Comparative Modelling

Summary

1. Basic concepts of Homology Modeling
2. Schema of the method
    1. Fold assignment
    2. Template selection
    3. Model building
    4. Evaluation
    5. Improvement

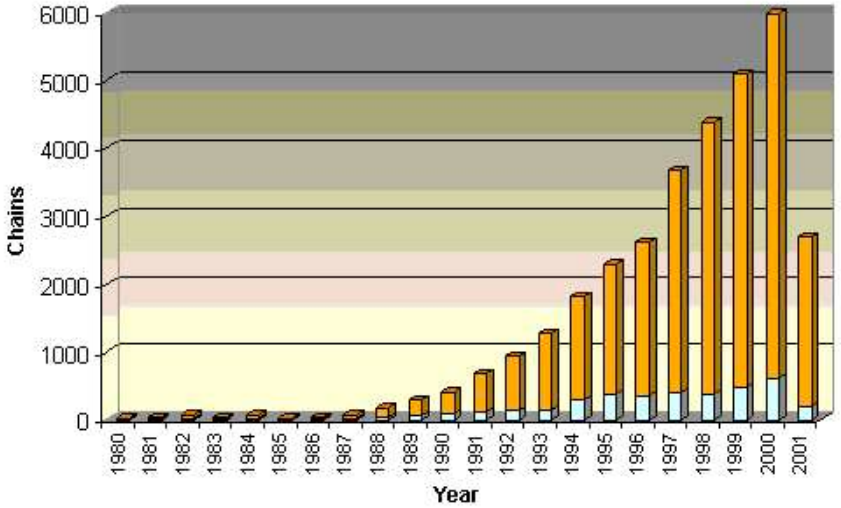
1. Basic concepts of Homology Modeling

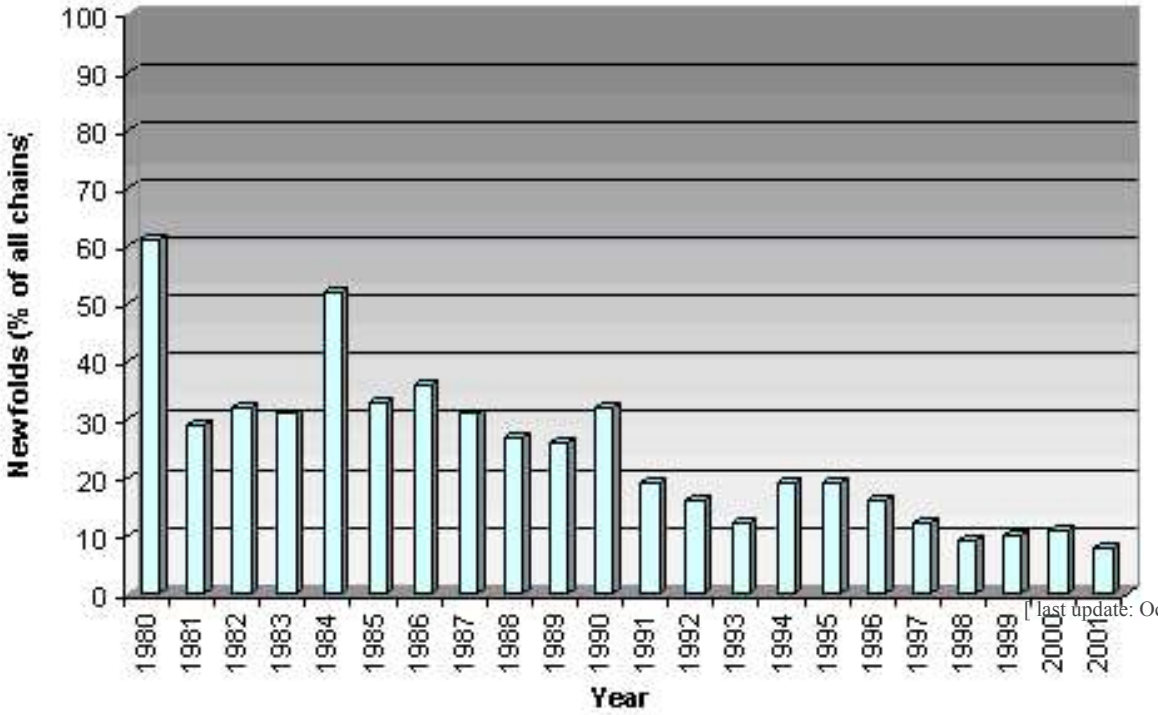
Definition

Extrapolation of the structure for a new (target) sequence from the known 3D-structures of related family members (templates).

1. Basic concepts of Homology Modeling

The number of different protein folds is limited:

