Was ist Bioinformatik?

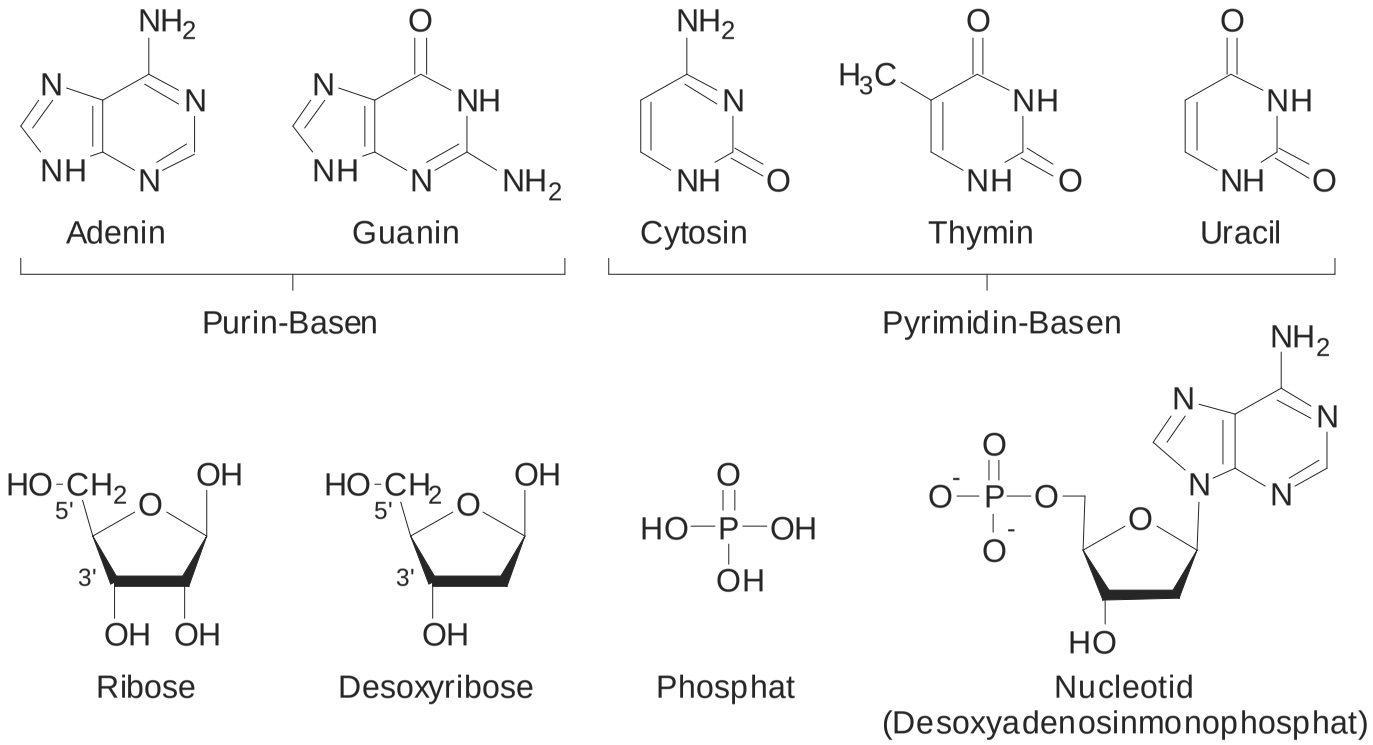
Alexander Vilbig

23. Oktober, 2001

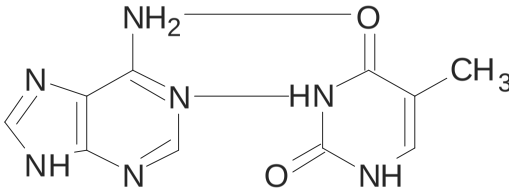
Übersicht

- Biologische Grundlagen
  - DNA, RNA, Gen, Protein, ...
- Informatik in der Biologie
  - Sequenz-Alignment
  - Molekulardynamik-Simulation
- Biologie in der Informatik
  - Evolutionäre Heuristiken
- Zusammenfassung & Ausblick
- Literatur und Ressourcen

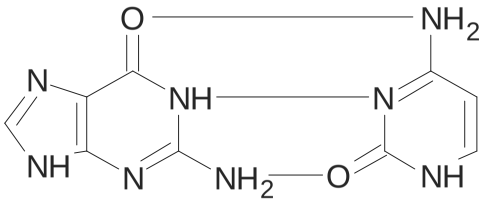
Nukleinsäuren I



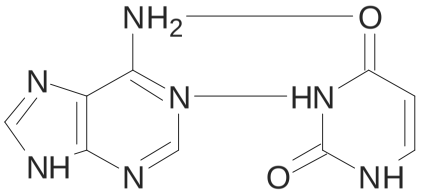
Nukleinsäuren II



Adenin Thymin



Guanin Cytosin



Adenin Uracil

roteine

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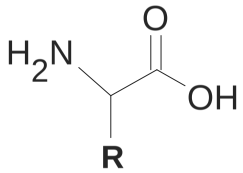

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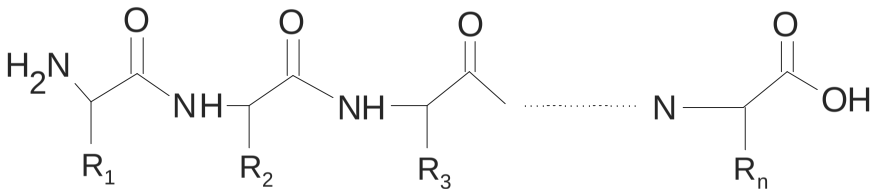

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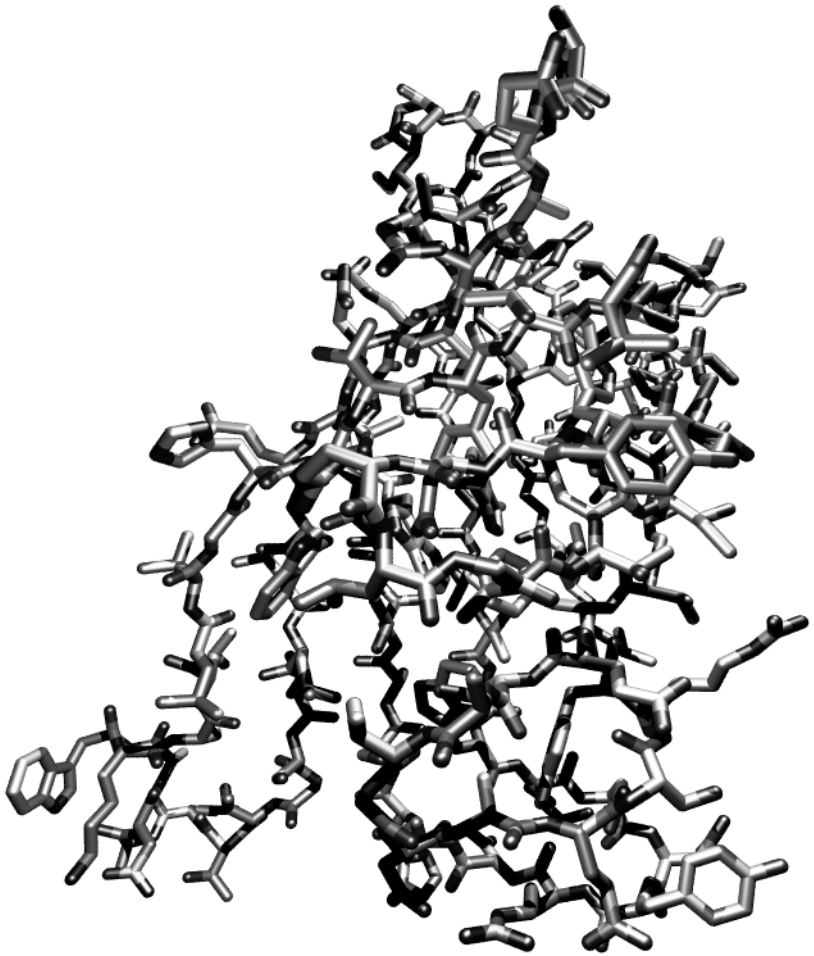

