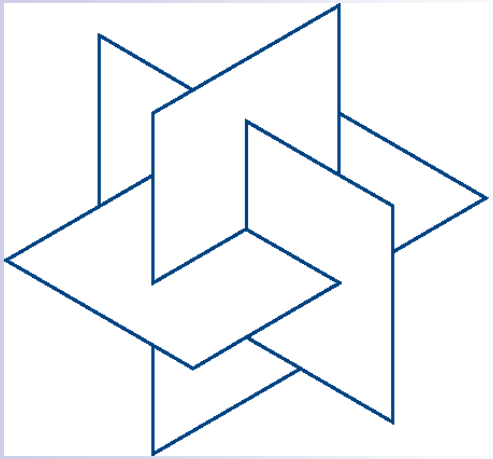
Mit Mathe zu neuen medizinischen Wirkstoffen



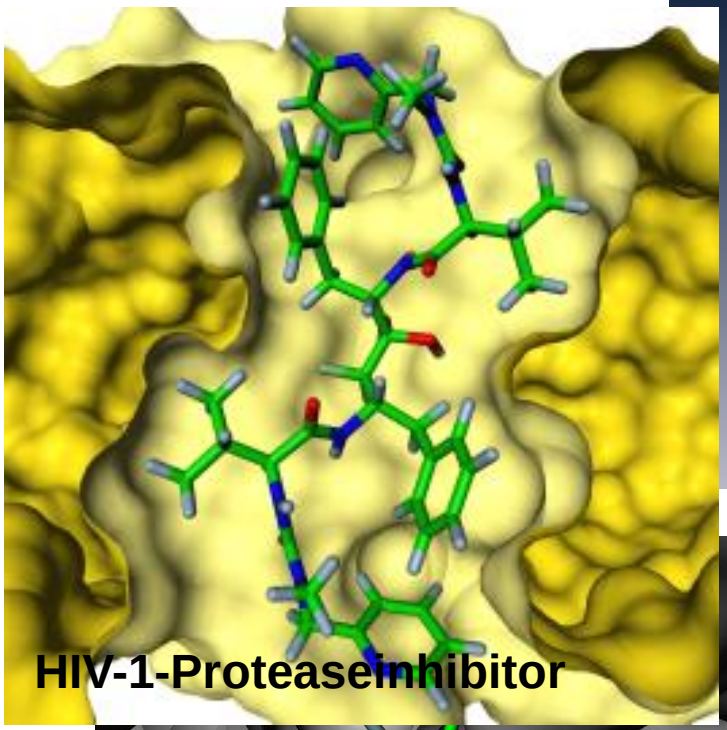
Dr. Marcus Weber
Arbeitsgruppenleiter
Computational Drug Design
Zuse-Institut Berlin (ZIB)

