

Semesterprojekt WS 17/18

Entwicklung einer Suchmaschine für  
Alternativmethoden zu Tierversuchen

23. Oktober 2017

# Semesterprojekt

- Kernidee: Erstellen eines mittel-komplexen Programms im Team über ein komplettes Semester hinweg
- Ziele:
  - Arbeiten in Teams: Gruppendynamik, Absprachen, ...
  - Softwareentwicklungsprozess von Anfang bis Ende miterleben
  - Anwenden vieler Tools der professionellen Softwareentwicklung
- Kein Ziel: Erstellen eines perfekten, umfangreichen Systems

# Vorstellung

- Prof. Dr. Ulf Leser
- Prof. Dr. med. Gilbert Schönefelder
- Dr. med. vet. Barbara Grune
- Dr. rer. nat. Daniel Butzke
- Dr. Ing. Mariana Lara Neves

# Deutsches Zentrum zum Schutz von Versuchstieren (Bf3R) am Bundesinstitut für Risikobewertung



# Gesetzlicher Auftrag

**TierSchG § 7a (2)** Unerlässlichkeit eines Tierversuchs:

„2. Es ist zu prüfen, ob der verfolgte Zweck nicht durch andere Methoden oder Verfahren erreicht werden kann.“

**TierSchG § 8 (1)** Wissenschaftlich begründete Darlegung im Genehmigungsantrag (u.a. **§ 7a (2) 2.**)

**TierSchVersV § 41 (1)** u.a. Inhalte der NTP

„In der Zusammenfassung (Anm.: = NTP) ist auf der Grundlage der Angaben im Genehmigungsantrag Folgendes darzustellen: ... die Erfüllung der Anforderungen des ... **§ 7a Absatz 2** Nummer 2 ... des Tierschutzgesetzes.“

**TierSchVersV § 46** Beratung zu Alternativen zu Tierversuchen

„Das Bundesinstitut (Anm: = BfR) berät die zuständigen Behörden in Angelegenheiten, die mit Alternativen zu Tierversuchen zusammenhängen.“

## 3R Konzept von Russell & BURCH The Principles of Humane Experimental Technique 1959, 1992



R.L. Burch and W.M.S. Russell  
<http://3rs.ccac.ca/en/about/three-rs.html>

- **REPLACE**      **VERMEIDEN**  
Ersatz von Tierversuchen durch alternative Methoden
- **REDUCE**      **VERMINDERN**  
Verminderung der Zahl benötigter Tiere
- **REFINE**      **VERBESSERN**  
Verminderung der Belastung der Tiere

# Problemstellung:

Die Prüfung „anderer Methoden oder Verfahren“ ist nur möglich, wenn ...

- 1.) solche im Labor etabliert sind bzw.
- 2.) bekannt sind bzw.
- 3.) im Stand der Technik recherchiert werden können.

Bei der Recherche gibt es zahlreiche Schwierigkeiten:

- Fehlende Recherchekompetenz, fehlende Ressourcen (Zeit, Datenbanken etc.)
- Alternativmethoden sind oft/meist nicht als solche gekennzeichnet.
- Existierende Recherchertools (z.B. „similarity“-Suche in PubMed) sind zu unspezifisch.

## Lösungsansatz (3R-Relevanz):

- Bereitstellung eines spezifischen anwenderorientierten Recherchetools für die versuchszweckgenaue 3R-Recherche.
- Ausgabe einer im Umfang begrenzten, priorisierten Liste von Alternativmethodenvorschlägen, die anschließend vom Anwender geprüft wird.
- Transparenz des automatisierten Rechercheprozesses



# Suchmaschine für Alternativmethoden zu Tierversuchen

## Input: Tierversuch-Publikation

J.Neurosci. 2005 Sep 28;25(39):8615-24.

### Encoding of movement direction in different frequency ranges of motor cortical local field potentials.

Ricker J<sup>1</sup>, Oliveira SC, Vaadia E, Aertsen A, Rotter S, Mehring C.

© Author information

#### Abstract

Recent studies showed that the low-frequency component of local field potentials (LFPs) in monkey motor cortex carries information about parameters of voluntary arm movements. Here, we studied how different signal components of the LFP in the time and frequency domains are modulated during center-out arm movements. Analysis of LFPs in the time domain showed that the amplitude of a slow complex waveform beginning shortly before the onset of arm movement is modulated with the direction of the movement. Examining LFPs in the frequency domain, we found that direction-dependent modulations occur in three frequency ranges, which typically increased their amplitudes before and during movement execution: < or =4, 6-13, and 63-200 Hz. Cosine-like tuning was prominent in all signal components analyzed. In contrast, activity in a frequency band approximately 30 Hz was not modulated with the direction of movement and typically decreased its amplitude during the task. This suggests that high-frequency oscillations have to be divided into at least two functionally different regimes: one approximately 30 Hz and one >60 Hz. Furthermore, using multiple LFPs, we could show that LFP amplitude spectra can be used to decode movement direction, with the best performance achieved by the combination of different frequency ranges. These results suggest that using the different frequency components in the LFP is useful in improving inference of movement parameters from local field potentials.

PMID: 16192371 DOI: 10.1523/JNEUROSCI.0816-05.2005



J.Neurosci. 2004 Jun 9;24(11):2668-76. Epub 2004 May 26.

### Comparing information about arm movement direction in single channels of local and epicortical field potentials from monkey and human motor cortex.

Mehring C<sup>1</sup>, Haenschel MP, de Oliveira SC, Vaadia E, Schulz-Bornhaagen A, Aertsen A, Rotter S.

© Author information

#### Abstract

Cortical field potentials have been used for decades in neurophysiological studies to probe spatio-temporal activity patterns of local populations of neurons. Recently, however, interest in these signals was spurred as they were proposed as potential control signals for neuronal motor prostheses, i.e., for devices fit to record and decode brain activity to restore motor functions in paralyzed patients. Little is known, however, about the functional significance of these cortical field potentials. Here we compared information about arm movement direction in two types of movement-related cortical field potentials, obtained during a four-direction center-out arm reaching paradigm: local field potentials (LFPs) recorded with intracortical micro-electrodes from monkey motor cortex, and epicortical field potentials (EFPs) recorded with macro-electrode arrays subdurally implanted on the surface of the human cerebral cortex. While monkey LFPs showed a typical sequence of positive and negative potential peaks, an initial negative peak was the most salient feature of human EFPs. Individual contralateral LFPs from the monkey motor cortex carried approximately twice as much decoded information (DI) about arm movement direction (median 0.27 bit) as did individual EFPs from the contralateral hand/arm area of primary motor cortex in humans (median 0.12 bit). This relation was similar to the relation between median peak signal-to-noise ratios for directional modulation of movement-related potentials (dMRPs) of both types of signals. We discuss possible reasons for the observed differences, amongst them: epi- vs. intracortical recording and the different electrode dimensions used to measure EFPs and LFPs.

PMID: 15131048 DOI: 10.1523/JNEUROSCI.2005.09.04

Electroencephalogr Clin Neurophysiol. 1994 Oct 93(5):390-403.

### 8-12 Hz rhythmic oscillations in human motor cortex during two-dimensional arm movements: evidence for representation of kinematic parameters.

Toro C<sup>1</sup>, Cui C, Fritsch S, Qianzhan C, Marrett S, Gates JG, Gurnett RJ, Eilon J.

