr Literaturverwaltungsprogramm beim Import „versteht“ herunterladen (im Falle von Medline im Format „MEDLINE“ und in einem normalen Textansichtsformat wie „Summary“).

3.1 Herunterladen aus Pubmed

Jeden Artikel, den Sie in PubMed (http://pubmed.gov) gefunden haben, können Sie herunterladen:

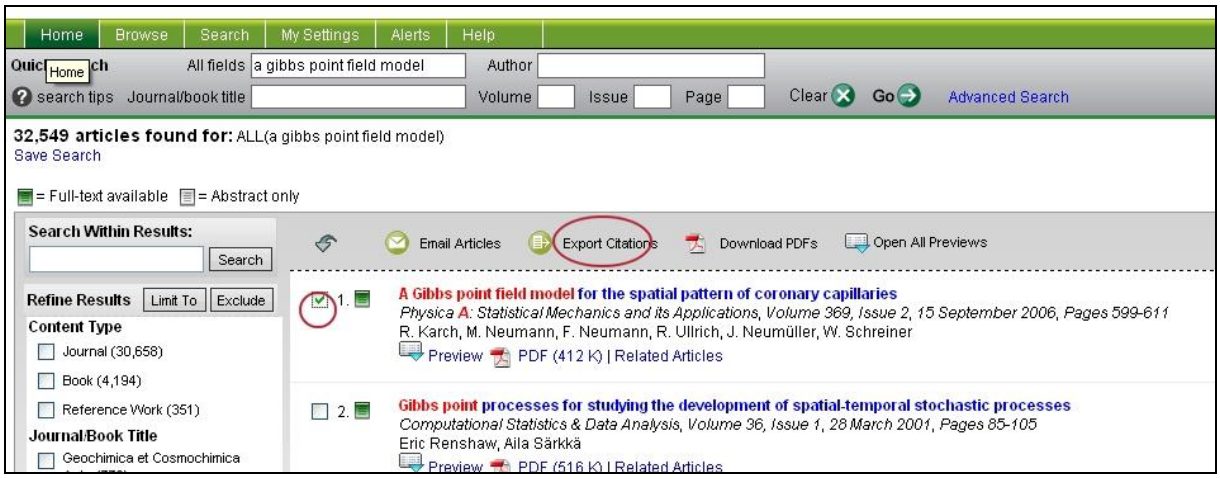
In der Ergebnisliste klicken Sie auf die gewünschten Artikel und wählen unter “Send to“ > “File“ das Format „MEDLINE“ aus.

Klicken Sie auf „“Create File“ und speichern Sie das Textfile in einem Ordner Ihrer Wahl (temporär – das File darf nachher wieder überschrieben werden).

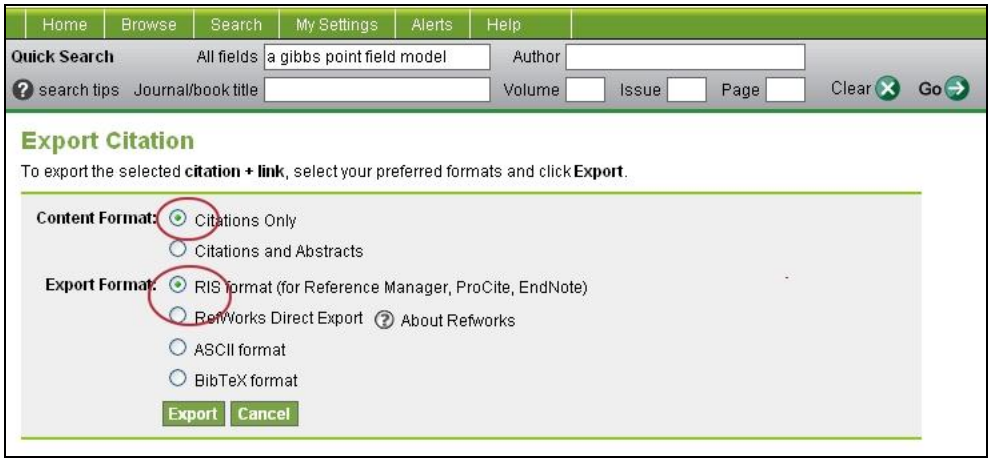


3.2 Herunterladen von Science direct-Artikeln

Manchmal suchen Sie nicht primär via PubMed, sondern befinden sich bereits in der „Subkultur“ eines Verlages, z.B. „Science direct“. Sie brauchen dann zum Herunterladen nicht wieder nach PubMed zu wechseln, sondern können gleich innerhalb der „Subkultur“ fortfahren: Lokalisieren Sie den gewünschten Artikel auf http://www.sciencedirect.com.



Klicken Sie auf den Artikel und dann auf „Export Citations“.



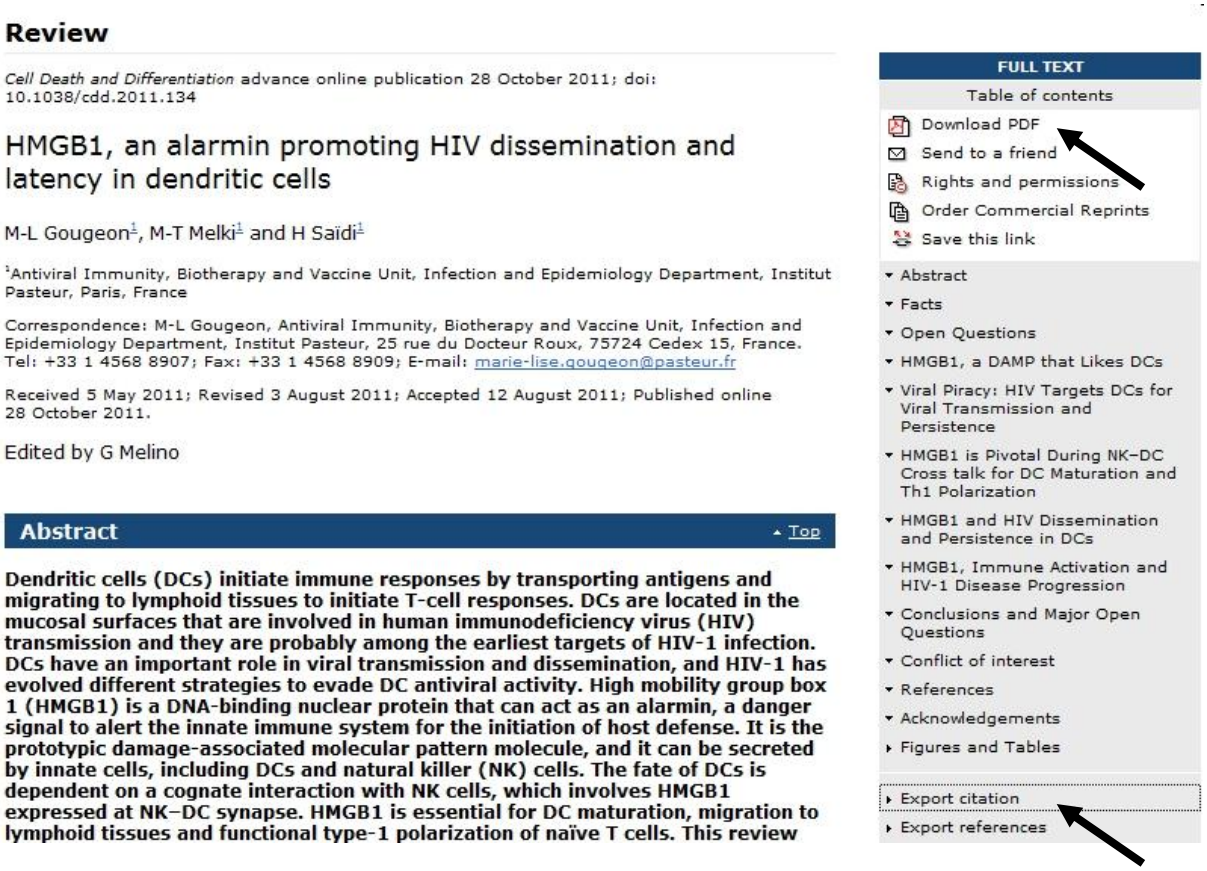
Lassen Sie alle Einstellungen bestehen und klicken Sie auf „Export“.

Im sich öffnendem Fenster wählen Sie nun „Speichern“ aus. Die Zitate werden im Format „RIS“ gespeichert. Dieses Format müssen sie dann als Option beim Import in EndNote angeben.

Wollen Sie den ganzen Artikel als PDF auf Ihrer Festplatte abspeichern, gehen Sie zurück und klicken statt auf „Export Citation“ auf „ Download PDFs“.

3.3 Herunterladen von ‚Nature'-Artikeln

Artikel aus ‚Nature' (http://www.nature.com), laden Sie folgendermaßen: Klicken Sie in der Volltextansicht auf „Export citation". Das Zitat wird im Format „RIS" gespeichert, das sie beim Import in EndNote als Option angeben müssen.



Review

Cell Death and Differentiation advance online publication 28 October 2011; doi: 10.1038/cdd.2011.134

HMGB1, an alarmin promoting HIV dissemination and latency in dendritic cells

M-L Gougeon[1], M-T Melki[1] and H Saïdi[1]

[1]Antiviral Immunity, Biotherapy and Vaccine Unit, Infection and Epidemiology Department, Institut Pasteur, Paris, France

Correspondence: M-L Gougeon, Antiviral Immunity, Biotherapy and Vaccine Unit, Infection and Epidemiology Department, Institut Pasteur, 25 rue du Docteur Roux, 75724 Cedex 15, France. Tel: +33 1 4568 8907; Fax: +33 1 4568 8909; E-mail: marie-lise.gougeon@pasteur.fr

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Edited by G Melino

Abstract Top

Dendritic cells (DCs) initiate immune responses by transporting antigens and migrating to lymphoid tissues to initiate T-cell responses. DCs are located in the mucosal surfaces that are involved in human immunodeficiency virus (HIV) transmission and they are probably among the earliest targets of HIV-1 infection. DCs have an important role in viral transmission and dissemination, and HIV-1 has evolved different strategies to evade DC antiviral activity. High mobility group box 1 (HMGB1) is a DNA-binding nuclear protein that can act as an alarmin, a danger signal to alert the innate immune system for the initiation of host defense. It is the prototypic damage-associated molecular pattern molecule, and it can be secreted by innate cells, including DCs and natural killer (NK) cells. The fate of DCs is dependent on a cognate interaction with NK cells, which involves HMGB1 expressed at NK–DC synapse. HMGB1 is essential for DC maturation, migration to lymphoid tissues and functional type-1 polarization of naïve T cells. This review

FULL TEXT

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- Abstract
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- Open Questions
- HMGB1, a DAMP that Likes DCs
- Viral Piracy: HIV Targets DCs for Viral Transmission and Persistence
- HMGB1 is Pivotal During NK–DC Cross talk for DC Maturation and Th1 Polarization
- HMGB1 and HIV Dissemination and Persistence in DCs
- HMGB1, Immune Activation and HIV-1 Disease Progression
- Conclusions and Major Open Questions
- Conflict of interest
- References
- Acknowledgements
- Figures and Tables

Export citation

Export references

Wollen Sie den ganzen Artikel als PDF auf Ihrer Festplatte abspeichern, gehen Sie zurück und klicken statt auf „Export Citation" auf „Download PDF".

4 Referenzen in EndNote einfügen

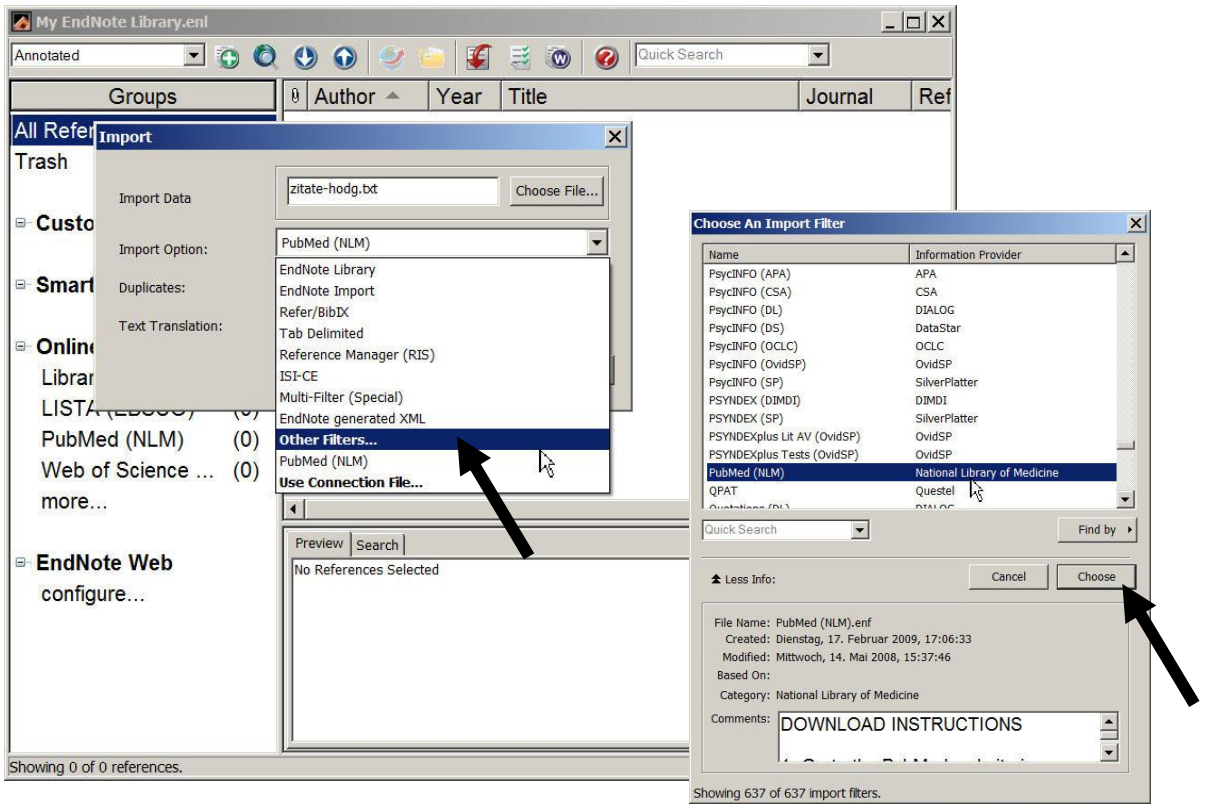
4.1 Heruntergeladene Referenzen importieren

Öffnen Sie den Reference Manager und importieren sie die Referenzen aus Medline in ihre Datenbank mit "File" > "Import".

Im Import Dialog müssen sie das zu importierende File und das entsprechende Importfilter zu der Datenbank angeben aus der sie die Referenzen exportiert haben. Zum Beispiel PubMed(NLM) im Fall von einem Download aus Medline.

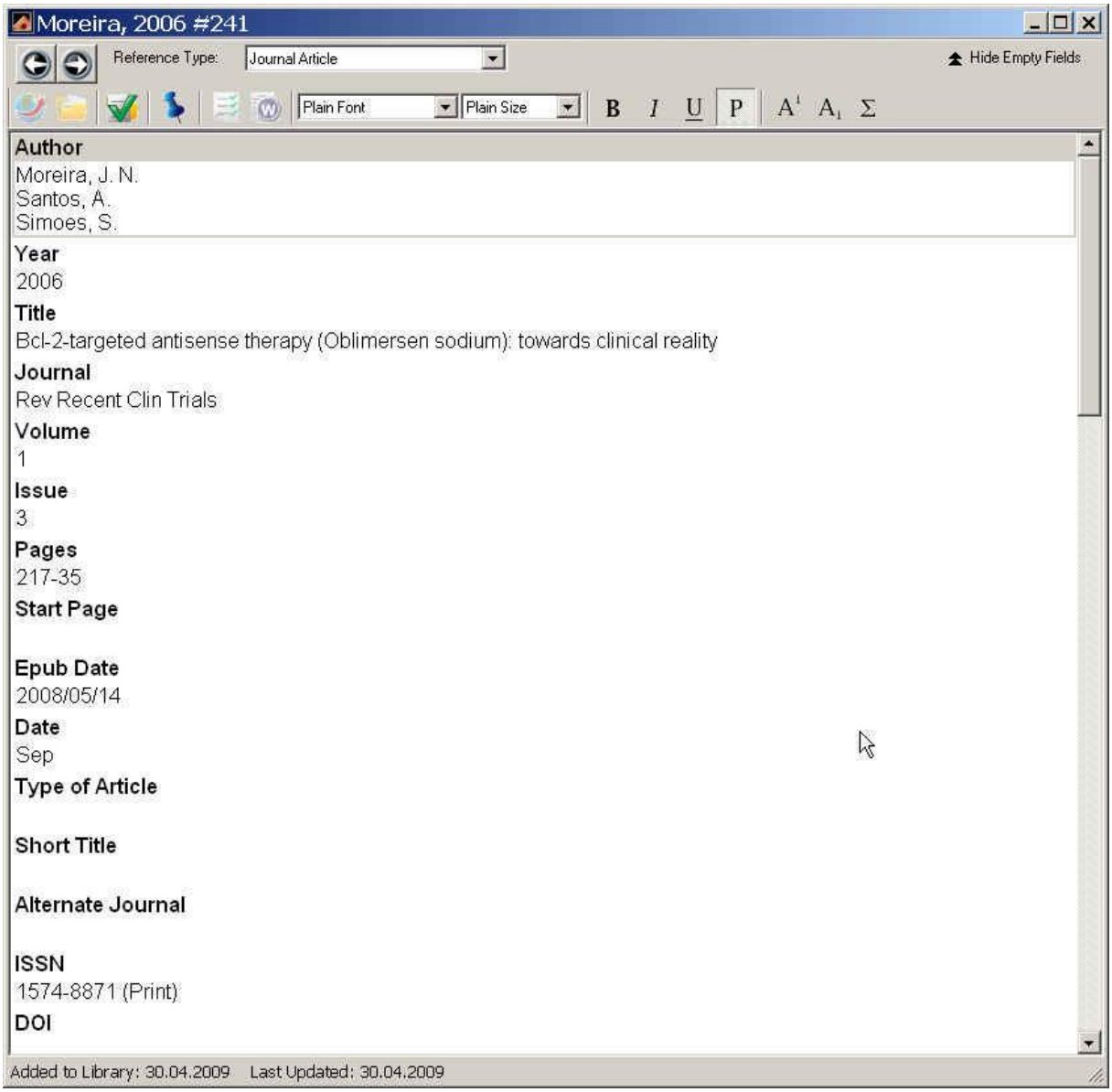
Wählen sie mit der Schaltfläche "Choose File…" in ihrem Ordner das File mit den gespeicherten Referenzen aus und klicken sie auf den Pfeil unter "Import Option:". Es wird eine Schnell-Auswahlliste mit voreingestellten und zuletzt verwendeten Filter angezeigt. Wählen sie das entsprechende Filter aus wenn es schon aufscheint.

Falls das Filter noch nicht angezeigt wird lassen sie sich mit der Auswahl „Other Filters…“ die Liste aller Filter anzeigen, wählen sie ein Filter aus und kehren mit der Schaltfläche "Choose" zum Dialog "Import" zurück.



Starten sie den Import durch Anklicken von "Import".

Durch Anklicken einer Referenz werden alle Felder (Autor, Titel, Journal etc.) im Detail angezeigt



Jede Referenz wird mit einer eindeutigen ID erstellt (oben). Die ID ist ein „unique key“, das heißt, sie kommt in der gesamten Datenbank nur einmal vor. Auch wenn Sie einen Artikel aus der Datenbank löschen, bleibt die ID (leer) bestehen. Doppelte Eingaben (die wir peinlich vermeiden wollen) würden denselben Artikel mit zwei unterschiedlichen IDs verknüpfen. Die möglichen Folgen möchten wir nicht näher beschreiben.

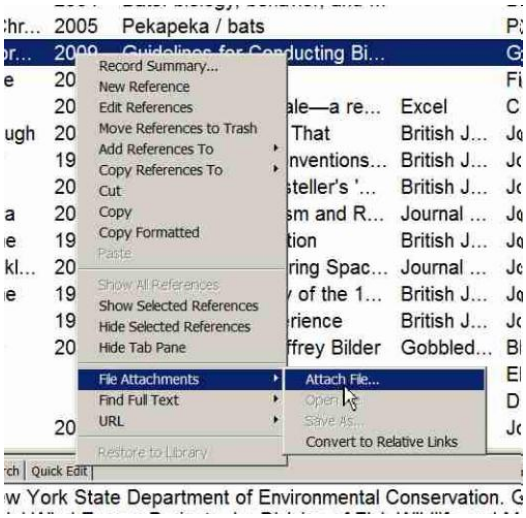
Es hat sich in der Praxis bewährt, die durch das System vergebene **ID auf jeder Papierkopie des Artikels zu vermerken.** Man kann auch die Artikel nach ID geordnet ablegen.

4.2 Verwalten der PDF-Dateien

Von Zeit zu Zeit ändert sich die Menge der für die MedUni Wien frei geschalteten Journale. Es kann vorkommen, dass ein Journal als Volltext verfügbar ist, dieser Zugriff jedoch später nicht mehr gestattet wird. Sichern Sie sich daher Ihre PDFs, „solange es noch geht“!

Es empfiehlt sich, alle PDFs in einem Ordner abzuspeichern (den Sie z.B. „Artikel Full Text“ nennen). Wählen Sie Dateinamen, die sich zusammensetzen aus Reference ID, Teilen des Titels und Journalabkürzung, z.B.: RefID1_A Gibbs_Physica.pdf

In EndNote suchen Sie die entsprechende Referenz, für die Sie gerade das PDF-File heruntergeladen haben. Klicken Sie mit der rechten Maustaste und wählen die Funktion “File Attachments“>„Attach File…“ aus. Wählen Sie das entsprechende pdf. Nun haben Sie den genauen Link in EndNote zum dazugehörigen pdf und Sie können leicht zugreifen.



4.3 Referenzen selbst eintippen

Wenn Sie einen Artikel nicht online finden, müssen Sie ihn händisch eintippen (mit “References“ > „New Reference“. Arbeiten Sie mit größtmöglicher Genauigkeit!