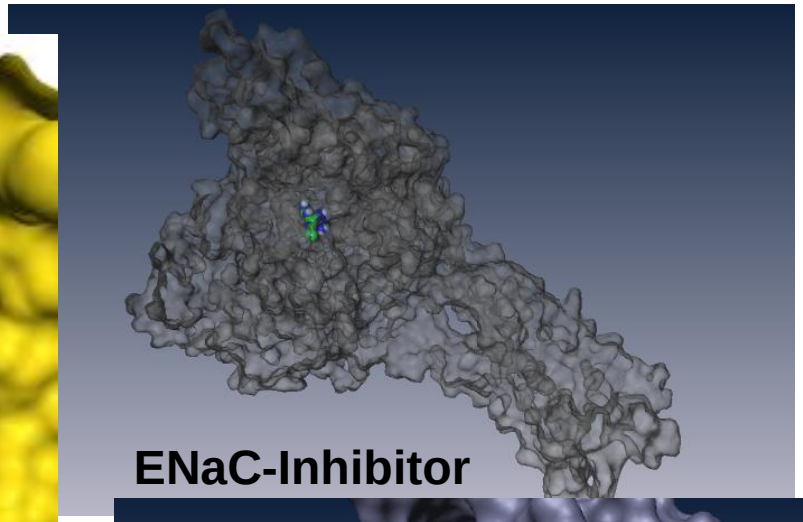
Mitglied im MATHEON

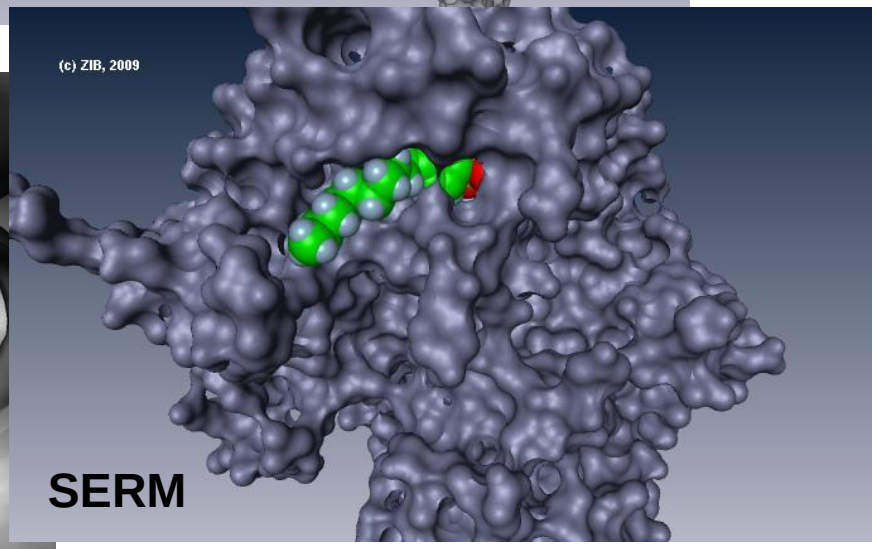
Geschäftsführer
molConcept GmbH

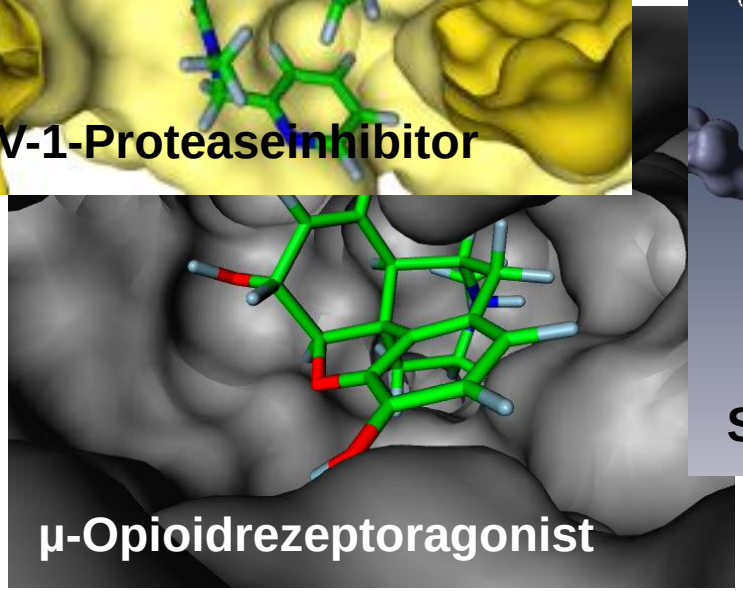
molConcept

Wirkstoffentwurf

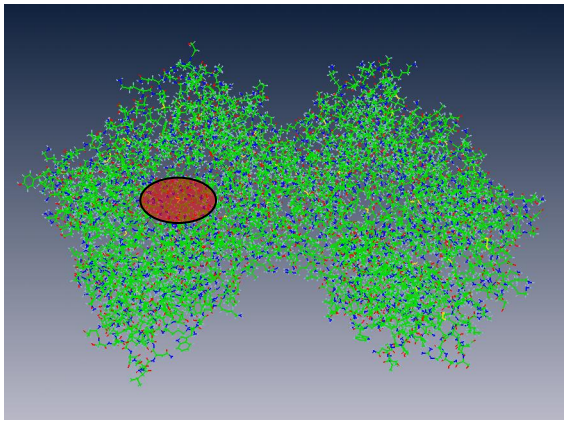








Beispiel: Inhibition von DPP-IV



Insulinausschüttung
Insulinsynthese
Beta-Zell-Proliferation

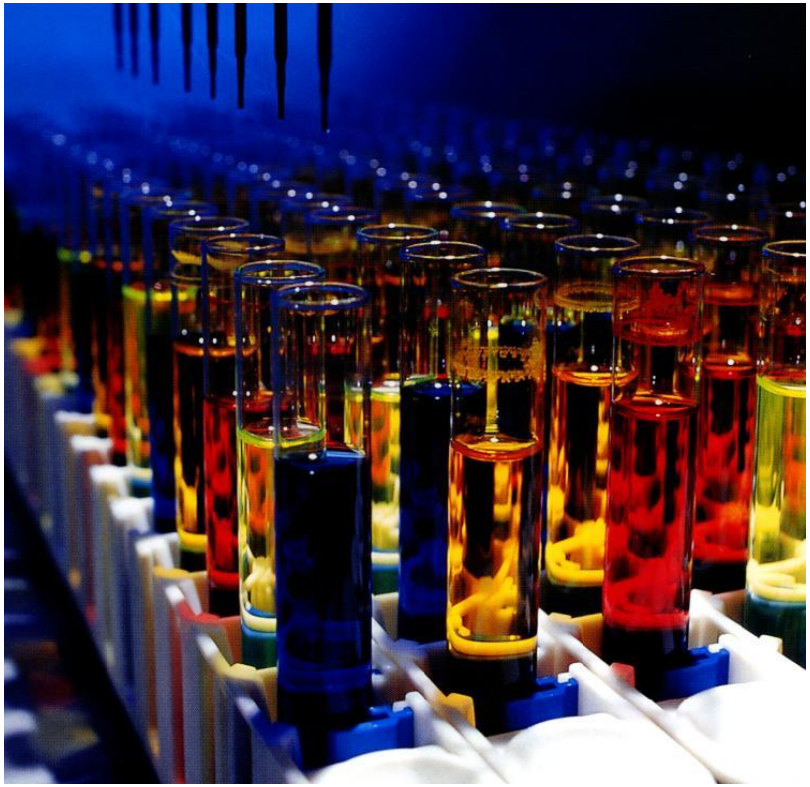
Magenentleerung
Glucagonausschüttung
Hungergefühl