© Author information

#### Abstract

Direct cortical recordings were taken from 12 patients with implanted subdural electrode arrays during performance of a 2-dimensional, multi-joint, visually guided arm movement task. Task-related changes in the amplitude of the motor cortex 8-12 Hz surface local field oscillations were evaluated for the encoding of direction and amplitude of movement in the 6 patients in whom no epileptogenic or ECoG background abnormalities were detected over the motor-sensory cortical areas under the recording electrode array. The topography, time of onset and duration of these responses were evaluated in the context of motor cortex somatotopy, as defined by cortical stimulation delivered through the electrode array. Multi-joint arm movements were accompanied by a decrease in the power of the 8-12 Hz frequency components of the ECoG signal. These power changes were spatially distributed over the upper extremity motor-sensory representation. Movement amplitude influenced the magnitude, duration, and extent of the spatial distribution of ECoG power changes in the 8-12 Hz band. These effects occurred predominantly over cortical areas corresponding to the upper extremity motor-sensory representations. Direction of movement had a weaker influence on the 8-12 Hz frequency components of the ECoG over the upper extremity motor-sensory representations, but influenced the patterns of 8-12 Hz ECoG response on adjacent cortical regions. These results show that the amplitude of surface electrical oscillations generated over the rolandic cortex are correlated with the kinematics of multi-joint arm movements. These changes in the ECoG signal appear to reflect shifts in the functional state of neuronal ensembles involved in the initiation and execution of motor tasks.

PMID: 1252347

J.Neurosci. 2014 Aug 13;34(32):8607-16. doi: 10.1523/JNEUROSCI.4607-14.2014. Epub 2014 Jun 12.

### Reliability of directional information in oriented spikes and local field potentials recorded in human motor cortex.

Fritsch S<sup>1</sup>, Zhang S, Haenschel MP, Horner ML, Cui C, Fritsch S, Eskandar EN, Oostenveld R, Hochberg LR.

© Author information

#### Abstract

**OBJECTIVE:** Action potentials and local field potentials (LFPs) recorded in primary motor cortex contain information about the direction of movement. LFPs are assumed to be more robust to signal instabilities than action potentials, which makes LFPs, along with action potentials, a promising signal source for brain-computer interface applications. Still, relatively little research has directly compared the utility of LFPs to action potentials in decoding movement direction in human motor cortex.

**APPROACH:** We conducted intracortical multi-electrode recordings in motor cortex of two persons (T2 and [S3]) as they performed a motor imagery task. We then compared the offline decoding performance of LFPs and spiking extracted from the same data recorded across a one-year period in each participant.

**MAIN RESULTS:** We obtained offline prediction accuracy of movement direction and endpoint velocity in multiple LFP bands, with the best performance in the highest (200-400 Hz) LFP frequency band, presumably also containing low-pass filtered action potentials. Cross-frequency correlations of preferred directions and directional modulation index showed high similarity of directional information between action potential firing rates (spiking) and high frequency LFPs (70-450 Hz), and increasing disparity with lower frequency bands (0-7, 10-40 and 50-65 Hz). Spikes predicted the direction of intended movement more accurately than any individual LFP band. However, combined decoding of all LFPs was statistically indistinguishable from spike-based performance. As the quality of spiking signals (i.e., signal amplitude) and the number of significantly modulated spiking units decreased, the offline decoding performance decreased 3.65 (5%/month) for T2 and [S3] respectively. The decrease in the number of significantly modulated LFP signals and their decoding accuracy followed a similar trend (2.42 (5%/month), ANCOVA,  $p = 0.270$  (5)).

**SIGNIFICANCE:** Field potentials provided comparable offline decoding performance to unsorted spikes. Thus, LFPs may provide useful external device control using current human intracortical recording technology.

**CLINICAL TRIAL REGISTRATION NUMBER:** NCT00912041.

PMID: 2481288 PMID: 24812882 DOI: 10.1523/JNEUROSCI.4607-14.2014

## Output: Nicht-Tierversuch (für ähnliche Versuchszwecke) Publikationen

# Case Report: Stroke (Schlaganfall)

J Cereb Blood Flow Metab. 2007 Apr;27(4):697-709. Epub 2006 Jul 19.

## Matrix metalloproteinase-mediated disruption of tight junction proteins in cerebral vessels is reversed by synthetic matrix metalloproteinase inhibitor in focal ischemia in rat.

Yang Y<sup>1</sup>, Estrada EY, Thompson JF, Liu W, Rosenberg GA.

### ⊕ Author information

#### Abstract

Matrix metalloproteinases (MMPs) disrupt the blood-brain barrier (BBB) during reperfusion. Occludin and claudins are recently described tight junction proteins (TJPs) that form the BBB. **We hypothesized that the opening of the BBB was because of the degradation of TJPs by the MMPs.** Spontaneously hypertensive rats had a 90 mins middle cerebral artery occlusion with reperfusion for 2, 3, or 24 h. Matrix metalloproteinases were measured by immunohistochemistry and in situ and gel zymography. Real-time polymerase chain reaction (PCR) measured mRNAs of MMP-2 and -9, furin, membrane-type MMP (MT1-MMP), occludin, and claudin-5. There was opening of the BBB in the piriform cortex after 3 h of reperfusion, and an MMP inhibitor, BB-1101 (30 mg/kg), prevented the opening. At 3 h, in situ zymograms showed gelatinase activity. Zymography and PCR showed greater increases in MMP-2 than in MMP-9. There were increased mRNA and immunohistochemistry for MT1-MMP and furin, which activate MMP-2. Claudin-5 and occludin mRNA expression decreased at 2 h in both hemispheres with fragments of both proteins seen on Western blot by 3 h on the ischemic side; treatment with BB-1101 reversed the degradation of the TJPs. Immunohistochemistry at 3 h showed fragmented TJPs within the endothelial cell clefts. By 24 h, in situ zymography showed gelatinase activity and gel zymography showed elevated levels of MMP-9. Disrupted TJPs previously seen in endothelial cells appeared in the surrounding astrocytes. Our results provide direct evidence that MMPs open the BBB by degrading TJPs and that an MMP inhibitor prevents degradation of the TJPs by MMPs.

PMID: 16850029 DOI: [10.1038/sj.jcbfm.9600375](https://doi.org/10.1038/sj.jcbfm.9600375)



### Similar articles

Early appearance of activated matrix metalloproteinase-9 and blo [Brain Res. 1999]

Immunohistochemistry of matrix metalloproteinases in reperi [Brain Res. 2001]

Synthetic gelatinases inhibitor attenuates electromagnetic pulse-induc [Toxicology. 2011]

**Review** Vasogenic edema due to tight junction disruption by [Neurosurg Focus. 2007]

**Review** Interaction of free radicals, matrix metalloproteina: [Front Biosci (Schol Ed). 2011]

[See reviews...](#)

[See all...](#)

(<https://www.ncbi.nlm.nih.gov/pubmed/?term=16855596>)

# Ähnliche Publikationen in PubMed

- ✘ [Matrix metalloproteinase-mediated disruption of tight junction proteins in cerebral vessels is reversed by synthetic matrix metalloproteinase inhibitor in focal ischemia in rat.](#)

1. Yang Y, Estrada EY, Thompson JF, Liu W, Rosenberg GA.  
J Cereb Blood Flow Metab. 2007 Apr;27(4):697-709. Epub 2006 Jul 19.  
PMID: 16850029  
[Similar articles](#)