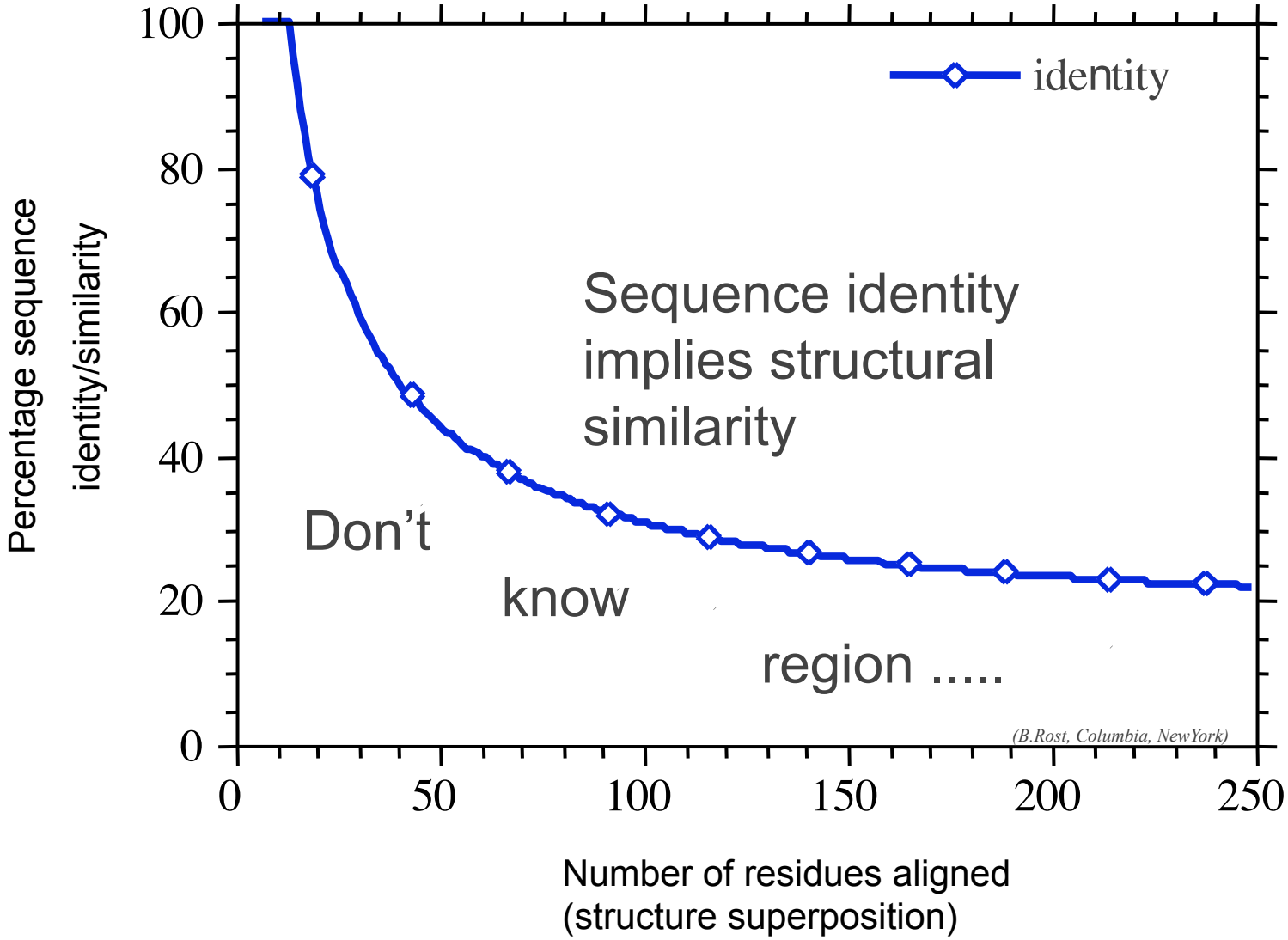




[last update: Oct 2001]

1. Basic concepts of Homology Modeling

Sequence similarity implies structural similarity?

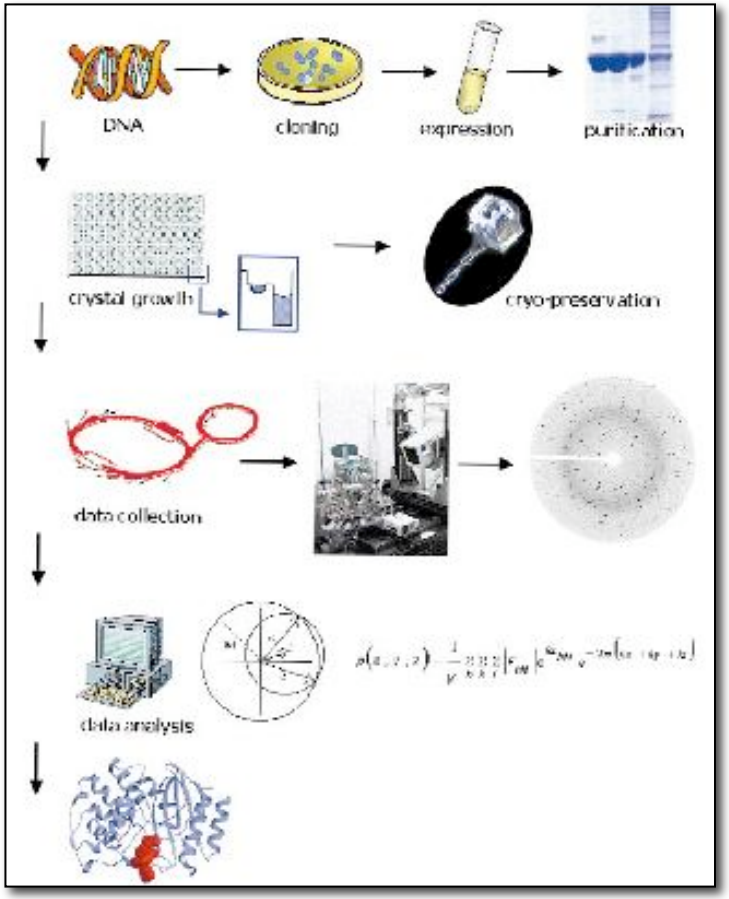


1. Basic concepts of Homology Modeling

- Fold is more conserved than sequence.
- Secondary structure are the most conserved parts
- Loops have the higher variability in structure.