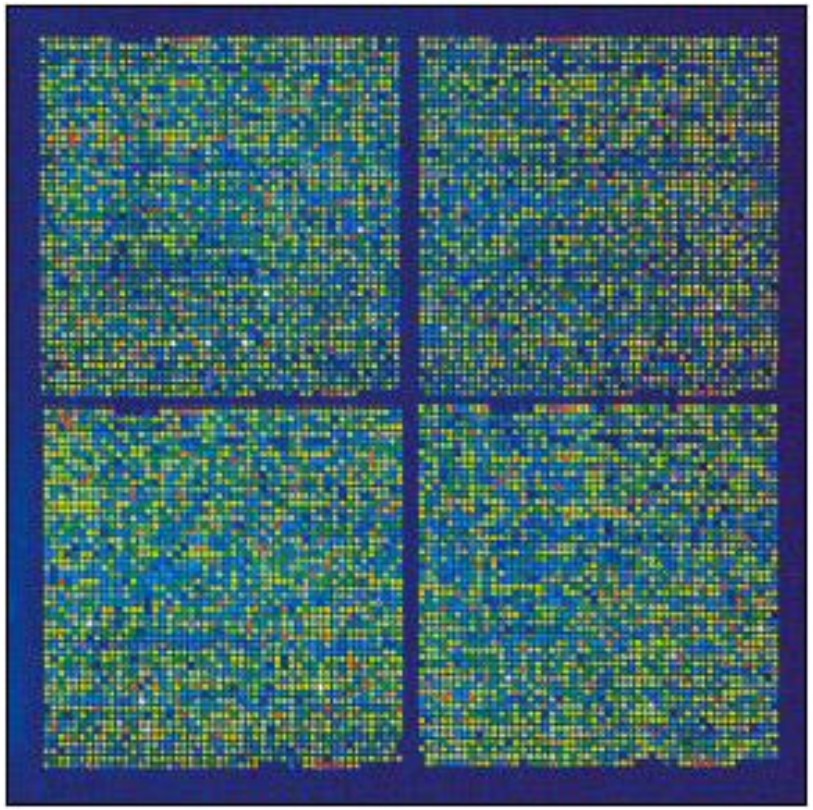
Inkretine

DPP-4

Diabetes Mellitus Typ 2

Screening zum Auffinden von Inhibitorkandidaten





Vom Inhibitorkandidaten zum Medikament

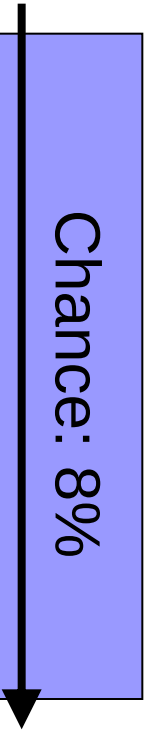
Screening	20.000 (oder viel mehr) -> 20

Phase 0	Pharmakokinetik, Dosen: subtherapeutisch
Phase I	Verträglichkeitsstudie, „First In Men“
Phase II	a: proof of concept, b: dose finding
Phase III	signifik. Wirkungsnachweis, Markteinführung
Phase IV	Nebenwirkungen, etc.

Vom Inhibitorkandidaten zum Medikament

Screening	20.000 (oder viel mehr) -> 20

Phase 0	bis ca. 15 Pers.	Dauer: Wochen
Phase I	bis ca. 80 Pers.	Dauer: Wochen
Phase II	bis ca. 200 Pers.	Dauer: Monate
Phase III	bis ca. 10.000 Pers.	Dauer: Jahre
Phase IV	je nach Medikament	Dauer: Jahre



Vom Inhibitorkandidaten zum Medikament

Screening	20.000 (oder viel mehr) -> 20
„Wirkstoffentwurf“	20 -> 1

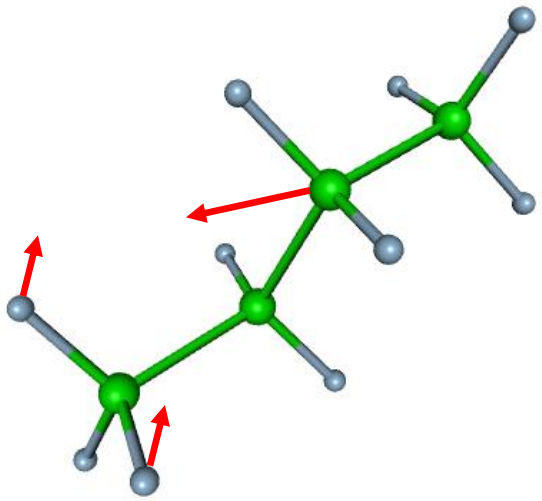
Phase 0	Pharmakokinetik, Dosen: subtherapeutisch
Phase I	Verträglichkeitsstudie, „First In Men“
Phase II	a: proof of concept, b: dose finding
Phase III	signifik. Wirkungsnachweis, Markteinführung
Phase IV	Nebenwirkungen, etc.