- ☐ [Early appearance of activated matrix metalloproteinase-9 and blood-brain barrier disruption in mice after focal cerebral ischemia and reperfusion.](#)

2. Fujimura M, Gasche Y, Morita-Fujimura Y, Massengale J, Kawase M, Chan PH.  
Brain Res. 1999 Sep 18;842(1):92-100.  
PMID: 10526099  
[Similar articles](#)

- ☐ [Immunohistochemistry of matrix metalloproteinases in reperfusion injury to rat brain: activation of MMP-9 linked to stromelysin-1 and microglia in cell cultures.](#)

3. Rosenberg GA, Cunningham LA, Wallace J, Alexander S, Estrada EY, Grossetete M, Razhagi A, Miller K, Gearing A.  
Brain Res. 2001 Mar 2;893(1-2):104-12.  
PMID: 11222998  
[Similar articles](#)

- ☐ [Synthetic gelatinases inhibitor attenuates electromagnetic pulse-induced blood-brain barrier disruption by inhibiting gelatinases-mediated ZO-1 degradation in rats.](#)

4. Qiu LB, Zhou Y, Wang Q, Yang LL, Liu HQ, Xu SL, Qi YH, Ding GR, Guo GZ.  
Toxicology. 2011 Jul 11;285(1-2):31-8. doi: 10.1016/j.tox.2011.03.019. Epub 2011 Apr 8.  
PMID: 21501651  
[Similar articles](#)

- ☐ [Vasogenic edema due to tight junction disruption by matrix metalloproteinases in cerebral ischemia.](#)

5. Rosenberg GA, Yang Y.  
Neurosurg Focus. 2007 May 15;22(5):E4. Review.  
PMID: 17613235  
[Similar articles](#)

- ☐ [Specific role of tight junction proteins claudin-5, occludin, and ZO-1 of the blood-brain barrier in a focal cerebral ischemic insult.](#)

6. Jiao H, Wang Z, Liu Y, Wang P, Xue Y.  
J Mol Neurosci. 2011 Jun;44(2):130-9. doi: 10.1007/s12031-011-9496-4. Epub 2011 Feb 12.  
PMID: 21318404  
[Similar articles](#)

- ☐ [Caveolin-1 regulates nitric oxide-mediated matrix metalloproteinases activity and blood-brain barrier permeability in focal cerebral ischemia and reperfusion injury.](#)

7. Gu Y, Zheng G, Xu M, Li Y, Chen X, Zhu W, Tong Y, Chung SK, Liu KJ, Shen J.  
J Neurochem. 2012 Jan;120(1):147-56. doi: 10.1111/j.1471-4159.2011.07542.x. Epub 2011 Nov 17.  
PMID: 22007835 **Free Article**  
[Similar articles](#)

- ☐ [Tissue inhibitor of metalloproteinases protect blood-brain barrier disruption in focal cerebral ischemia.](#)

8. Fujimoto M, Takagi Y, Aoki T, Hayase M, Marumo T, Gomi M, Nishimura M, Kataoka H, Hashimoto N, Nozaki K.  
J Cereb Blood Flow Metab. 2008 Oct;28(10):1674-85. doi: 10.1038/jcbfm.2008.59. Epub 2008 Jun 18.  
PMID: 18560439  
[Similar articles](#)

- ☐ [Early upregulation of matrix metalloproteinases following reperfusion triggers neuroinflammatory mediators in brain ischemia in rat.](#)

9. Amantea D, Russo R, Gliozzi M, Fratto V, Berliocchi L, Bagetta G, Bernardi G, Corasaniti MT.  
Int Rev Neurobiol. 2007;82:149-69.  
PMID: 17678960  
[Similar articles](#)

- ☐ [Pre-ischemic exercise reduces matrix metalloproteinase-9 expression and ameliorates blood-brain barrier dysfunction in stroke.](#)

10. Guo M, Cox B, Mahale S, Davis W, Carranza A, Hayes K, Sprague S, Jimenez D, Ding Y.  
Neuroscience. 2008 Jan 24;151(2):340-51. Epub 2007 Oct 18.  
PMID: 18160227  
[Similar articles](#)

# Dokument #2:

## Tierversuch, nicht ähnlich genug!

Brain Res. 1999 Sep 18;842(1):92-100.

### **Early appearance of activated matrix metalloproteinase-9 and blood-brain barrier disruption in mice after focal cerebral ischemia and reperfusion.**

Fujimura M<sup>1</sup>, Gasche Y, Morita-Fujimura Y, Massengale J, Kawase M, Chan PH.

⊕ Author information

#### **Abstract**

Blood-brain barrier (BBB) disruption is thought to play a critical role in the pathophysiology of ischemia/reperfusion. Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that can degrade all the components of the extracellular matrix when they are activated. Gelatinase A (MMP-2) and gelatinase B (MMP-9) are able to digest the endothelial basal lamina, which plays a major role in maintaining BBB impermeability. The present study examined the expression and activation of gelatinases before and after transient focal cerebral ischemia (FCI) in mice. **Adult male CD1 mice** were subjected to 60 min FCI and reperfusion. Zymography was performed from 1 to 23 h after reperfusion using the protein extraction method with detergent extraction and affinity-support purification. MMP-9 expression was also examined by both immunohistochemistry and Western blot analysis, and tissue inhibitors to metalloproteinase-1 was measured by reverse zymography. The BBB opening was evaluated by the Evans blue extravasation method. The 88-kDa activated MMP-9 was absent from the control specimens, while it appeared 3 h after transient ischemia by zymography. At this time point, the BBB permeability alteration was detected in the ischemic brain. Both pro-MMP-9 (96 kDa) and pro-MMP-2 (72 kDa) were seen in the control specimens, and were markedly increased after FCI. A significant induction of MMP-9 was confirmed by both immunohistochemistry and Western blot analysis. The early appearance of activated MMP-9, associated with evidence of BBB permeability alteration, suggests that activation of MMP-9 contributes to the early formation of vasogenic edema after transient FCI.

PMID: 10526099

# Dokument #3:

## Beide - Tierversuch und Zelllinie, aber nicht ähnlich genug!

[Brain Res.](#) 2001 Mar 2;893(1-2):104-12.

### **Immunohistochemistry of matrix metalloproteinases in reperfusion injury to rat brain: activation of MMP-9 linked to stromelysin-1 and microglia in cell cultures.**

[Rosenberg GA](#)<sup>1</sup>, [Cunningham LA](#), [Wallace J](#), [Alexander S](#), [Estrada EY](#), [Grossetete M](#), [Razhaqi A](#), [Miller K](#), [Gearing A](#).