4.4 Ein Wort zu Keywords

Beim Herunterladen von Zitaten aus dem Netz kommen die gespeicherten Keywords mit. Es kann nützlich sein, zusätzliche Keywords im Rahmen der Arbeitsgruppe zu definieren. Wir raten, diesen Prozess sorgfältig abzustimmen, Details werden im Publikationsworkshop vorgeschlagen. Ungeschickt gewählte Keywords sind eher eine Last als ein Nutzen.

Sie können selbst gewählte Keywords speziell kennzeichnen (z.B. vorangestellter Stern, etc.), um Sie von den automatisch heruntergeladenen zu unterscheiden.

4.5 Eine Notiz zu den Notes

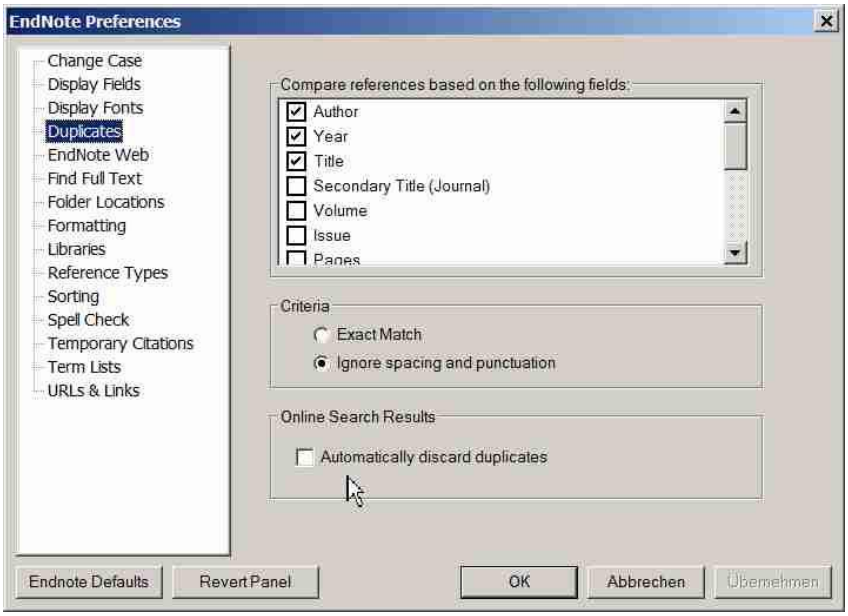
EndNote erlaubt die Eingabe von „Notes“. Bereits beim Herunterladen kommen einige Informationen automatisch in dieses Feld. Sie können es aber auch nutzen, indem Sie Ihre privaten Kommentare, Beurteilungen und Verweise dort einfügen. Auch ein Vermerk (Namenskürzel), wer die Arbeit gelesen und die Kommentare gemacht hat, ist nützlich. Manchmal genügen sehr kurze Vermerke, wie z.B. „B.S“ = „bull shit“, „M.S“. = „more shit“

oder gar „PhD“= „piled, higher and deeper“. Kurzum: Notes ersetzen die „Randnotizen“ und können Sie davor schützen, Teile von Artikeln unnötigerweise mehrfach zu lesen.

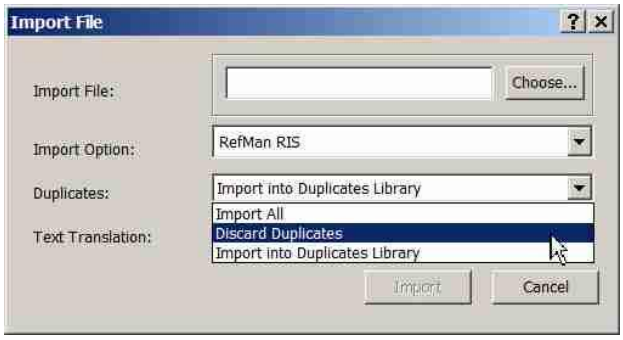
4.6 Duplikate vermeiden

Es könnte passieren, dass Sie einen Artikel unabsichtlich zweimal in Ihre Datenbank laden. Das führt zu problematischen Unübersichtlichkeiten! Sie sollten daher vermeiden, dass es zu Duplikaten kommt!

Mit “Edit“ > “Preferences“ könnten sie die Felder festlegen, die für das Erkennen von Duplikaten verwendet werden sollen.



Beim Import von Referenzen (“Import“ > “File…“) bestimmen sie mit der Auswahl „Import Option“ ob die Duplikate gelöscht oder in einem eigenen Bereich gespeichert werden sollen.

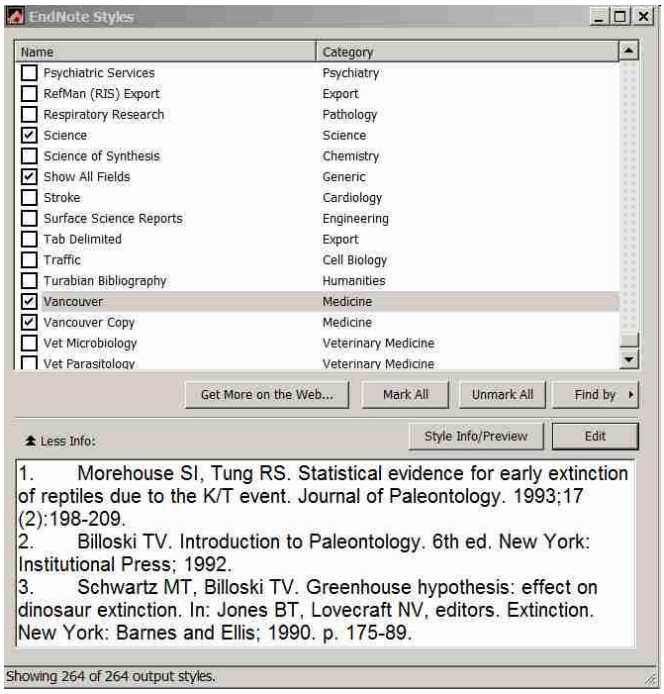


5 Fertige Journalformate

Der Lieferumfang von EndNote enthält zahlreiche Journalformate (sogenannte „Output Styles“) zur unmittelbaren Verwendung. In diesen Formaten ist definiert, wie für das betreffende Journal die „In-text-citations“ und die „List of references“ auszusehen haben.

Dennoch kann es vorkommen, dass das von Ihnen gewünschte Journalformat nicht mitgeliefert wurde. Wir empfehlen folgende Vorgangsweise:

- Verwenden Sie, wenn möglich, ein anderes mitgeliefertes Journalformat, das die gleiche oder eine ausreichend ähnliche Formatierung liefert. Beim Durchsuchen der verfügbaren Journalformate („Edit“ > Output Styles“ > „Open Style Manager…“) können sie sich eine Vorschau auf die Formatierung anzeigen lassen.



- Sollte kein Format mit ausreichender Ähnlichkeit verfügbar sein, können Sie ein neues Journalformat definieren. Dazu editieren sie ein möglichst ähnliches Journalformat (anklicken eines Formats) und speichern es unter einem neuen (!) Namen ab.

Hinweis: Die Definition von Journalformaten erfordert Geduld und Genauigkeit.

6 Zusammenwirken: Word ↔ EndNote

Einfügen von Literaturstellen in Word und Erstellen von Literaturlisten

Nach der Installation von EndNote erscheint in Word eine neue Registrierkarte EndNote X2“ die alle Funktionen enthält.

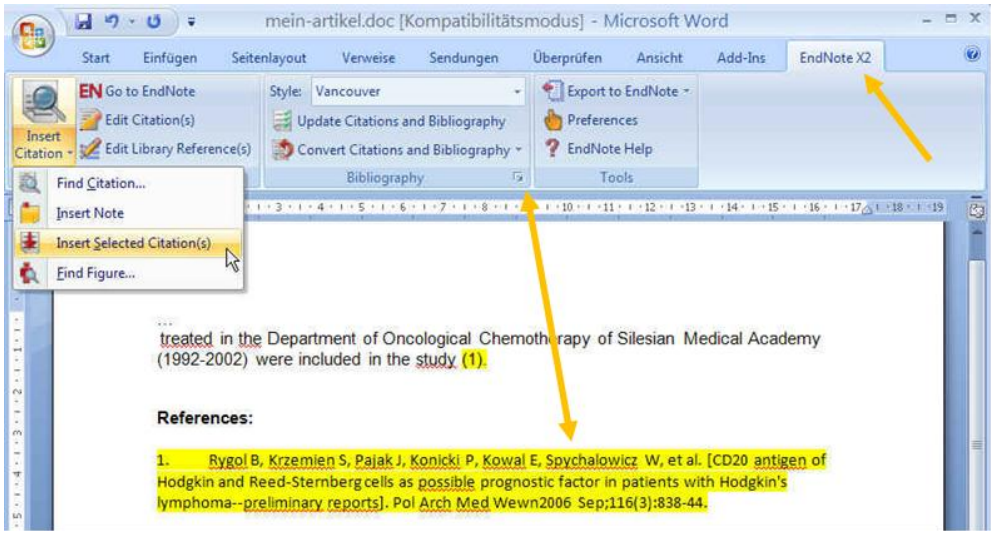
Die zwei wichtigsten Funktionen sind:

1. Zitat(e) einfügen

Sie markieren in EndNote ein oder mehrere Referenzen und fügen sie in Word an der gewünschten Textstelle durch den Befehl „Insert Selected Citation“ ein.

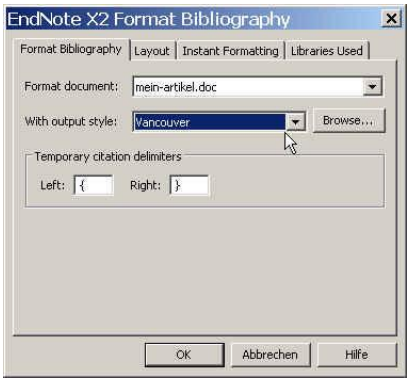
2. Literaturliste erstellen

Mit „Format Bibliography“ und Auswahl des gewünschten Formats (entsprechend dem Journal bzw. den Instruktionen für Autoren) wird die Referenzliste generiert.



Die von EndNote eingefügten Zitate sind Teile Ihres Originalmanuskripts und sollten von Ihnen keinesfalls händisch verändert werden!! (Ausnahme: vollständiges Weglöschen einzelner Zitate).

Wenn sie den Stil der Literaturliste ändern möchten, formatieren sie mit der Funktion „Format Bibliography“ und Auswahl eines neuen „Output Style“ die Literaturliste neu.



Medizinische Universität Wien
Zentrum für
Medizinische Statistik, Informatik und Intelligente Systeme
A-1090 Wien, Spitalgasse 23

Publizieren mit EndNote

Folien

Anleitung zum Publikationsworkshop
im Rahmen der postgraduellen Fortbildung an der MUW

W. Schreiner, B. Knapp, W. Gall

7. November 2011

Publizieren mit EndNote

(1) Referenzen

(2) Richtig zitieren

(3) Literaturverwaltung

(4) Literaturquellen

(5) Programm EndNote

(6) Übung – von Medline über EndNote zur Referenzliste

(1) Referenzen

- Was sind Referenzen?
- „Supporting information“ zum Text
  - Figures and Tables
  - References
- Wozu Zitate?
  1) Autor würdigen
  2) Pfad zu weiteren Informationen

Referenzen - Qualität

- Referenzen sind ein Aushängeschild für die Qualität ihrer wissenschaftlichen Arbeit
- Oft 1. Blick (des Reviewers) auf Zitate
- Anzahl
- Typ
  - Nicht nur Internet-Referenzen
  - Review Prozess

Formatierungsstile

- Unterschiedlichste Formatierungsstile
- 2 Hauptvarianten
  - Zitat: Name + Jahr, Liste: alphabetische Sortierung
    - z.B. Harvard
  - Zitat: Nummer, Liste: Reihenfolge im Artikel
    - z.B. Vancouver
- Mischvarianten >>
- Jeden Typ in einer Arbeit einheitlich formatieren

(2) Richtig zitieren

- Direkte (wörtliche) Zitate sparsam
- Indirekte (sinngemäße) Zitate bevorzugen
- Abbildungen und Tabellen zitieren
  - „entnommen aus []“, „adaptiert von []“
- Immer Original zitieren (versuchen)
  - Peter Karall, Aurelia Weikert. Universität Wien. Das Verfassen wissenschaftlicher Arbeiten. http://www.univie.ac.at/ksa/elearning/cp/schreiben/schreiben-43.html (UmbertoEco2002)

Zitieren - Richtlinien

- Details Harvard Stil
  - z.B. mehrere Autoren, Bücher, elektronische Quellen
  - Anglia Ruskin University. Chelmsford und Cambridge, UK. Harvard System of Referencing Guide. http://libweb.anglia.ac.uk/referencing/harvard.htm
- Wissenschaftliches Schreiben
  - z.B. parallele Formen (Phrasen, Sätze)
  - >> Buch: Mimi Zeiger. Essentials of Writing Biomedical Research Papers. McGraw-Hill. 1999
    - Summary of Guidelines for References (Figures, Tables) >>

Summary Guidelines - 1

References give credit to the ideas and findings of others and direct readers to sources of further information.

Select the most valid, the most available, and the fewest references.

- Valid: journal articles, books, Ph.D. theses, reviewed conference proceedings.
- Less valid: abstracts for meetings, unreviewed conference proceedings.
- Available: journal articles either published or in press, books.
- Less available: Ph.D. theses, conference proceedings.
- Not available: journal articles submitted or in preparation; do not include these in the reference list; cite them in the text as personal communications or unpublished observations.
- For the fewest references, select the first, most important, most elegant, and most recent papers. Use review articles when possible.

References must be accurate in every detail: authors' names, authors' initials, title of the paper, title of the journal, year of publication, volume number, first and last page numbers.

Summary Guidelines - 2

Quotations must be exact.

Paraphrases must be accurate and fair.

Every reference in the text must be in the reference list, and vice versa.

When naming the authors of a paper in the text, include all authors. For papers by three or more authors, use the form "Jackson et al." and the pronoun "they" (not "he").

Put reference citations after the idea you are citing or after the authors' names if names are included.

If you draw a conclusion based on another author's findings, put the citation after the author's finding, not after your conclusion.

For several references in one sentence, cite each reference after the appropriate point rather than grouping all references at the end of the sentence.

Summary Guidelines - 3

Use either authors and years or numbers to identify references in the text, whichever the journal requests.

For more than one reference for one point, cite references in chronological order.

In the reference list, use alphabetical order when authors and years are cited in the text. Use numerical order according to first citation in the text when numbers are used for citations, unless the journal prefers alphabetical order.

Follow the journal's style for details in the reference list. If the journal has adopted the Vancouver style, use it.

„Instructions for authors“

- Gute Journale und Kongresse legen die Formierung der Referenzen im Detail fest
- Sammlung Instruktionen
  - The University of Toledo. Instructions to Authors in the Health Sciences. http://mulford.meduohio.edu/instr/
    - z.B. Medical Anthropology
      - Verschiedene Stile für Text und Liste
    - z.B. Genes to Cell
      - „et.al“ erst ab 15 Autoren

Schlechtes (übliches) Benehmen

- Selbst-Plagiat
- Journal Shopping
- Artikel duplizieren
  - Tagungspaper > Journalpaper
- Artikel von Journal Editoren >>
  - R. A. Miller, T. Groth2, A. Hasman, C. Safran, E. H. Shortliffe, R. Haux, A. T. McCray. On Exemplary Scientific Conduct Regarding Submission of Manuscripts to Biomedical Informatics Journals.

(3) Literaturverwaltung

- Motivation: Unterschiedliche Formatierungen der Bibliographien

1. Quellen: unterschiedliche Exportformate der Literaturdatenbanken

2. Verwendung: unterschiedliche Formatierungsregeln der Journale, Kongresse („instructions for authors“)

Literaturverwaltungsprogramme

- Referenzmanager unterstützen durch
  - Importieren aus Datenbanken
  - Formatieren der Referenzen in der Publikation

- EndNote, Reference Manager, Citavi, RefDB, …
  - Liste: OpenOffice.org. Bibliographic Software. http://wiki.services.openoffice.org/wiki/Bibliographic_Software_and_Standards_Information
    - Betriebssystem, Preis, Lizenz

Referenzmanager – Funktionen - 1

- „private“ Literaturdatenbank
- Persönlich oder Arbeitsgruppe
- Verwaltung von Referenzen unterschiedlicher Publikationstypen
- Plus Volltext (PDF), Bilder, …
- Verzeichnis aller in Erwägung gezogener / gelesener / bearbeiteter Zitate und Artikel

Referenzmanager – Funktionen - 2

- „Hunderte vorbereitete Formate
  - Import-Filter
  - Datenbank-Schnittstellen
  - Formatierungs-Stile
- Vorbereitete Journal-Templates
- Hinzufügen von Keywords
  - zusätzlich zu den automatisch importierten
- Hinzufügen von Kommentaren

Nützen sie die Vorteile

- Synergieeffekte durch gemeinsame Nutzung
- Zeitersparnis

- Qualität
  - Wenn möglich Zitate und Artikel immer herunterladen
  - Manuelle Eingabe mit größtmöglicher Genauigkeit

(4) Literaturquellen

- 2 Arten
  - Bibliographie-Datenbank
    - nur Zitat
  - Fakten-Datenbank
    - Volltext
    - Multimedia

- Exakte Suche in Datenbanken (zum Unterschied von Google)

Literaturquellen

- Sammlung medizinischer Datenbanken
  - Josef König. Linz. http://www.meddb.info/
  - Josef König et al. Erfolgreiche Suche in medizinischen Datenbanken. Springer. 1996

- Bibliothek MedUni Wien
  - Datenbanken, e-journals, e-books
  - Ampelsystem für Zugriffsberechtigung
  - http://ub.meduniwien.ac.at

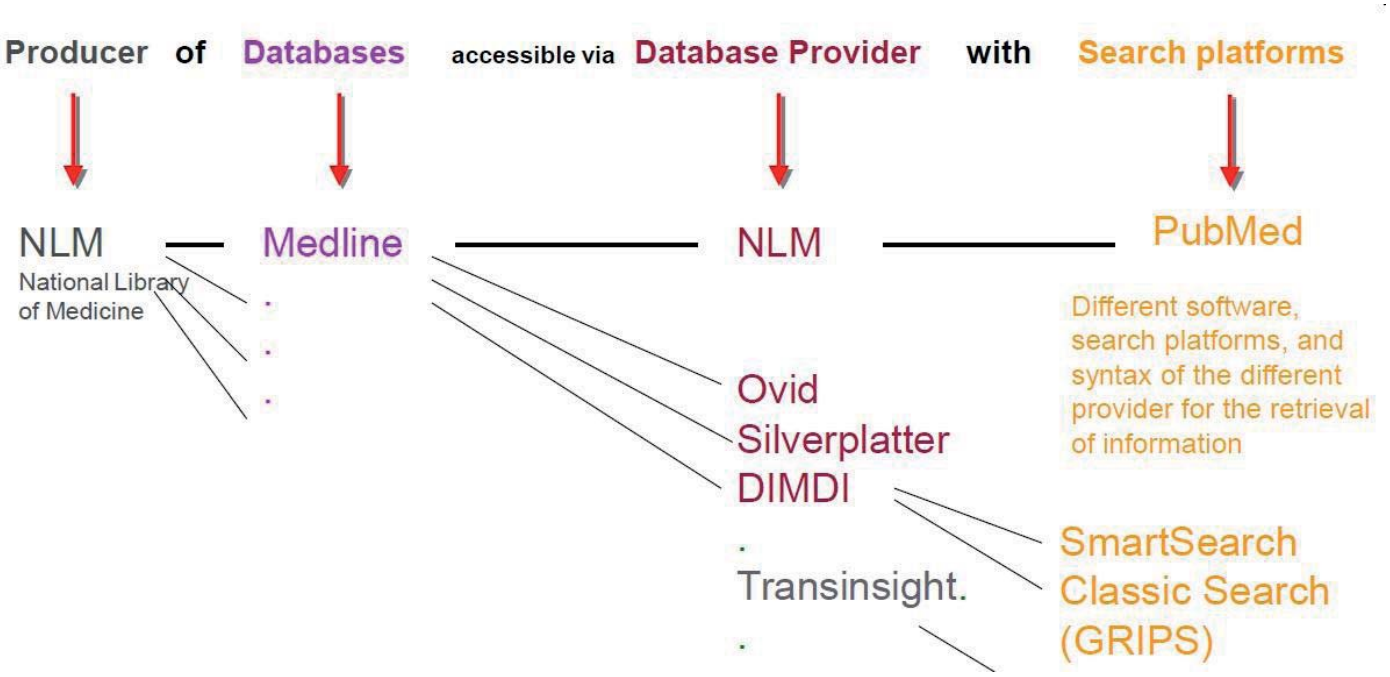
Wichtige Datenbanken - 1

- Medline – Service „PubMed“ der National Library of Medicine
- über 5000 Journale
- Über 15 Millionen Artikelreferenzen
- Viele Volltexte

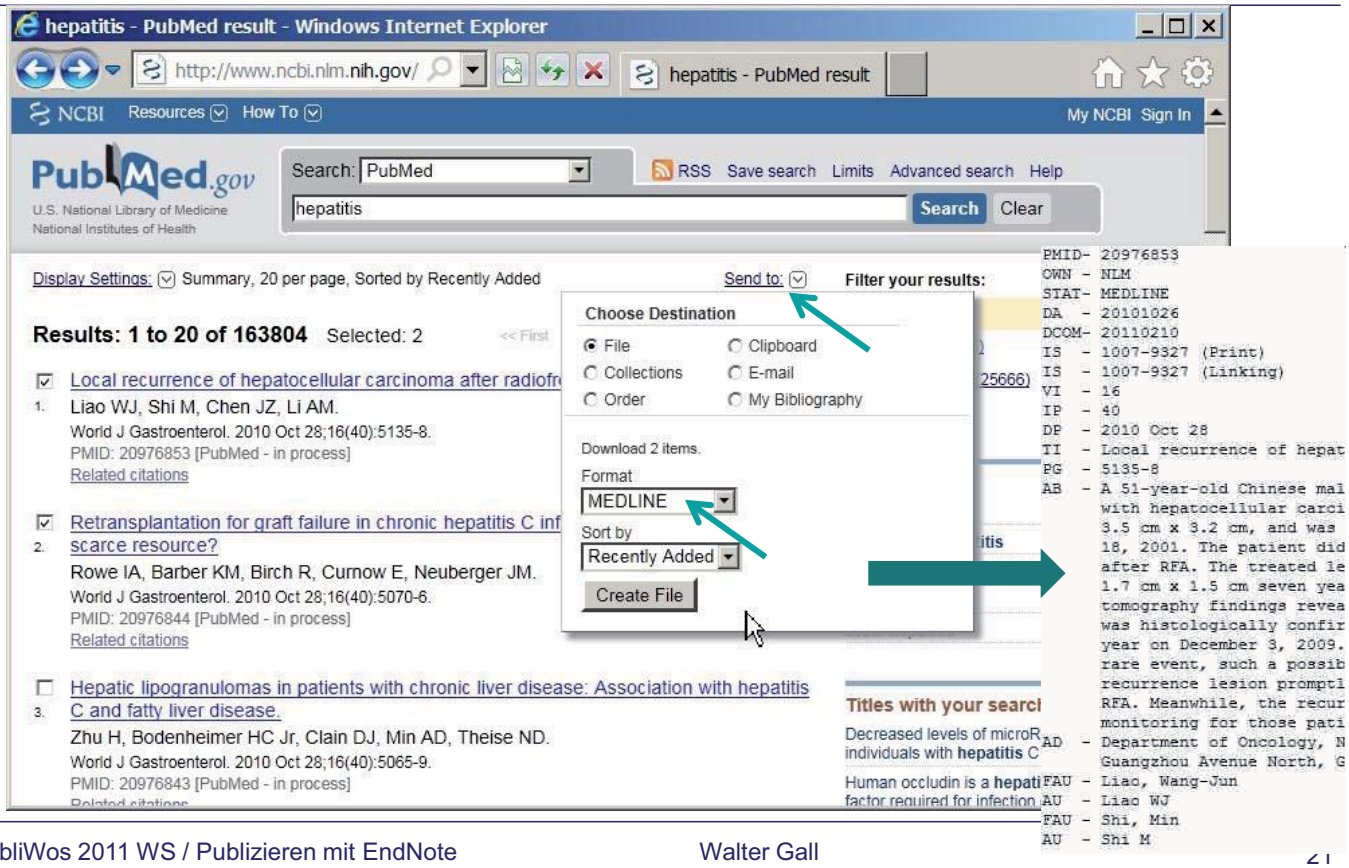
- http://www.pubmed.gov

- Zitate abspeichern im Format „Medline“

Medline - PubMed – NLM – OVID ??