Zustandsraum

Molekulares System mit N Atomen

$p \in \Gamma$: 3N Koordinaten für die Impulse

$q \in \Omega$: 3N Koordinaten für die Atompositionen



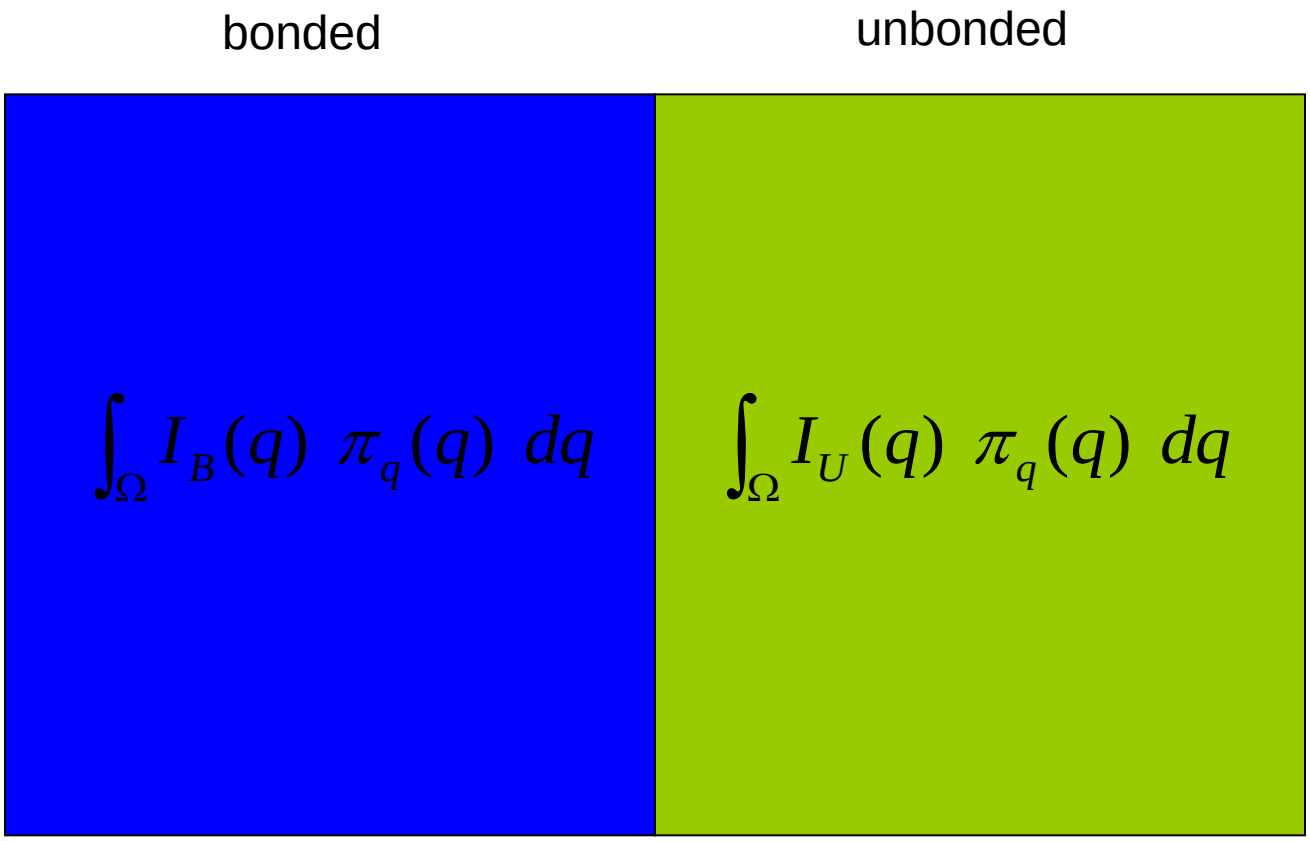
Kanonisches Ensemble

Boltzmann-Verteilung der Molekülzustände bei Temperatur T

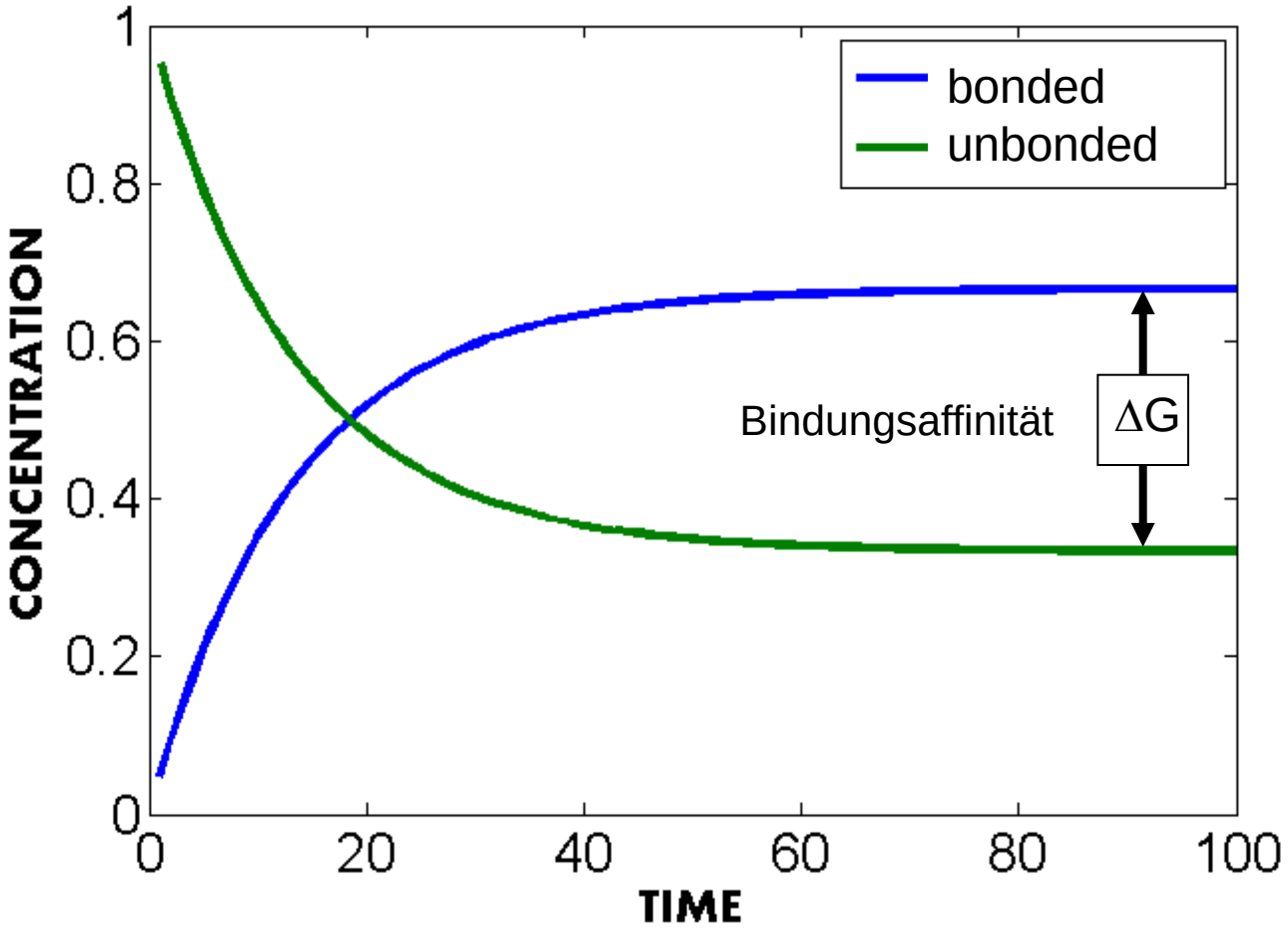
$$H(p,q) = K(p) + V(q) \quad \Rightarrow$$

$$\pi \propto \exp\left(-\frac{1}{k_B T} H\right) \Rightarrow \begin{cases} \pi_p(p) \propto \exp\left(-\frac{1}{k_B T} K(p)\right) \\ \pi_q(q) \propto \exp\left(-\frac{1}{k_B T} V(q)\right) \end{cases}$$