#### ⊕ Author information

#### Abstract

Reperfusion damages the blood-brain barrier (BBB). Matrix metalloproteinases (MMPs) are associated with the opening of the BBB, but their cellular localization and activation mechanisms are uncertain. We used immunohistochemistry to determine the cellular localization of the MMPs in reperfused rat brain, and cell cultures to study their activation. **Spontaneously hypertensive rats** (SHR) had a 90 min middle cerebral artery occlusion (MCAO) followed by reperfusion for times from 3 h to 21 days. Frozen sections were immunostained with antibodies to gelatinase A (MMP-2), stromelysin-1 (MMP-3), and gelatinase B (MMP-9). Sham-operated control rats showed MMP-2 immunostaining in astrocytic processes next to blood vessels. After 3 h of the onset of reperfusion MMP-2 immunostaining increased in astrocytes. At 24 h immunoreactivity for MMP-3 and MMP-9 appeared. MMP-3 co-localized with activated microglia (Ox-42+) and ischemic neurons (NeuN+). MMP-9 immunostaining was seen at 48 h in endothelial cells, neutrophils, and neurons. At 5 and 21 days intense MMP-2 staining was seen in reactive astrocytes around the ischemic core. Studies of activation of the MMP were done in lipopolysaccharide (LPS)-stimulated **astrocyte and microglia cultures**. Stimulated astrocytes produced an activated form of MMP-2. When microglia were stimulated, they activated MMP-9. Immunostaining showed MMP-3 in cultures of enriched microglial cells. The hydroxamate-type, MMP inhibitor, BB-1101, blocked the activation of MMP-2 and MMP-9 by LPS in mixed glial cultures. We propose that MMP-2 is normally present in astrocytic end feet, and that during ischemia MMP-9 and MMP-3 are produced. MMP-3 in microglia/macrophages may be activating proMMP-9. Our results show that a differential expression of MMPs by astrocytes, microglia, and endothelial cells at the blood vessels is involved in the proteolytic disruption of the BBB.

PMID: 11222998

# Ähnliche Publikationen in PubMed (nach Bewertung)

1. [Matrix metalloproteinase-mediated disruption of tight junction proteins in cerebral vessels is reversed by synthetic matrix metalloproteinase inhibitor in focal ischemia in rat.](#)

Yang Y, Estrada EY, Thompson JF, Liu W, Rosenberg GA.  
J Cereb Blood Flow Metab. 2007 Apr;27(4):697-709. Epub 2006 Jul 19.

PMID: 16850029

[Similar articles](#)

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PMID: 10526099

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3. [Immunohistochemistry of matrix metalloproteinases in reperfusion injury to rat brain: activation of MMP-9 linked to stromelysin-1 and microglia in cell cultures.](#)

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4. [Synthetic gelatinases inhibitor attenuates electromagnetic pulse-induced blood-brain barrier disruption by inhibiting gelatinases-mediated ZO-1 degradation in rats.](#)

Qiu LB, Zhou Y, Wang Q, Yang LL, Liu HQ, Xu SL, Qi YH, Ding GR, Guo GZ.

Toxicology. 2011 Jul 11;285(1-2):31-8. doi: 10.1016/j.tox.2011.03.019. Epub 2011 Apr 8.

PMID: 21501651

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5. [Vasogenic edema due to tight junction disruption by matrix metalloproteinases in cerebral ischemia.](#)

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PMID: 22007835 **Free Article**

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8. [Tissue inhibitor of metalloproteinases protect blood-brain barrier disruption in focal cerebral ischemia.](#)

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J Cereb Blood Flow Metab. 2008 Oct;28(10):1674-85. doi: 10.1038/jcbfm.2008.59. Epub 2008 Jun 18.

PMID: 18560439

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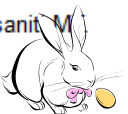
9. [Early upregulation of matrix metalloproteinases following reperfusion triggers neuroinflammatory mediators in brain ischemia in rat.](#)

Amantea D, Russo R, Gliozzi M, Fratto V, Berliocchi L, Bagetta G, Bernardi G, Corasaniti M.

Int Rev Neurobiol. 2007;82:149-69.

PMID: 17678960

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Guo M, Cox B, Mahale S, Davis W, Carranza A, Hayes K, Sprague S, Jimenez D, Ding Y.

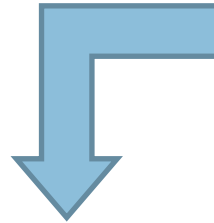
Neuroscience. 2008 Jan 24;151(2):340-51. Epub 2007 Oct 18.

PMID: 18160227

[Similar articles](#)

# Aber: es gibt Alternativmethoden!

z.B.



[J Cereb Blood Flow Metab.](#) 2007 Apr;27(4):697-709. Epub 2006 Jul 19.

## Matrix metalloproteinase-mediated disruption of tight junction proteins in cerebral vessels is reversed by synthetic matrix metalloproteinase inhibitor in focal ischemia in rat.

[Yang Y<sup>1</sup>](#), [Estrada EY](#), [Thompson JF](#), [Liu W](#), [Rosenberg GA](#).

### ⊕ Author information

#### Abstract

Matrix metalloproteinases (MMPs) disrupt the blood-brain barrier (BBB) during reperfusion. Occludin and claudins are recently described tight junction proteins (TJPs) that form the BBB. We hypothesized that the opening of the BBB was because of the degradation of TJPs by the MMPs. Spontaneously hypertensive rats had a 90 mins middle cerebral artery occlusion with reperfusion for 2, 3, or 24 h. Matrix metalloproteinases were measured by immunohistochemistry and in situ and gel zymography. Real-time polymerase chain reaction (PCR) measured mRNAs of MMP-2 and -9, furin, membrane-type MMP (MT1-MMP), occludin, and claudin-5. There was opening of the BBB in the piriform cortex after 3 h of reperfusion, and an MMP inhibitor, BB-1101 (30 mg/kg), prevented the opening. At 3 h, in situ zymograms showed gelatinase activity. Zymography and PCR showed greater increases in MMP-2 than in MMP-9. There were increased mRNA and immunohistochemistry for MT1-MMP and furin, which activate MMP-2. Claudin-5 and occludin mRNA expression decreased at 2 h in both hemispheres with fragments of both proteins seen on Western blot by 3 h on the ischemic side; treatment with BB-1101 reversed the degradation of the TJPs. Immunohistochemistry at 3 h showed fragmented TJPs within the endothelial cell clefts. By 24 h, in situ zymography showed gelatinase activity and gel zymography showed elevated levels of MMP-9. Disrupted TJPs previously seen in endothelial cells appeared in the surrounding astrocytes. Our results provide direct evidence that MMPs open the BBB by degrading TJPs and that an MMP inhibitor prevents degradation of the TJPs by MMPs.

PMID: 16850029 DOI: [10.1038/sj.icbfm.9800375](#)

[Brain Res.](#) 2004 Jan 9;995(2):184-96.

## Tyrosine phosphatase inhibition induces loss of blood-brain barrier integrity by matrix metalloproteinase-dependent and -independent pathways.