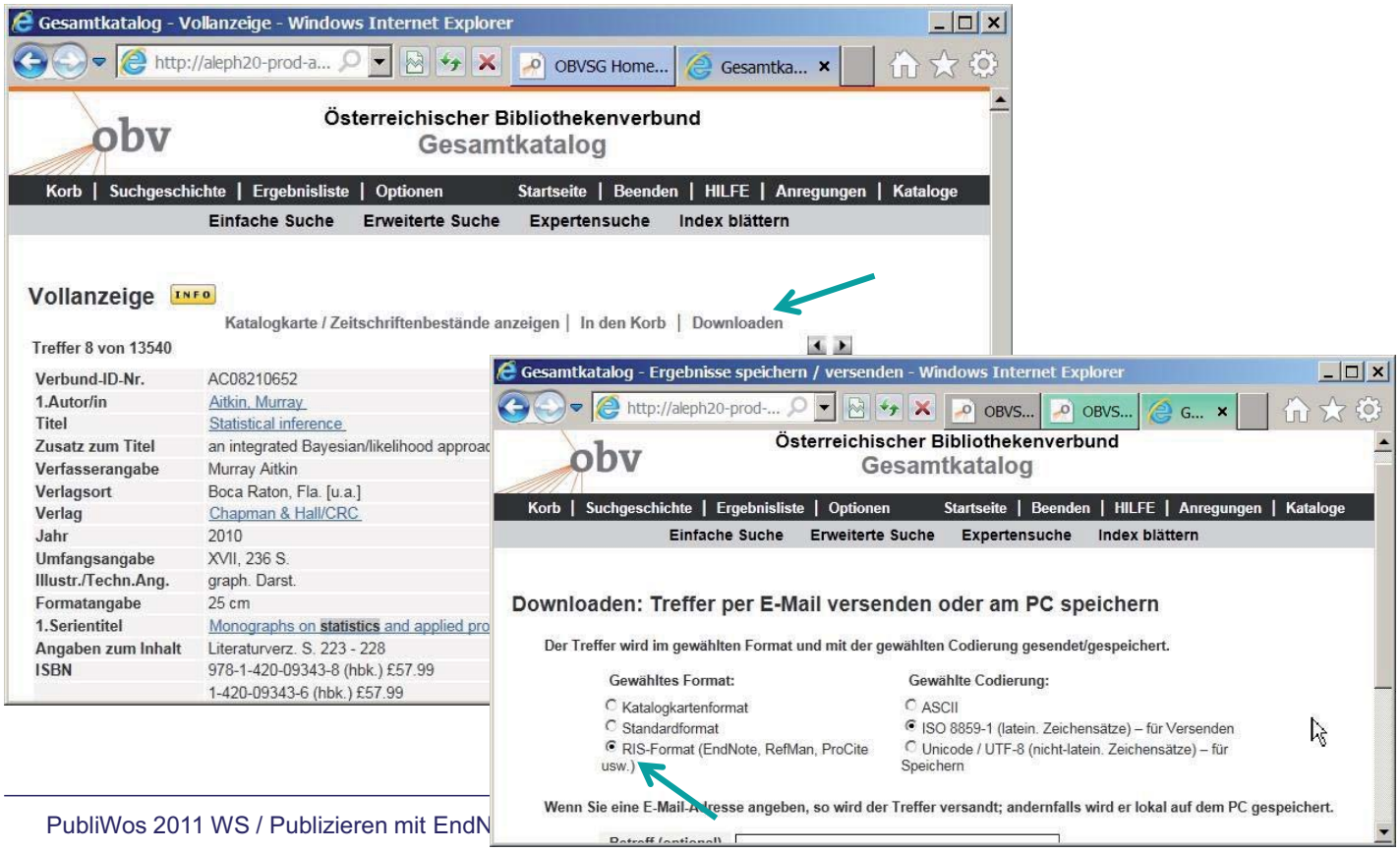
Zitate aus Medline abspeichern



Wichtige Datenbanken - 2

- Österreichischer Bibliothekenverbund
- Kataloge
  - Universitäten, Museen , Kirchliche Einrichtungen
- Bücher, Dissertationen
- http://www.obvsg.at
- Persönliche Literaturverwaltung
  - Zitate abspeichern oder direkte Verbindung aus eigener Literaturdatenbank
  - http://www.obvsg.at/services/verbundsystem/persoenliche-literaturverwaltung/

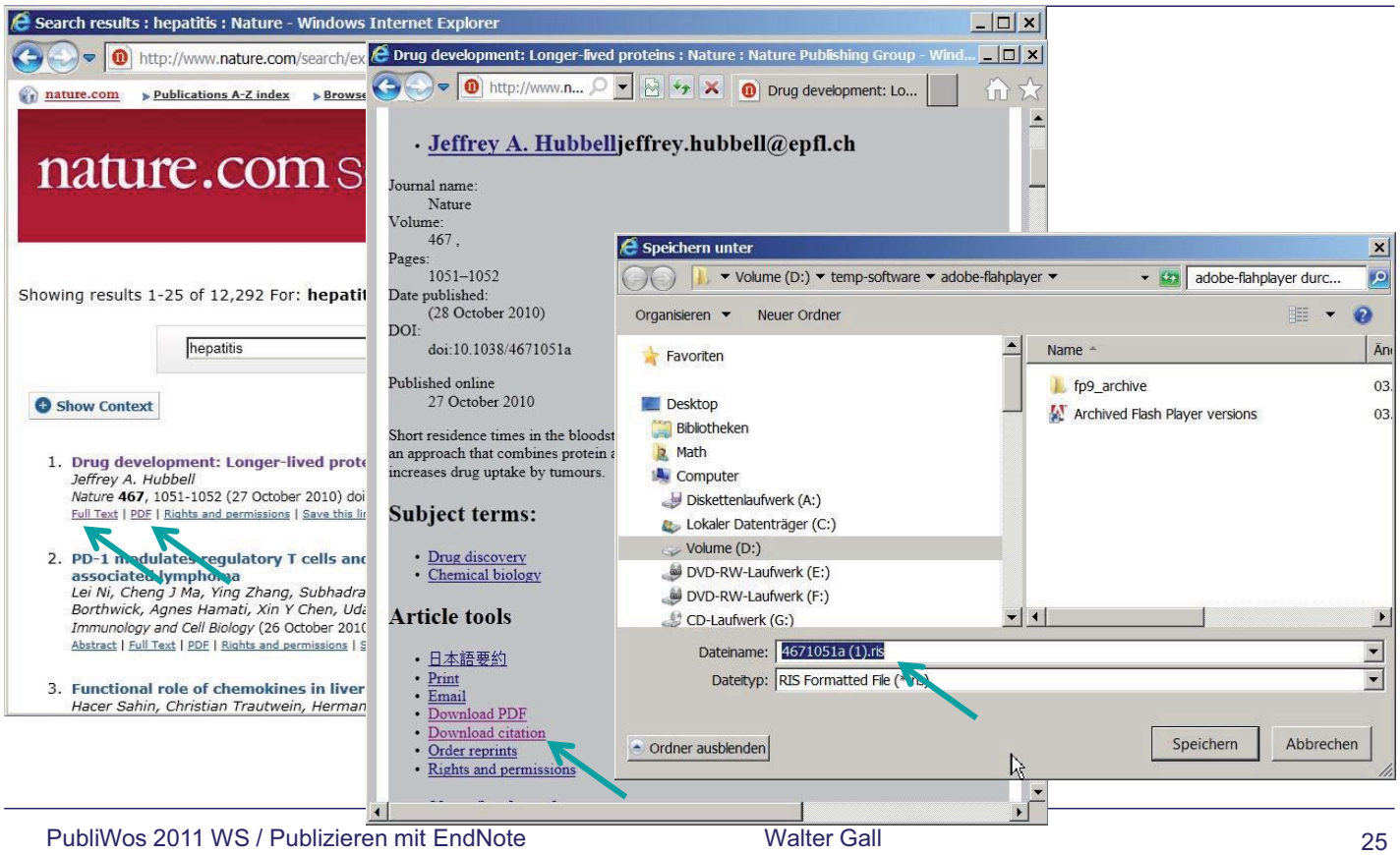
Zitate aus ÖBV abspeichern



Literatur Services

- Standard Services
  - Benachrichtigungen
  - Download
- Wer wurde wo zitiert?
  - ISI Web of Knowledge: http://apps.isiknowledge.com
- Online-Zeitschriften
  - Springer: http://link.springer.de
  - The Lancet: http://www.thelancet.com
  - Nature: http://www.nature.com

Zitate aus Nature abspeichern



(5) Programm EndNote

- Import, Editieren und Export von Bibliographien
- Direkte Recherchen in Online-Datenbanken

- Arbeitet sehr gut mit Word zusammen
- Kopiert „AddIns“ ins vorher installierte Word

- Neu: EndNoteWeb
- Aktuell: Version X4

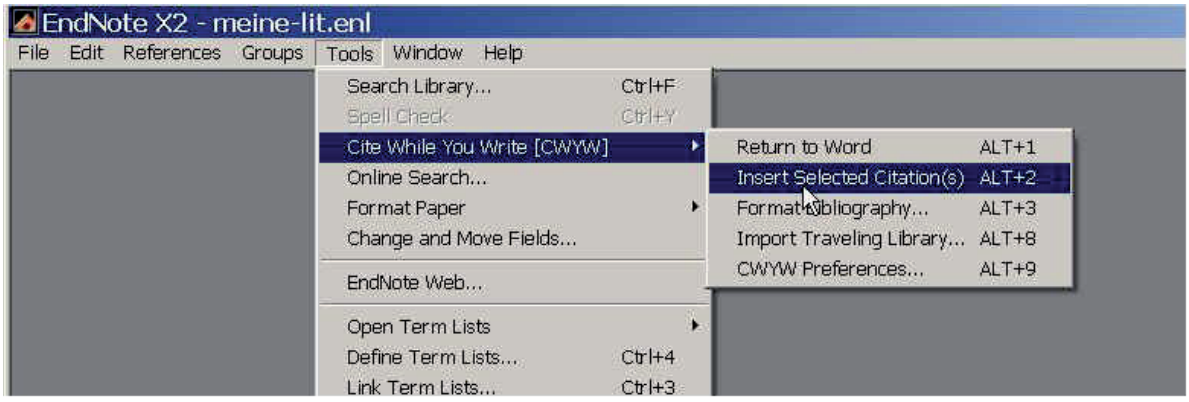
EndNote Homepage

- http://www.endnote.com

- Produkt Infos
  - Kompatibilität der Versionen mit Betriebssystemen (Windows, Mac, ..)
- Support
  - Download neuer Schnittstellen (Input-Filter, Datenbank-Schnittstellen, Formatierungs-Stile)

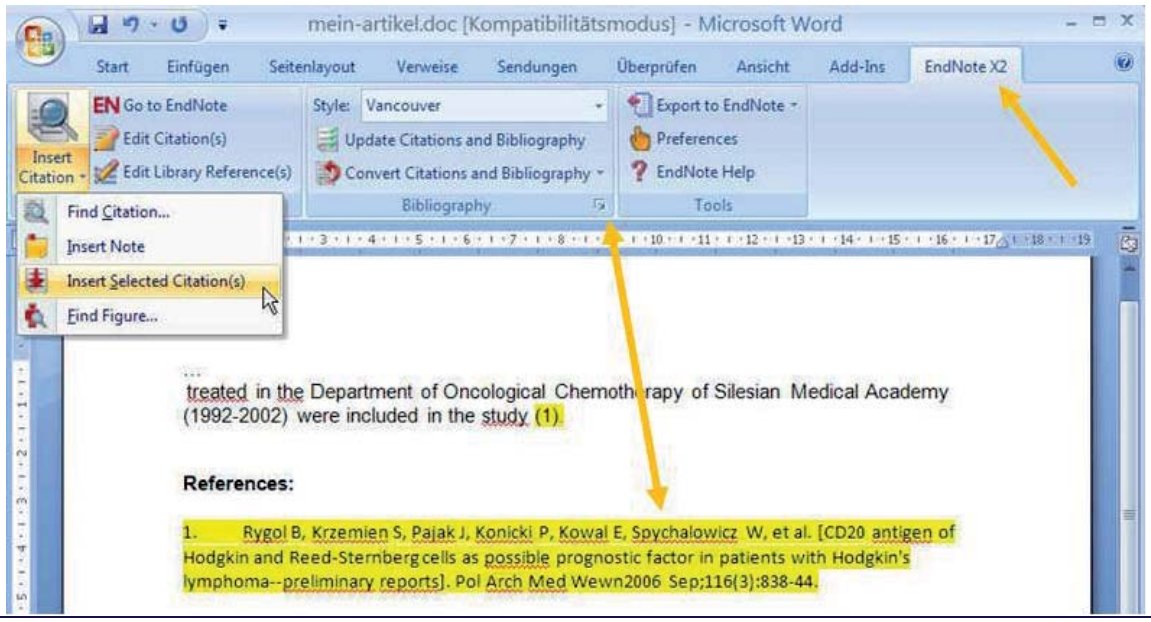
Verknüpfung von EndNote und Word

- In EndNote über Menü „Tools“ > „Cite While You Write“

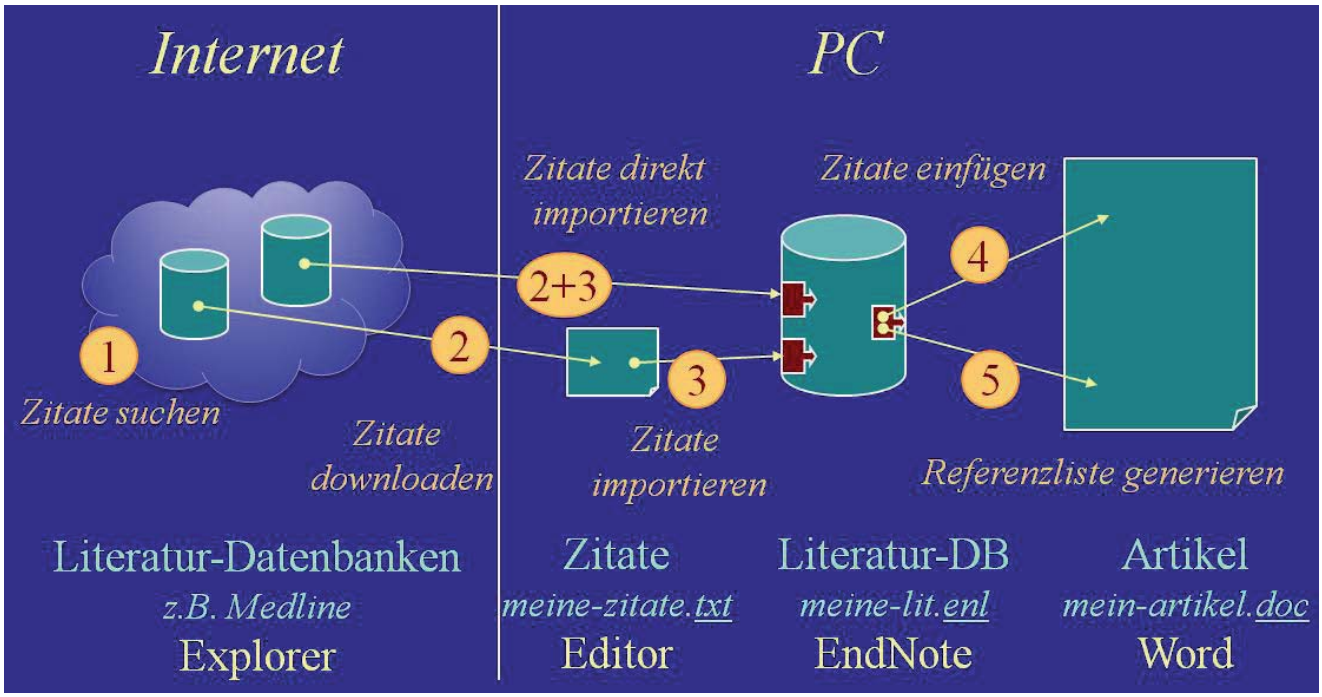


In Word mit Registrierkarte „EndNote X2“

- Zitat(e) einfügen mit „Insert Selected Citation(s)“
- Referenzliste einfügen mit „Bibliography“ (kleiner Pfeil)



Von Medline über EndNote zur Referenzliste



EndNote Features - 1

- Zugriff durch gesamte Arbeitsgruppe
  - Gemeinsamer Speicherort, Webversion
- Zugriff auf Quelle
  - Feld „URL“
- Volltext speichern wenn möglich
  - Feld „File Attachments“ -> Link zu lokalen File (PDF)
- Referenz aus PDFs generieren
  - Import Option „PDF“ (ab Version X4)

EndNote Features - 2

- Referenzen gruppieren
  - „Groups > Create Group“
  - Smart Groups (dynamische Filter)
- Thematisch sortierte Biographien
  - „Tools > Subject Bibliography…“ (z.B. über Keywords)
- Direkter Zugriff auf Datenbanken aus EndNote
  - Freie oder mit Account
- Einfacher Export in allen Stilen
  - „File > Export…“ (z.B. als HTML für ihre Homepage)

EndNote Features - 3

- Journal Templates
  - Vorformatierte Artikel
- Duplikate vermeiden
  - Option bei Import
- Individuell einstellbar
  - z.B. zusätzliche persönliche Felder
- Format-Manager
  - Formate editieren (Import Filters, Output-Stiles)
  - persönliche generieren

Tip: Vernetzung der Services nutzen !

- „Wissenschaftlichen „Arbeitsplatz“ einrichten
- z.B: Artikel zu Substanz Malathion suchen und zitieren
  - Datenbank in Resourcen-Center (z.B. König) suchen http://www.meddb.info/
    - Substanz in Datenbank ChemID suchen
      - Direkte Literaturabfrage in Medline aus ChemID
        - Abstract, Volltexte (wenn verfügbar) ansehen
        - Zitate exportieren im Format-Medline
          - Zitate in private Literaturdatenbank importieren
            - Zitate im Artikel zitieren und Referenzliste generieren

(6) Übung - von Medline über EndNote zur Referenzliste

1. Literatur in Medline suchen und speichern
2. Literatur in EndNote importieren
3. Zitieren und Referenzliste erstellen in Word

3 Programme:

- Start > Webexplorer > http://pubmed.gov (Medline)
- Start > Programme > EndNote
- Start > Programme > Microsoft Office > Word 2007

@: walter.gall@meduniwien.ac.at Tel: +43-1-40400-6694

Editorial

On Exemplary Scientific Conduct Regarding Submission of Manuscripts to Biomedical Informatics Journals

R. A. Miller[1], T. Groth[2], A. Hasman[3], C. Safran[3], E. H. Shortliffe[4], R. Haux[5], A. T. McCray[5]
[1]Journal of the American Medical Informatics Association
[2]Computer Methods and Programs in Biomedicine
[3]International Journal of Medical Informatics
[4]Journal of Biomedical Informatics
[5]Methods of Information in Medicine

Summary
As the Editors of leading international biomedical informatics journals, the authors report on a recent pattern of improper manuscript submissions to journals in our field. As a guide for future authors, we describe ethical and pragmatic issues related to submitting work for peer-reviewed journal publication. We propose a coordinated approach to the problem that our respective journals will follow. This Editorial is being jointly published in the following journals represented by the authors: *Computer Methods and Programs in Biomedicine, International Journal of Medical Informatics, Journal of Biomedical Informatics, Journal of the American Medical Informatics Association,* and *Methods of Information in Medicine.*

Methods Inf Med 2006; 45: 1–3

As the Editors of leading international biomedical informatics journals, the authors report on a recent pattern of improper manuscript submissions to journals in our field. As a guide for future authors, we describe ethical and pragmatic issues related to submitting work for peer-reviewed journal publication. We propose a coordinated approach to the problem that our respective journals will follow. This Editorial is being jointly published in the following journals represented by the authors: *Computer Methods and Programs in Biomedicine*, *International Journal of Medical Informatics*, *Journal of Biomedical Informatics*, *Journal of the American Medical Informatics Association*, and *Methods of Information in Medicine.*

As Editors, we have collectively experienced at least one of the following occurrences recently:

1) Concurrent duplicate submissions: The same set of authors submits essentially identical manuscripts to two separate journals concurrently, without disclosure to the Editorial staffs of either. The authors may mistakenly believe that it is permissible to do so because the respective journals have minimally overlapping audiences.
2) Serial unaltered submissions ("journal shopping"): Authors submit a manuscript to one biomedical informatics journal, and, after peer review, it is not accepted for publication, and a critique is provided. The authors do not make any of the changes suggested by the previous review, and instead submit the unchanged manuscript immediately to a

second journal, without disclosing the existence or results of the previous review by the first journal.