1. Basic concepts of Homology Modeling

Structural Genomics



express & purify

cristallize

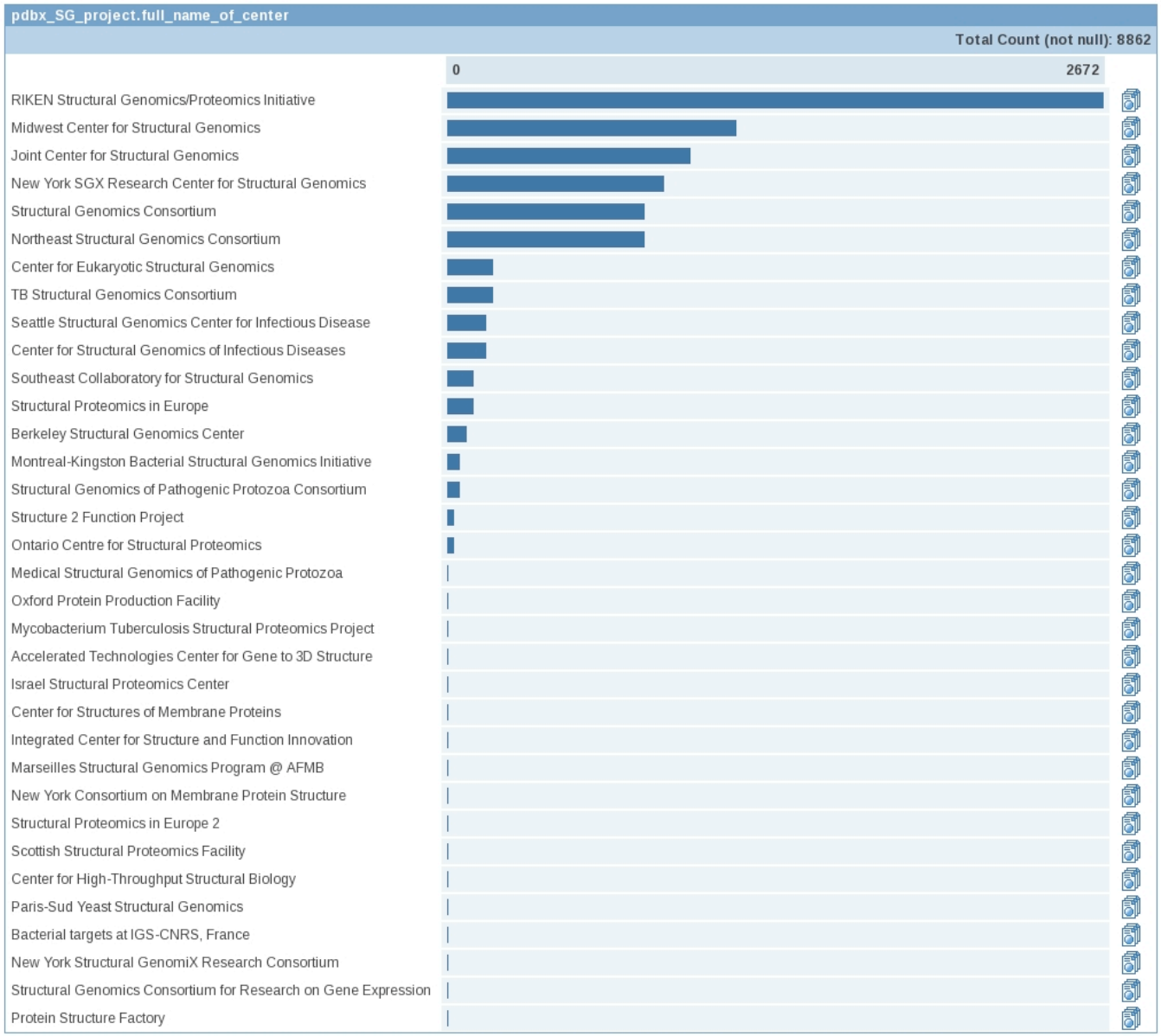
X-ray

analises

structure

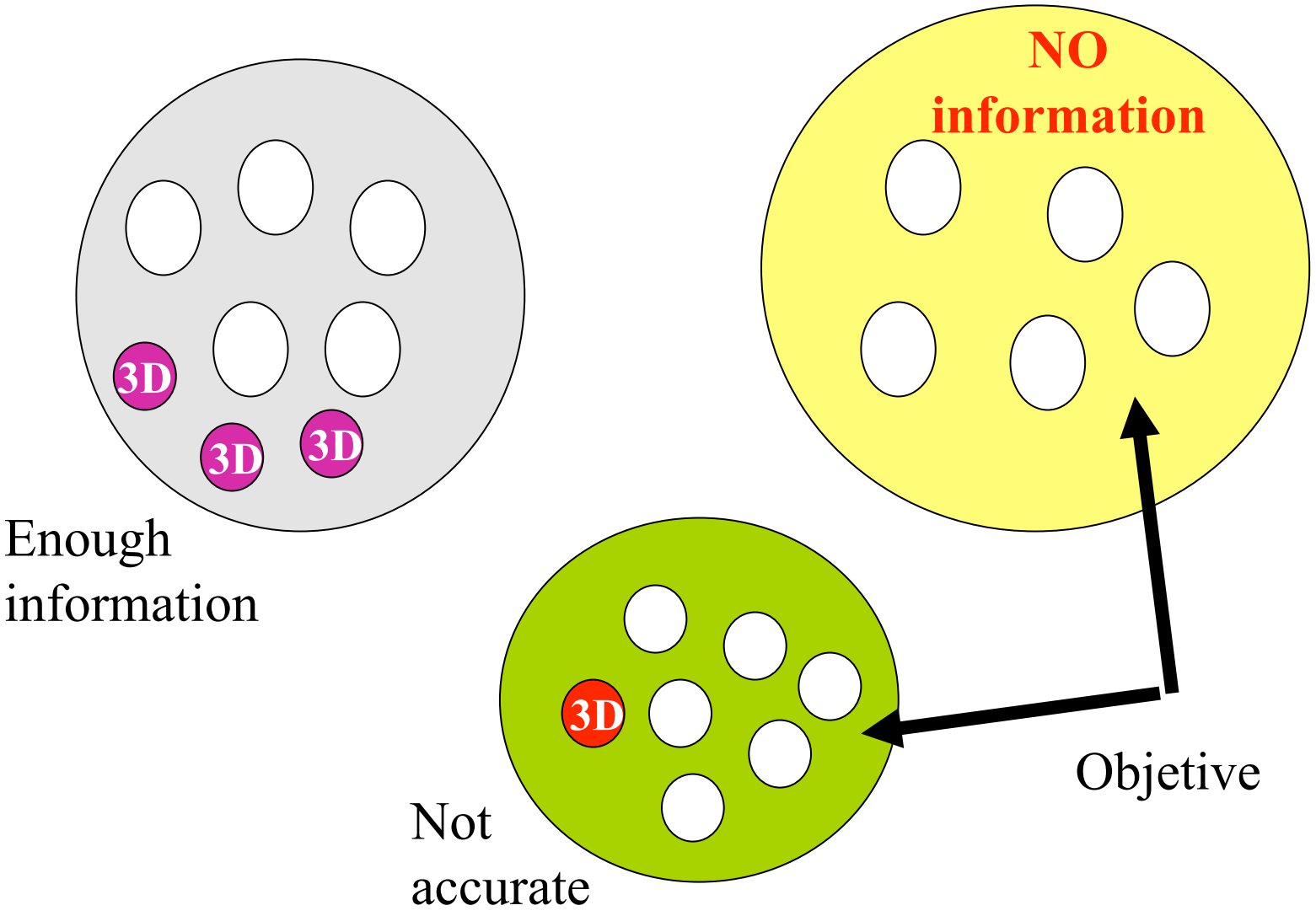
1. Basic concepts of Homology Modeling