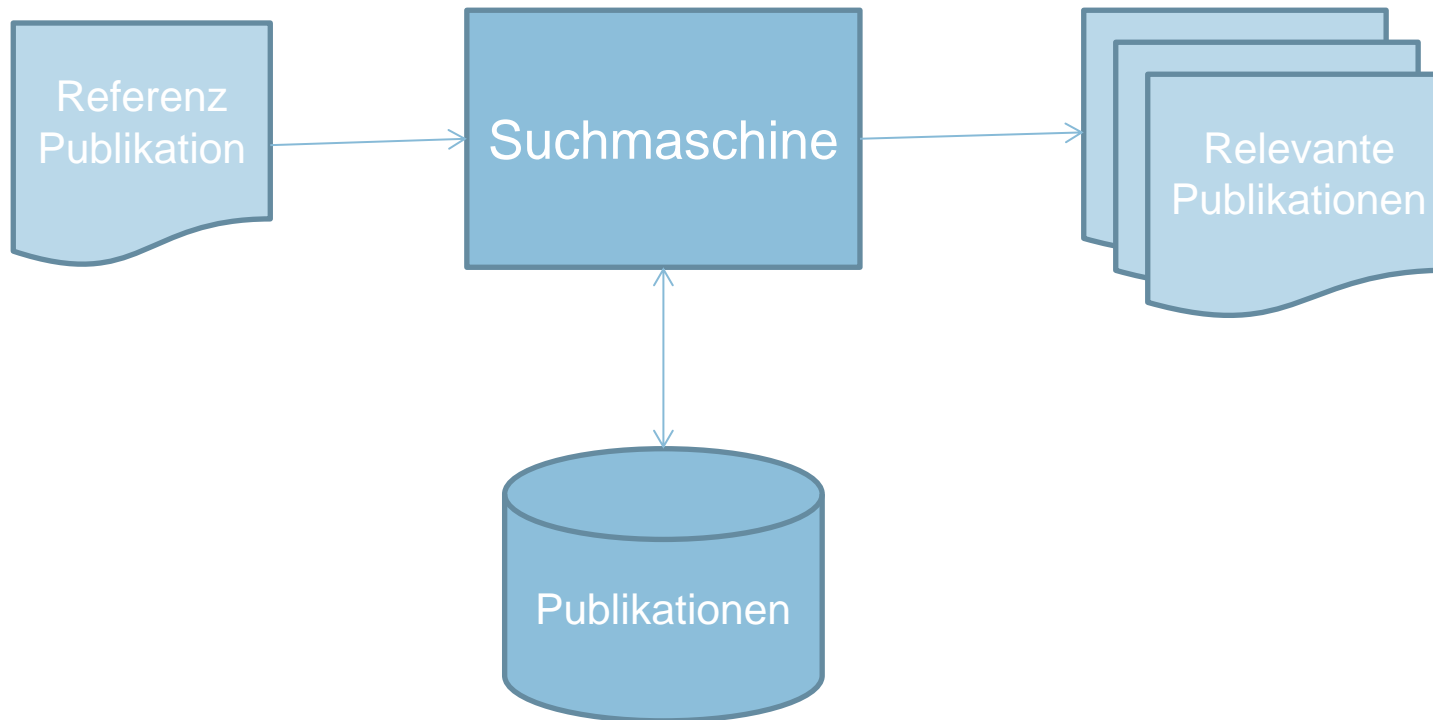
[Lohmann C<sup>1</sup>](#), [Krischke M](#), [Wegener J](#), [Galla HJ](#).

### ⊕ Author information

#### Abstract

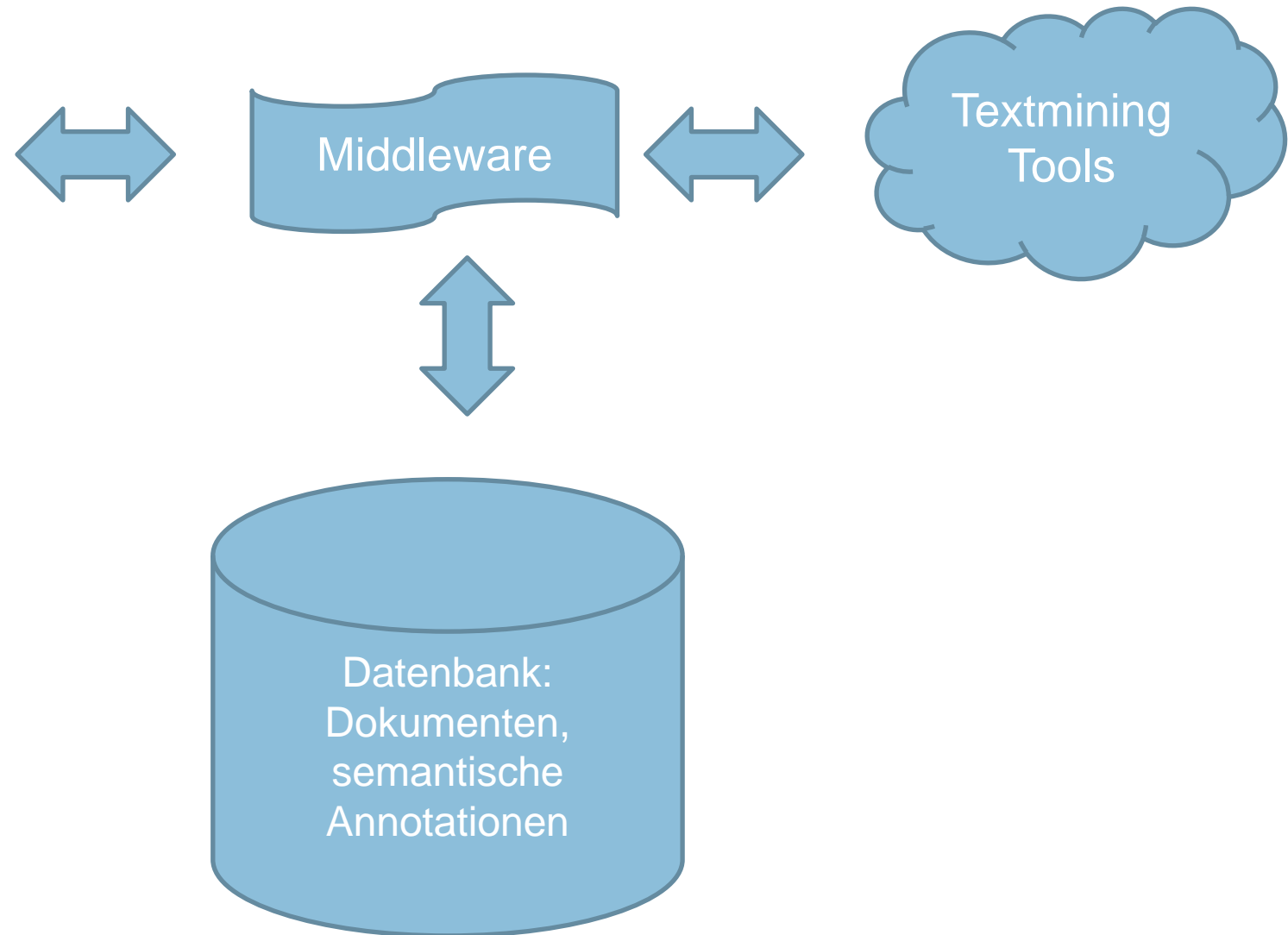
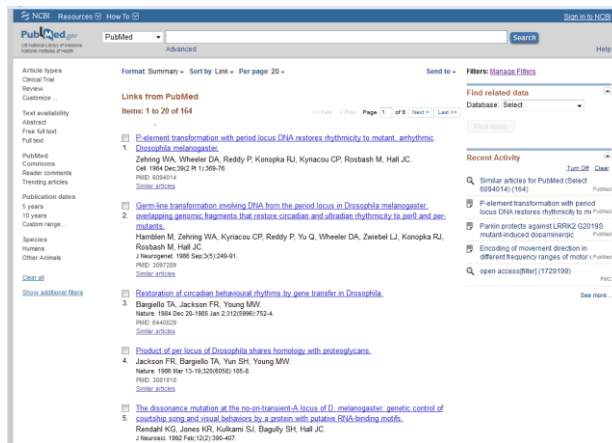
Tight junctions between endothelial cells of brain capillaries form the structural basis of the blood-brain barrier (BBB), which controls the exchange of molecules between blood and CNS. Regulation of cellular barrier permeability is a vital and complex process involving intracellular signalling and rearrangement of tight junction proteins. We have analysed the impact of tyrosine phosphatase inhibition on tight junction proteins and endothelial barrier integrity in **a primary cell culture model based on porcine brain capillary endothelial cells (PBCEC) that closely mimics the BBB in vitro.** The tyrosine phosphatase inhibitor phenylarsine oxide (PAO) induced increased matrix metalloproteinase (MMP) activity, which was paralleled by severe disruption of cell-cell contacts and proteolysis of the tight junction protein occludin. ZO-1 and claudin-5 were not affected. Under these conditions, the transendothelial electrical resistance (TEER) was markedly reduced. PAO-induced occludin proteolysis could be prevented by different MMP inhibitors. Pervanadate (PV) reduced the TEER similar to PAO, but did not increase MMP activity. Cell-cell contacts of PV-treated cells appeared unaffected, and occludin proteolysis did not occur. Our results suggest that tyrosine phosphatase inhibition can influence barrier properties independent of, but also correlated to MMPs. Evidence is given for a role of MMPs in endothelial tight junction regulation at the BBB in particular and probably at tight junctions (TJs) in general.

