Announcements

Videos: SciVe / www.rostlab.org
THANKS:
   Tim Karl + ?

Special lectures:
   • May 16, 23, 28: Andrea Schafferhans
   • June 27: Thomas Hopf

No lecture:
   • May 9 Thu (Ascension)
   • May 14 Tue (Student assembly)
   • May 21 Tue (Whitsun break)
   • May 30 Thu (Corpus Christi)

LAST lecture: Jul 4

Examen: Jul 9, 13:15 (likely this room + others)
   • Makeup: Oct 17 - morning

CONTACT: Marlena Drabik assistant@rostlab.org
Thanks for slides

Andrea Schafferhans
TUM
Notation: protein structure 1D, 2D, 3D
Goal of structure prediction

• Epstein & Anfinsen, 1961: sequence uniquely determines structure

• INPUT: sequence
• OUTPUT:
Goal of structure prediction

- Epstein & Anfinsen, 1961: sequence uniquely determines structure

- INPUT: sequence
- OUTPUT: 3D structure and function
Comparative modeling 1
(homology modeling)
Comparative modeling in perspective
Using structure to predict function

ConSurf

F Glaser, T Pupko, I Paz, RE Bell, D Bechor-Shental, E Martz and N Ben-Tal
2003 Bioinformatics 19 163-4
Using structure to predict function

ConSurf


GRASS:


© Burkhard Rost (TU Munich)
Tuning immune system response with costimulation

RCSB - PDB: PSI/nature StructuralBiologyKnowledgebase Feature June 2013
Universe of protein structures

Christine Orengo 1997 Structures 5 1093-1108

© Burkhard Rost (TU Munich)
Universe of protein structures

Christine Orengo et al. 1997 Structures 5 1093-1108
3D & Comp. Model. in numbers

Estimate for 1999

Number of entries 05/2013

Uniprot/TREMBL: 33,995,348
Uniprot/Swissprot: 414,816
PDB: 84,051

13%
Redundancy in the PDB

Number of proteins in PDB

- 30
- 40
- 50
- 70
- 90
- 95
- 100
- all

Sunday May 26, 2013
Idea of comparative modeling

WHAT IF

<table>
<thead>
<tr>
<th>Structure</th>
<th>Percentage</th>
<th>Sequence</th>
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<td>lshf</td>
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<td>VTLFVALYDYEARTEDDLSFHKGGEKFQILNSSEGDNWYDLTGETGYIPSNYVAPVD</td>
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<td>39%</td>
<td>....VAEHDNPAGSPDELSFKRGNTLKVNLKDEPHWYKAE....DNDGFIPSNYIRMTE</td>
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Comparative modeling: idea

- **assumption:** H and U similar in 3D structure
- **strategy:** modeling of U based on H
Zones

Midnight Zone

Twilight Zone

Save Zone

sequences similar

structures similar

0 20 40 60 80 100
3D & Comp. Model. in numbers

Estimate for 1999

Number of entries 05/2013

Uniprot/TREMBL: 33,995,348
Uniprot/Swiss-prot: 414,816
PDB: 84,051

Experimental
HoMo

© Andrea Schafferhans & Burkhard Rost (TU Munich)
Sequence conservation of protein structure

C Sander & R Schneider 1991 *Proteins* 9:56-69
B Rost 1999 *Prot Engin* 12, 85-94

© Burkhard Rost (TU Munich)
Sequence conservation of protein structure

C Sander & R Schneider 1991 *Proteins* 9:56-69
B Rost 1999 *Prot Engin* 12, 85-94
Twilight zone = false positives explode!!

B Rost 1999 Prot Engin 12, 85-94
3D & Comp. Model. in numbers

Estimate for 1999

Number of entries 05/2013

Uniprot/TREMBL: 33,995,348
Uniprot/Swiss-prot: 414,816
PDB: 84,051
Evolution into the Midnight zone

B Rost 1997 Folding & Design 2, S19-S24

© Burkhard Rost (TU Munich)

Sunday May 26, 2013
Notation: protein structure 1D, 2D, 3D

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1D  2D  3D

kcal/mol
3D & Comp. Model. in numbers

Estimate for 1999

Number of entries 05/2013

Uniprot/TREMBL: 33,995,348
Uniprot/Swiss-prot: 414,816
PDB: 84,051

- Experimental: 44%
- HoMo: 22%
- FoRc: 20%
- 1D: 13%
Protein structure prediction in reality

1D

HoMo

FoRc
Protein structure prediction in reality

**SWISS-PROT view**

**Genome view**

1D

….the art of being humble

HoMo

FoRc
Improving prediction by waiting it out ...
Improving prediction by waiting it out …
Jinfeng Liu

- 1995-2003 MS Rutgers Univ.
- 1998-2004 PhD
  Columbia Univ. Pharmacology

PhD with 16 publications!