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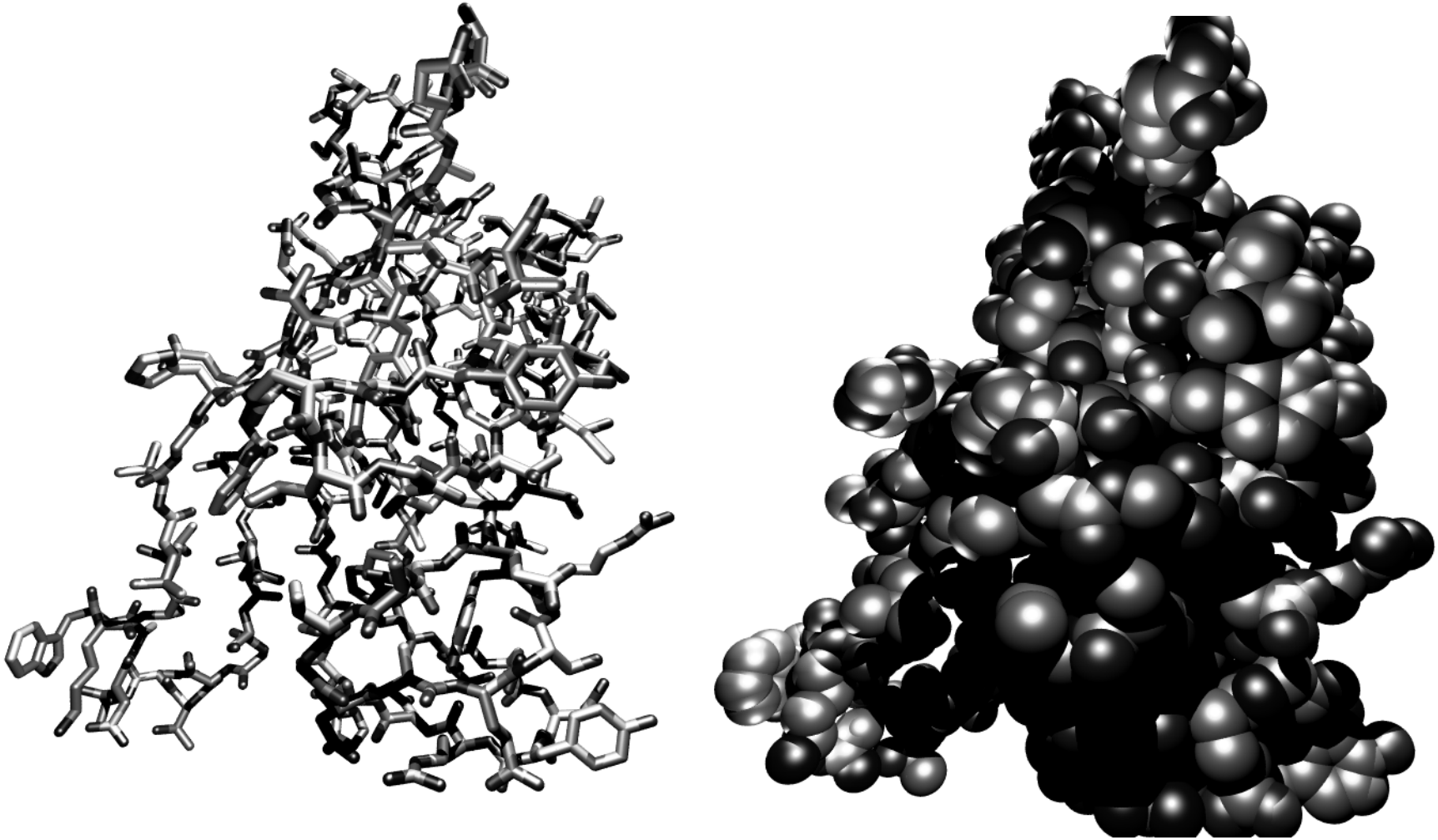

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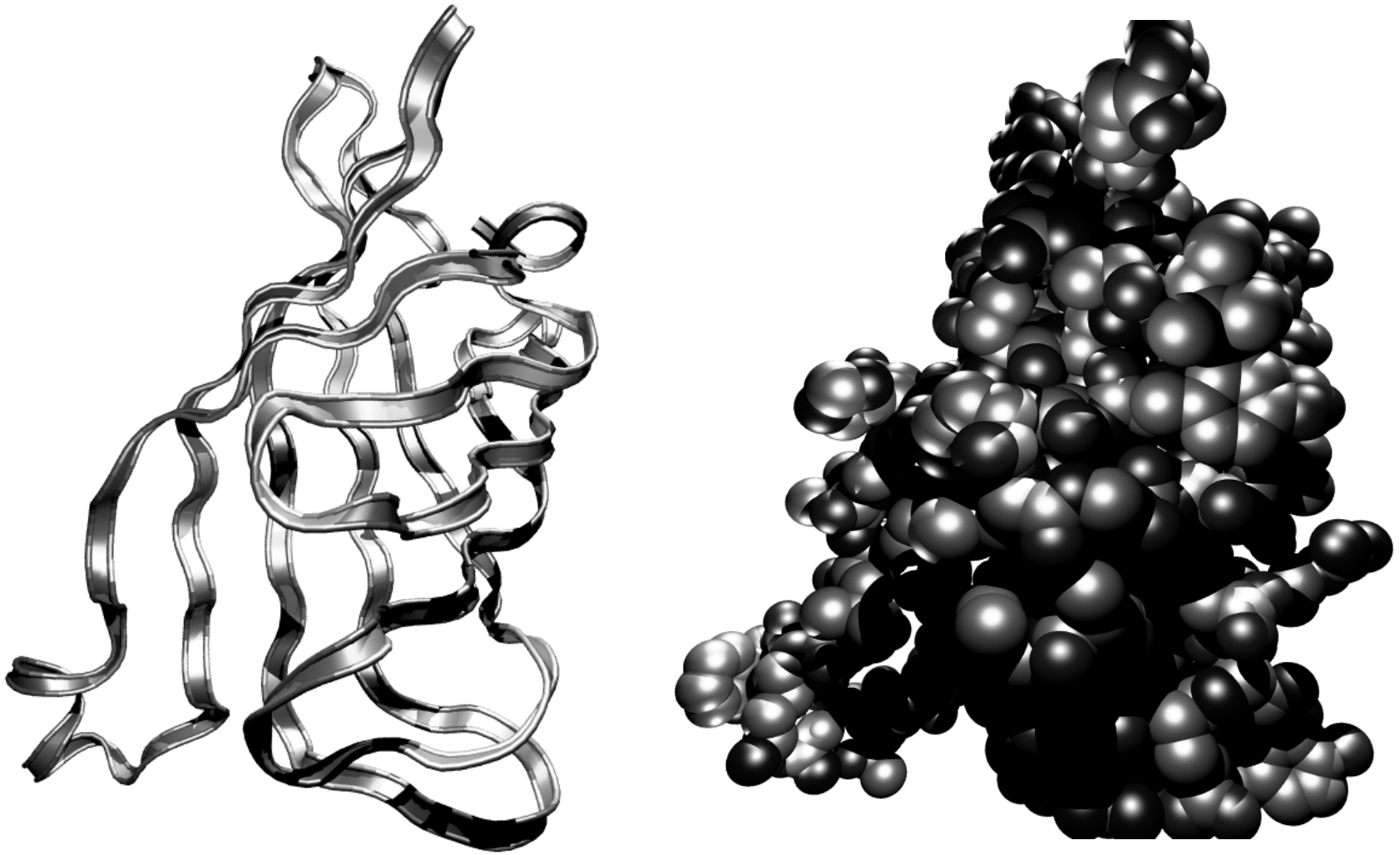