# Suchmaschine für Alternativmethoden zu Tierversuchen





# Suchmaschine für Alternativmethoden zu Tierversuchen



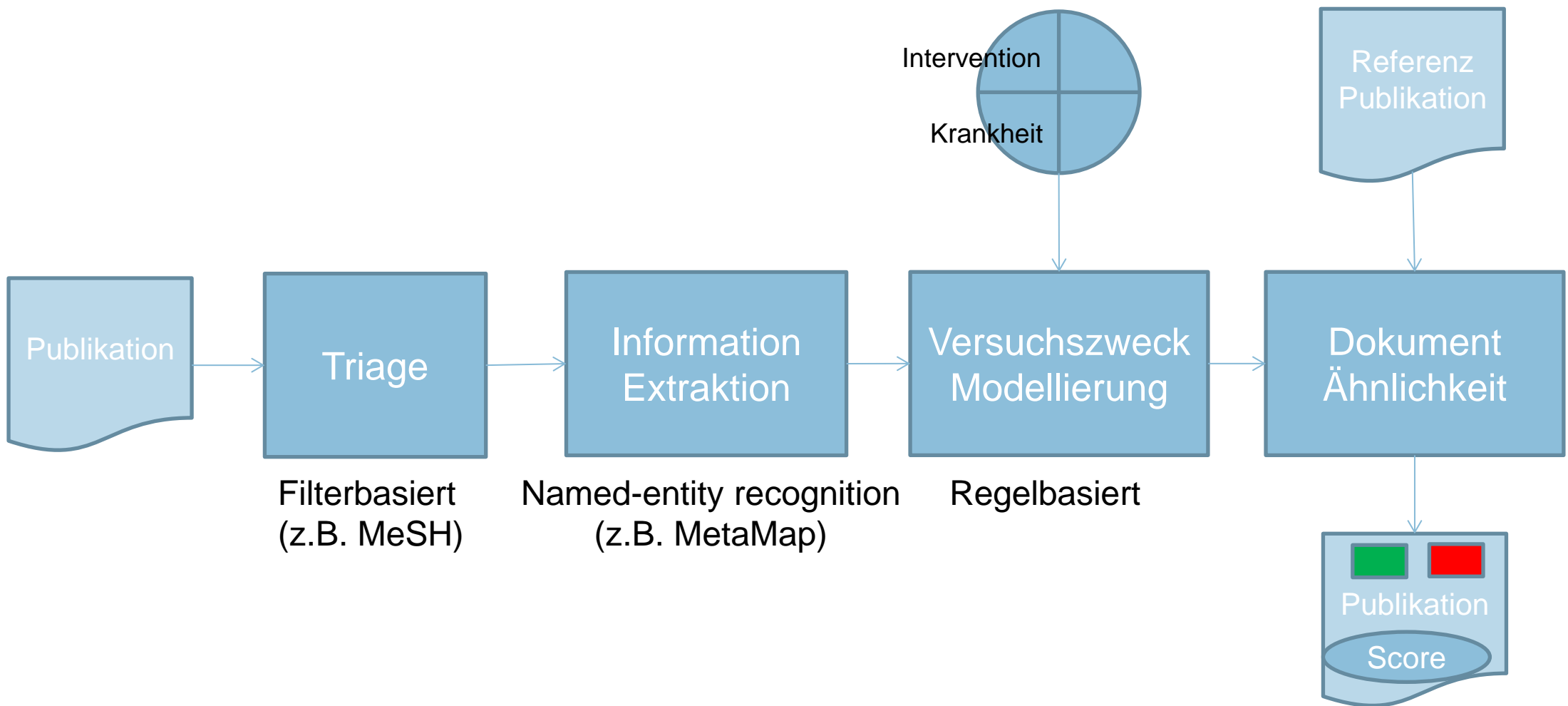


Input: PMID

Andere Visualisierung, z.B. Word Clouds

<input type="checkbox"/>	Dokument 1	87% Ähnlichkeit	Grund für Ähnlichkeit: MeSH Terms, ähnliche Wörter, Versuchszweck, usw.
<input type="checkbox"/>	Dokument 2		
<input type="checkbox"/>	Dokument 3		
	...		



# Suchmaschine: Workflow Textmining



Filterbasiert  
(z.B. MeSH)

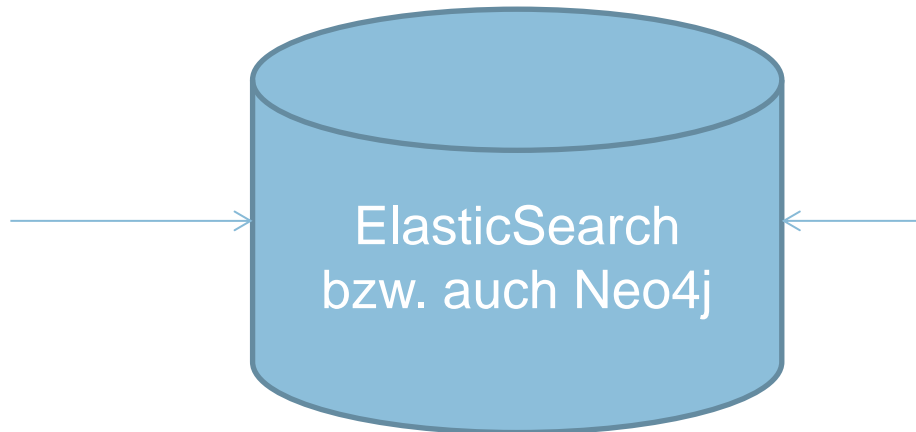
Named-entity recognition  
(z.B. MetaMap)