- 2004-2007 Sr. Research Assistant
  Columbia Univ. Biochemistry & Molecular Biophysics
- 2007-now Genentech, CA
Homology modeling for entire genomes

Number of proteins

Organism

- H sapiens
- H sapiens (chr. 22)
- D melanogaster
- C elegans
- S cerevisiae
- U urealyticum
- T pallidum
- S PCC6803
- R prowazekii
- N meningitidis
- M tuberculosis
- M pneumonias
- M genitalium
- H pylori
- H influenzae
- E coli
- C trachomatis
- C pneumoniae
- C jejuni
- B burgdorferi
- B subtilis
- A aeolicus
- T maritima
- D radiodurans
- P horikoshii
- P abyssi
- M thermoautotrophicus
- M jannaschii
- A fulgidus
- A pernix

Number of ORFs

Number of ORFs with PDB hit
Homology for protein universe

Organism

Percentage of all ORFs in genome

H sapiens(chr. 22)
H sapiens
D melanogaster
C elegans
S cerevisiae
U urealyticum
T pallidum
S PCC6803
R prowazekii
N meningitidis
M tuberculosis
M pneumoniae
M genitalium
H pylori
H influenzae
E coli
C trachomatis
C pneumoniae
C jejuni
B burgdorferi
B subtilis
A aeolicus
T maritima
D radiodurans
P horikoshii
P abyssi
M thermoautotrophicum
M jannaschii
A fulgidus
A pernix

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Comparative modeling: concepts
Comparative modeling: words

- Comparative modeling vs. Homology modeling

- Lingo:
  - Target: protein to model
  - Template: protein to model from
Idea of comparative modeling

WHAT IF

1shf 100% VTLFVALLYDYEARTEDDDLSFHKGEKFQILNSSEGDWWEARSLTTGETGYIPSNYVAPVD
1srm 78% VTTFVALLYDYESRTETDDLSFKGERLQIVNNTEDGWLASHSLTTGQTGYIPSNYVAPSD
1sem 39% ....VAEHDFQAGSPDELSFKRGNTLKVNLKDEDPHWYKAEL.DGNEGFIIPSNYIRMTE
Comparative modeling: idea

- assumption: H and U similar in 3D structure
- strategy: modeling of U based on H
Comparative modeling: steps

- Identify template database search (one or many)
Comparative modeling: steps

- Identify template
  database search (one or many)
- Align target/template
Comparative modeling: steps

- Identify template
database search (one or many)
- Align target/template
- Build model
Comparative modeling: steps

- Identify template
database search (one or many)
- Align target/template
- Build model
- Assess model
Comparative modeling: steps

- Identify template
database search (one or many)
- Align target/template
- Build model
- Assess model
- (refine)
Extending cm: threading

- Correct first hit:
  ≈ 20-30%

- Alignment correct to some extent:
  ≈ 10-25%

- Remote homology modelling (3D) correct:
  < 10%

Percentage of pairwise identical residues:

- 100% Region of homology modelling (sequence alignment suffice)
- 25% Fold recognition
- 0%

Accuracy of automatic fold recognition: Sunday May 26, 2013
Comparative modeling: steps

- Identify template
database search (one or many)
  - PSI-BLAST
  - HHblits
  - threading
- Align target/template
- Build model
- Assess model
- (refine)
Comparative modeling: quality

**Percentage of pairwise identical residues**

- 100%
- 75%
- 50%
- 25%
- 0%

**Limiting factor in homology modelling**

- SPEED of modelling
- QUALITY of model
- ALIGNMENT accuracy
- DETECTION of homology

Increasing accuracy

Increasing coverage
Comparative modeling: steps

- Identify template / database search
  - PSI-BLAST / HHblits / threading

- Align target/template
  - dynamic programming
  - structural alignment of targets to template-relatives
  - threading-like
  - profile-profile