3) Serial minimally altered republication: Authors publish a preliminary manuscript as part of conference proceedings. Mistakenly believing that conference publications do not count as "official" publications (of note, several informatics conference proceedings, such as MEDINFO, MIE, and the AMIA Fall Symposium, are indexed in MEDLINE), the authors later submit the same work, with minimal alteration or expansion, to a peer-reviewed journal for publication.
4) Self-plagiarism [1]: Authors, mistakenly believing that any text that they have written is "theirs", submit a new manuscript for publication in a different, peer-reviewed journal, and include major sections (paragraphs or larger) of the previous peer-reviewed publication that they authored – and do so without proper attribution to the original source or without obtaining permission from the copyright holder.
5) Non-disclosure of conflict of interest by one or more of the authors: Authors with a financial interest related to the scientific content of the paper fail to disclose this information in a cover letter to the Editor at the time of submission or in the acknowledgment section of the manuscript prior to the time of publication.

The peer-reviewed literature constitutes the main archival source of knowledge in biomedicine. Authors, editors, and publishers must respect reasonable, common-sense ethical and legal imperatives in order to maintain the integrity of the peer-reviewed literature as a vital and important resource. Peer review is conducted by busy professional colleagues who are experts in a given field, and who are not compensated for their efforts. The burden on editors and publishers grows over time due to the seemingly exponential rate of increase in biomedical publications. Peer review is based on trust, respect and the principle of "behave toward others as you would like them to behave toward you". There is little room for the sort of behaviors detailed above, which potentially involve dishonesty, deception, and disrespect for the work of those carrying out peer review. Submitting duplicative material for publication unnecessarily consumes editorial staff time and expert reviewer resources. If the deception is not caught, duplicate publication also violates copyright laws, since authors assign copyright on a work to the publisher of the journal in which it appears. Duplicative submissions burden the peer review system, creating inefficiencies that may lengthen the time before anyone's submitted manuscript is reviewed and published.

With respect to submissions to biomedical informatics journals, prospective authors should follow several common, standard practices. To avoid burdening an already labor-intensive peer review process, authors should, at the time of submission of a work, disclose confidentially to the editorial staff of the target journal any potentially overlapping materials, whether already published, or currently in peer review. It is best if the authors attach clearly labeled copies of any such potentially duplicative work, along with their original submission to the journal. In addition, if a manuscript recently underwent peer review by another journal, authors should disclose this information. They should include either the previous critique, or a cover letter with the new submission that explains how the authors have modified the manuscript to address the previous (outside) critique. Similarly, authors should fully disclose any potential conflicts of interest of any of the authors (e.g., commercial ownership of the intellectual product being evaluated, potential financial benefit to an author related to the subject of the publication, or commercial sponsorship of an evaluation study of that company's product) Most importantly, if there is any question regarding appropriate procedures for submission or disclosure, authors should contact the editorial office and discuss the situation with the Editor or editorial staff well in advance of submitting a manuscript.

The Editors who have authored this paper note that there are many "gray" or borderline areas where individual journals will have different policies from one another. We also point out that, by contacting the Editor(s) of journals in advance of a submission, it may be possible and reasonable to arrange for "duplicate" publication by obtaining mutual consent from the Editor(s). For example, if a manuscript is important to both a clinical audience and a technical audience, and has potentially great significance to both fields, Editors of journals with relatively non-overlapping readerships might be willing to publish similar versions of the same work concurrently, so long as this is disclosed before submission and in the manuscripts as they are published. Such a disclosure with joint publication occurred for a position paper recommending how the United States Food and Drug Administration (FDA) might approach regulation of clinical software systems [2, 3]. Some policy differences among the journals represented by the authors include that, for example, *JAMIA* with few exceptions will not publish work that has previously appeared with global distribution on the World Wide Web – whereas other journals are not as restrictive. *JAMIA* has historical standards for how much new material (methods and results) must be added to a preliminary paper published in conference proceedings in order to qualify as a new original publication, while other journals have different standards for what is required in such settings. *Methods of Information in Medicine*, for example, generally does not publish material that has already appeared elsewhere, but accepts some papers that have been published as abstracts, and some high-quality manuscripts that have already appeared in a language other than English. The *International Journal of Medical Informatics* may approach authors of the best presentations at certain conferences (e.g. MIE and MEDINFO) for permission to republish the manuscripts (often as extended versions) in special issues. The *Journal of Biomedical Informatics* occasionally publishes special issues based on conferences, but the individual papers are greatly expanded from what occurs in any Proceedings and the review process is as rigorous as it would be for any journal submission.

The Editors of the respective journals listed above mutually agree that any work submitted to any of our journals that represents duplicative publication (as defined by the common standards above) will be im-

mediately rejected without peer review, and returned to the authors. It will not subsequently be considered for publication in the journal to which it was submitted, even if substantially revised. In addition, as a deterrent to duplicative publication in our field, the Editors have agreed to share among themselves the list of authors and the title of any manuscript that each of the journals accepts for publication, immediately at the time that the work is accepted for publication, with the possibility that duplicative submissions discovered through this process will be rejected prior to publication.

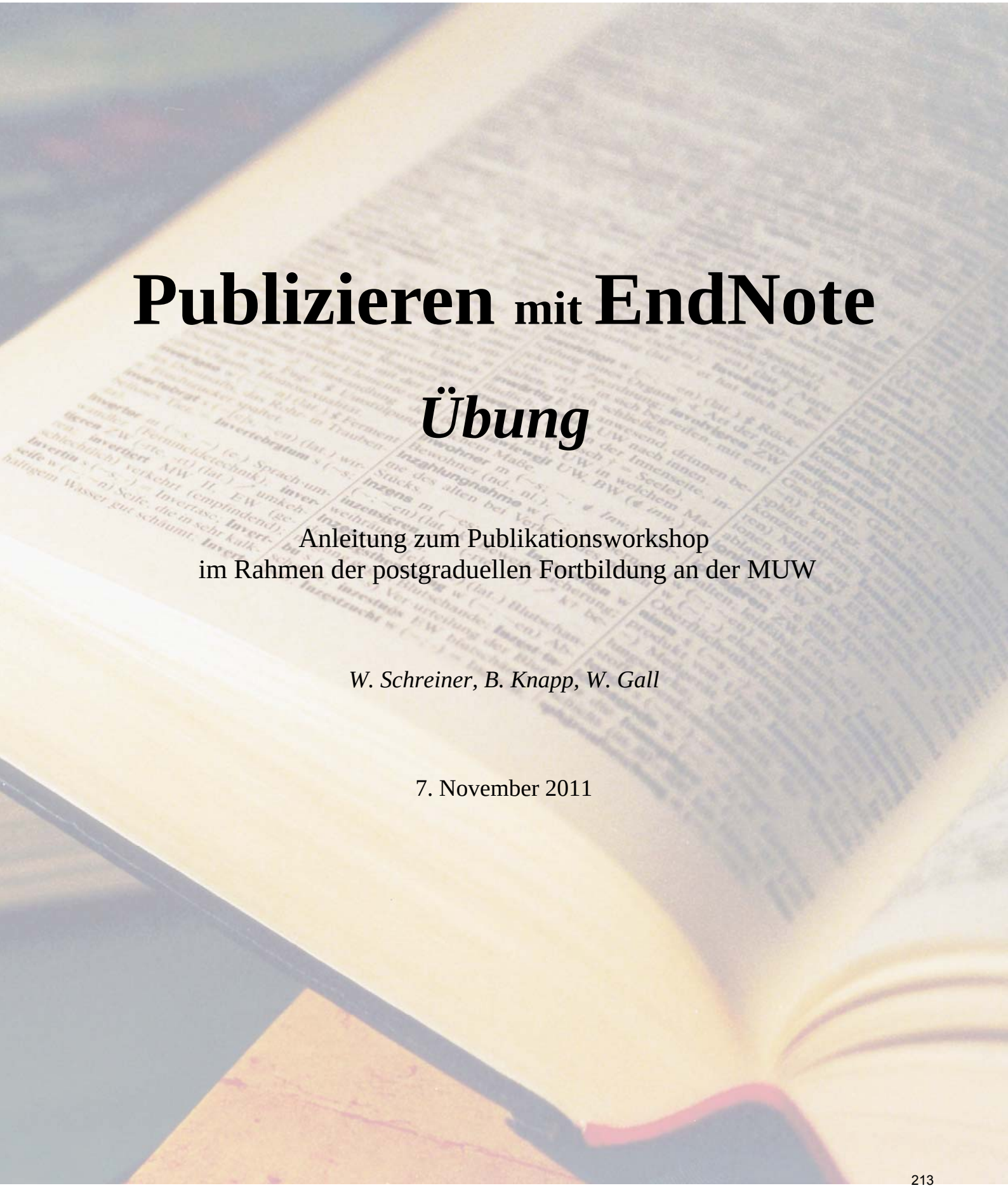
Authors should avoid duplicative publications because it damages not only their reputation, but weakens the integrity of the peer review process, and results in needless efforts by dedicated individuals who participate in the peer review process. We thank future authors for their careful consideration of these matters.

References

1. Collberg C, Kobourov S. Self-plagiarism in computer science. Commun ACM 2005; 48 (4): 88-94.
2. Miller RA, Gardner RM. Summary Recommendations for Responsible Monitoring and Regulation of Clinical Software Systems. Ann Intern Med 1997; 127 (9): 842-5.
3. Miller RA, Gardner RM. Recommendations for Responsible Monitoring and Regulation of Clinical Software Systems. J Am Med Inform Assoc 1997; 4 (6): 442-57.

Correspondence to:
Randolph A. Miller, MD
Editor-in-Chief, JAMIA
Room B003C Eskind Biomedical Library
2209 Garland Avenue
Nashville, TN 37232-8340
USA
E-mail: Randolph.A.Miller@Vanderbilt.Edu

Medizinische Universität Wien
Zentrum für
Medizinische Statistik, Informatik und Intelligente Systeme
A-1090 Wien, Spitalgasse 23



Publizieren mit EndNote

Übung

Anleitung zum Publikationsworkshop
im Rahmen der postgraduellen Fortbildung an der MUW

W. Schreiner, B. Knapp, W. Gall

7. November 2011

0. Aufgabenstellung

Für einen Journalartikel sollen sie

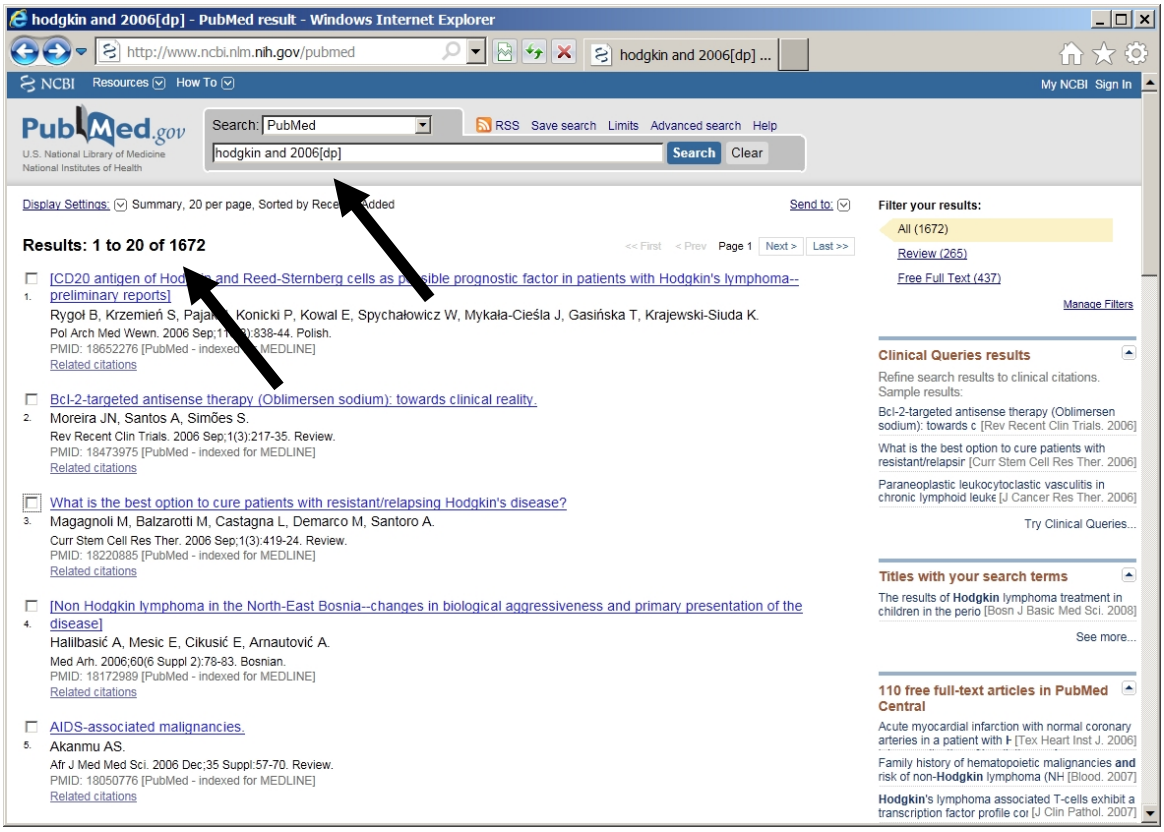
1. Literatur (bibliographische Daten) in 'Medline' suchen,
2. die Referenzen im Datenbankformat speichern,
3. die Referenzen in das Literverwaltungsprogramm 'EndNote' importieren,
4. die Referenzen im Text eines Artikels in 'Word' einfügen,
5. die Referenzliste formatieren.

1. Literatur in Medline suchen

- Starten sie PubMed (Medline) durch die Eingabe von „pubmed.gov“ im Webbrowser.

- Suchen sie Artikel mit dem Text ‘Hodgkin‘ aus dem Jahre 2006 durch die Abfrage „Hodgkin AND 2006[dp]“.
  - Bei dieser Abfrage wird der Text ‘Hodgkin‘ in allen Feldern gesucht (‘Hodgkin‘ kann im Titel, im Abstract, aber auch als Autor vorkommen). Das Filter ‘[dp]‘ schränkt hingegen die Suche nach ‘2006‘ genau auf das Feld ‘Publikationsdatum‘ ein.

- Es werden 1672 Artikel gefunden.

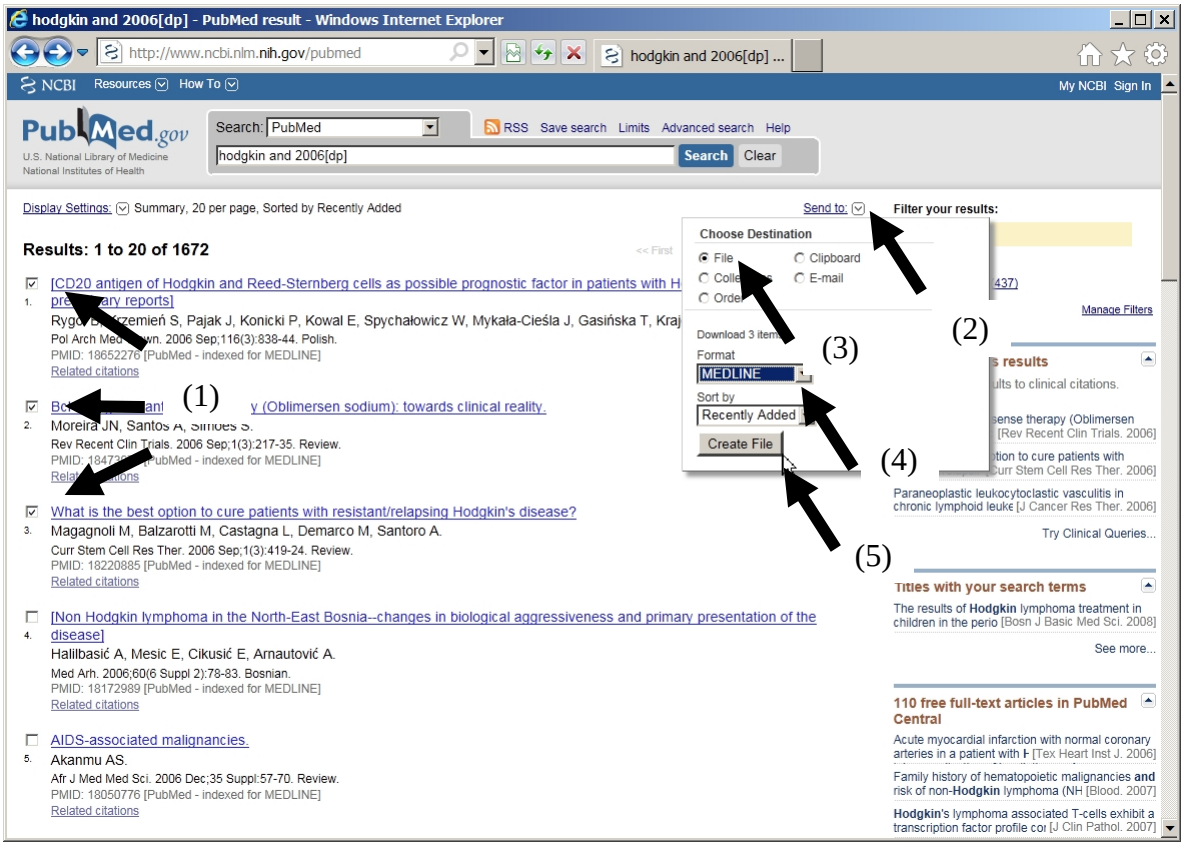


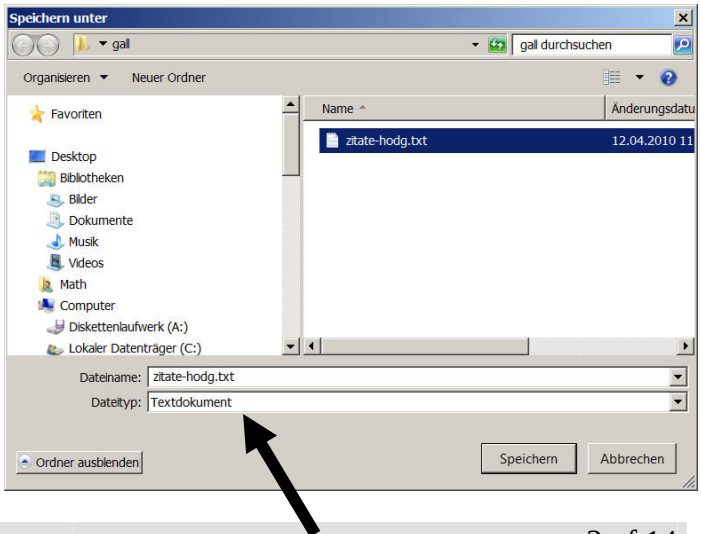
2. Referenzen im Datenbankformat abspeichern

- Erstellen sie am Desktop einen Ordner mit ihrem Namen für die zu erstellenden Übungsfiles. Löschen sie ihn bitte am Ende der Übungen.

- Markieren sie die ersten drei Referenzen (1).

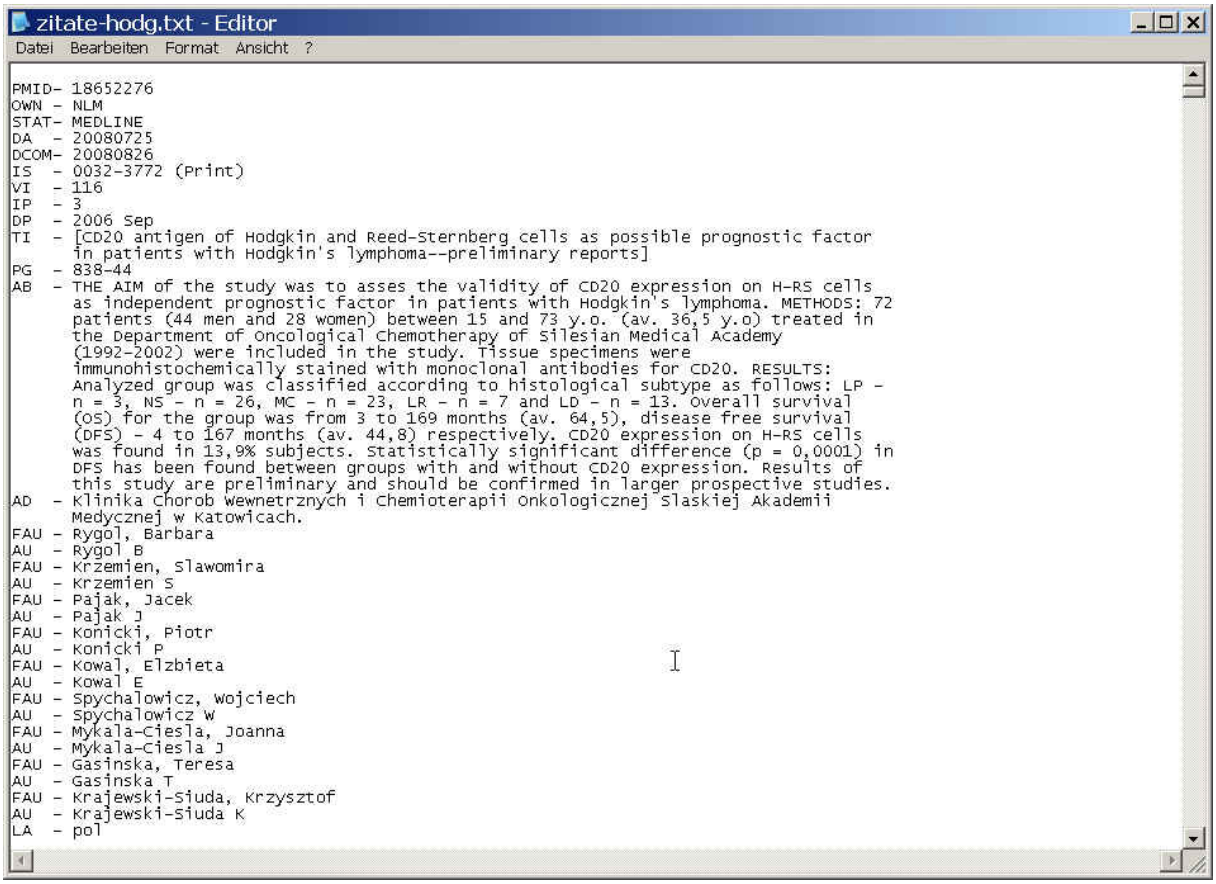
- Speichern sie die drei Referenzen mit "Send to" unter dem Namen 'zitate-hodg.txt' in ihrem Ordner ab (2).
  - Wählen sie als Destination „File“ aus (3).
  - Wählend sie als Format „Medline“ aus (4).
  - Erzeugen sie das File mit „Create File“ (5).