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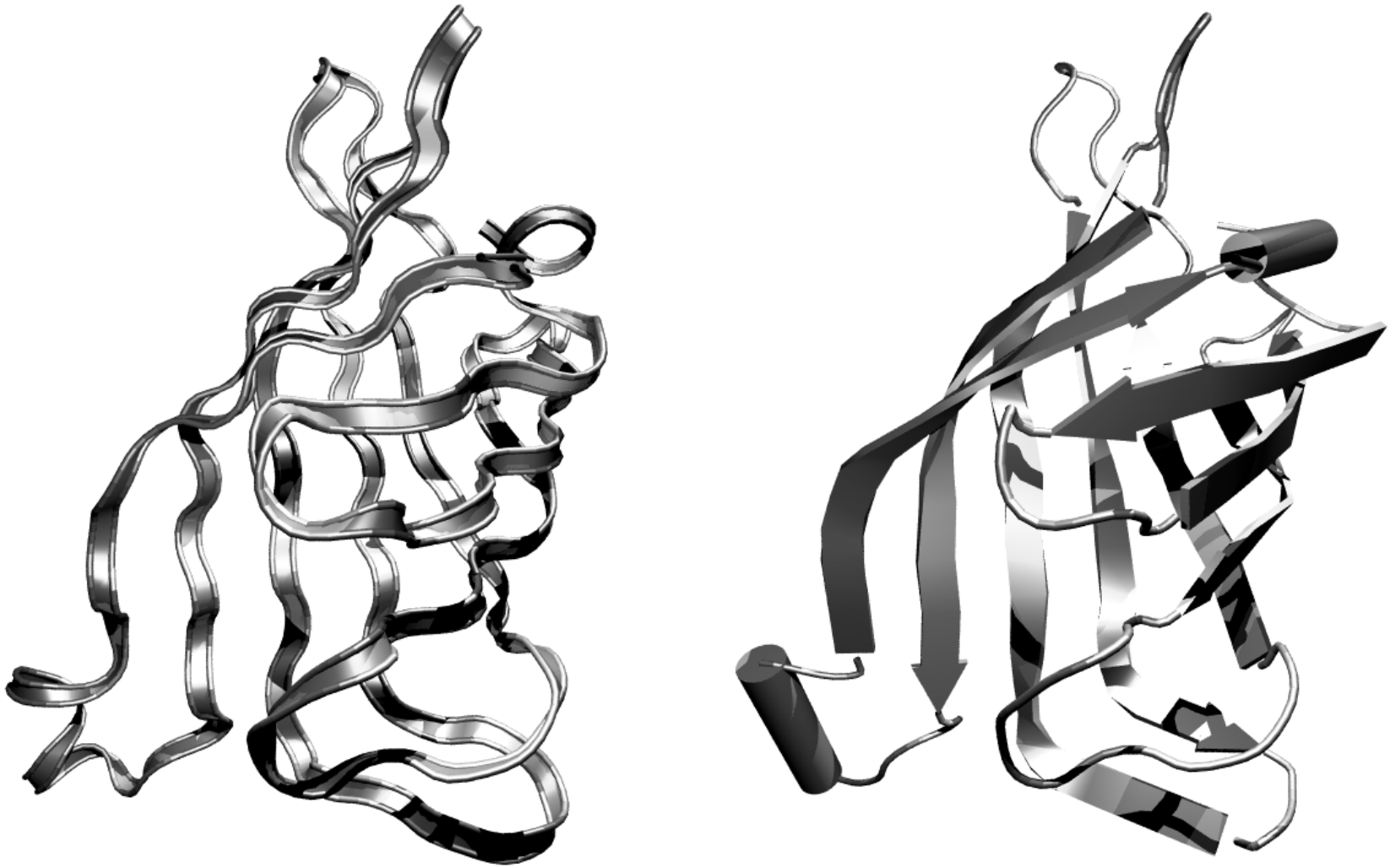

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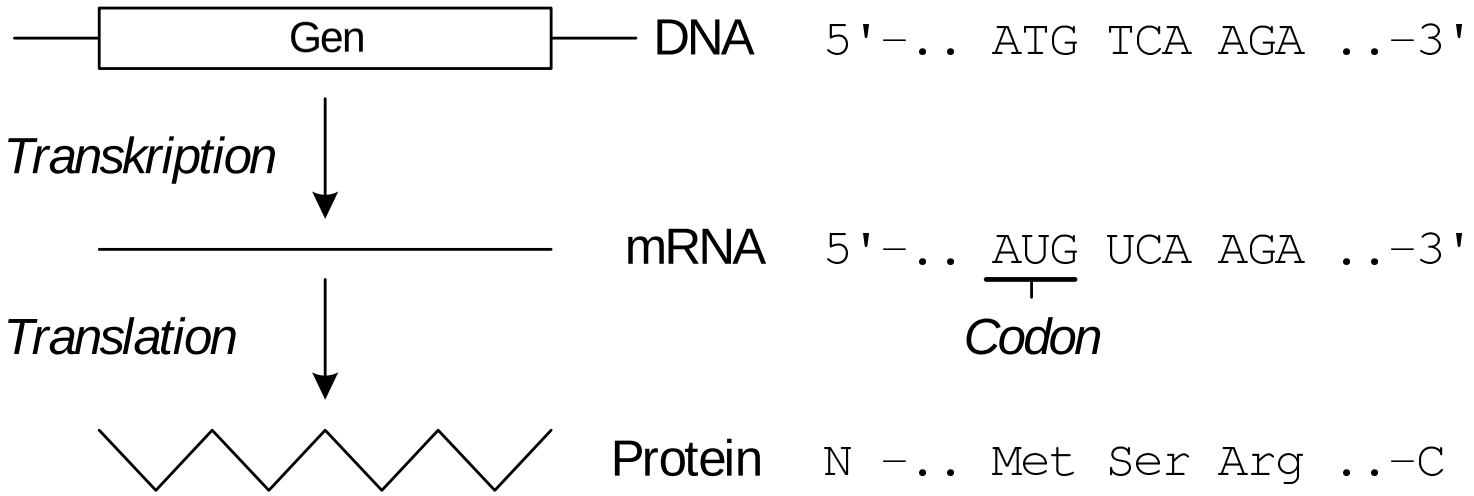
Gen
DNA
5'-.. ATG TCA AGA ..-3'
Transkription
mRNA
5'-.. AUG UCA AGA ..-3'
Translation
Codon
Protein
N -.. Met Ser Arg ..-C

□as menschliche □enom

- □mfa□t ca. □,□□□□□ Basen□aare
- Geschätzte □- □□□□ Gene
- Physisch verteilt auf □□□hromosomen
- Sequenzierung in □□□□□□□□□□raktisch abgeschlossen
  - Human Genome Pro□ect □ffentlich□
  - □elera Genomics Inc. □kommerziell□

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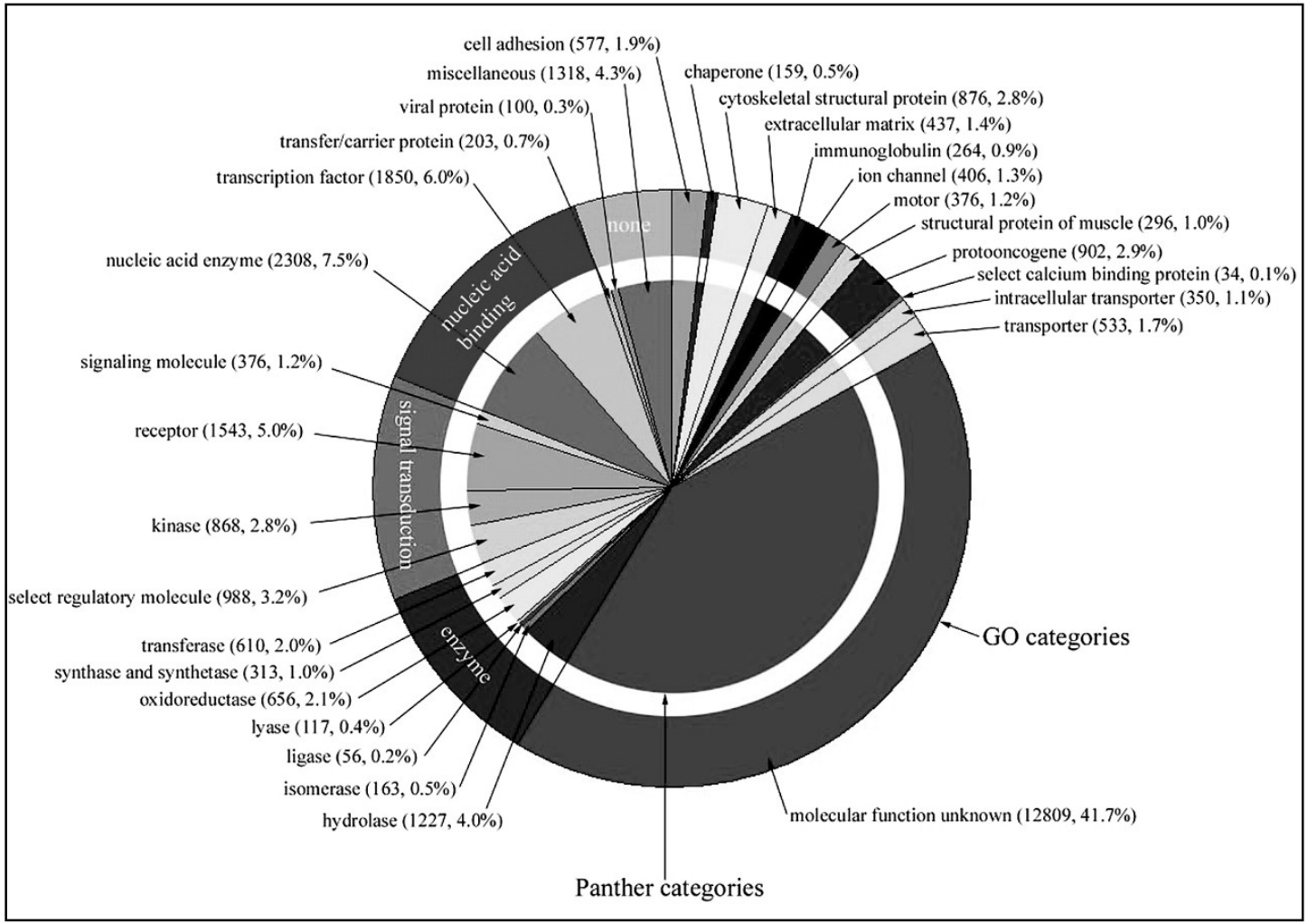