Bindungsaffinität ΔG



Optimierung von Wirkstoffkandidaten

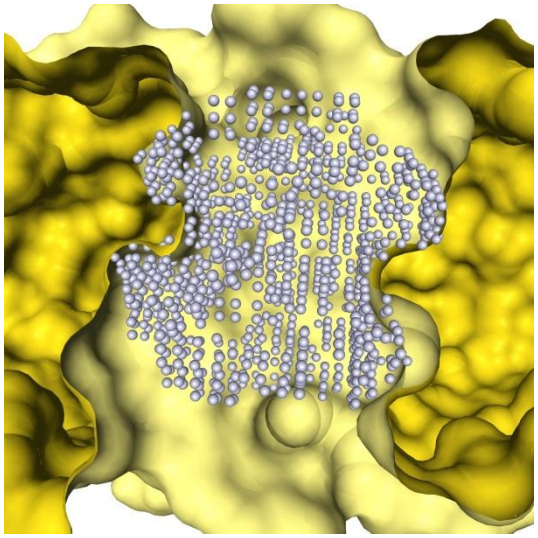


Alte Herangehensweise!

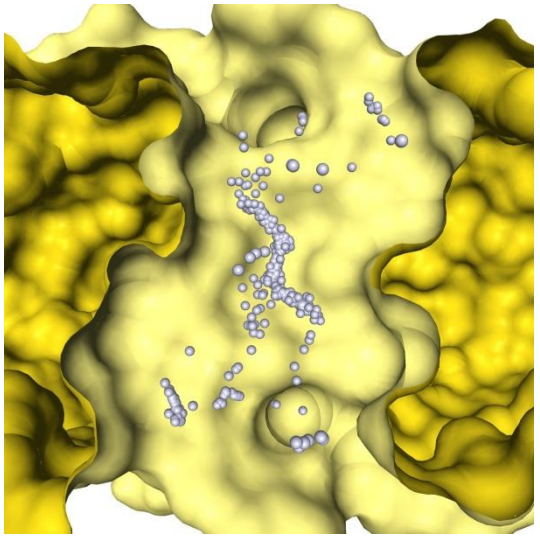
Docking-Software FaDo

Alte Herangehensweise!