Überprüfen sie ob im abgespeicherten File alle drei Zitate im Datenbankformat (Format ‚Medline') vorhanden sind.

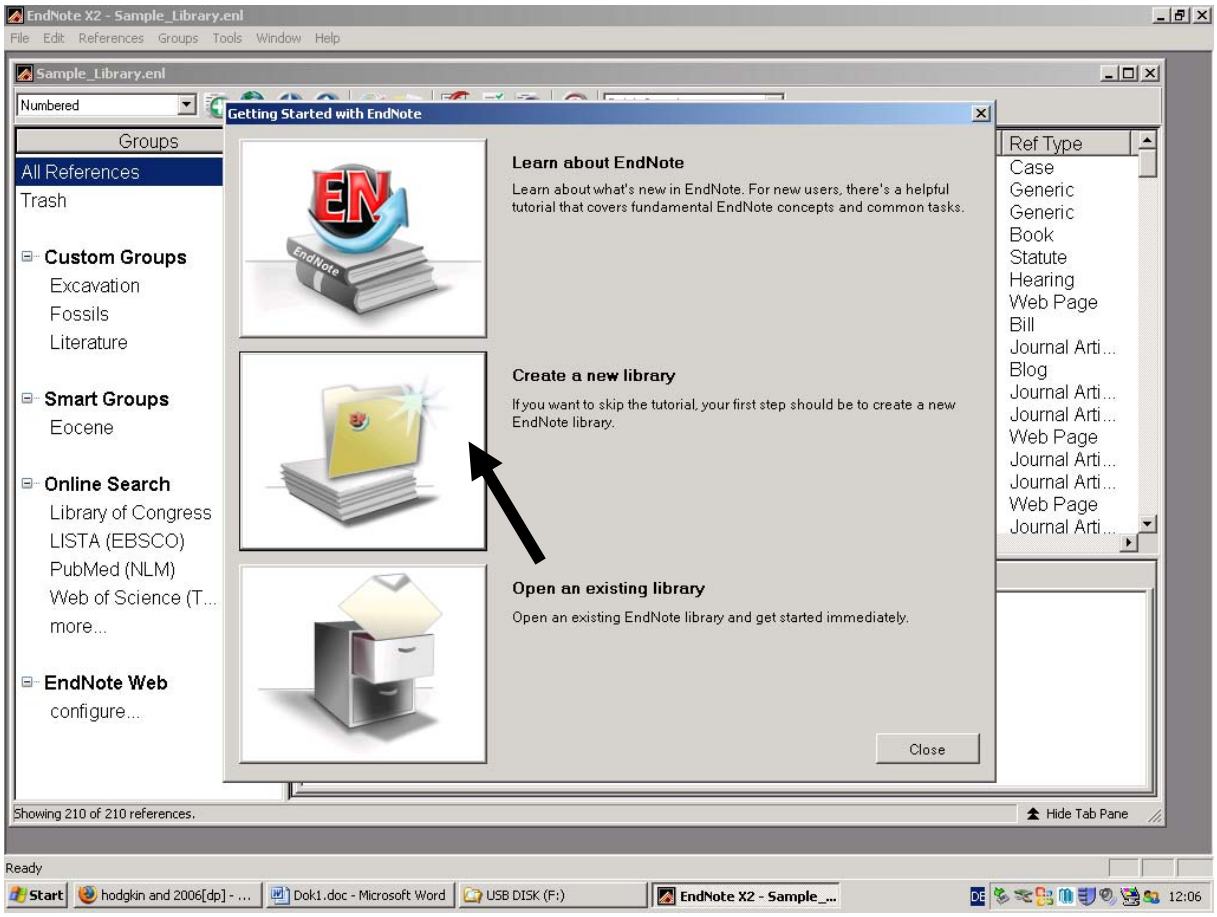
- Durch Anklicken des Files öffnet sich der Editor.
- Im Format 'Medline' sind alle Felder mit einem Kürzel gekennzeichnet und können dadurch von einem Programm automatisch identifiziert werden. Zum Beispiel 'TI' für den Titel oder ‚AB' für das Abstract.

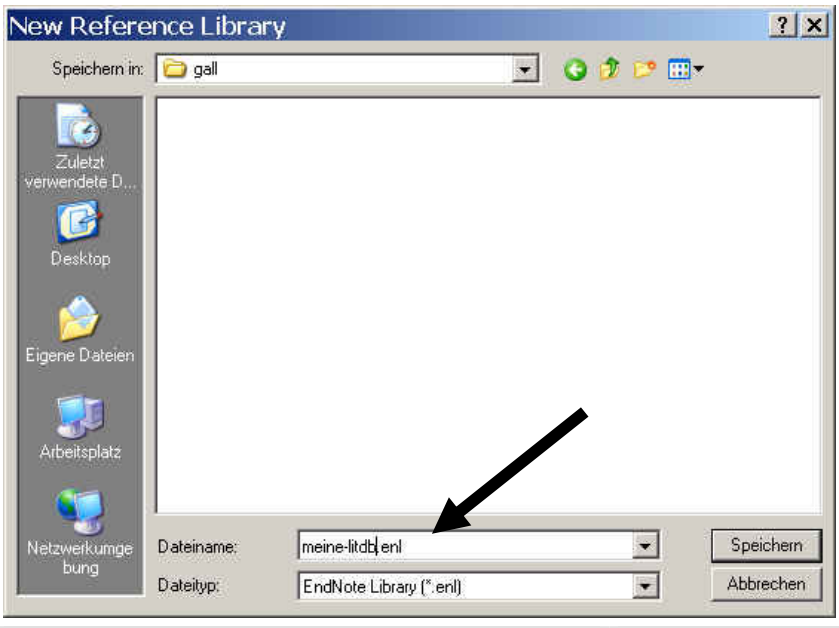


- Schließen sie anschließend den Editor wieder.

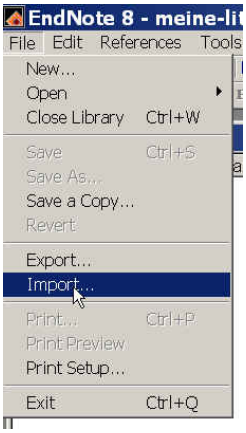
3. Referenzen in EndNote importieren

- Starten sie EndNote mit "Start" > "Alle Programme" > "EndNote" > "EndNote Programm".
- Legen sie eine neue Literaturdatenbank mit dem Namen 'meine-litdb.enl' in ihrem Ordner an. Entweder im Startdialog mit Anklicken von „Create a new Library“ oder im Hauptmenü durch "File" > "New".





➢ Importieren sie die Referenzen aus Medline in ihre Datenbank mit "File" > "Import".

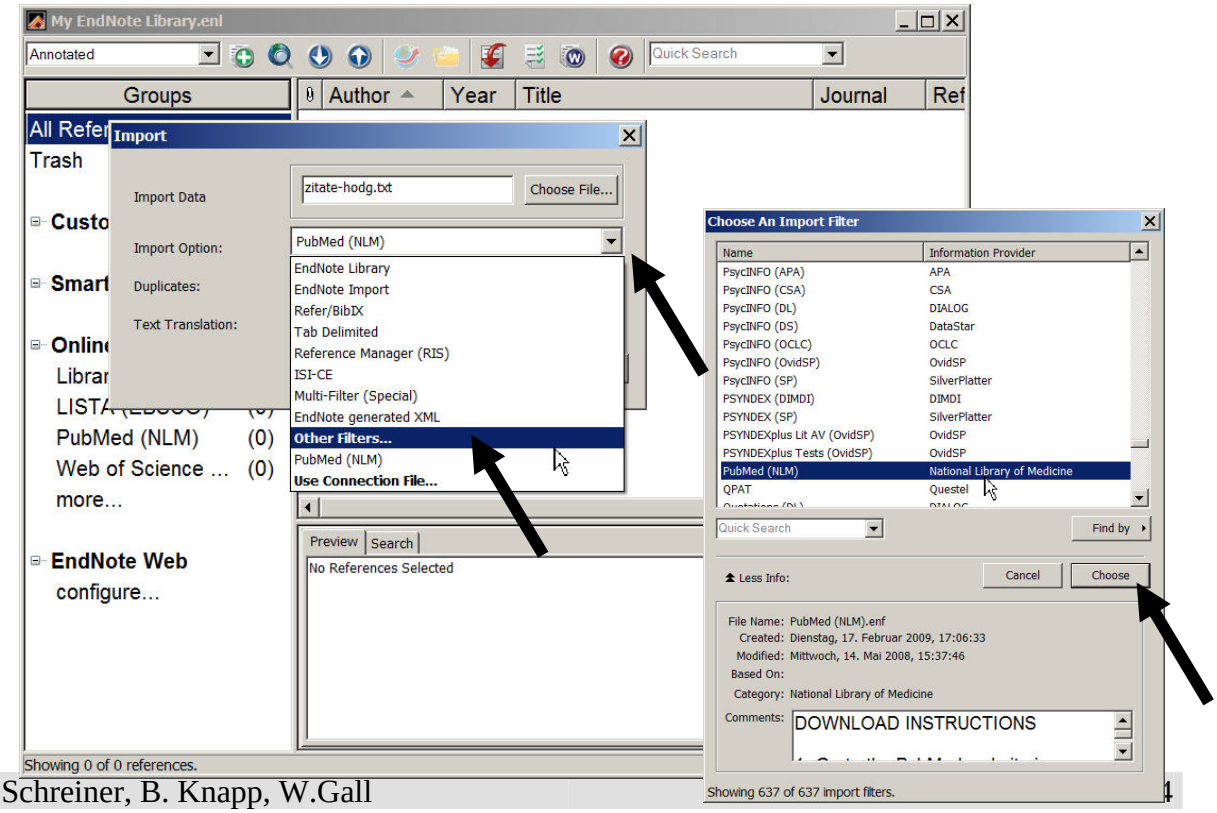


- Im Import Dialog müssen sie das zu importierende File und das entsprechende Importfilter zu der Datenbank angeben aus der sie die Referenzen exportiert haben. In unserem Fall PubMed(NLM).

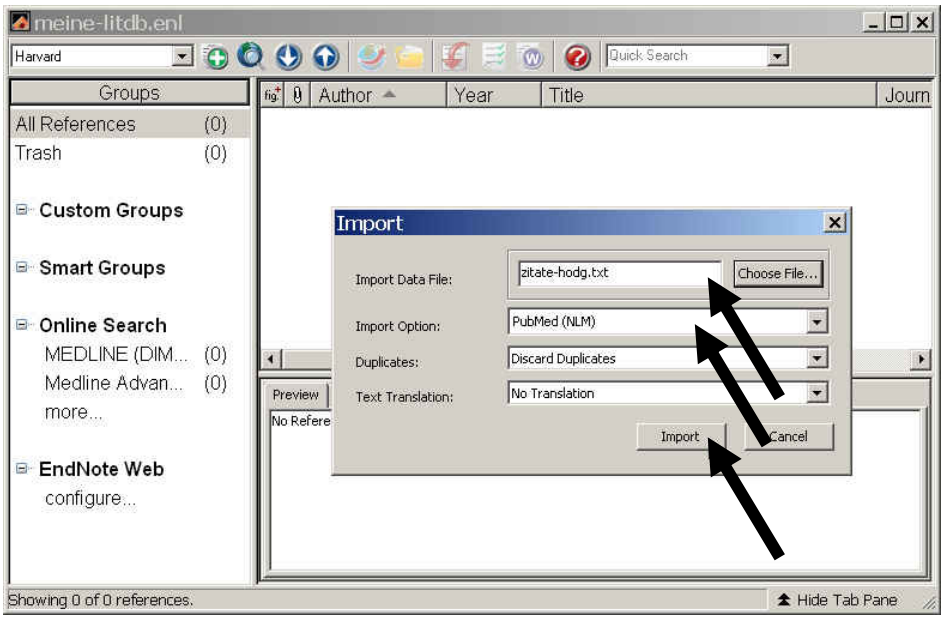
➢ Wählen sie mit der Schaltfläche "Choose File…" in ihrem Ordner das File 'zitate-hodg.txt' mit den aus Medline gespeicherten Referenzen aus und

➢ Klicken sie auf den Pfeil unter "Import Option:". Es wird eine Schnell-Auswahlliste mit voreingestellten und zuletzt verwendeten Filter angezeigt. Wählen sie das Filter "PubMed(NLM)" aus wenn es schon aufscheint.

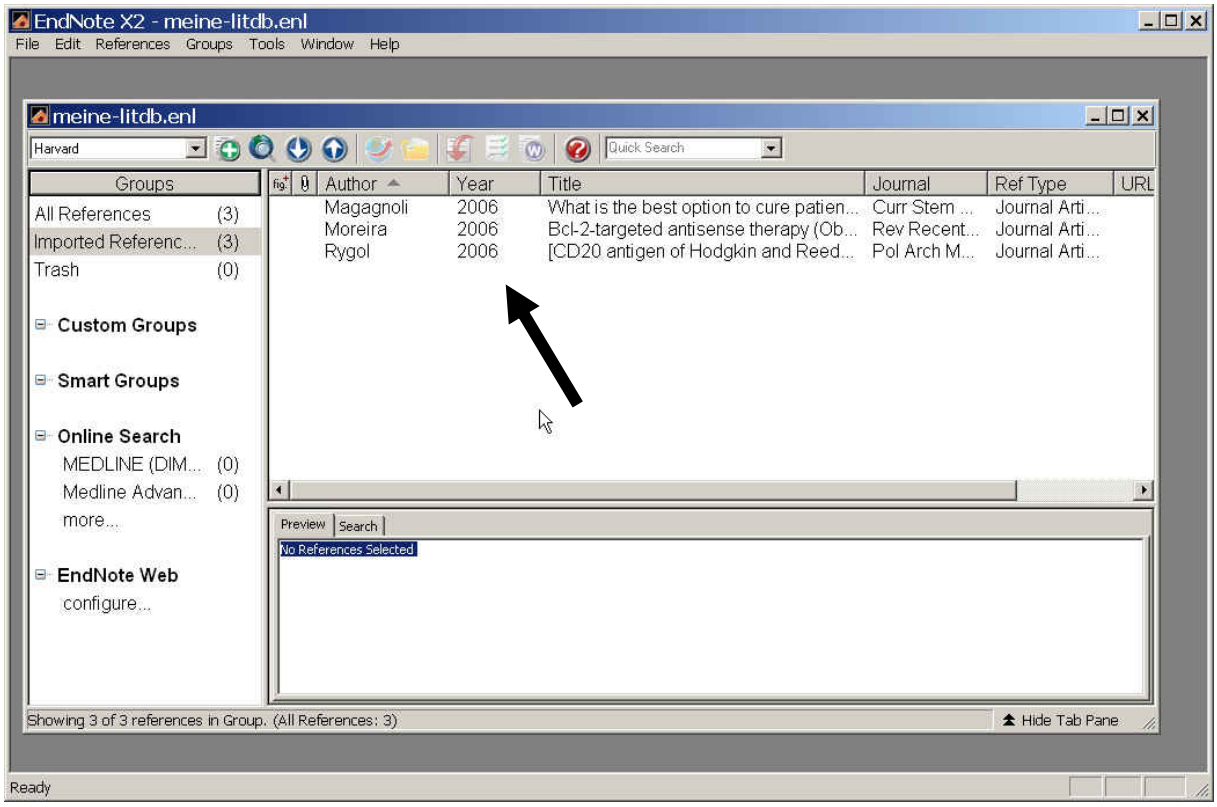
Falls dieses Filter noch nicht angezeigt wird lassen sie sich mit der Auswahl „Other Filters…“ die Liste aller Filter anzeigen, wählen aus dieser "PubMed(NLM) " aus und kehren mit der Schaltfläche "Choose" zum Dialog "Import" zurück.



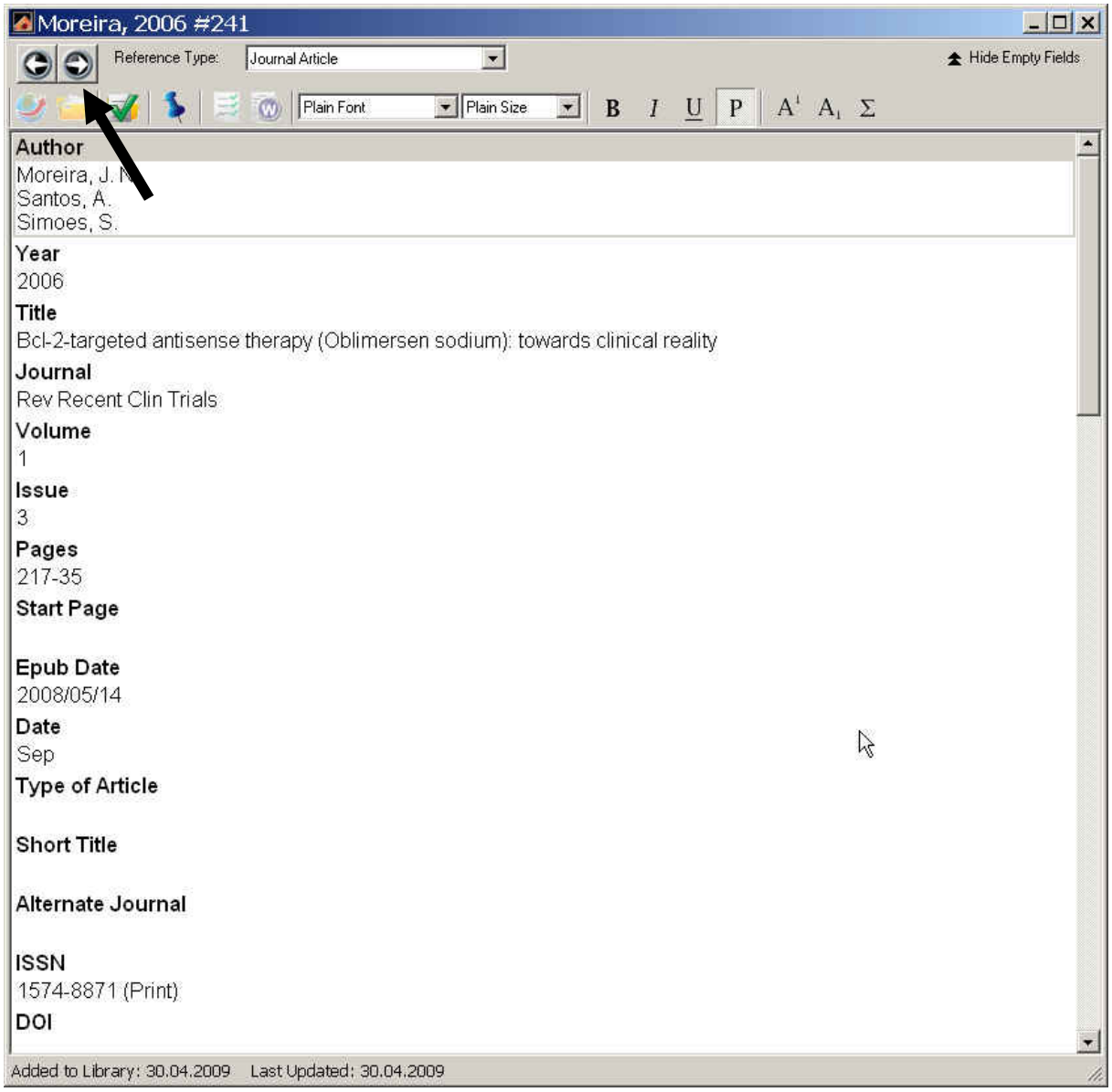
➢ Starten sie den Import durch Anklicken von "Import".



- Sie bekommen die drei importierten Referenzen angezeigt.



- Durch Anklicken einer Referenz werden alle Felder (Autor, Titel, Journal etc.) im Detail angezeigt.
- Mit den Pfeilen "Go to next reference" und "Go to previous reference" können sie durch die Referenzen blättern.



- Schließen sie das Fenster mit der Einzel-Anzeige.