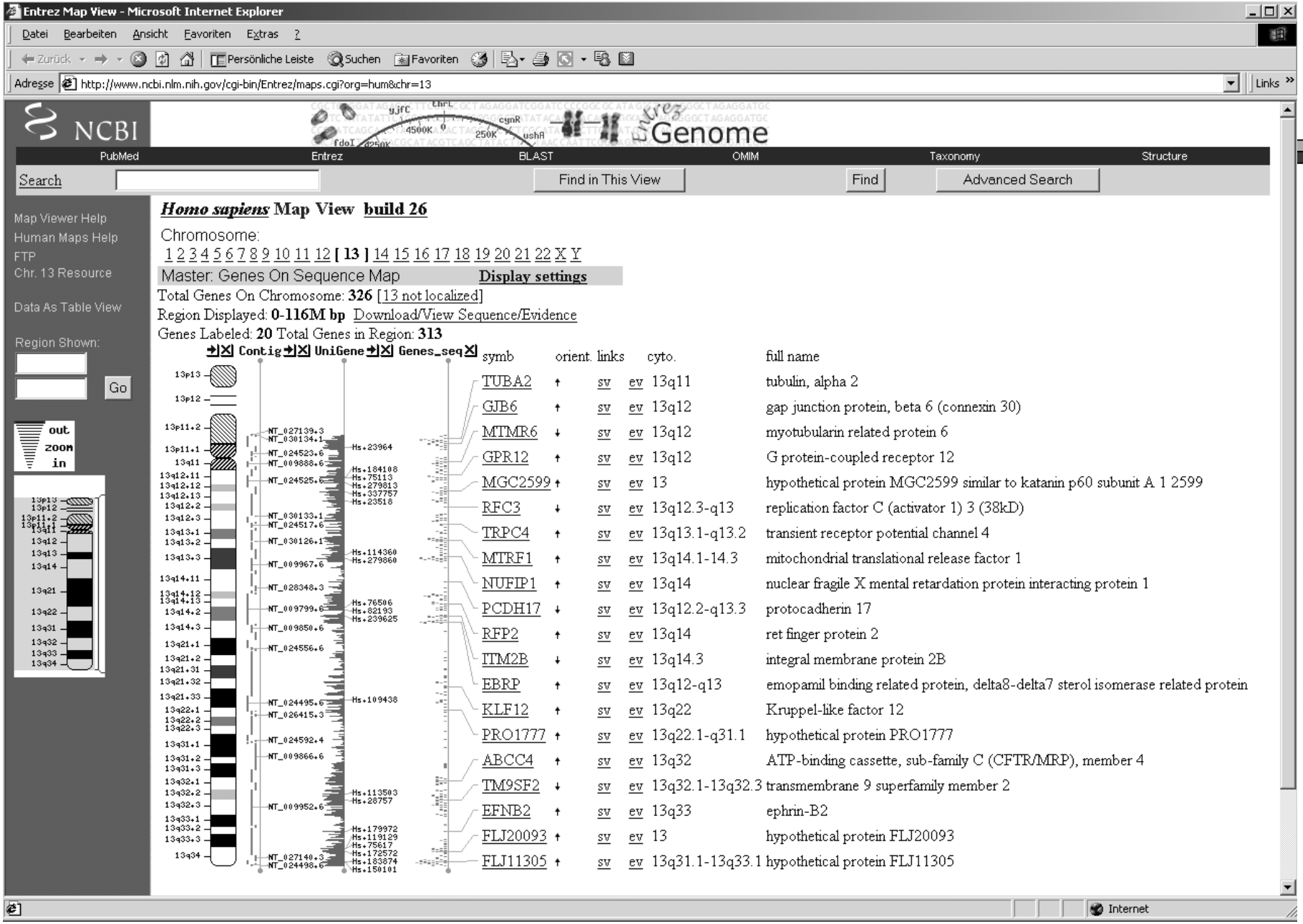
Entrez Map View - Microsoft Internet Explorer
Datei Bearbeiten Ansicht Favoriten Extras ?
Zurück Persönliche Leiste Suchen Favoriten
Adresse http://www.ncbi.nlm.nih.gov/cgi-bin/Entrez/maps.cgi?org=hum&chr=13
Links
NCBI
Entrez Genome
PubMed Entrez BLAST OMIM Taxonomy Structure
Search
Find in This View
Find
Advanced Search
Map Viewer Help
Human Maps Help
FTP
Chr. 13 Resource
Data As Table View
Region Shown:
Go
out
zoom
in
Homo sapiens Map View build 26
Chromosome:
1 2 3 4 5 6 7 8 9 10 11 12 [13] 14 15 16 17 18 19 20 21 22 X Y
Master: Genes On Sequence Map
Display settings
Total Genes On Chromosome: 326 [13 not localized]
Region Displayed: 0-116M bp Download/View Sequence/Evidence
Genes Labeled: 20 Total Genes in Region: 313
Contig UniGene Genes_seq
symb orient. links cyto. full name
TUBA2 + sv ev 13q11 tubulin, alpha 2
GJB6 + sv ev 13q12 gap junction protein, beta 6 (connexin 30)
MTMR6 - sv ev 13q12 myotubularin related protein 6
GPR12 + sv ev 13q12 G protein-coupled receptor 12
MGC2599 + sv ev 13 hypothetical protein MGC2599 similar to katanin p60 subunit A 1 2599
RFC3 - sv ev 13q12.3-q13 replication factor C (activator 1) 3 (38kD)
TRPC4 + sv ev 13q13.1-q13.2 transient receptor potential channel 4
MTRF1 + sv ev 13q14.1-14.3 mitochondrial translational release factor 1
NUFIP1 + sv ev 13q14 nuclear fragile X mental retardation protein interacting protein 1
PCDH17 - sv ev 13q12.2-q13.3 protocadherin 17
RFP2 + sv ev 13q14 ret finger protein 2
ITM2B - sv ev 13q14.3 integral membrane protein 2B
EBRP + sv ev 13q12-q13 emopamil binding related protein, delta8-delta7 sterol isomerase related protein
KLF12 + sv ev 13q22 Kruppel-like factor 12
PRO1777 + sv ev 13q22.1-q31.1 hypothetical protein PRO1777
ABCC4 + sv ev 13q32 ATP-binding cassette, sub-family C (CFTR/MRP), member 4
TM9SF2 - sv ev 13q32.1-13q32.3 transmembrane 9 superfamily member 2
EFNB2 + sv ev 13q33 ephrin-B2
FLJ20093 + sv ev 13 hypothetical protein FLJ20093
FLJ11305 + sv ev 13q31.1-13q33.1 hypothetical protein FLJ11305
Internet

Informatik in □er Biolo□ie

- Datenerfassung und -ver□altung
  - Steuerung von Laborgeräten
  - Labormanagement, Sequence Assembly, ...
  - Datenbanken, □ueries, Präsentation, □□□-Anbindung, ...
- Datenanalyse
  - Sequenzbasiert□Alignment, Phylogenie, ...
  - Strukturbasiert□Molecular Docking, Structure Prediction, ...
  - □isualisierung
- Simulation theoretischer Modelle
  - Biochemische Reaktionen
  - Metabolismus
  - □ntogenese, ...