Structural Genomics



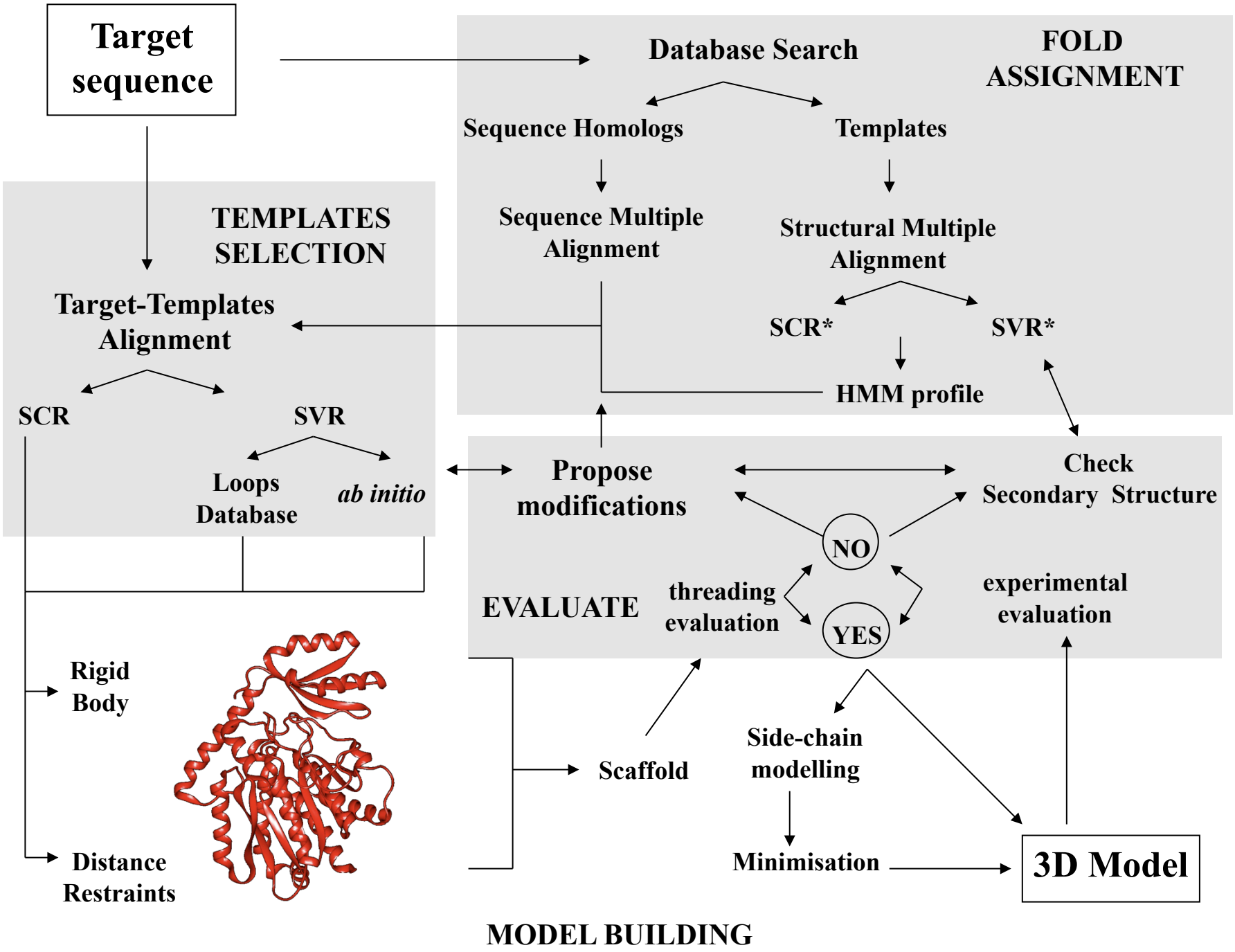
1. Basic concepts of Homology Modeling

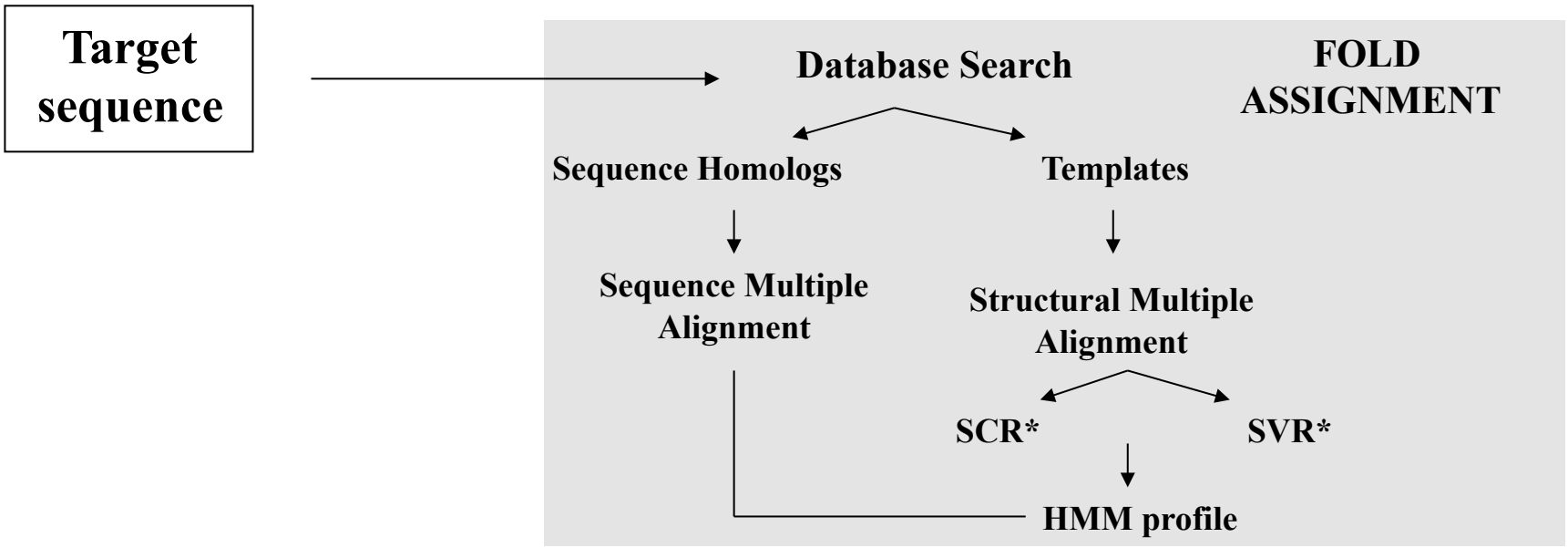
Structural Genomics



2. Schema of the method

1. Fold assignment
2. Template selection
3. Model building
4. Evaluation
5. Improvement


Target sequence
Database Search
FOLD ASSIGNMENT
Sequence Homologs
Templates
Sequence Multiple Alignment
Structural Multiple Alignment
TEMPLATES SELECTION
Target-Templates Alignment
SCR*
SVR*
HMM profile
SCR
SVR
Loops Database
ab initio
Propose modifications
Check Secondary Structure
NO
EVALUATE
threading evaluation
YES
experimental evaluation
Rigid Body
Scaffold
Side-chain modelling
Distance Restraints
Minimisation
3D Model
MODEL BUILDING