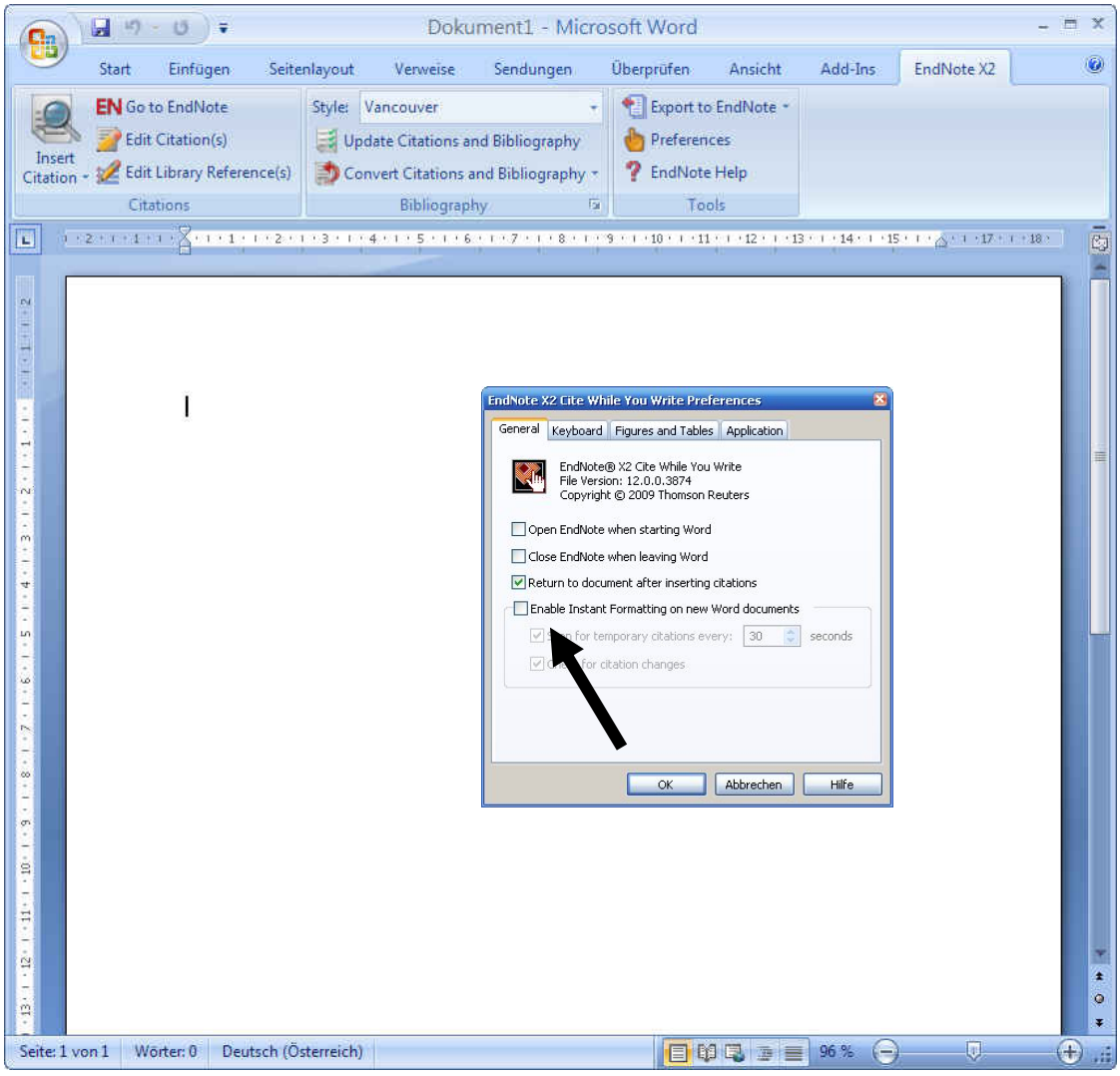
4. Zitate im Text eines Artikels einfügen

➢ Starten sie Word mit "Start" > "Microsoft Office" > "Word 2007"

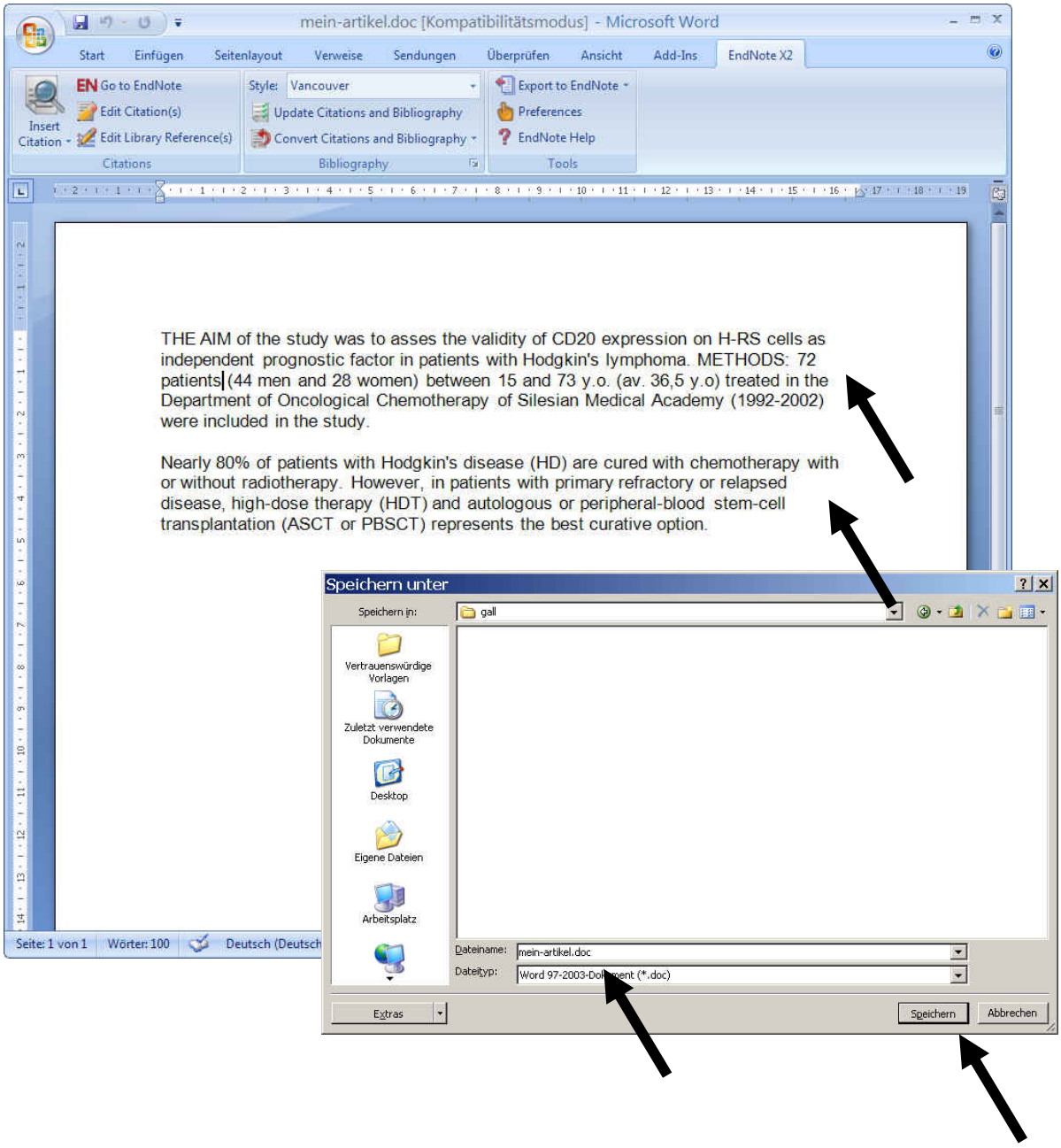
- In Word sind alle Funktionen in Verbindung mit EndNote in der Registrierkarte "EndNote X2" enthalten

- In EndNote sind alle Funktionen in Verbindung mit Word im Menü "Tools" > "Cite While You Write" enthalten.

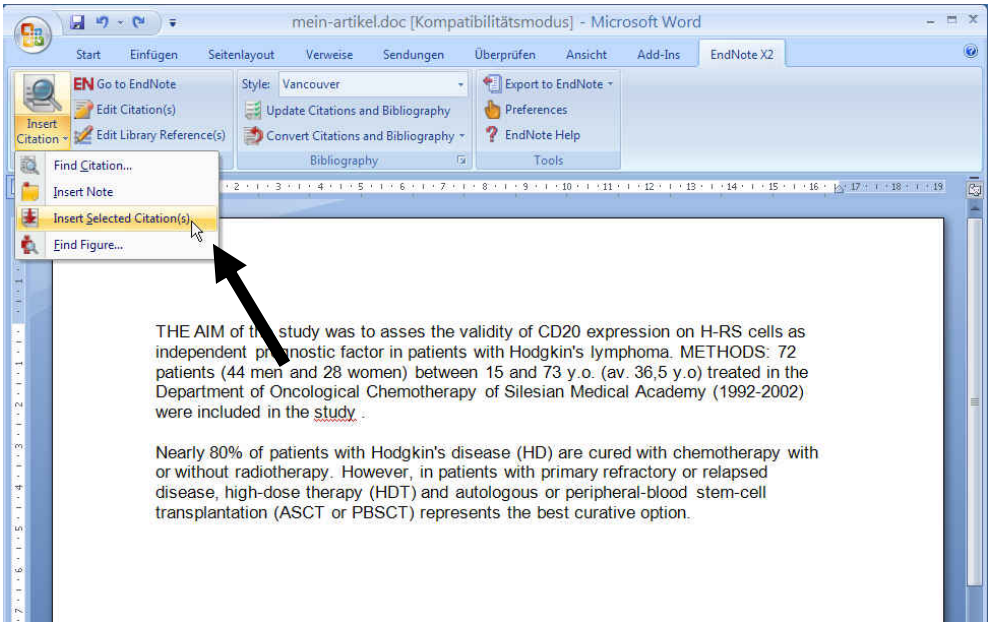
➢ Schalten sie in Word die Option “Enable Instant Formatting ..” aus um zu verhindern dass beim Einfügen des ersten Zitats die Referenzliste automatisch formatiert wird.



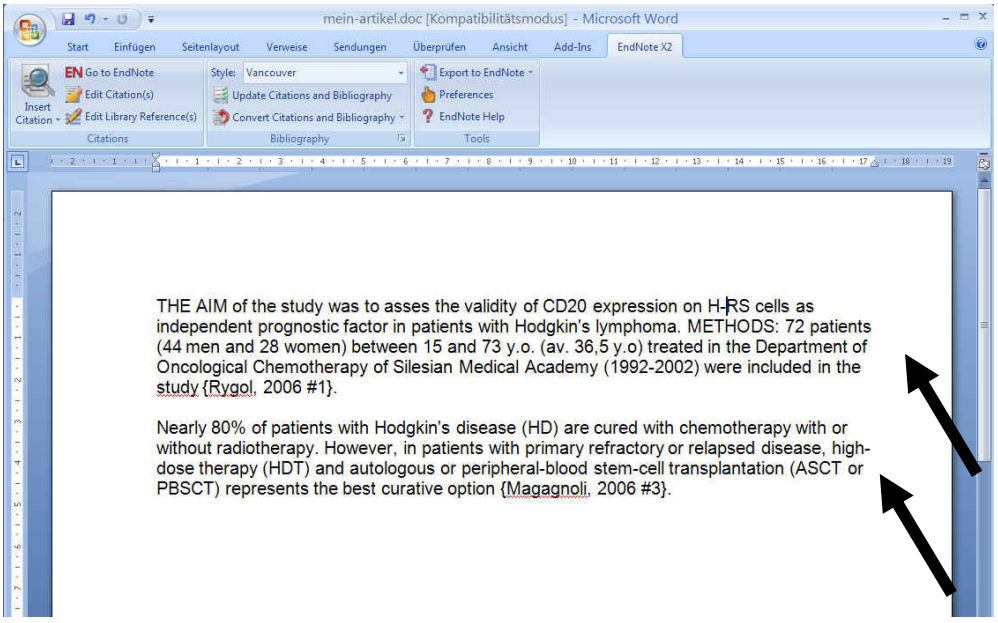
- Erzeugen sie etwas Text (2-3 Absätze) und speichern sie den Artikel in ihrem Ordner unter 'mein-artikel.doc'.



- Fügen sie nach den beiden ersten Absätzen je ein Zitat ein
- Wählen sie ein Zitat in EndNote durch einfachen Klick in der Liste aus.
- Dann klicken sie in Word auf die Stelle wo sie ein Zitat einfügen wollen (z.B. das Ende eines Absatzes).
- Dann fügen sie das Zitat ein durch Auswählen der Funktion "Insert Selected Citation(s)" des Icons „Insert Citations“ (auf der Registrierkarte "EndNote X2" in der Gruppe „Citations“).
- Fügen sie das 2. Zitat nach dem 2. Absatz ein.



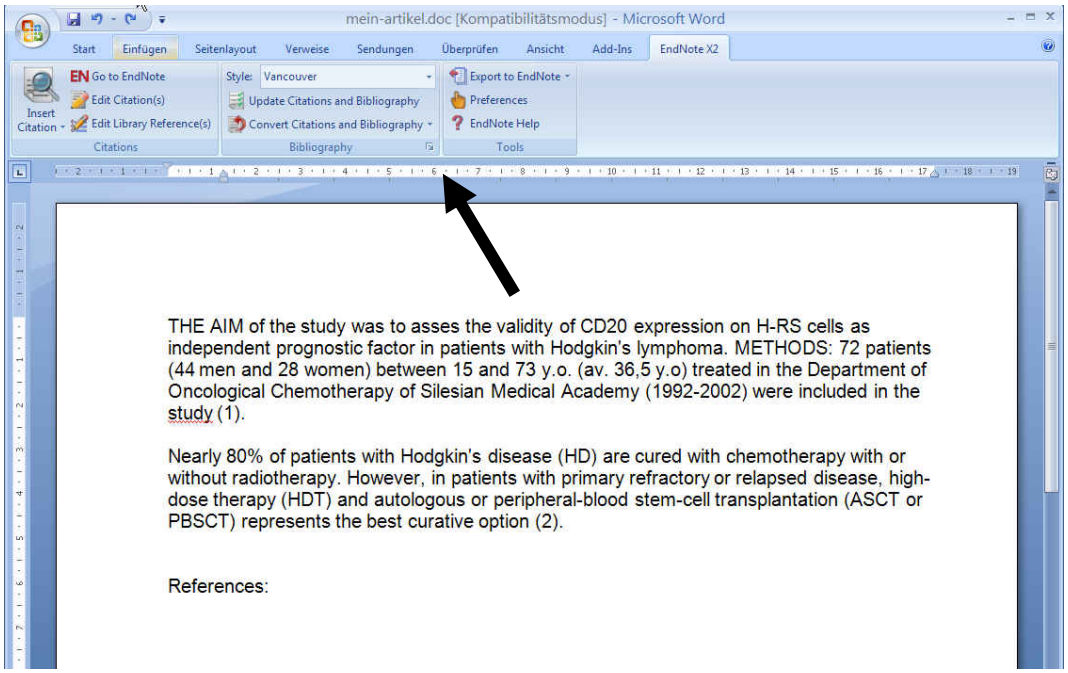
- Die beiden Referenzen werden in geschwungenen Klammern eingefügt.



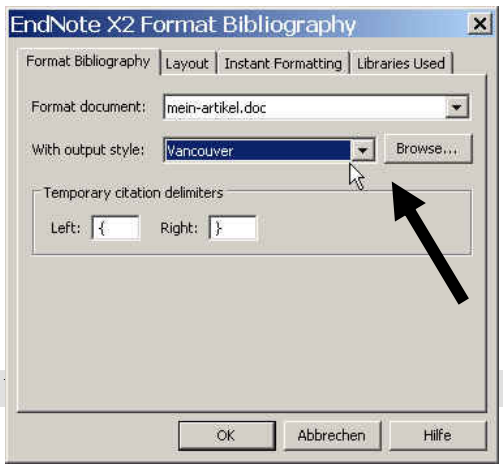
5. Referenzliste im Artikel formatieren

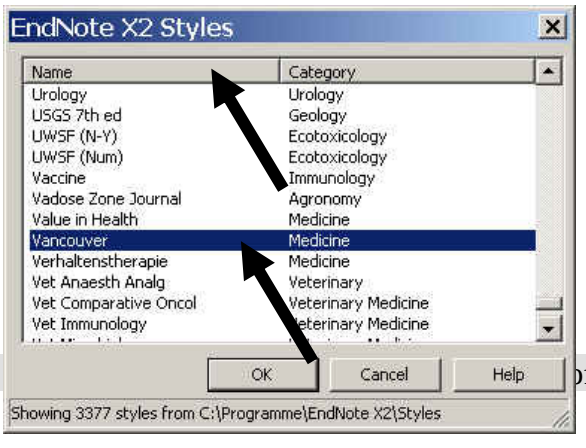
- Die Formatierung der Referenzliste hängt von den Instruktionen des Journals (der Konferenz, etc.) ab.
- In EndNote sind hunderte Formatierungsstile vorbereitet. Wir möchten die Referenzliste im häufig verwendeten Stil 'Vancouver' formatieren.

  - Fügen am Ende ihres Artikels die Überschrift 'References:' ein.
  - Klicken sie auf den kleinen Pfeil der Gruppe "Bibliography" auf der Registrierkarte "EndNote X2".

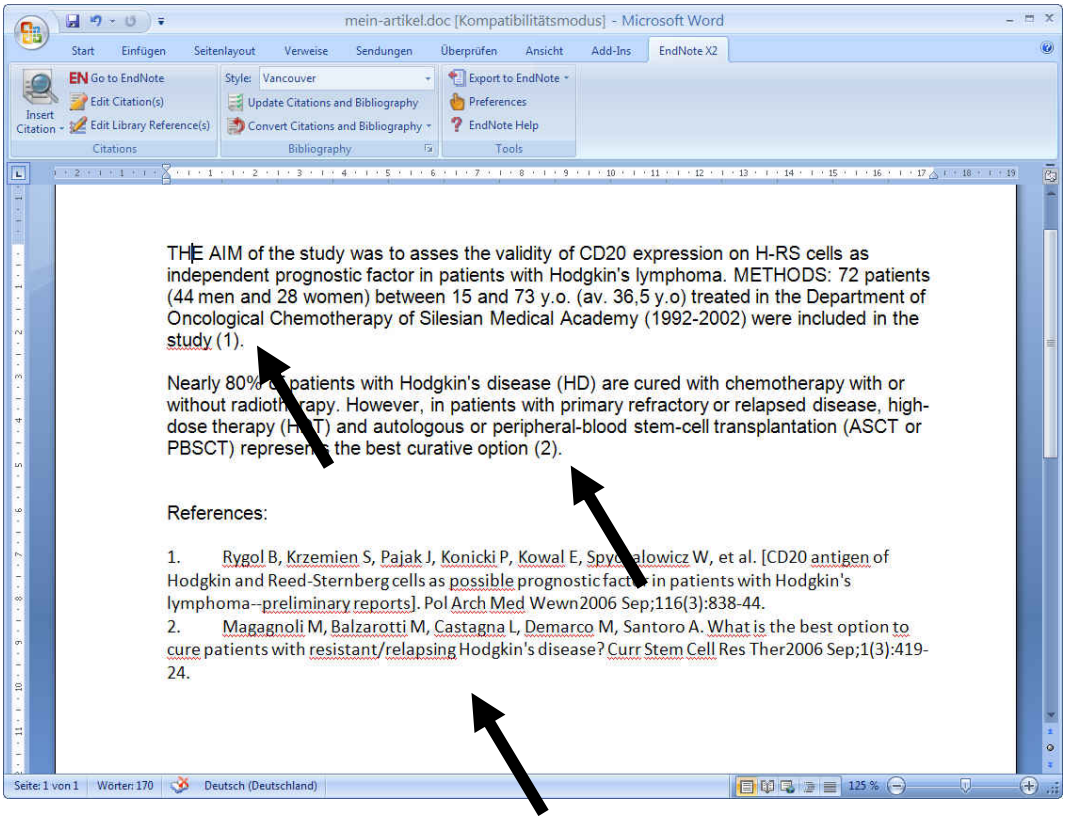


- Der Dialog 'EndNote X2 Format Bibliography' wird angezeigt. Ihr Artikel ist unter "Format-document" schon ausgewählt.
  - Durch Anklicken des Pfeils der Option "With output style:" wird analog zu den Import Filtern eine Schnellauswahlliste mit Stilen angeboten. Wählen sie den Stil 'Vancouver' aus.
    - Wenn der Stil 'Vancouver' nicht in der Schnellauswahlliste aufscheint, wählen sie ihn mit "Browse…" aus der Gesamtliste der Stile aus (sortieren der Liste durch Anklicken des Headers „Name“).
  - Klicken sie auf "OK" um den Stil auszuwählen und noch einmal „OK um die Formatierung durchzuführen.





- Sie erhalten die Referenzliste und die Zitate im Text im Stile 'Vancouver' formatiert.
  - Die Zitate im Text werden mit einer laufenden Nummer in runden Klammern formatiert.
  - Die Referenzliste enthält alle bibliographischen Details der durchnummerierten Zitate.



- Durch das Auswahlfeld „Style“ und den Funktionen „Update Citations and Bibliography“ und „Convert Citations and Bibliography“ auf der Gruppe „Bibliography“ der Registrierkarte „EndNote X2“ kann die Formatierung der Referenzliste wieder rückgängig gemacht oder in einem anderen Stil neu formatiert werden.

6. Optionale Übungen

- Formatieren sie die Referenzen ihres Artikels in einem anderen Format.
  - Verwenden sie zum Beispiel den Stil 'Harvard'.
  - Wenden sie die Funktionen "Format Bibliograpy" in Word noch einmal an und wählen den neuen Stil aus.
  - Beachten sie die Änderungen der Referenzliste als auch der Zitate im Text.

- Sehen sie sich die Beispieldatenbank von EndNote ('Sample_Library.enl') an.
  - Sie finden sie im Ordner "C:\Programme\EndNote X2\Examples\".
  - Betrachten sie die Details der verschiedenen Publikationstypen (z.B. Books, Figures).

- Holen sie Referenzen mit einer direkten Datenbank-Verbindung
  - Verbinden sie sich mit “Tools > Online Search…“ zu ‚Pubmed(NLM)‘.
  - Formulieren sie eine Anfrage.
  - Die gefundenen Referenzen werden in der Gruppe ‚Online Search - PubMed(NLM)‘ angezeigt.

- Sehen sie sich weitere Funktionen von EndNote an.
  - Sie können mehrere Datenbanken gleichzeitig öffnen.
  - Kopieren sie Referenzen aus der Beispieldatenbank durch 'Drag-and-Drop' in ihre Datenbank.
  - Suchen sie nach Referenzen mit "Tools" > "Search Library".