□n□ en□un□sbeis□iel □□□e□uen□□□ li□nment

- □Bestm□gliche□Ausrichtung biomolekularer Sequenzen
  - Insertion, Deletion, Substitution, Match

A = TTAAGCACTTGGATTCTCGGCAGCGTGG
B = TTAAAGGATTCTCCGTAG

□n□ en□un□sbeis□iel □□□e□uen□□□ li□nment

- □Bestm□gliche□Ausrichtung biomolekularer Sequenzen
  - Insertion, Deletion, Substitution, Match

A = TTAAGCACTTGGATTCTCGGCAGCGTGG
B = TTAAAGGATTCTCCGTAG

Global

A□= TTAA-GCACTTGGATTCTCGGCAGCGTGG
B□= TTAAA------GGATTCT---C--CGTAG

□n□ en□un□sbeis□iel □□□e□uen□□□ li□nment

- □Bestm□gliche□Ausrichtung biomolekularer Sequenzen
  - Insertion, Deletion, Substitution, Match

A = TTAAGCACTTGGATTCTCGGCAGCGTGG
B = TTAAAGGATTCTCCGTAG

Global	A□= TTAA-GCACTTGGATTCTCGGCAGCGTGG B□= TTAAA------GGATTCT---C--CGTAG
Semi-global	A□= TTAAGCACTTTT---GGATTCTCGGCAG B□= ----------TTAAAGGATTCTCCGTAG

□n□ en□un□sbeis□iel □□□e□uen□□□ li□nment

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  - Insertion, Deletion, Substitution, Match

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B = TTAAAGGATTCTCCGTAG

Global	A□= TTAA-GCACTTGGATTCTCGGCAGCGTGG B□= TTAAA------GGATTCT---C--CGTAG
Semi-global	A□= TTAAGCACTTTT---GGATTCTCGGCAG B□= ----------TTAAAGGATTCTCCGTAG
mit Ga□s	A□= TTAA-GCACTTGGATTCTCGGCAGCGTGG B□= TTAAAG------GATTCTC-----CGTAG

Berechnung eines globalen Alignments I

Distanz $d(A,B) = \min \sum_{i=1}^{k} d(a_i', b_i')$ $\quad d(a_i, b_j) = \begin{cases} 0, a_i = b_j \\ > 0, \text{sonst} \end{cases}$

$$D_{i,j} = \min \begin{pmatrix} D_{i-1,j} + d(a_i, -), \\ D_{i-1,j-1} + d(a_i, b_j), \\ D_{i,j-1} + d(-, b_j) \end{pmatrix}$$

$$D_{i-1,j} = \min \begin{pmatrix} D_{i-2,j} + d(a_{i-1}, -), \\ D_{i-2,j-1} + d(a_{i-1}, b_j), \\ D_{i-1,j-1} + d(-, b_j) \end{pmatrix}$$

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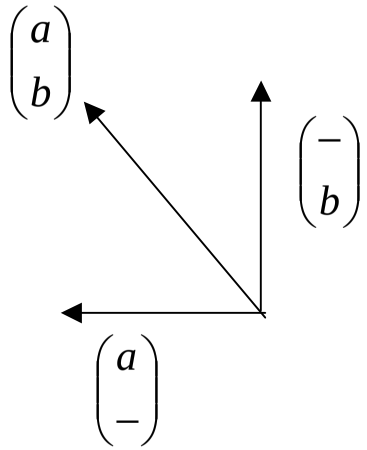
$$D_{i-1,j} = \min \begin{pmatrix} D_{i-2,j} + d(a_{i-1}, -), \\ D_{i-2,j-1} + d(a_{i-1}, b_j), \\ D_{i-1,j-1} + d(-, b_j) \end{pmatrix}$$

Berechnung eines globalen Alignments II

		S	O	N	N	E
	0	1	2	3	4	5
M	1	1	2	3	4	5
O	2	2	1	2	3	4
N	3	3	2	1	2	3
D	4	4	3	2	2	3

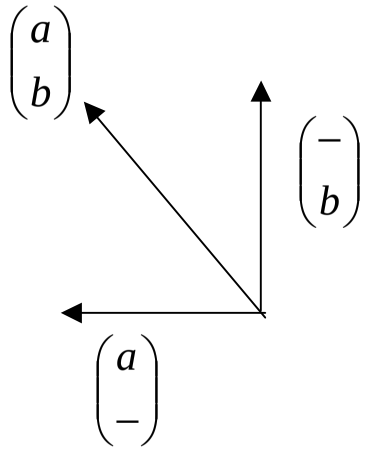


s o n n e

m o - n d

Berechnung eines globalen Alignments II

		S	O	N	N	E
	0	1	2	3	4	5
M	1	1	2	3	4	5
O	2	2	1	2	3	4
N	3	3	2	1	2	3
D	4	4	3	2	2	3

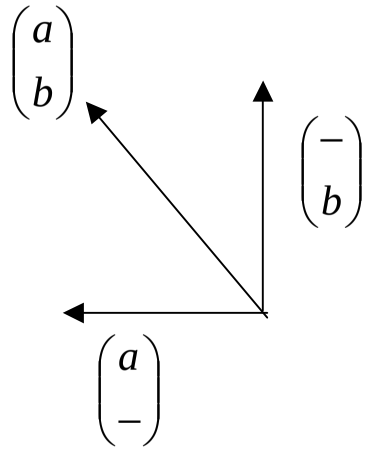


s o n n e

m o - n d

Berechnung eines globalen Alignments II

		S	O	N	N	E
	0	1	2	3	4	5
M	1	1	2	3	4	5
O	2	2	1	2	3	4
N	3	3	2	1	2	3
D	4	4	3	2	2	3

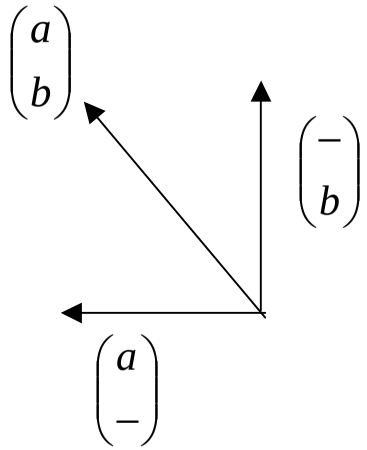


s o n n e

m o - n d

Berechnung eines globalen Alignments II

		S	O	N	N	E
	0	1	2	3	4	5
M	1	1	2	3	4	5
O	2	2	1	2	3	4
N	3	3	2	1	2	3
D	4	4	3	2	2	3



s o n n e sonne

m o - n d mond-

□n□ en□un□sbeis□iel □□
□ olekular□□namik□□imulation

- Simulation des □erhaltens molekularer Systeme
  - Detaillierungsgrad□individuelle Atome oder funktionale Gru□□en
  - Systemgr□□e□□□□- □□□Atome □L□sungsmittelatome
  - Zeitr□ume□□□-□□- □□-□s □Pico- bz□. Nanosekunden□
- Zielsetzung
  - □ntersuchung von Bindungsvorg□ngen
  - Berechnung thermodynamischer Gr□□en
  - Drug Design, ...
- □heoretisches Modell
  - □lassische Mechanik vs. □uantenmechanik
  - Ne□tonsche Be□egungsgleichungen f□r gro□e Systeme