- Build model
- Assess model
- (refine)
Comparative modeling: quality

D Baker & A Sali (2001)
Science: 93-96
Comparative modeling: State-of-the-art methods
Modeller
Sali lab
UCSF
Andrei Sali - UCSF

CV
- PhD Birkbeck - Tom Blundell
- PD Harvard - Martin Karplus
- Rockefeller Univ.
- UCSF

Publications (2011/06)
- > 400 publications
- 1x ~4,000
- 45x >100
- H-index > 64

Andrej Sali, UCSF
Comparative modeling: MODELLER

MODELLER:


Andrej Sali, UCSF
Comparative modeling: MODELLER

MODELLER:


Marc Marti-Renom, CIPF Barcelona (here at ISCB-Africa in Bamako, Mali)

Andrej Sali, UCSF
Comparative modeling: MODELLER

MODELLER: overview

N Eswar et al. & A Sali (2008) Methods Mol Biol 426: 145-59 (Fig. 1)
MODELLER: constraint satisfaction

1. Align sequence with structures
   Target sequence
   
   Template structure(s)

   SWQTYVDNLVTGAGVTQA · · A
   · · · · · · ·
   GWNAYIDNLMADGTCDQDAIVG

2. Extract spatial restraints

3. Satisfy spatial restraints

Figure 1.1: First, the known, template 3D structures are aligned with the target sequence to be modeled. Second, spatial features, such as $C_\alpha - C_\alpha$ distances, hydrogen bonds, and mainchain and sidechain dihedral angles, are transferred from the templates to the target. Thus, a number of spatial restraints on its structure are obtained. Third, the 3D model is obtained by satisfying all the restraints as well as possible.

Source: MODELLER manual

MODELLER: constraint satisfaction: fits

\[ p(x_1 \leq x < x_2) = \int_{x_2}^{x_1} p(x) \, dx \]

with

\[ \int p(x) \, dx = 1 \]

\[ p(x) > 0 \]

Source: MODELLER manual


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MODELLER: constraint satisfaction

- Find the model with highest probability
- Variable Target function:
  - Start model close to the template conformation
  - First only local constraints
  - Minimize using conjugate gradient optimization
  - Repeat, introduce more and more long-range constraints

![Graph of Objective function vs Iteration](chart.png)
MODELLER: multiple models

- Run optimization repeatedly
- Starting point: template coordinates with random fluctuations
- Explore different local minima

N Eswar et al. & A Sali (2008) Methods Mol Biol 426: 145-59 (Fig. 3)
MODELLER: typical errors

side chain packing

mis-alignment

wrong template

Chapter 5 - Unit 5.6.1-30 (Fig. 5.6.12)
MODELLER: Identify best models

DOPE score
Discrete Optimized Protein Energy
Based on knowledge-based pair potentials

MODELLER: loop modeling

Andras Fiser, Richard Kinh Gian Do & Andrej Sali (2000) Protein Science 9:1753-73: Fig. 9

Fig. 9. Accuracy of loop modeling in the correct environment as a function of loop length. Models were calculated for 40 loops at each length from 1 to 14 residues, as described in Theory and algorithms. Fifty independent optimizations were used to make each prediction. Average accuracy and the standard deviation of the accuracy are shown for each length for (A) local and (B) global superposition.
Comparative modeling methods

- MODELLER
  lots of whistles and bells
  downloadable
  very accurate

- SWISS-MODEL
CV
- PhD in X-ray crystallography
- SIB
- Biocenter Basel

Publications (2011/06)
- > 45 publications
- 1x ~2,000
- 5x >100
- H-index > 19

Web presence
- 1000s of accesses / day

Shapers and Shakers
Torsten Schwede - Biocenter Basel

© Burkhard Rost (TU Munich)
Comparative modeling: SWISS-MODEL

Manuel Peitsch, Philip Morris Internatl. Basel

Nicolas Guex, Vital-IT

© Burkhard Rost (TU Munich)
Comparative modeling: SWISS-MODEL


Shapers and Shakers

Sunday May 26, 2013
Comparative modeling: SWISS-MODEL


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Comparative modeling: SWISS-MODEL

- Underlying “philosophy”:
  fully automated
  for non-expert users/experimental biologists
  do less -> you do fewer mistakes

- original:
  1. alignment by BLAST/PSI-BLAST
  2. copy co-ordinates
  3. end

Comparative modeling: SWISS-MODEL

Things got more complicated ...