Unit 09:

Revising the Manuscript

REVISING the Manuscript

RECEIVING THE REVIEW:

(...and not loosing self confidence...) ☺

- reviews contain serious and objective criticism ☝
- specific references addressed in reviews often reveal the person reviewing
- reviews can be formulated in aggressive, non-polite style, making the worst possible of your work, e.g. *„This is a mediocre research paper in a field of limited interest, which is hardly alive.“* ☝☝☝☝☝

FIGURE 7-1
Don't despair when you get that rejection.

Reproduced from Martha Davis, Scientific Papers and Presentations

REVISING, Types of Actions

Classify reviewer's comments:

Check each point of reviews and decide how to react.

Affix (mnemonic) labels ☝ to reviews, classifying the reactions you plan:

T	Text change	CTR	*Comments to reviewer*
F	Figure change	A	argue against (criticism)
C	Contents change	I	ignore

Try to end up with a „revising action" in 80-90% of the reviewers' items, be it of type T, F or C. You can then state in the letter to the editor: *„we closely followed the suggestions of the reviewers and were thus able to improve the manuscript in many respects".*

REVISING, List of Actions

1) [make a list (informal notepad): „revision agenda"] ☝
2) Carry out all additional research activities necessary (measurements, evaluations, preparation of new figures, tables etc.)
3) Correction Pass: Use WORD-facilities to identify and mark changes:
   - Menü: „Extras/Änderungen nachverfolgen" ☝
   - Menü: „Einfügen/Kommentar"

   Manche Journals (z.B. AJP) verlangen Korrekturen im Änderungsmode
4) Write list of changes performed (describe your reaction to the reviewers in your letter to the editor) ☝
5) final formatting in WORD (falls nicht im Änderungsmode verlangt):
   - „Alle Änderungen annehmen"
   - Kommentare löschen
6) Letter to the Editor (...praising how useful the changes were...) ☝

How to deal with reviewers: Example 1

"The problem of this paper is that its content is shallow. I believe it can be published in some form, also because the authors were able to present it properly, but I doubt whether it deserves [..] a journal as this one. [..]

On the other hand, though it is more about a small technical achievement rather than a noteworthy scientific advance, publication in this journal would not be totally inappropriate either, as the presented plug-in is useful, and the paper may be cited several times by people who use it."

We fully agree with the reviewer. Although, in this paper no huge scientific jump is described we think that publishing this paper in the [redacted] would be a benefit for the journal and the community since this plug-in makes research in molecular dynamics astonishing easier (as we could observe in our own lab). Therefore we do not want to withhold the plug-in from the scientific community and publication in a well known Journal as the [redacted] will make it visible to a broader audience.

How to deal with reviewers: Example 2

"As an alternative to resorting to a lower impact journal if this manuscript will be turned down by the editor, the authors could present their plug-in together with a new scientific result where the plug-in was an important tool. [..]
Historically, some notable advances in simulation technique (which this is not) where presented in an appendix to a paper with a different primary focus;"

Fortunately, the manuscript was seen as appropriate for the [redacted]. Therefore we refer here to our discussion above why we think it is worth publishing the manuscript in this journal.

How to deal with reviewers: Example 3

"[..] The MD simulations are expertly conducted; nevertheless the MD data is suggestive - and by no means definitive [..]"

We understand the reviewer's concerns about computer simulations and want to point out that …

How to deal with reviewers: Example 4

"Add the time necessary to compute the trajectories while doing an on-the-fly analysis (at least for step size 1), and add the size of at least one of the trajectories on disk (the size of the others result from the number of atoms and the step size). Giving this extra time information is relevant for the objection on the possible superiority of on-the-fly analyses for large systems. The authors should demonstrate their statement that their plug-in helps to save CPU time (see e.g. the last sentence of the last section) by showing how much analysing a precomputed trajectory is faster than analysing it on the fly while GROMACS computes it; of course the speed will increase with the step size used for the analysis, but now we do not know this figure even for a single step size for the case of an on-the-fly analysis."

We suppose that our statements on runtime issues/comparisons have been misleading, therefore we understand the reviewer's concern to attach performance figures for the on-the-fly-analysis. However, we would like to point out, that vmdICE doesn't mean to compete with on-the-fly analysis regarding runtime. The aim of vmdICE is explorative graphical analysis prior to full numerical evaluations. CPU time is saved since not all (potentially not interesting) areas are investigated if the trajectory is inspected with vmdICE first. Therefore, a runtime comparison between Gromacs and vmdICE would not be in the sense of the reader. If one evaluates the whole trajectory in detail he will clearly be faster using Gromacs (e.g. about 2.8 times for SASA), however if one pre-inspects the trajectory with vmdICE (using a big time step) then he will get a rough impression of the trajectory and hints which parts are potentially interesting for detailed evaluation. These evaluations are then performed with Gromacs. The amount of time saved depends mainly on the decisions of the user which parts he wants to evaluate in detail and is therefore very subjective. We try to point this out in the discussion in a more elaborative way now. Hence, we thank the reviewer that we can clarify this now to avoid any confusion for the readers.

How to deal with reviewers: Example 5

"number of peptides studied is insufficient to support the conclusions. Please consider a rewrite of the paper that presents the research results without making the unsupported claims. [..]
The main weakness to this report is that the correlation observed is based on just three data points (three different peptides) and a qualitative rank order correlation. From three quantitative data points, six different rank orders are possible (3!). Thus, the matching of rank orders would occur by chance ~17% of the time. Thus, even if a set of characteristics are truly independent, if enough characteristics are assessed a rank correlation can be found 1 out of every 6 times."

We think that even the descriptive data presented in this study (without predictions for other peptides) may be of great interest to the field. The idea that the conformation and spatial dynamics of the pMHC interface may contribute to immunogenicity may trigger a lot of further research and responses on this topic. Therefore, we toned the language of our manuscript down and we hope that the editor will agree with this.

REVISING: Final Checks and Benefit

The revised version: Was it worth while?

- more contents (results, methods ☝ ☝)
- clearer thread of thought?
- additional (side) aspects treated/discussed? ☝
- important references added? (confirming, contradictory)
- limitations ☝ and underlying assumptions discussed, which were formerly neglected
- More ideas for coming work?

Some reviewers provide very detailed suggestions.....

20 APR 1998

Define shear stress as the force per unit area between adjacent moving lamina of a viscous fluid:

$$S = \frac{F}{A} = \eta \frac{dv}{dx} \qquad (1)$$

where $\frac{dv}{dx}$ = velocity gradient
F = resisting force
A = area

Assuming Poiseuille's law, the velocity gradient at the vessel wall is:

$$\frac{dv}{dx} = \frac{4\bar{v}}{r} \qquad (2)$$

where $\bar{v}$ = average linear velocity of flow

Since $Q = \pi r^2 \bar{v}$, $\bar{v} = \frac{Q}{\pi r^2}$ (3)

Substitute (3) into (2) and (2) into (1), yielding: $S = \frac{4\eta Q}{\pi r^3}$ equation 2, page 5

Referring to Poiseuille's law: $Q = \frac{\pi r^4 \Delta p}{8 \eta L}$

where Δp = pressure difference
L = length of segment

and substituting for Q in equation 2 yields:

$$S = \frac{4\eta Q}{\pi r^3} = \frac{r \Delta p}{2L}$$

This second expression for the vessel wall shear stress is important

(see reverse side)

Assuming viscosity is constant (viscosity does vary with shear stress on blood, and in small vessels),
then shear stress varies only because velocity gradient varies (1)
Velocity gradient varies as flow (expressed as Q or $\bar{v}$) or radius varies (2)
Velocity gradient varies also with radial position in a segment, being maximum ($\frac{4\bar{v}}{r}$) at the vessel wall and zero at the vessel center.

$$\dot{\gamma} = \frac{4Q}{\pi r^3} = \frac{4}{\pi r^3} \frac{\pi r^4 \Delta p}{8 \eta L} = \frac{r \Delta p}{2 \eta L}$$

University of Vienna

Department of Medical Computer Sciences

A-1090 Vienna, Spitalgasse 23/Austria

phone: (+43)(1) 40400-6678
(+43)(1) 40400-1639
fax: (+43)(1) 40400-6667
(+43)(1) 40400-6677
e-mail: imc@akh-wien.ac.at
DVR-Nr. 0509477/0065528

Beschwerde über einen Review

Prof. L. Wolpert
c/o Academic Press Editorial Office
10D St Edwards Passage
Cambridge, CB2 3PJ
United Kingdom

Vienna, July 29, 2001

Dear Prof. Wolpert!

Regarding the manuscript „Shear Stress Distribution....“ submitted to the Journal of Theoretical Biology I thank you for informing me about the referee’s opinion.

The quality of his review is in my opinion very poor, however. To me his statements are only understandable under the assumption that he expected a hydrodynamic simulation, which the present paper is not about. Also it is rather strange to hear that computer simulations are considered irrelevant (1st paragraph). This is only understandable in the light of another general idea expressed, namely that any kind of simplification introduced in a model makes the model all in all meaningless.

As a matter of fact, models can either represent a few (say 5 or so) vascular segments and their bifurcations realistically and simulate „full hydrodynamics“, thereby disregarding the (major) rest of the vascular tree. Or else, a larger number of segments is considered while each segment is treated in less detail (as done in fractal models and in the CCO approach). Introducing e.g. details of the 3-dimensional shape of bifurcations for several thousand segments is far beyond the capacity of any computers at hand: All segments in full detail would represent reality itself.

Among the multi branch models, I think that the CCO approach is not the most unsophisticated one, in particular regarding the fact that very realistic structures are derived from first principles. We consider this an achievement rather than a drawback (as indicated in 2nd paragraph).

All in all I regret having to comment negatively on this particular review, even more so since for all our preceding papers in the JTB we received reviews which really helped to improve our

manuscripts, which we did and were grateful for. May I ask you to give us a short comment on how to proceed with the present manuscript, in particular if it is possible to obtain a second opinion.

Yours sincerely,

Wolfgang Schreiner, PhD, FACA
Professor of Medical Informatics

How to digest bad reviews

on JTB97/091

REVIEWER #:

Title: **Shear Stress Distribution in Arterial Tree Models Generated by Constrained Constructive Optimization**

Authors: **W Schreiner, F Neumann, R Karch, M Neumann, S M Roedler and A End**

COMMENTS: I HAVE TO SAY THAT I DO NOT VIEW THIS PAPER AS COMING UP TO J. THEOR. BIOL.'S NORMALLY HIGH STANDARDS. THE EDITORS ASK REFEREES TO BE WARY OF 'PURELY SPECULATIVE SUGGESTIONS'; AND, ON THAT BASIS, I PERSONALLY FEEL VERY DOUBTFUL ABOUT THIS PAPER.

FIRST OF ALL, I HAVE DOUBTS ABOUT THE BIOLOGICA RELEVANCE OF COMPUTER 'SIMULATIONS' OF VASCULAR TREES, OF K WHICH ARE UNINFLUENCED BY ANATOMICAL INFORMATION OR DATA FROM DEVELOPMENTAL BIOLOGY.

SECONDLY, I FIND THE OPENING SENTENCE OF THE INTRODUCTION WHOLLY UNCONVINCING. IF ALL OF THE AUTHORS' WORK INVOLVED IN (SO-CALLED) 'GENERATION' OF (HYPOTHETICAL) VASCULAR TREES IS MEANT TO UNDERPIN 'SIMULATIONS OF HEMODYNAMIC PHENOMENA' THEN WHY DO THEY SO DRASTICALLY

"ON HOW TO DIGEST REVIEWER'S COMMENTS"

REVIEWER 1:

However, I was drawn into reading it nevertheless, and wish to report that I found it an interesting paper worthy of publication. It demonstrates the power and utility of the computer in modeling blood flow in arterial trees, and in developing thereby greater theoretical insight into the functional geometry of the cardiovascular system.

Subject: **Re: JTB97/091**
Date: Wed, 29 Apr 1998 11:20:30 -0400
From: [redacted]
To: Wolfgang Schreiner <Wolfgang.Schreiner@akh-wien.ac.at>

Dear Professor Schreiner letter to urge review

Re : JTB97/091

Thank you for your email.

I am afraid that your manuscript is still undergoing review. So far we have received two reports from our referees and I have been in contact with the third reviewer and he should send his comments within the next few days. Please be ensured that I will inform you of Professor [redacted] decision as soon as possible.

With best wishes
[redacted]

From: Wolfgang Schreiner Wolfgang.Schreiner@akh-wien.ac.at AT ~internet on 28/04/98 10:35 EDT

To: [redacted]
cc: [redacted]
Subject: JTB97/091

Dear [redacted]

Re: JTB97/091

Thank you for your e-mail dated 11 Feb 98. Since quite a long time has elapsed since our paper was sent to be reviewed, I would like to ask you about the present state of decision.

Yours sincerely

W. Schreiner
--
Univ.Prof. Dr. Wolfgang Schreiner
Department of Medical Computer Sciences
University of Vienna, General Hospital
Spitalgasse 23
A-1090 Wien / AUSTRIA

phone: (+43) 1 40400-6679
fax: (+43) 1 40400-6677

University of Vienna
Department of Medical Computer Sciences
A-1090 Vienna, Spitalgasse 23/Austria

phone: (+43)(1) 40400-6678
(+43)(1) 40400-1639
fax: (+43)(1) 40400-6667
(+43)(1) 40400-6677
e-mail: imc@akh-wien.ac.at
DVR-Nr. 0509477/0065528

Thanks for Review and ask for more time to reassess the work

[redacted]

Vienna, 28/03/2001

Dear Professor [redacted]

Re: Manuscript reference number JTB97/091

thank you very much for having our manuscript reviewed. The comments of the reviewers are very substantial and hit key issues of our work. It will take some time to re-assess parts of our work and change the manuscript accordingly. We are looking forward to submit an improved version within three months.

Yours sincerely,

Wolfgang Schreiner, PhD
Professor of Medical Informatics

most important to emphasize that this possibility of scaling flows does neither depend on the particular connective structure (topology) nor on the particular geometry (segment coordinates) of the tree.

CCO TREES RESCALED FOR SHEAR RATE

In the present work we shall add the "adaptation to a given value of shear rate" as one additional type of scaling to the CCO procedure as follows:

The shear rate (i.e. the velocity gradient) between a fluid and the wall of segment i (cylindrical tube) is given by (Fung, 1984; Milnor, 1989)†

$$\dot{\gamma}_i = \frac{4}{\pi} \cdot \frac{Q_i}{r_i^3} \tag{2}$$

and thus only depends on the flow Q[m^3 s^{-1}] and the radius r_i [m]. First we note that a cons[t] factor c multiplied into *all* radii of a C[C] has the following consequences:

1. it does *not* change relative r[adii] ...lore does *not* change the relati[ve]
2. it does *not* change r[elative] ...ents, neither across single segm[ents] ... the whole tree;
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$$r_i^* = c \cdot r_i \tag{3}$$

change i[n] ...flow into the tree [Poiseuille's law for consta[nt] viscosity (Fung, 1984)], if the overall pressure gradient Δp is kept constant. As opposed to that, in order to keep the flow unchanged and adapted to the value preset according to physiological data, the overall pressure gradient has to be rescaled ($\Delta p \rightarrow \Delta p^*$) according to

$$\frac{\Delta p^*}{\Delta p} = \left(\frac{r_i}{r_i^*}\right)^4 = c^{-4} \tag{4}$$

Note that *relative* pressure gradients within the tree remain unaffected by this procedure;

4. as a consequence of changes in radii and pressure gradient (at constant flows) the shear rate in all segments changes according to

$$\frac{\dot{\gamma}_i^*}{\dot{\gamma}_i} = \left(\frac{r_i}{r_i^*}\right)^3 = c^{-3} \tag{5}$$

This dependency can be used to select the pressure gradient (e.g. via selecting p_{term}) such that the shear rate in a deliberat[e] segment of the tree assumes a desired val[ue] ...cifically, one can select the p_{term} such [that] ... rate in the root segment assum[es] ...mpatible with experimental da[ta]

$$\frac{\Delta p^*}{\Delta p} = \left(\frac{\dot{\gamma}_{root}^*}{\dot{\gamma}_{root}}\right)^{\frac{4}{3}} \tag{6}$$

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STEPWISE GROWING OF THE TREE

The first step in each lap of adding a new terminal is tossing for its location within a perfusion area representing the piece of tissue in question. Locations are accepted only if they are not too close to any of the pre-existing segments, thereby imitating an enforced vascularization of

*In the scientific literature the symbol γ[dimensionless] is widely used for the bifurcation exponent and $\dot{\gamma}$[s^{-1}] is used for the shear rate. In order to keep notation compatible we stick to these conventions and hope not to cause confusion. In the present context γ is a constant and $\dot{\gamma}$ *is not* its time derivative.

new method for rescaling introduced

added due to comments of reviewers

however, is the shear stress τ_i[N m^{-2}] induced by the viscous friction (Fung, 1984; Milnor, 1989) due to blood viscosity η[Pa·s]:

$$\tau_i = \frac{4\eta \cdot Q_i}{\pi \cdot r_i^3} = \eta \cdot \dot{\gamma}_i \qquad (11)$$

Assuming viscosity to be constant, shear stress is simply proportional to shear rate. The CCO algorithm implicitly has to make this assumption, since it is in fact a mandatory prerequisite for scaling any given tree to meet the CCO constraints. However, we know that blood viscosity is larger at low shear rates, and gradually declines to a limiting value ($\eta_\infty \approx 0.0036$ Pa·s) for shear rates above 700–1000 s^{-1} (Lipowsky *et al.*, 1980; Lipowsky & Zweifach, 1977). Therefore, proportionality between shear stress and shear rate prevails only at high shear rates and is impaired at low shear rates. In order to evaluate the consequences for CCO trees, we computed the changes in key quantities affected (viscosity, shear stress and radii) over the frequency distribution of shear rates, as shown in Fig. 3 for the reference tree.

RESCALING CCO TREES FOR SHEAR-RATE-DEPENDENT VISCOSITY

Within the reference tree generated by CCO under "shear-rate scaling" (see above) shear rates can be computed exactly (solid bars in Fig. 3). Over a log-abscissa, the distribution appears close to normal which is also confirmed by the normal probability plot. Values of shear rate range approximately between ($10^2 =$) 100 and ($10^{3.5} \approx$) 3200 s^{-1}. Across this interval we have to consider a decline in viscosity from approximately 0.0051 to 0.0038 Pa·s, as shown by the solid line in Fig. 3. Values of viscosity (η) have been represented by a regression vs. shear rate ($\dot{\gamma}$)

$$\eta = \eta_\infty + a \cdot (\dot{\gamma})^b \qquad (12)$$

taken from the literature (Lipowsky *et al.*, 1980; Lipowsky & Zweifach, 1977), yielding $a = 0.0236 \pm 0.007$ and $b = -0.591 \pm 0.014$. If we would insert η depending on shear rate into Poiseuille's law for segment i

$$Q_i = \frac{\pi}{8\eta_i} \cdot \frac{r_i^4}{l_i} \cdot \Delta p_i \qquad (13)$$

we would get flow values smaller than those obtained under CCO scaling of radii, where the smaller value $\eta_\infty = 0.0036$ Pa·s $< \eta_i$ was used. Since different segments experience different shear rates, changes in η and flow would be different for individual segments of the tree. As a consequence, there cannot be any such universal factor by which one could rescale (radii of) a CCO tree in order to compensate for shear-rate-dependent viscosity and still comply with the constraints.

However, we can present a method to rescale CCO trees for shear-rate-dependent η on a segment-individual basis as follows:

for each individual segment we require Δp_i and Q_i to remain constant and unaffected by rescaling, and thus automatically fulfil the original CCO boundary conditions for pressures and flows. This implies—according to eqn (13)—that the desired process of rescaling radii must be designed such that for each individual segment

$$\frac{\eta}{r^4} = \text{const.} = \frac{\eta_\infty}{r_\infty^4} \qquad (14)$$

where r_∞ is the segment radius originally adopted by CCO under the assumption of constant $\eta \approx \eta_\infty$. However, the new pair of (η,r) we are looking for, must not only yield the correct flow [i.e. fulfil eqn (13)] but also be consistent in that

new approximation method developed

$$\eta_\infty \left[1 - \left(\frac{r}{r_\infty}\right)^4\right] + a\left(\frac{4Q}{\pi \cdot r^3}\right)^b = 0 \qquad (15)$$

It can be solved iteratively [e.g. by a gradient method (Press *et al.*, 1992)] and yields a new segment radius from which "consistent" values for shear rate and viscosity can be computed, with flow and pressure gradient remaining constant. However, these radii no longer fulfil the bifurcation constraint [eqn (9)].