□ olekular□□namik□□imulation I

- Algorithmus von □erlet
  - Integration der Be□egungsgleichungen
  - □ombination der □aylor-Ent□icklung an den Stellen t+Δt und t-Δt

$$\frac{\partial \boldsymbol{r}_i(t)}{\partial t} = \boldsymbol{v}_i(t) \qquad \frac{\partial \boldsymbol{v}_i(t)}{\partial t} = \frac{\boldsymbol{F}_i(t)}{m_i}$$

Molekulardynamik-Simulation I

- Algorithmus von Verlet
  - Integration der Bewegungsgleichungen
  - Kombination der Taylor-Entwicklung an den Stellen $t+\Delta t$ und $t-\Delta t$

$$\frac{\partial \boldsymbol{r}_i(t)}{\partial t} = \boldsymbol{v}_i(t) \qquad \frac{\partial \boldsymbol{v}_i(t)}{\partial t} = \frac{\boldsymbol{F}_i(t)}{m_i}$$

$$\boldsymbol{r}_i(t+\Delta t) = 2\,\boldsymbol{r}_i(t) - \boldsymbol{r}_i(t-\Delta t) + \frac{\boldsymbol{F}_i(t)}{m_i}\Delta t^2 + O\left(\Delta t^4\right)$$

Molekulardynamik-Simulation I

- Algorithmus von Verlet
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$$\boldsymbol{r}_i(t+\Delta t) = 2\,\boldsymbol{r}_i(t) - \boldsymbol{r}_i(t-\Delta t) + \frac{\boldsymbol{F}_i(t)}{m_i}\Delta t^2 + O\left(\Delta t^4\right)$$

$$\boldsymbol{F}_i(t) = -\frac{\partial U\left[\boldsymbol{r}_1(t), \boldsymbol{r}_2(t), \ldots, \boldsymbol{r}_N(t)\right]}{\partial \boldsymbol{r}_i(t)}$$

Molekulardynamik-Simulation I

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  - Kombination der Taylor-Entwicklung an den Stellen t+Δt und t-Δt

$$\frac{\partial \boldsymbol{r}_i(t)}{\partial t} = \boldsymbol{v}_i(t) \qquad \frac{\partial \boldsymbol{v}_i(t)}{\partial t} = \frac{\boldsymbol{F}_i(t)}{m_i}$$

$$\boldsymbol{r}_i(t+\Delta t) = 2\boldsymbol{r}_i(t) - \boldsymbol{r}_i(t-\Delta t) + \frac{\boldsymbol{F}_i(t)}{m_i}\Delta t^2 + O\left(\Delta t^4\right)$$

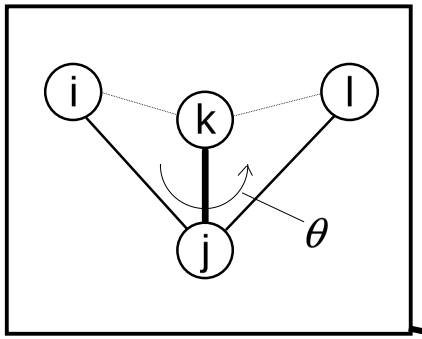
$$\boldsymbol{F}_i(t) = -\frac{\partial U\left[\boldsymbol{r}_1(t), \boldsymbol{r}_2(t), \ldots, \boldsymbol{r}_N(t)\right]}{\partial \boldsymbol{r}_i(t)}$$

$$U\left(\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots, \boldsymbol{r}_N\right) = E_B + E_\theta + E_\varphi + E_\psi + E_{VDW} + E_C$$

Molekulardynamik-Simulation I

- Algorithmus von Verlet
  - Integration der Bewegungsgleichungen
  - Kombination der Taylor-Entwicklung an den Stellen t+Δt und t-Δt

$$\frac{\partial \boldsymbol{r}_i(t)}{\partial t} = \boldsymbol{v}_i(t) \qquad \frac{\partial \boldsymbol{v}_i(t)}{\partial t} = \frac{\boldsymbol{F}_i(t)}{m_i}$$



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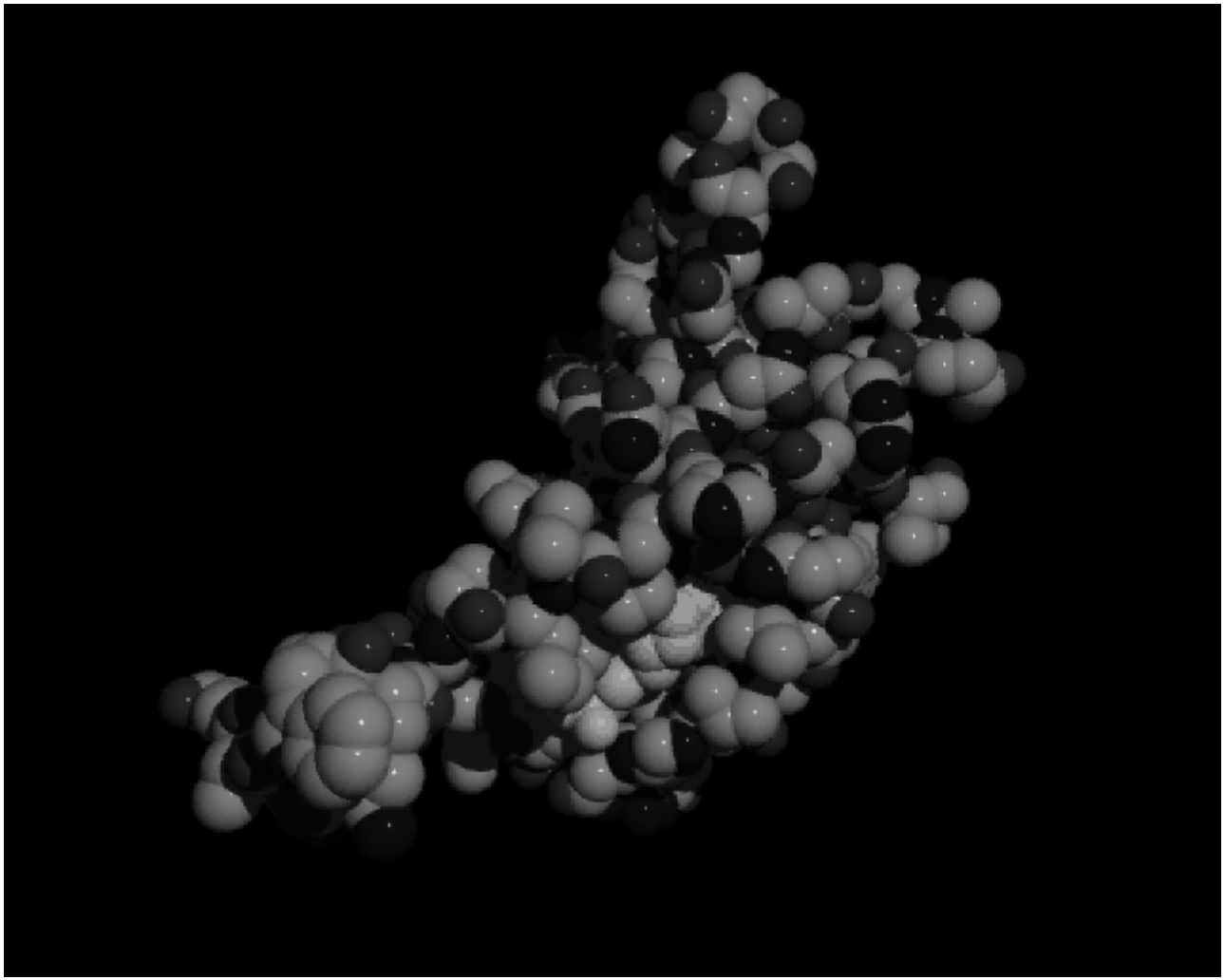
$$\boldsymbol{F}_i(t) = -\frac{\partial U\left[\boldsymbol{r}_1(t), \boldsymbol{r}_2(t), \ldots, \boldsymbol{r}_N(t)\right]}{\partial \boldsymbol{r}_i(t)}$$