Regelbasiert

-  ähnliche Eigenschaften
-  nicht-ähnliche Eigenschaften

# Suchmaschine: Datenbank

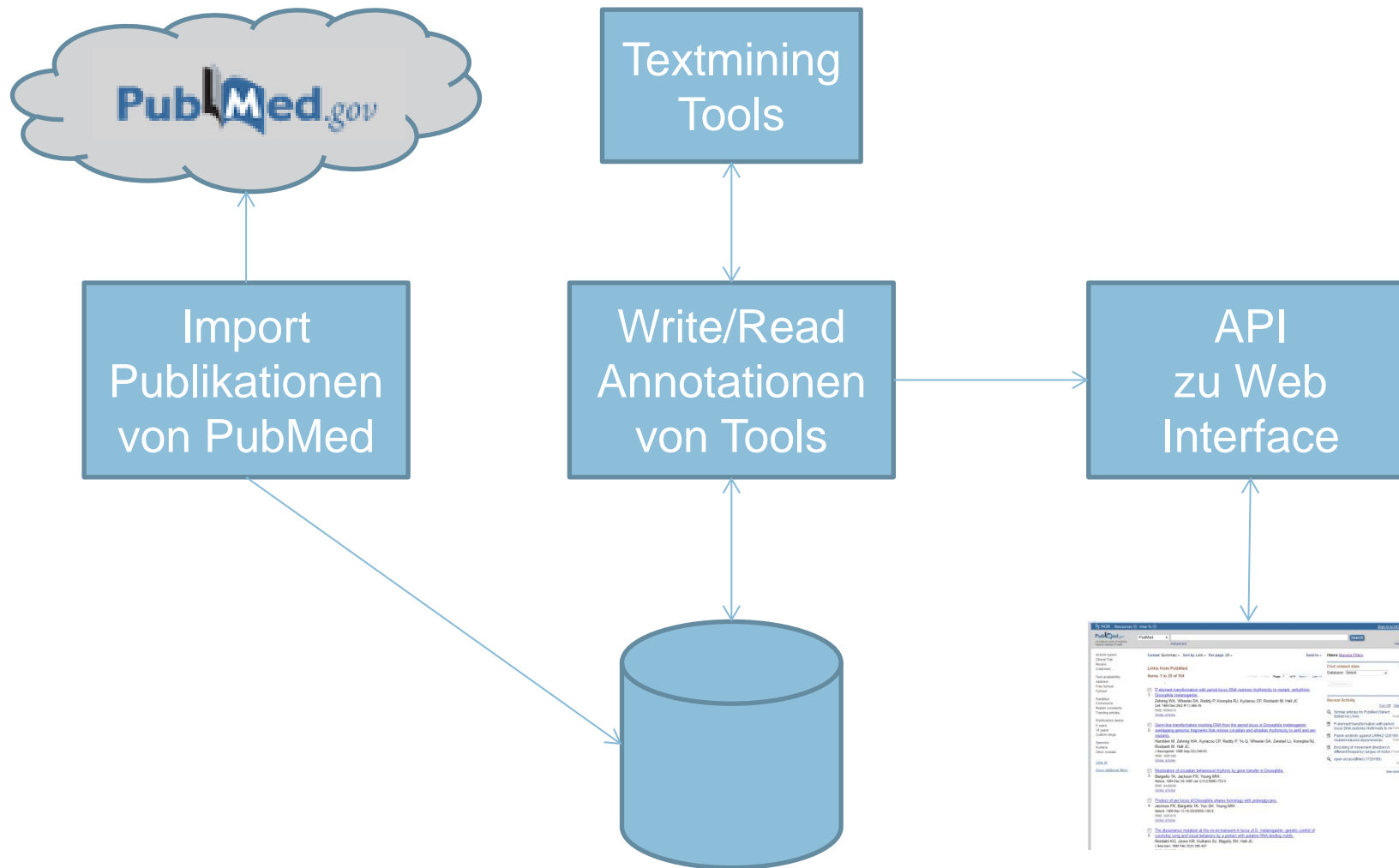
Publikationen  
von PubMed  
(Abstract,  
Fulltext)



ElasticSearch  
bzw. auch Neo4j

Entitäten  
von MetaMap,  
MeSH, usw.

# Suchmaschine: Middleware



# Funktionsumfang

- Suche nach Ähnlichkeit für input (PubMed-) Publikation
- Ranking der Publikationen, die Alternativenmethoden für Tierversuch beschreiben
- Web-basierte Visualisierung von Dokumenten mit Gründen für die Ähnlichkeit , bzw. auch Word Clouds
- Skalierbarkeit, intuitive Benutzbarkeit, ansprechendes Design
- Read und Write bzgl. Datenbasis
- ... genaueres folgt ...

# Ablauf

- Wir übernehmen die **Benutzerrolle**: Angabe, \*was\* wir wollen, nicht, wie es (technisch) umgesetzt wird
- Aber auch Kontrolle
- Sie übernehmen die **Anbieterrolle**: Spezifikation des Funktionsumfangs, Aufteilung in Teilprojekte, Modellierung, Implementierung, Test, Abnahme (wir moderieren)
- Typischerweise: Drei oder Vier Teilprojekte (TP) plus Projektleitung (PL)
- Engmaschige Aufgaben mit Abgaben, die diskutiert werden
- Begleitung durch GitHub

# Begleitprogramm

- An 4-6 Terminen werden zusätzlich Hintergrund und Anwendungswissen in 45-90 Minuten Vorträgen präsentiert
- Biomedizinische Textmining (Neves)
- Grundlagen von Suchmaschinen und semantische Suchmaschinen (Neves)
- Tierversuch und Alternativenmethoden (Butzke/Grune)
- Literaturrecherche in der Biomedizin (Butzke)
- Benutzung von GitHub (Bux)
- Webprogrammierung (Starlinger)



# Ablauf Überblick 1/4

- Oktober (Spezifikation)
  - Spezifikation des Funktionsumfangs, Formulierung von Use Cases
  - Aufteilung in Teilprojekte und Teams
  - Funktionale Charakterisierung der Teilprojekte
  - Initiale Festlegung benutzter Technologien (alle)
  - Benennung zentraler Schnittstellen (alle)

# Ablauf Überblick 2/4

- November (Spezifikation, Modellierung, Implementierung)
  - Definition Style-Guide (PL)
  - Initiale Projektplanung inkl. Meilensteine (Benutzer und PL)
  - Festlegung der Teilprojektschnittstellen (insb. PL)
  - Software-Modellierung der Teilprojekte (alle)
  - Planung Testfälle (Teilprojekte und PL)
  - Mock-Ups der Benutzeroberfläche (entsprechendes TP)
  - Besuch im BfR (Labore und Background-Vorträge): 03.11.

# Ablauf Überblick 3/4

- Dezember (Implementierung)
  - Implementierung der Teilprojekte
  - Implementierung und Durchführung der TP-Testfälle

# Ablauf Überblick 4/4

- Januar (Implementierung, Integration, Test)
  - Integrationstests
  - Fehlerdokumentation und Zuweisung
  - Bug Fixing
  - Code Dokumentation
  
- Februar (Abnahme)
  - Abnahme
  - Präsentationen, Projektdokumentation (Wiki in GitHub), Poster
  - Projektabschluss

# Teilnehmer

Die Mindestzahl ist acht (8) Teilnehmer,  
die Höchstzahl ist sechzehn (16) Teilnehmer.