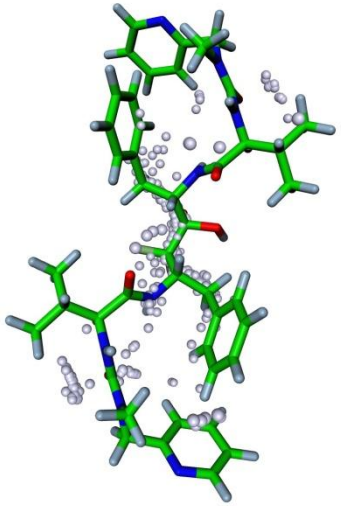
I



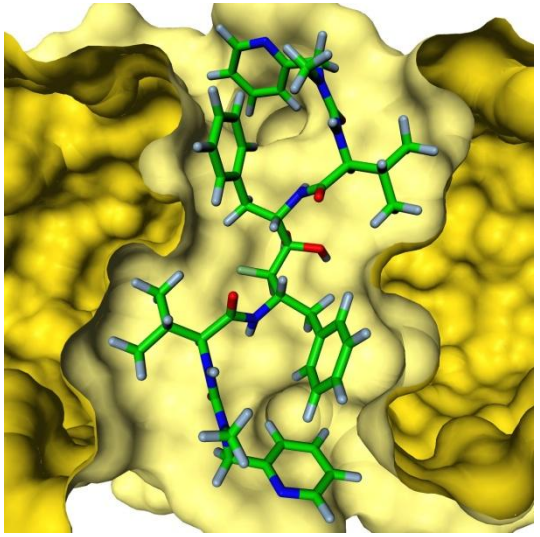
II



III

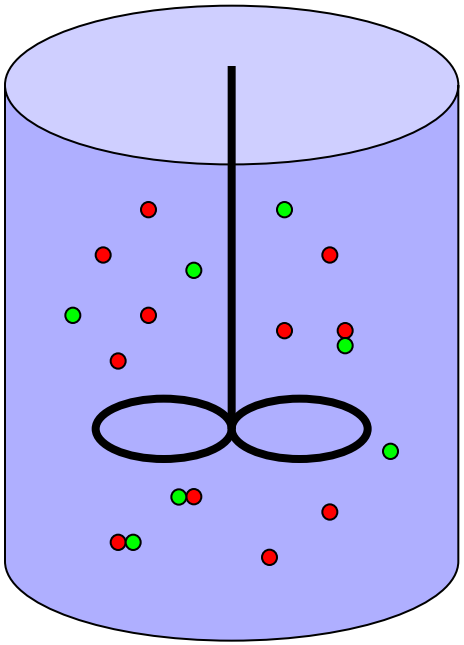


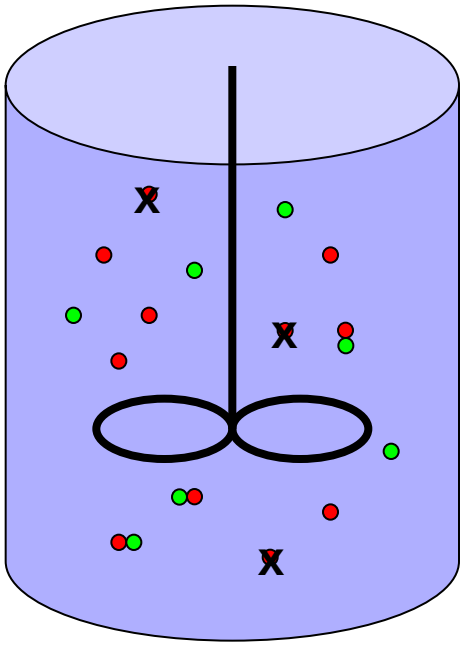
IV



A. Guerler, S. Moll, M. Weber, H. Meyer, F. Cordes (2008)

Metabolismus





unbonded

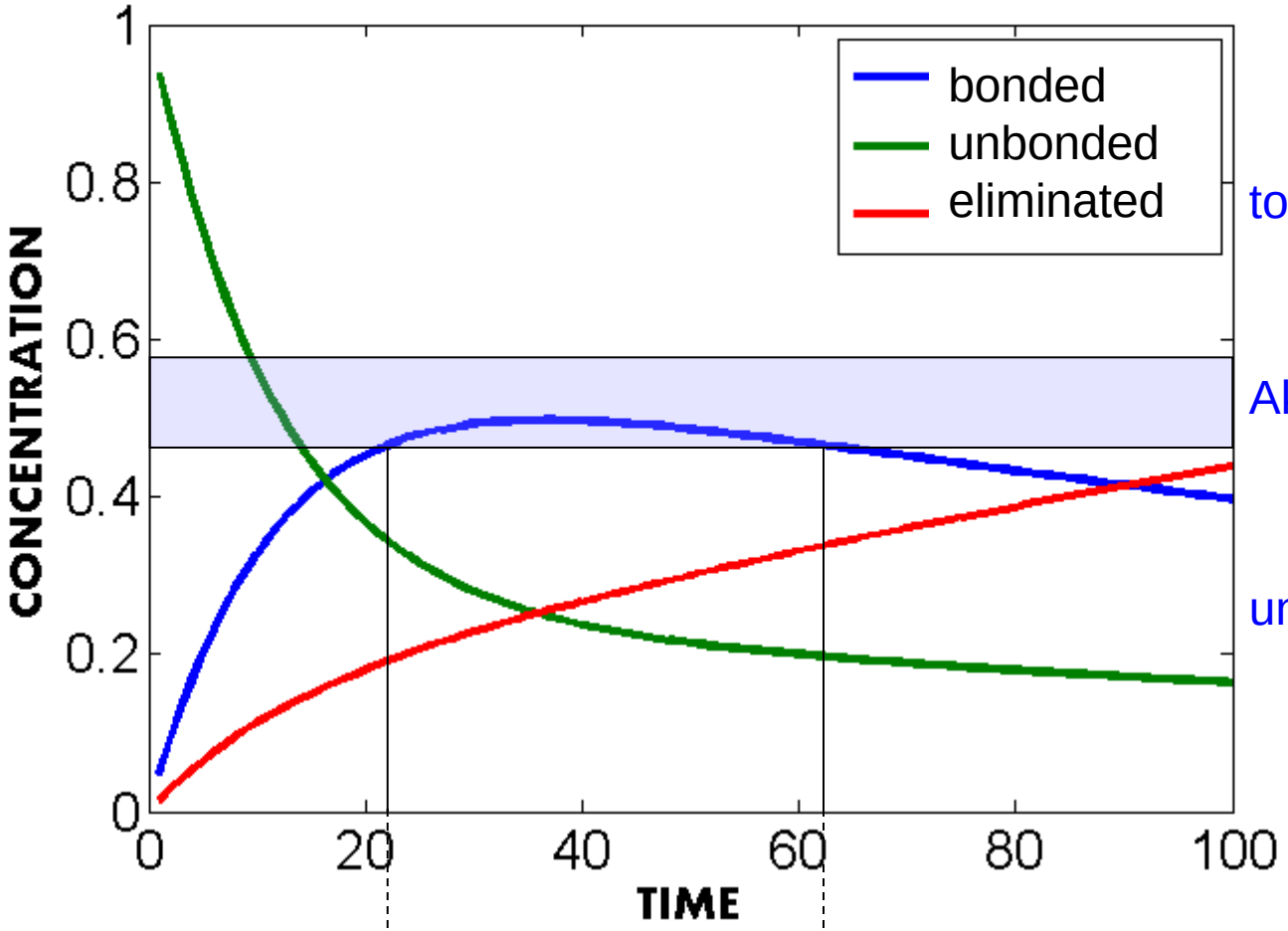
bonded

eliminated

drug molecules

Änderung des Konzepts!