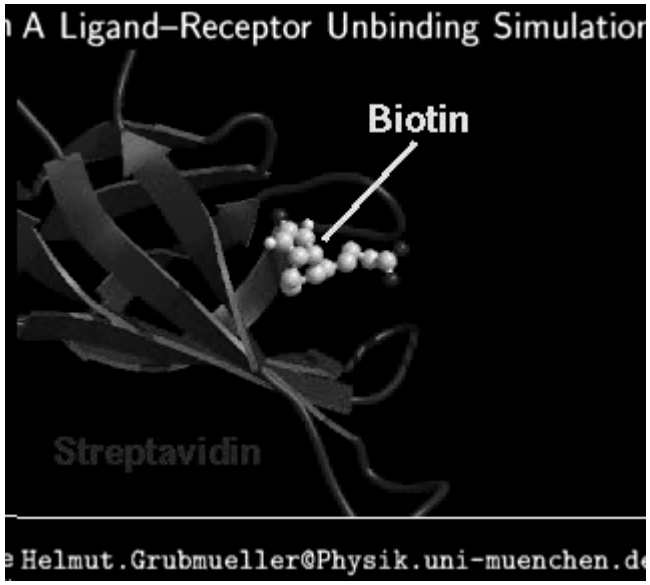
$$U\left(\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots, \boldsymbol{r}_N\right) = E_B + E_\theta + E_\varphi + E_\psi + E_{VDW} + E_C$$