## Literatur bis Freitag 27.10.17

- Sauer UG, Wächter T, Grune B, Doms A, Alvers MR, Spielmann H, Schroeder M. Go3R - semantic Internet search engine for alternative methods to animal testing. ALTEX. 2009; 26(1):17-31. ([http://www.altex.ch/resources/altex\\_2009\\_1\\_17\\_31\\_Sauer.pdf](http://www.altex.ch/resources/altex_2009_1_17_31_Sauer.pdf))
- Thomas P, Starlinger J and Leser U. (2013). Experiences from Developing the Domain-Specific Entity Search Engine GeneView. BTW, Magdeburg, Germany. ([https://www.informatik.hu-berlin.de/de/forschung/gebiete/wbi/research/publications/2013/btw\\_geneview.pdf](https://www.informatik.hu-berlin.de/de/forschung/gebiete/wbi/research/publications/2013/btw_geneview.pdf))

## Literatur bis Freitag 15.11.17

- Hirschman L, Burns GA, Krallinger M, Arighi C, Cohen KB, Valencia A, Wu CH, Chatr-Aryamontri A, Dowell KG, Huala E, Lourenço A, Nash R, Veuthey AL, Wiegers T, Winter. Text mining for the biocuration workflow. Database (Oxford). 2012 Apr.  
(<https://academic.oup.com/database/article/doi/10.1093/database/bas020/434747/Text-mining-for-the-biocuration-workflow>)
- Jovanović J and Bagheri E. Semantic annotation in biomedicine: the current landscape. Journal of Biomedical Semantics, 2017; 8:44  
(<https://jbiomedsem.biomedcentral.com/articles/10.1186/s13326-017-0153-x>)

# Ähnliche Suchmaschine für Biomedizin

- PolySearch2:

- Paper: <https://academic.oup.com/nar/article-lookup/doi/10.1093/nar/gkv383>

- Application: <http://polysearch.cs.ualberta.ca/>

- Semedico:

- Paper: <http://www.aclweb.org/anthology/P17-4016>

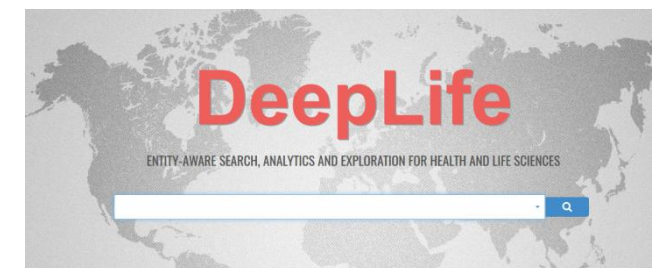
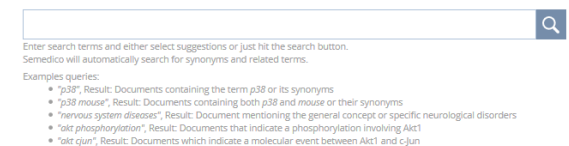
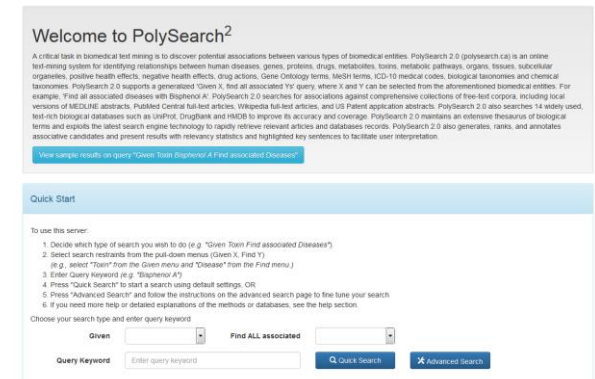
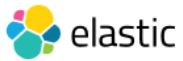
- Application: <http://www.semedico.org/>

- DeepLife:

- Paper:

- <https://www.aclweb.org/anthology/P/P16/P16-4004.pdf>

- Application: <https://gate.d5.mpi-inf.mpg.de/deeplife/en-health/>





# Ähnliche Suchmaschine für Biomedizin

- GeneView:

- Paper:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3394277/>

- Application: <http://bc3.informatik.hu-berlin.de/>

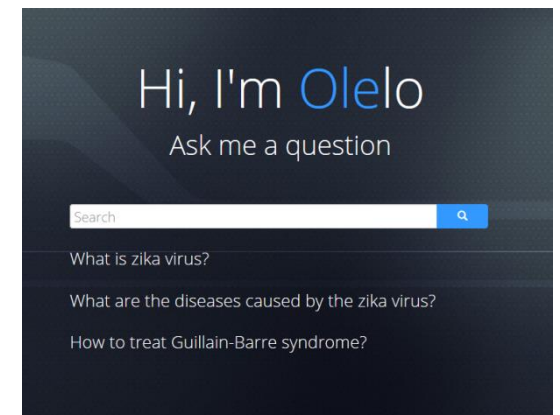
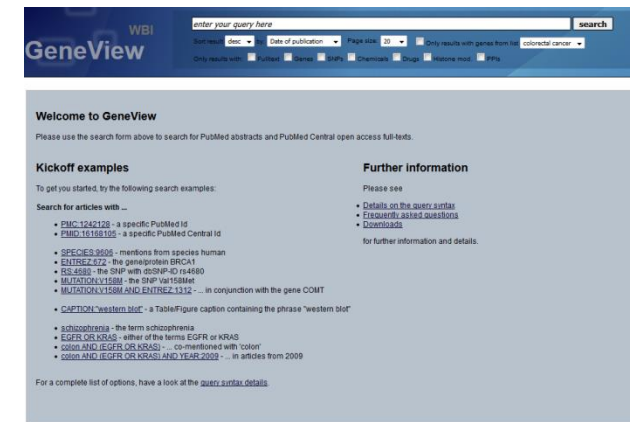


- Olelo:

- Paper:

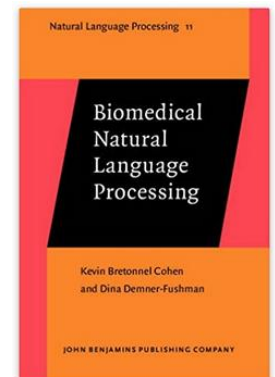
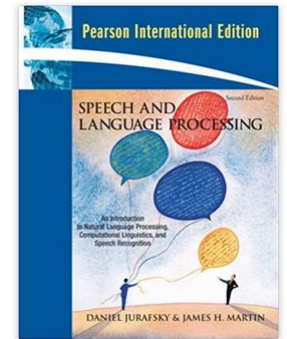
<https://academic.oup.com/nar/article/doi/10.1093/nar/gkx363/3791211/Olelo-a-web-application-for-intuitive-exploration>

- Application: <http://www.hpi.de/plattner/olelo>



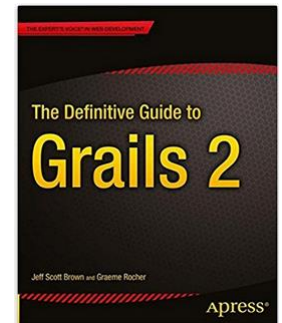
# Zusätzliche Literatur für die nächsten Wochen

- Textmining und “Natural Language Processing”
  - Daniel Jurafski und James H. Martin. (2008) Speech and Language Processing, Prentice Hall, 2<sup>nd</sup> edition.
  - 3<sup>rd</sup> edition online: <https://web.stanford.edu/~jurafsky/slp3/>
  - Kevin Bretonnel Cohen und Dina Dehmen-Fushman. (2014) Biomedical Natural Language Processing, John Benjamins Publishing Co.



# Zusätzliche Literatur für die nächsten Wochen

- Software, z.B., Grails
  - Jeff Scott Bown und Graeme Rocher (2013) The Definitive Guide to Grails 2, Apress; 1<sup>st</sup> edition
  
- Projektmanagement
  - Tom DeMarco und Doris Märtin (1998). Der Termin: Ein Roman über Projektmanagement. Hanser Fachbuch



# Kontakt

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