Performing this procedure for all segments of the reference tree shows that relative changes of η and $\dot{\gamma}$ lie on straight lines in a double-log plot

Given a tree with only one bifurcation located (at the center of the dashed circle) so that both daughters have equal lengths ($l_1^* = l_2^*$), see the hatched segments in Fig. 2. Since both terminals have to carry equal flows ($Q_1 = Q_2 = Q_{term}$) across equal pressure gradients ($p_{bif} - p_{term}$), it follows that $r_1^* = r_2^*$. Evidently, such a symmetric bifurcation exhibits uniform shear rates in all three segments (provided that $\gamma = 3$). Now suppose we move (for example in order to optimize) the bifurcation to a different location (shown in solid fill) and rescale radii to re-establish the constraints in CCO-like manner. The resulting segment lengths will in general b unequal, e.g. $l_1 > l_2$. To maintain equal fl radii have to compensate, yielding $r_1 > r$ present example. As a consequence s will become unequal

$$\dot{\gamma}_1 = \frac{4}{\pi} \cdot \frac{Q_{term}}{r_1^3} < \frac{Q_{terr}}{} \qquad (10)$$

despite $\gamma = 3$ in the bifurcati other words, the mother's shear s into a "smaller daughter valu a "larger daughter value ($\dot{\gamma}_1$)". er ($\dot{\gamma}_1 < \dot{\gamma}_2$) or ($\dot{\gamma}_1 \geqslant \dot{\gamma}_2$). Since the ument applies to each bifurcation splits successively as one proceeds f ot towards the terminal branches c tree, finally showing a frequenc on which broadens towards the p e Fig. 3 (full bars).

hods 2: Considering Blood Rheology

TRODUCING SHEAR-RATE-DEPENDENT VISCOSITY

The method of CCO, as introduced above, draws on the concept of constant blood viscosity η and can therefore readily be scaled for shear rate (which does not depend on η). What the endothelial cells at the inside of a vessel "really feel" and what is relevant for physiology,

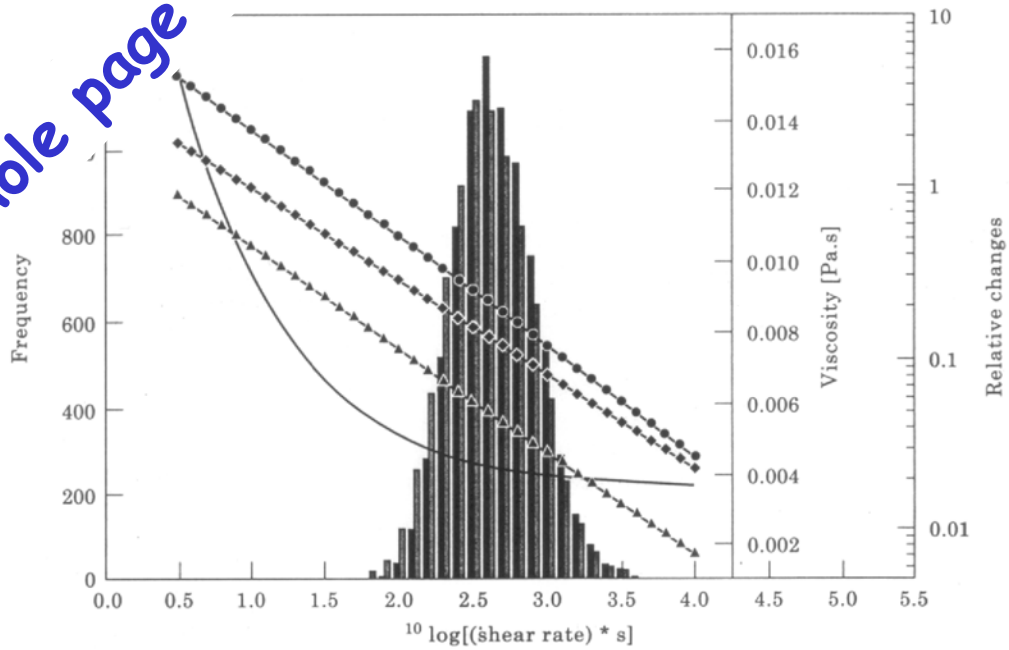


FIG. 3. Frequency distribution of shear rate and its impact on CCO models. Values of shear rate ($\dot{\gamma}$[s^{-1}]) were calculated in each segment of the CCO-reference-tree according to eqn (2) and logarithms (of $\dot{\gamma}\cdot s$) were taken to the base 10 (x-axis). The resulting frequency distribution (full bars, left y-scale: frequency) is seen to be close to normal, as can be verified by the normal probability plot. For $^{10}\log(\dot{\gamma}\cdot s)$, in a second step shear rates were re-evaluated after rescaling for shear-rate dependent viscosity; the resulting distribution of $^{10}\log(\dot{\gamma})$ is shown by hatched bars (median = 2.58, mean = 2.59). Rescaling for shear-rate-dependent viscosity induces relative changes in η (●) and $\dot{\gamma}$ (◆) which lie on straight lines in a double-log plot (see the regression lines referring to the rightmost y-axis). Note that η increases (●) and $\dot{\gamma}$ decreases (◆) according to the definitions in eqns (16) and (17). The effect on shear stress (▲) is about five times smaller. Medium y-axis: viscosity η [Pa·s] (shown as solid line) as it depends on logarithm of shear rate, $^{10}\log(\dot{\gamma}\cdot s)$.

(see the regression lines referring to the right scale in Fig. 3).

$$^{10}\log\left(\frac{\eta-\eta_\infty}{\eta_\infty}\right)=\underbrace{0.974}_{\pm 0.0003}-\underbrace{0.637}_{\pm 0.0001}\cdot{}^{10}\log\left(\dot\gamma_\infty\right) \quad (16)$$

$$^{10}\log\left(\frac{\dot\gamma_\infty-\dot\gamma}{\dot\gamma_\infty}\right)=\underbrace{0.533}_{\pm 0.0003}-\underbrace{0.544}_{\pm 0.0001}\cdot{}^{10}\log(\dot\gamma_\infty) \quad (17)$$

where regression coefficients are given ±SD, and the subscript "∞" refers to those values prevailing in the respective segment prior to rescaling*. As can be seen from the plot, changes in η and $\dot\gamma$ increase from approximately $0.04 = 4\%$ to $0.3 = 30\%$ with decreasing shear rate across the range of the shear-rate distribution. For example, at a representative shear rate of 1000 s^{-1} the changes are: 11% increase in η, 2.7% increase in r, and an 8% *decrease* in $\dot\gamma$. The frequency distribution of "η-rescaled-$\dot\gamma$" can be seen from the empty bars in Fig. 3. Using the above equations one can show analytically for the rescaled radii the relative change

$$\frac{r^4-r_\infty^4}{r_\infty^4} \quad (18)$$

must follow exactly the same [illegible] as η and is therefore not shown separately in Fig. 3.

The change in shear [illegible]sults from the *joint effect of an increase in* η *and a decrease in* $\dot\gamma$ [cf. eqn (11)] remains significantly (approximately [illegible]s) smaller (2.8% increase at $\dot\gamma$ = [illegible], than the changes in η and $\dot\gamma$. The con[illegible]es for the frequency distribution are the[illegible]ore even *less* than those for the distribution of $\dot\gamma$, shown in Fig. 3. We conclude that in CCO trees the effects on shear stress induced by shear-rate-dependent viscosity are a correction in the order of a few percent and we may assume for most purposes that η = constant = 0.0036 Pa·s, see also the discussion. Under this approximation shear stress is proportional to shear rate, as will be assumed in the following.

*For reasons of conciseness we suppress units of measurements to be multiplied into physical quantities to make arguments of logarithms, exponents, etc. dimensionless.

Results

EXPERIMENTAL MEASUREMENTS COMPARED WITH RADII OF CCO MODELS

It has been shown (Kassab *et al.*, 1993, 1997) that the Strahler system samples segments with considerable spread of radii within each of its orders. This is also true for the [illegible] models, as can be seen from Fig. 4(a) [illegible]plot with circles, bottom axis). In [illegible]rphometric analysis Kassab *et al* [illegible]troduced the "diameter-defined S[illegible]dering" ($^{dd}\Lambda_{str}$), which was shown [illegible] the spread of radii within each $^{dd}\Lambda$ [illegible]astically, thus offering a much bette[illegible]ion of segments in terms of radii. I[illegible] validate our CCO model we applied [illegible] same ordering procedures and obta[illegible] similar results: ranges of radii in di[illegible]ahler orders are wide and largely [illegible] [Fig. 4(a), HiLo-plot with circles], [illegible]s with diameter-defined Strahler ordering [illegible]ges are narrow and overlap only to a small [illegible]xtent [Fig. 4(a), HiLo-plot with diamonds]. Moreover, diameter-defined Strahler ordering produces seven orders ($0 \leqslant {}^{dd}\Lambda_{str} \leqslant 7$, top scale) instead of six orders for regular Strahler ordering ($0 \leqslant \Lambda_{str} \leqslant 6$, bottom scale).

Experimental measurements (Kassab *et al.*, 1997) of segment radii extend up to $^{dd}\Lambda_{str} = 11$ for the root segment of a pig's left common coronary artery. Our CCO model represents the arterial tree only to a lower degree of detail (4000 terminal segments only) and therefore reaches only a lower maximum of $^{dd}\Lambda_{str} = 7$ for the root segment. In order to allow for a comparison of results, we use the maximum level encountered in the CCO model to transform the experimental data according to

$$^{dd}\Lambda^*_{str} = {}^{dd}\Lambda_{str} - \left(\max_{exp}\left\{{}^{dd}\Lambda_{str}\right\} - \max_{CCO}\left\{{}^{dd}\Lambda_{str}\right\}\right) \quad (19)$$

and thus "line up" orders in the measurements with orders in the model downwards from the root $\left\{{}^{dd}\Lambda_{str}\right\} \equiv 7$. (As a consequence, those levels in experimental data which penetrate beyond the scope of the model—and can be disregarded in the comparison—would belong to "negative" levels). With levels thus lined up, we can display

Introduction

Perfusion is defined as the amount of blood delivered to a unit mass of tissue per unit time. Average perfusion of an organ can be calculated by dividing the flow through the supplying artery by the mass of the organ. However, local perfusion values within the organ have been found to vary significantly and to show positive correlation in space [1, 2, 17]. This means that it is likely that the area surrounding a highly perfused region of the organ is also highly perfused. More importantly, the correlation has been found to be independent of the size (scale) of the measurement volumes, which implies that perfusion heterogeneity is a self-similar or fractal quantity [2, 17]. This statement is equivalent to the observation that perfusion heterogeneity as a function of scale can be described by a power law (see ~~Appendix I~~ Methods section). Differences in local perfusion arise from differences in the resistance of the supplying vascular pathways. Consequently, we can learn something about vascular structure and resistance by measuring the heterogeneity and spatial correlation of perfusion.

C3-8

Recently, imaging techniques like PET (Positron Emission Tomography) [8] and MRI (Magnetic Resonance Imaging) [4] have been used to acquire data on perfusion heterogeneities. However, without a convincing model, which establishes a link between the measured parameters and the underlying vascular structure, a physiologically useful interpretation of these measurements is difficult.

In this paper, we present a model that suggests a connection between fractal perfusion heterogeneities and the scaling of vessel resistance as well as branching asymmetry. The model is based on the assumption of fractal vessel resistance meaning that vessel resistance also obeys a power law as a function of scale similar to the heterogeneity of perfusion. The scale of an artery will here be defined as the volume of tissue that it supplies. This definition of scale also leads to

Author's Response to Referees

Response to Referees: H-00510-2002
(The decision letter with all Referee comments will appear below the author's response.)

REVIEWERS' COMMENTS TO AUTHOR AND REPLIES:

Referee 1 Comments:
1)
This paper treads carefully between "modeling" and "physiology". It would do well to delve more deeply into one or the other, or ideally both. The proposed concept of vessel ordering based on tissue volume being perfused is a very intersting novel concept which is certainly worth pursuing.

Reply:
We have made an attempt to address your concerns keeping in mind that the paper is already very long.

2)
- As a modeling paper, the three appendices should be integrated into the main body of the paper where all equations should be numbered. Within these equations, more attention need be paid to mathematical notation and logic. The notation in Eqs.3,4 in Appendix II is confusing, with unclear use of primes and commas and the unfortunate use of 'o' as a symbol. The notation in Fig.3 is particularly confusing.

Reply C1-1: p. 6, 8, 13 ? All appendices have been integrated into the Methods section.
p. 8 - The symbol ?o? has been replace by ?u?. Equations 3 and 4 are now 4 and 5.
p. 32 ? There was a printing problem with Figure 3.

- As a paper in physiology, the concept of "the volume of tissue that is being supplied by an artery", which is central to the whole paper, should be discussed more thoroughly. How is this volume determined experimentally? How was it defined for the purpose of computer simulations? What is the basis for the volume order number?

Reply C1-2: p. 9, 10, 11

- What is the basis of relations used for vessel length and diameter under Assumptions 2?

Reply C1-3: p. 8, 13

- The caption of Fig.1 should explain the purpose for which the figure is shown. How does the figure relate to data used in the paper? How were measurements taken etc..?

Unit 10:

In Press & Proofs

„In press...“

- receiving the letter of acceptance! ☺
- from now on your work counts as being published
- page charges (additional charges for excessive length, color illustrations)
- submit halftone figures on CD if possible or requested to ensure optimal resolution. Use Zip-files if necessary. Don‘t hesitate to get technical assistance if needed.
- ordering reprints (like grandfathers did…)

Proofs (to be corrected)

- Die Autoren bekommen eine (meist mit sehr kurzem Zeitfenster verbundene) Möglichkeit Setzungsfehler bzw. falsche Ausbesserungen zu revidieren
- have *another person* correct the manuscript
- Lektoren, die meist nicht vom Fach sind, setzen den Text des Manuskripts in jene finale Form, die im Druck erscheint……*mit oftmals überaschenden „Effekten“*
- Meist gibt es auch einige Fragen wie z.B. „Please check if short title is okey“
- correct accurately and unambiguously
  Aber: Inhaltliche Korrekturen sind in diesem Stadium nicht mehr möglich!

Correcting proofs, technical issues

Meist 4 Möglichkeiten (abhängig vom Journal) für Textkorrekturen :

Paper-Proofs“: Ausbesserungen im ausgedruckten Manuskript (veraltet und kaum mehr üblich). Wenn dennoch

- verwenden Sie die genormten Korrekturzeichen ☝ ☝
- schrecken Sie nicht zurück vor „komplex“ aussehenden Korrekturen ☝ , die Setzer „sind einiges gewohnt“

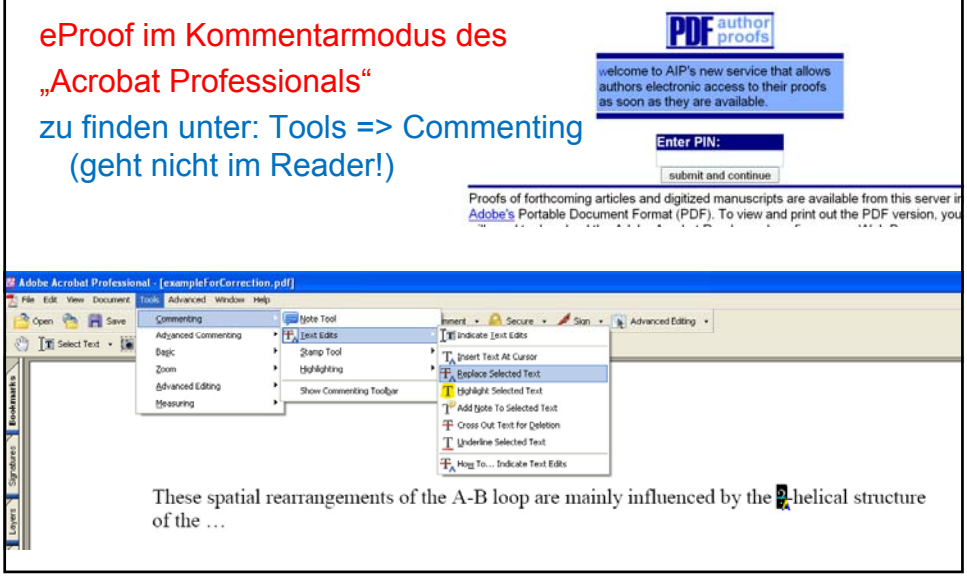
„List of Changes“: Tabellarische Liste mit Änderungen z.B. Page 3, Line 5, replace „?“ by „α“

- komplexe Korrekturen sind in diesem Modus fehleranfällig → liefern Sie ganzen Satz oder Absatz in „neuer Fassung“.

Correcting proofs, technical issues

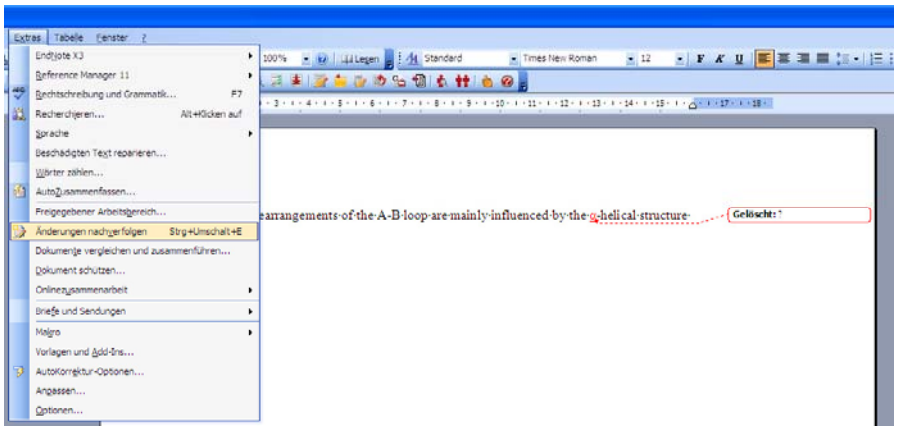
eProof im Kommentarmodus des „Acrobat Professionals“

zu finden unter: Tools => Commenting (geht nicht im Reader!)



Correcting proofs, technical issues

eProof im Änderungsmodus von MS-Word



Readers' marks

Marginal mark	Meaning	Corresponding mark in text
	Leave unchanged	under characters to remain
New matter followed by 	Insert the letter(s) indicated in the margin	
	Delete	/ through characters or ⟷ through words to be deleted
	Delete and close up	 through character(s) or through character e.g. character; character
	Set in or change to italic	under character(s) to be set or changed
	Set in or change to capital letters	 under character(s) to be set or changed
	Set in or change to small capital letters	 under character(s) to be set or changed
	Set in or change to bold type	 under character(s) to be set or changed
	Change capital letters to lower case letters	Encircle character(s) to be changed
	Change small capital letters to lower case letters	Encircle character(s) to be changed
	Change italic letters to upright type	Encircle character(s) to be changed
	Substitute or insert character in 'inferior' position	/ or 
 e.g. 	Substitute ligature e.g. ffi for separate letters	⟷ through characters affected
Write out separate letters	Substitute separate letters for ligature	⟷
	Substitute or insert apostrophe	/ or  where required
 and/or 	Substitute or insert single quotation marks	/ or  where required
 and/or	Substitute or insert double quotation marks	/ or where required
•••	Substitute or insert ellipsis	/ or where required
	Substitute or insert hyphen	/ through character or where required
	Substitute or insert rule	/ through character or where required
	Substitute or insert oblique	/ through character or  where required
	Start new paragraph	
	Run on (no new paragraph)	
	Transpose characters or words	between characters or words, numbered when necessary

Marginal mark	Meaning	Corresponding mark in text
1 2 3	Transpose a number of characters or words	3 2 1
1 2 3	Transpose a number of lines	3 2 1
	Transpose lines	
	Cancel indent	
	Centre	enclosing matter to be centred
	Set line justified to specified measure	and/or
	Set column justified to specified measure	
	Move matter specified distance to the right	enclosing matter to be moved to the right
	Move matter specified distance to the left	enclosing matter to be moved to the left
	Raise matter	over matter to be raised under matter to be raised
	Lower matter	over matter to be lowered under matter to be lowered
	Insert space between characters	between characters affected
	Insert space between words	between words affected
	Reduce space between characters	between characters affected
	Reduce space between words	between words affected
	Make space appear equal between characters or words	between characters or words affected
(each side of column linking lines)	Close up to normal interline spacing	(each side of column linking lines)
or	Insert space between lines or paragraphs	or
or	Reduce space between lines or paragraphs	or

emphasize that this possibility of scaling flows does neither depend on the particular connective structure (topology) nor on the particular geometry (segment coordinates) of the tree.

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In the present work we shall add the "adaptation to a given value of shear rate" as one additional type of scaling to the CCO procedure as follows:

The shear rate (i.e. the velocity gradient) between a fluid and the wall of segment i (cylindrical tube) is given by (Fung, 1984; Milnor, 1989)†

$$\dot{\gamma} = \frac{4}{\pi} \cdot \frac{Q_i}{r_i^3} \qquad (2)$$

$\dot{\gamma}_i$

and thus only depends on the flow Q[m^3 s^{-1}] and the radius r_i [m]. First we note that a constant factor c multiplied into *all* radii of a CCO tree has the following consequences:

1. it does *not* change relative radii and therefore does *not* change the relative flows;
2. it does *not* change pressure gradients, neither across single segments nor over the whole tree;
3. the changes in absolute values of all radii

$$r_i \rightarrow r_i^* = c \cdot r_i \qquad (3)$$

change the total flow into the tree [Poiseuille's law for constant viscosity (Fung, 1984)], if the overall pressure gradient Δp is kept constant. As opposed to that, in order to keep the flow unchanged and adapted to the value preset according to physiological data, the overall pressure gradient has to be rescaled ($\Delta p \rightarrow \Delta p^*$) according to

$$\frac{\Delta p^*}{\Delta p} = \left(\frac{r_i}{r_i^*}\right)^4 = c^{-4} \qquad (4)$$

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This dependency can be used to select the pressure gradient (e.g. via selecting p_{term}) such that the shear rate in a deliberate segment of the tree assumes a desired value. Specifically, one can select the p_{term} such that the shear rate in the root segment assumes a value compatible with experimental data:

$$\frac{\Delta p^*}{\Delta p} = \left(\frac{\dot{\gamma}_{root}^*}{\dot{\gamma}_{root}}\right)^{\frac{4}{3}} \qquad (6)$$

In other words: any given CCO tree (with terminal pressure $p_{term} = p_{perf} - \Delta p$) can be rescaled to a different (appropriate) terminal pressure ($p_{term}^* = p_{perf} - \Delta p^*$), and the radius of the root will change accordingly to keep flow constant and make the shear rate in the root (or any other arbitrary segment) assume a desired value. We call this procedure "shear-rate scaling", and it replaces one constraint (p_{term}) by a different one (shear rate in a given segment). The procedure can be applied to fully grown CCO trees or to intermediate stages, or it can be performed after each step of adding a new terminal segment. In the latter case, p_{term} will gradually drift as the tree grows and at any stage of development be compatible with the value of shear rate assigned to one deliberate segment according to physiologic considerations. p_{term} thus obtained does not represent a deliberate choice any more (as it hitherto was), but is adequately adapted to a given resolution (N_{term}) of the model tree, which represents arterial vasculature distal to the feeding segment into a certain depth of arterial branchings.

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Unit 10a:

Conclusion

"Your work and ideas are now in the literature"

a baby is beeing born - a paper is being published

- how long lasted pregnancy? -

- Many people will know you from your work before you meet them personally.
- You have now plenty of material (figures etc.) to draw upon when giving lectures at meetings etc. Suggestion: Prepare *hic et nunc* colored versions from all the figures of your paper, suitable for presentations (slides, video beam).
- You have added another piece to the puzzle of your total scientific work.
- You may receive estimations from readers ☝ or at meetings.
- You have built solid ground where upon to base your next investigation within your field of research. ☝ ☝