Molekulardynamik-Simulation II

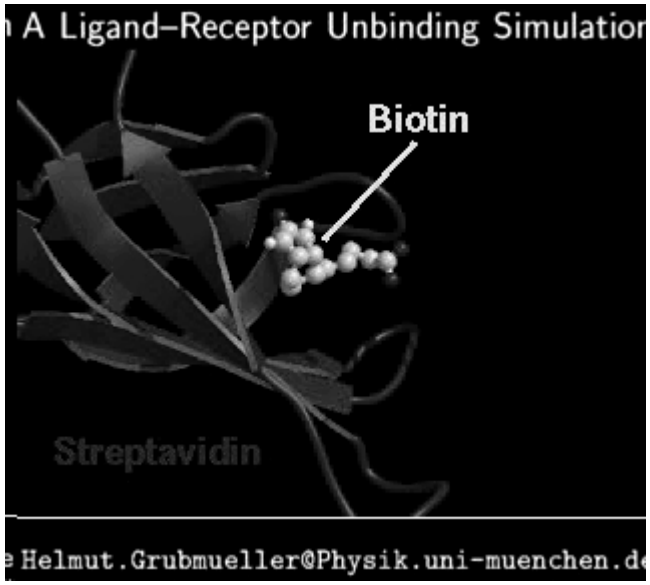
Molekulardynamik-Simulation II

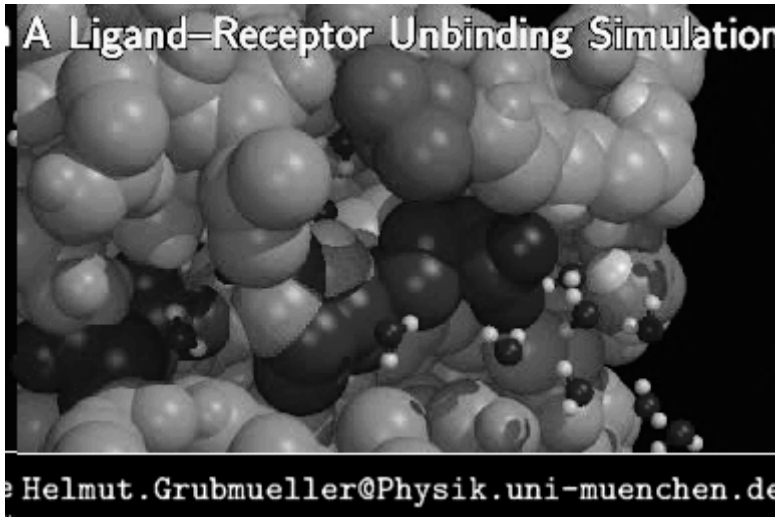


Molekulardynamik-Simulation II



Molekulardynamik-Simulation II





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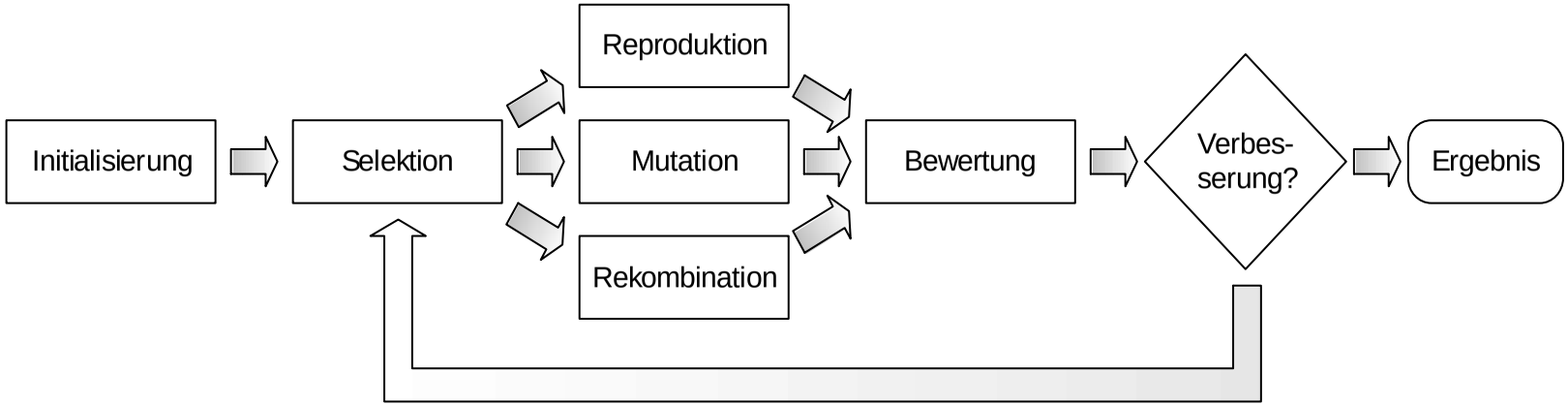
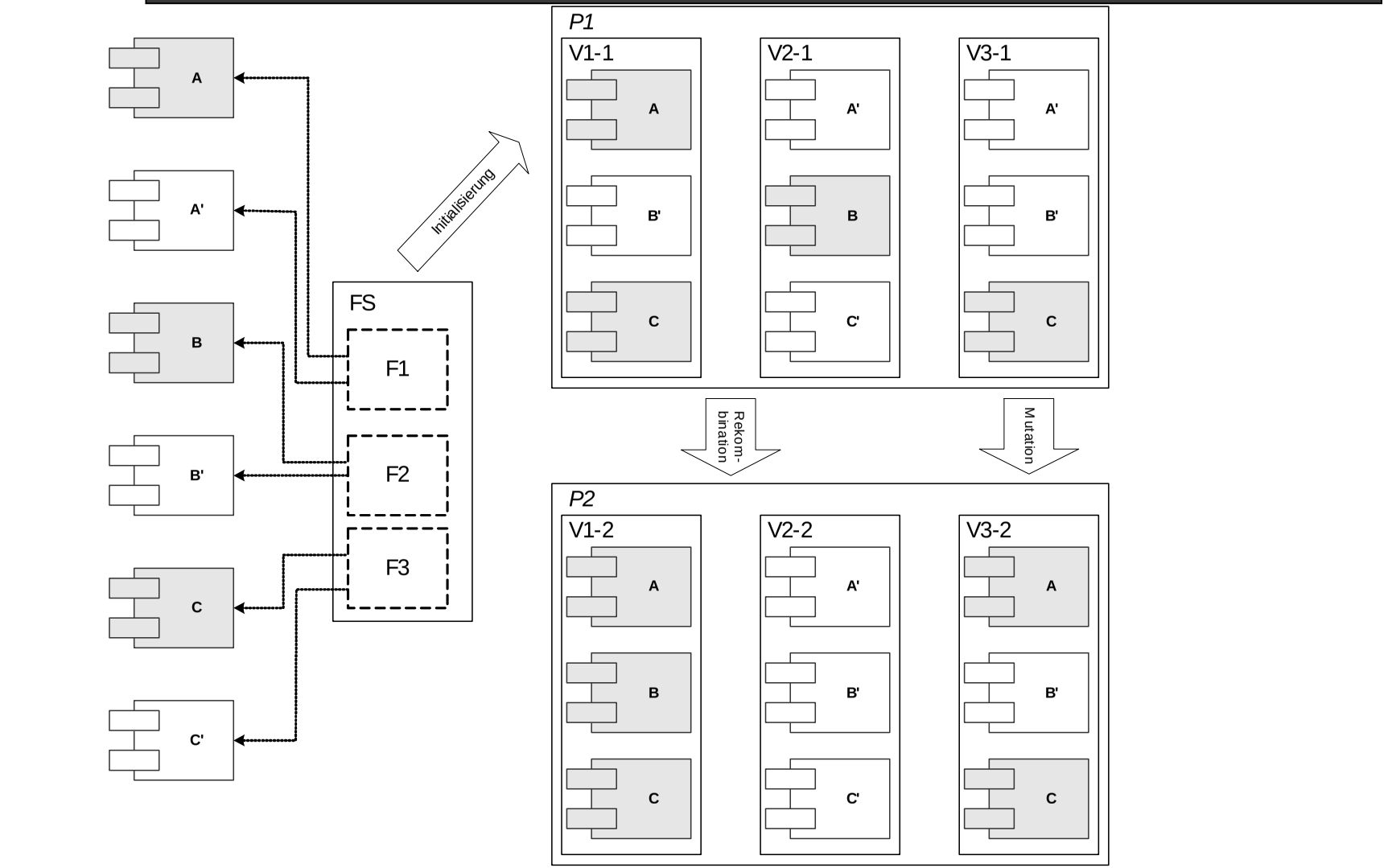
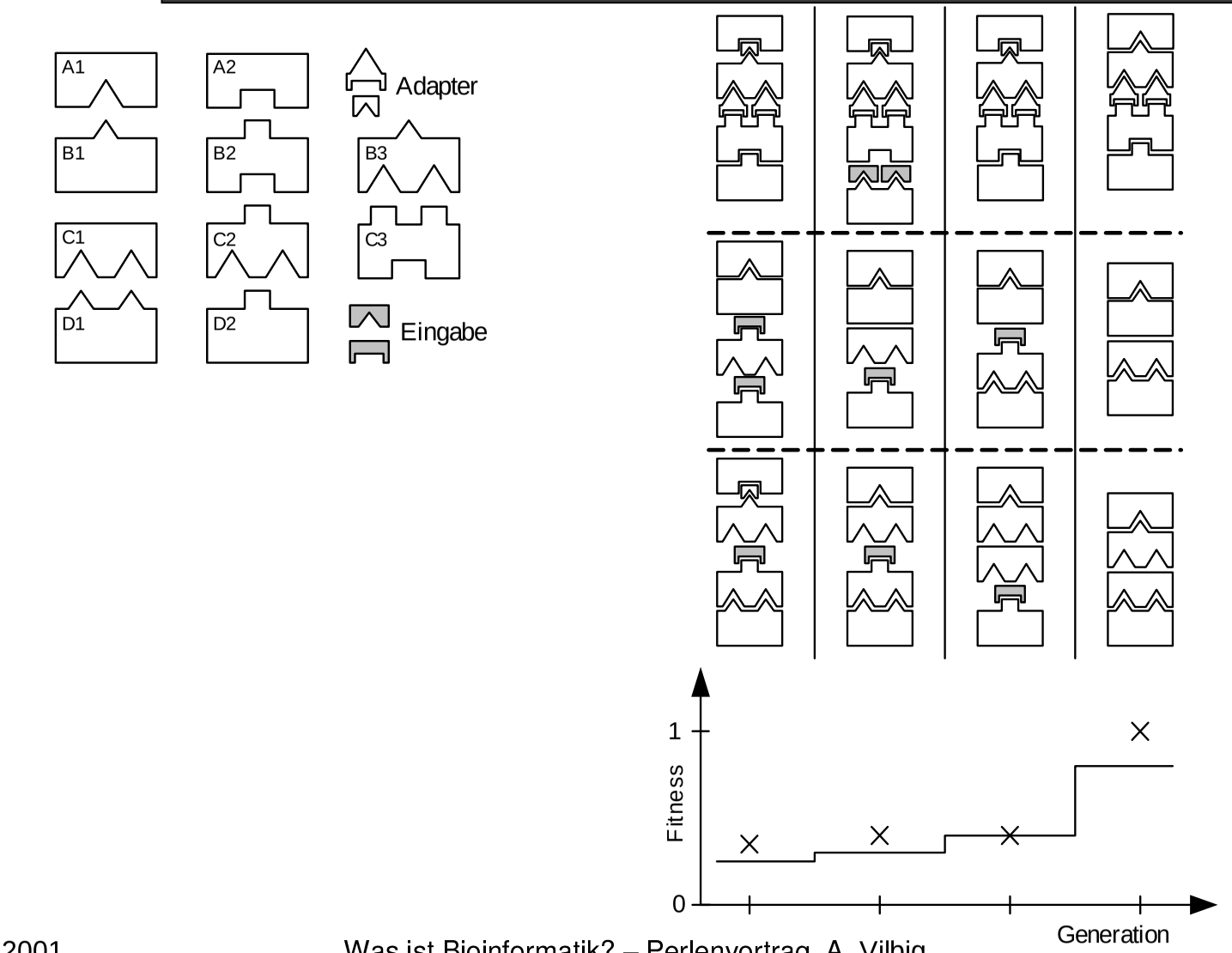
- Evolutionäre Heuristik zur kombinatorischen Optimierung
  - Anwendung bei komplexer, nicht-stetiger Zielfunktion
  - Betrachtung einer Menge von Lösungen als *Individuen* einer *Population*, welche sich durch *Selektion* und fortgesetzte Anwendung der *Genetischen Operatoren* weiterentwickelt
  - Lineare Kodierung der Lösung erforderlich $\leftrightarrow$ *Chromosom*
  - Theorie nur für einfache Kodierung ausgearbeitet („Bitstrings")
  - Anpassung der *Fitneß-Funktion* und Gen. Operatoren erforderlich



Genetische Algorithmen I



Genetische Algorithmen II



Zusammenfassung & Ausblick

- Informatik in der Biologie
  - Essentiell zur Bewältigung großer Datenmengen
  - Anwendung „traditioneller" Algorithmen zur Klärung wichtiger biologischer Fragestellungen
  - Vielfältige Lösungsansätze
- Biologie in der Informatik
  - Evolutionäre Heuristiken als interessante Alternative zu bekannten Verfahren
  - Erfassung und Verarbeitung unscharfer Informationen
  - Potential bei weitem nicht ausgeschöpft
- Zukünftige Fragestellungen & Ansätze
  - Genomics, Proteomics: Holistische Betrachtung komplexer biomolekularer Systeme
  - Protein Folding: Zusammenhang zwischen Sequenz und Struktur
  - Vision: „Organic Software Engineering" - Analogie zwischen Software-System und Organismus?

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  - J. M. Haile, *Molecular Dynamics Simulation: Elementary Methods.* Wiley-Interscience, New York, 1992.
- Genetische Algorithmen
  - D. Goldberg, *Genetic Algorithms in Search, Optimization, and Machine Learning*. Addison-Wesley 1989.

WWW-Ressourcen

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  - www.ornl.gov/hgmis/, www.nhgri.nih.gov/HGP/
- Forschungseinrichtungen
  - National Center for Biotechnology Information: www.ncbi.nlm.nih.gov/
  - European Bioinformatics Institute: www.ebi.ac.uk/
  - European Molecular Biology Laboratory: www.embl-heidelberg.de/
- Online-Dokumente und URLs
  - Folding@Home: www.stanford.edu/group/pandegroup/cosm/
  - MD Simulation des Streptavidin-Biotin Komplexes (MPI Göttingen) www.mpibpc.gwdg.de/abteilungen/071/streptavidin.html
  - BioComputing Hypertext Coursebook der Universität Bielefeld www.techfak.uni-bielefeld.de/bcd/Curric/welcome.html
  - Vorlesung Scientific Computation an der ETH Zürich linneus20.ethz.ch:8080/wsrscript.html
  - Lehrstuhl für effiziente Algorithmen der TU München wwwmayr.informatik.tu-muenchen.de/