Optimierung von Wirkstoffkandidaten



toxisch

Aktivitätsfenster

unwirksam

Aktivitätsperiode

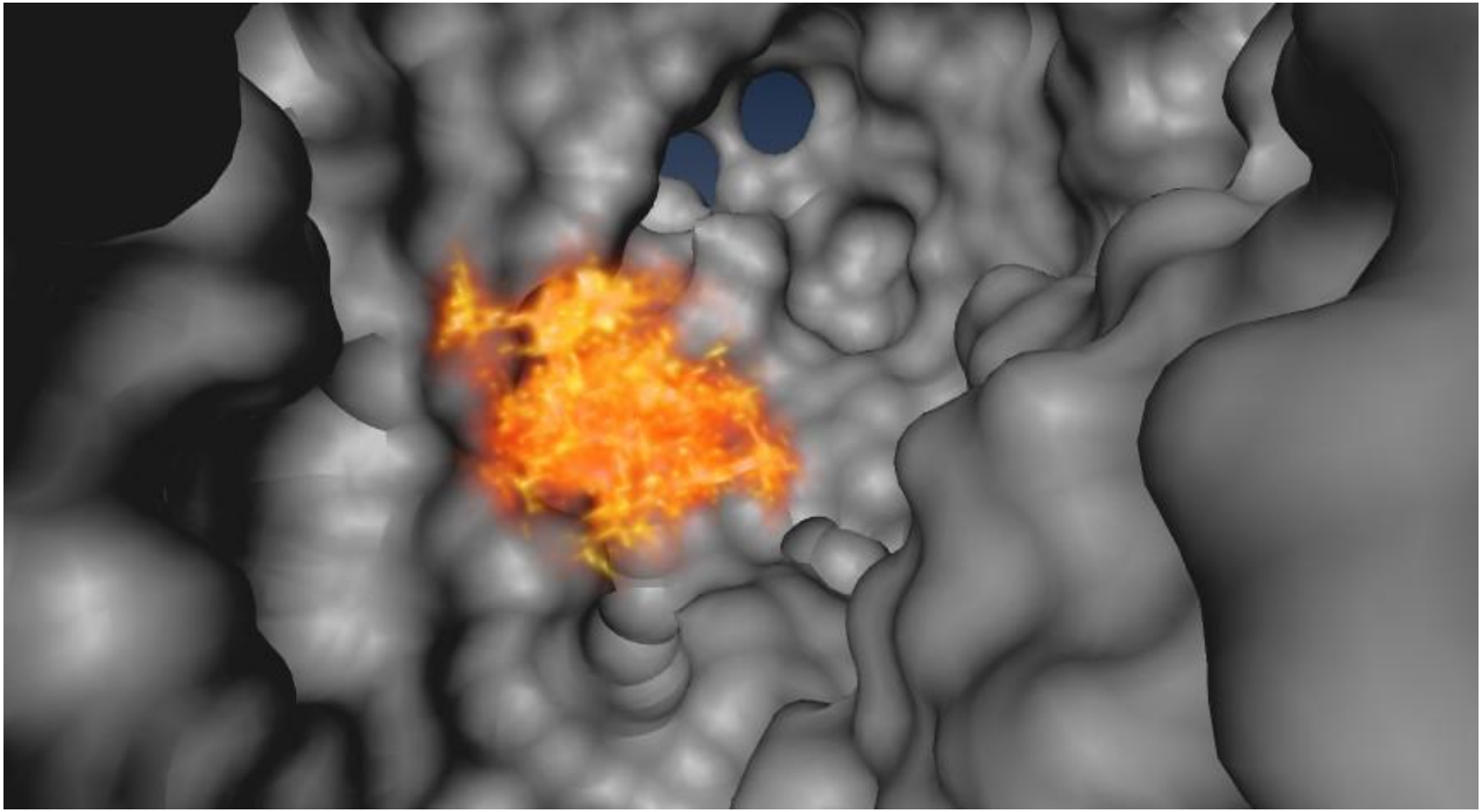
Neuer Ansatz!

Optimierung der Wirkstoffkandidaten durch Optimierung des Bindungsprozesses

Moleküldynamik

$$\dot{p} = -\frac{\partial H}{\partial q}, \quad \dot{q} = \frac{\partial H}{\partial p}$$

Simulation bei konstanter Temperatur



MD kann das Simulationsproblem nicht lösen

Gizmodo - Anton: 512-Processor Supercomputer Being Built to Simulate Molecules... Seite 1 von 1

Display: Condensed Most recent

Gizmodo

SUPERCOMPUTERS

Anton: 512-Processor Supercomputer Being Built to Simulate Molecules, Drugs

Named for microbiology pioneer Anton van Leeuwenhoek, Anton is currently being built with 512 highly specialized processors. These are clocked at just 400MHz, and the machine has modest memory, but its architecture lets it process problems in a massively-parallel way. Ultimately, that'll offer a performance boost of 1000x over current complex molecular simulations. And that's great news: these bits of math are how drug design works. It's different to processing done by existing supercomputers like BlueGene/L in that it will look at molecular behavior over a longer interval. That means scientists could discover new biological processes. "If you can do 1,000 times longer, real proteins come into play" as team leader David Shaw puts it. Anton should be in operation later this year. [ACM Library via NYTimes]

ANTON:

270 Jahre Simulationszeit, um eine Sekunde „Echtzeit“ zu simulieren.

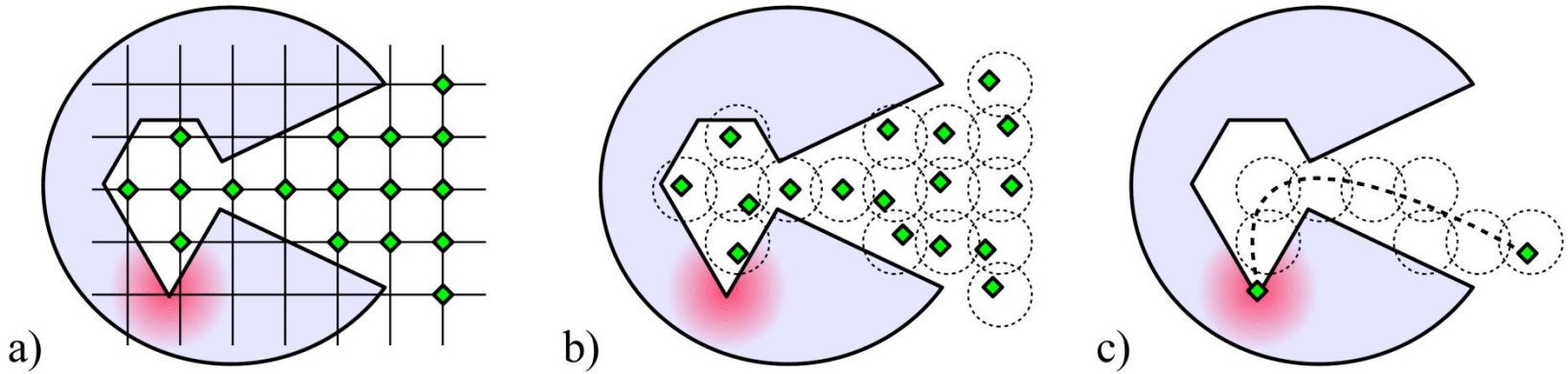
http://gizmodo.com/5022928/anton-512+processor-supercomputer-being-built-to-simulate-molecules-drugs

http://en.wikipedia.org/wiki/Anton_(computer)

(Stand: 26.06.2009)