Lorenza Bordoli, Florian Kiefer, Konstantin Arnold, Pascal Benkert, James Battey & Torsten Schwede (2009) Nature Protocols doi:10.1038/nprot.2008.197; Fig. 2
"I aim to provide quality services and applications that are clear, useful, and user-friendly. The continuing enrichment of my knowledge and programming skills gained over the past four years, together with my high attention to detail, strong problem-solving skills and fast learning abilities, all help me to achieve that aim."
SWISS-MODEL: template search

- BLAST
- PSI-BLAST
- HHsearch

© Chris Wilton (Helsinki)
SWISS-MODEL: template search

- BLAST
- PSI-BLAST
- HHsearch

© Chris Wilton (Helsinki)
SWISS-MODEL: template selection

- Template quality
- Bound substrate
- InterPro annotations
- Secondary structure prediction
- Transmembrane helices

© Chris Wilton
(Helsinki)
SWISS-MODEL: building structure

- find structurally conserved core regions
- build model core
- loop (insertion) modeling
- side-chain placement
  - use information from similar structures
  - back-bone dependent rotamer libraries
  - energetic and packing criteria
- energy minimization
  (GROMOS 96, steepest descent)
SWISS-MODEL: result after many steps

© Chris Wilton (Helsinki)
SWISS-MODEL: model assessment

Sum scores:
- QMEAN
- DFIRE (statistical potential)

Local scores:
- ANOLEA (mean force potential)
- GROMOS (empirical force field)
- ProQres (neural network)
SWISS-MODEL:

- Long stretches above zero probably loops
- Most-negative regions well buried in core
- Functional residues above zero!
- Majority of residues must be below zero
- Compare your model to pdb template!

© Burkhard Rost (TU Munich)
Comparative modeling methods

- MODELLER
  lots of whistles and bells, downloadable, very accurate

- SWISS-MODEL
  automated, increasingly comprehensive and flexible
Other top comparative modeling methods:

HHpred, 3D-Jigsaw, WhatIf, COMA
Comparative modeling: HHpred

HHpred:
- J Soeding, A Biegert & AN Lupas (2005) NAR 33:W244-8

Johannes Soeding, LMU
photo: http://www.lmb.uni-muenchen.de/soeding/images/soeding.jpg

Andrei Lupas, MPI Tuebingen
photo: http://www.mph.tuebingen.mpg.de/pix/perspics/pic444.jpg
Comparative modeling: HHpred

HHpred:
- J Soeding, A Biegert & AN Lupas (2005) NAR 33:W244-8

Major step:
HMM-HMM
(profile-profile) alignment
+ many details right
HHpred: major steps

- build target sequence profile with PSI-Blast
- build HMM of target
- search template HMM database
  (HMM-HMM alignment = profile-profile)
- re-rank potential templates
- reduce diversity of multiple sequence alignments
- re-rank alternative alignments
- pick best template for each region
- run MODELLER
Comparative modeling methods

- **MODELLER**
  lots of whistles and bells, downloadable, very accurate

- **SWISS-MODEL**
  automated, increasingly comprehensive and flexible

- **HHpred/HHsearch**
  very accurate, automated

- **3D-JIGSAW**
Comparative modeling: 3D-JIGSAW

3D-JIGSAW:

Paul A Bates,
London Res Inst
photo: http://www.bmm.icnet.uk/~bates03/

Michael JE Sternberg
photo: http://www3.imperial.ac.uk/pls/portallive/docs/1/63011698.JPG
Comparative modeling: 3D-JIGSAW

bmm.cancerresearchuk.org/~3djigsaw/

fragment-based approach:
1. identify all similar fragments in PDB
2. assemble fragments to structure
Comparative modeling methods

- **MODELLER**
  lots of whistles and bells, downloadable, very accurate

- **SWISS-MODEL**
  automated, increasingly comprehensive and flexible

- **HHpred/HHsearch**
  very accurate, automated

- **3D-JIGSAW**
  automated, accurate

- **WHAT IF**
Comparative modeling: WHAT IF

WHAT IF:
- G Vriend (1990) J Mol Graph 8:52-6

Gert Vriend
CMBI Nijmegen
photo: http://swift.cmbi.ru.nl/gv/start/IMAGE/VRIEND.jpg

© Burkhard Rost (TU Munich)
Comparative modeling: WHAT IF & YASARA

YASARA

- E Krieger, JE Nielsen, C Spronk & G Vriend (1990) J Mol Graph 8:52-6

Elmar Krieger
YASARA
Biosciences, Vienna

photo: http://www.yasara.org/ekrieger_small.jpg
Comparative modeling methods

- **MODELLER**
  lots of whistles and bells, downloadable, very accurate

- **SWISS-MODEL**
  automated, increasingly comprehensive and flexible

- **HHpred/HHsearch**
  very accurate, automated

- **3D-JIGSAW**
  automated, accurate

- **WHAT IF**
  expert users, does anything incl. chess
Comparative modeling methods

- MODELLER
  lots of whistles and bells, downloadable, very accurate

- SWISS-MODEL
  automated, increasingly comprehensive and flexible

- HHpred/HHsearch
  very accurate, automated

- 3D-JIGSAW
  automated, accurate

- WHAT IF
  expert users, does anything incl. chess

- COMA
Comparative modeling: COMA

COMA:
- M Margelevicius, M Laganeckas & Ceslovas Venclovas (2010)
  Bioinformatics in press

Ceslovas Venclovas
Inst Biotechnology,
Vilnius, Lithuania

Comparative modeling: COMA

- comparison of multiple alignments
- mostly through good profile-profile alignments
- special features:
  - position specific gap penalty
  - global score

Comparative modeling: COMA


M Margelevicius & Ceslovas Venclovas (2010) BMC Bioinformatics 11:89, 9-14; Fig. 3

- global: entire 3D domain
- local
Comparative modeling methods

- MODELLER
  lots of whistles and bells, downloadable, very accurate

- SWISS-MODEL
  automated, increasingly comprehensive and flexible

- HHpred/HHsearch
  very accurate, automated

- 3D-JIGSAW
  automated, accurate

- WHAT IF
  expert users, does anything incl. chess

- COMA
  reaches deep into twilight zone, automated
i-Tasser

zhanglab.ccmb.med.umich.edu/I-TASSER/

Yang Zhang, University of Michigan

Y Zhang 2008 BMC Bioinf 9:40
i-Tasser: workflow

- Template identification: threading
- Structure assembly: put together contiguous fragments
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  - general knowledge-based statistics terms
  - spatial restraints from threading templates
  - Sequence-based contact predictions from SVMSEQ
- Multiple domain proteins: dock models of individual domains
- Special:
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  - Optimise global and local structural packing
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Models and reality

René Margritte
(1989-1967)

Leci n'est pas une pipe.
Models and reality

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**Models and reality**

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“A model is a tool that helps to interpret biochemical data.” (Thorsten Schwede)
Lecture plan (PP1: Structure)

- 01: 2013/04/16 Tue: welcome: who we are
- 02: 2013/04/18 Thu: no room, no lecture
- 03: 2013/04/23 Tue: intro I - acids/structure
- 05: 2013/04/30 Tue: intro IIa - 3D comparisons
- 06: 2013/05/02 Thu: CANCELED alignment 1
- 07: 2013/05/07 Tue: alignment 1
- 08: 2013/05/09 Thu: holiday (Ascension Day)
- 09: 2013/05/14 Tue: no lecture: student assembly
- 10: 2013/05/16 Thu: no lecture
- 11: 2013/05/21 Tue: Whitsun holiday
- 12: 2013/05/23 Thu: alignment 1 contd
- 13: 2013/05/28 Tue: alignment 2
- 14: 2013/05/30 Thu: Fronleichnam=Corpus Christi
- 15: 2013/06/04 Tue: comparative modeling 1
- 16: 2013/06/06 Thu: comparative modeling 2
- 17: 2013/06/11 Tue: 3D->1D: sec str, sec str pred 1
- 18: 2013/06/13 Thu: sec str pred 3
- 19: 2013/06/18 Tue: transmembrane helix prediction
- 20: 2013/06/20 Thu: transmembrane strand prediction, solvent accessibility
- 21: 2013/06/25 Tue: 2D prediction, intro
- 22: 2013/06/27 Thu: 2D prediction - Thomas Hopf
- 23: 2013/07/02 Tue: 3D prediction
- 24: 2013/07/04 Thu: summary: what we do in our group
- 25: 2013/07/09 Tue: examen, no lecture
- 26: 2013/07/11 Thu: no lecture
- 27: 2013/07/16: no lecture
- 28: 2013/07/18: no lecture

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