MD kann das Simulationsproblem nicht lösen

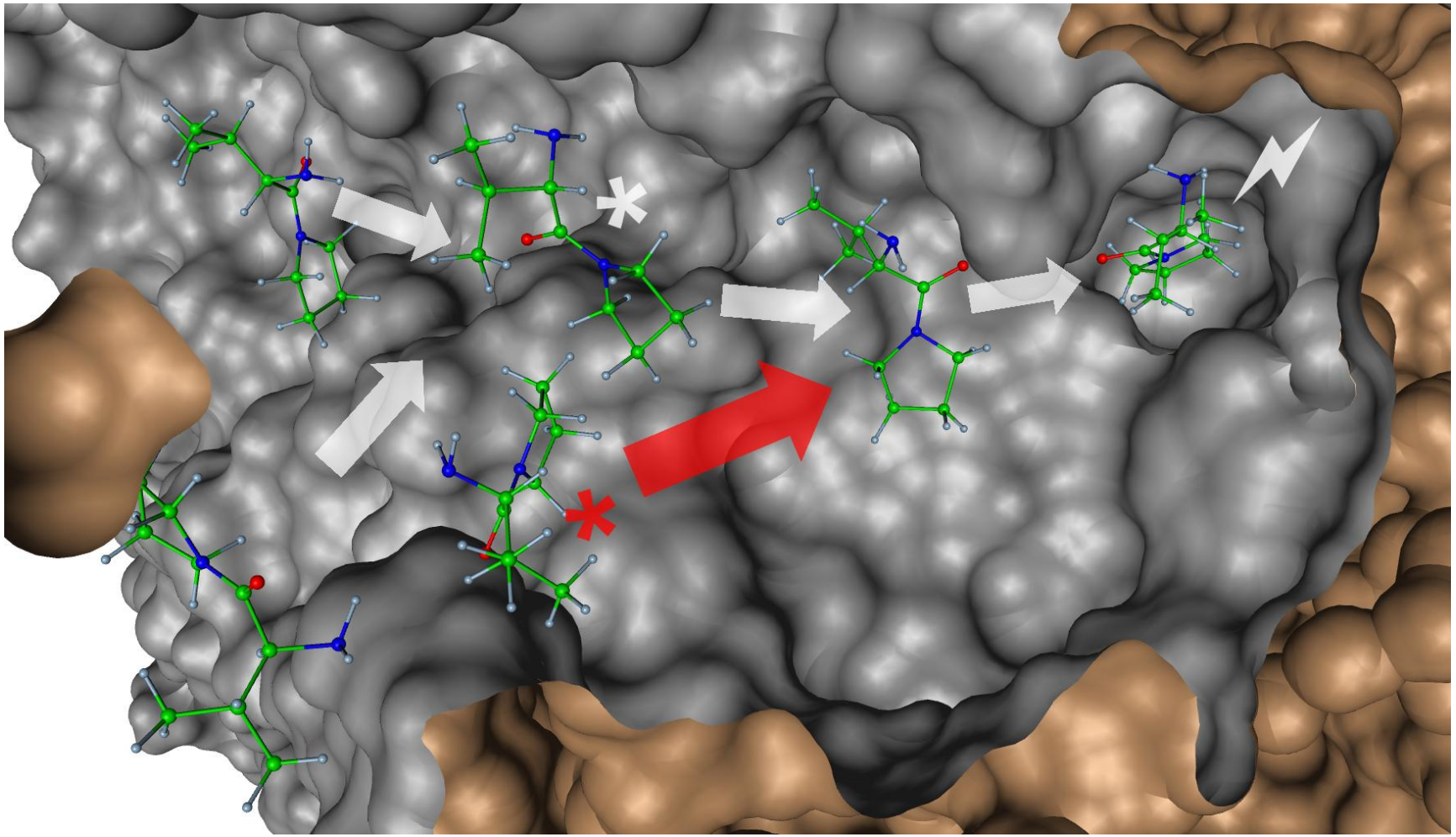
Gebietszerlegungsansatz



Der Gebietszerlegungsansatz kann das Simulationsproblem lösen (ZIB)

A. Bujotzek, M. Weber (2009)
S. Röblitz (2008); N. Singhal-Hinrichs, V. Pande (2005,2007)

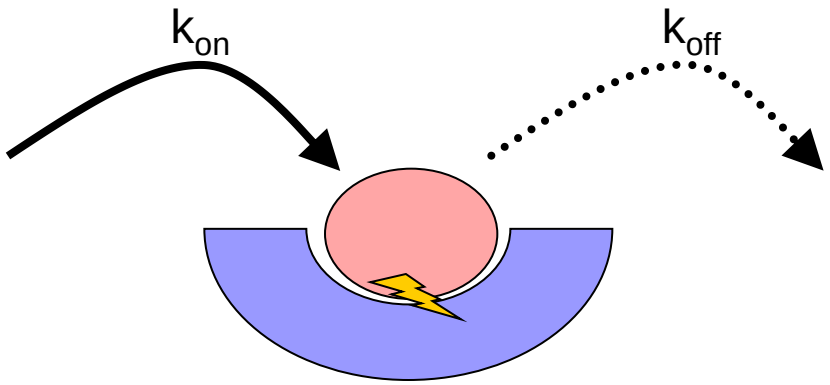
Simulation-Software: ZIBgridfree



7 Tage Rechenzeit für eine 8-AMD-Opteronprozessor-Einheit (je 2×2.6 GHz)

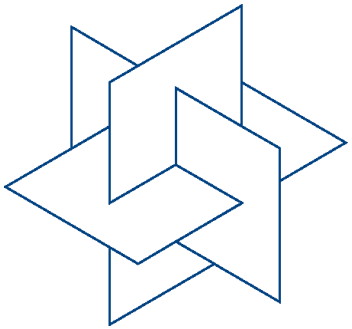
Simulation von Bindungsprozessen

- Optimierung von Wirkstoffkandidaten
- Trennsäulendesign
- Enzymdesign
- Entwurf von biologischen Filtermembranen…



Computational Drug Design

http://www.molconcept.com



http://www.zib.de/weber

http://www.matheon.de/research/show_project.asp?id=11