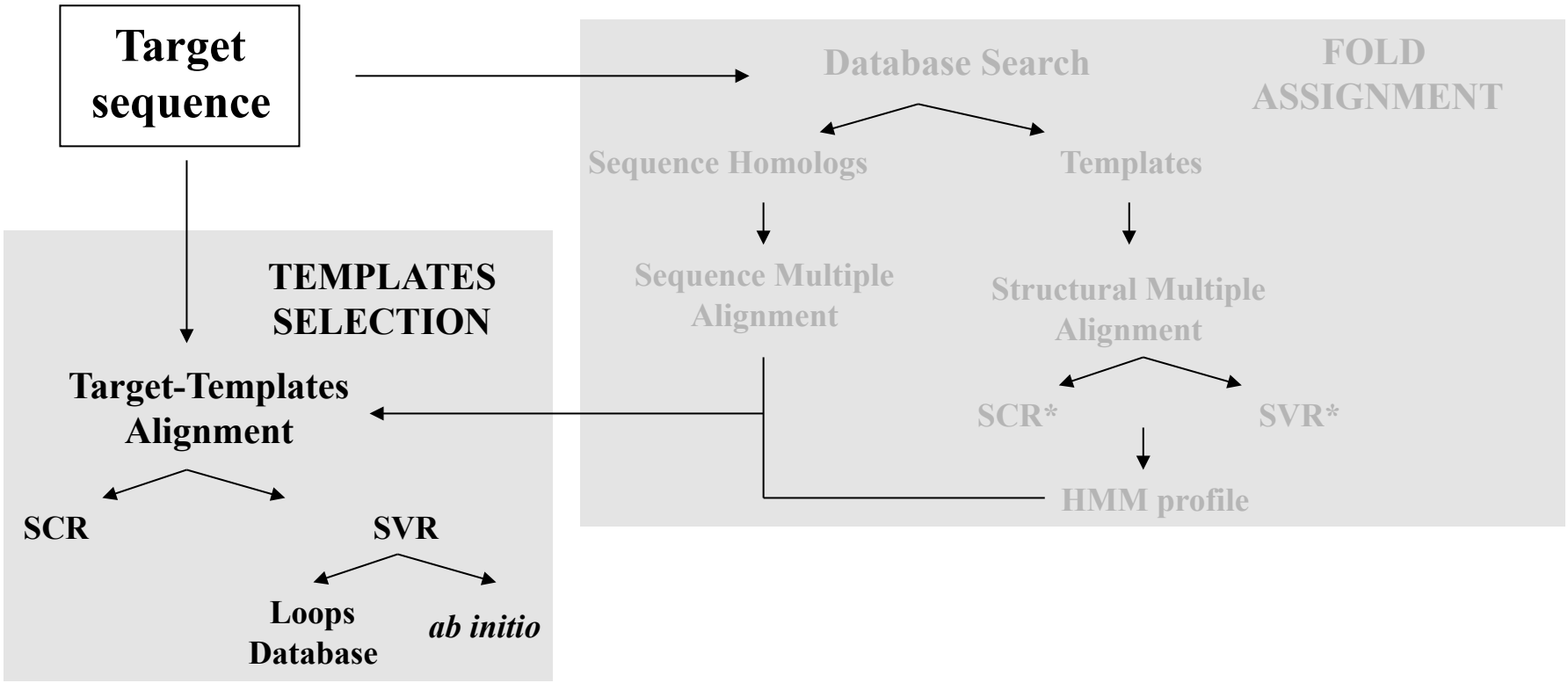

Target sequence
Database Search
FOLD ASSIGNMENT
Sequence Homologs
Templates
Sequence Multiple Alignment
Structural Multiple Alignment
SCR*
SVR*
HMM profile

2. Schema of the method

1. Fold assignment

Sequence search with the target

1. Compares the sequence of the target with a set of sequences with known structure
2. Ranking the comparisons by scores.
3. Scores are related to P-values or E-values (high score implies low P-value). P-value is the probability of obtaining the same alignment by chance.
4. Scores are calculated using a residue-substitution matrix:
    1. PAM: based on the alignment of sequences of homologs
    2. BLOSUM: based on the alignment of blocs of similar sequences
5. One sequence can have more than one domain, therefore we can obtain the best scores for partial parts of the target.
6. Methods (see practice)
    1. BLAST algorithm, matches words from a pre-calculated and indexed set and joints them into sentences (forming the sequence)
    2. FastA: Smith & Waterman algorithm
    3. Scanning PFAM: algorithm of Hidden Markov Models


Target sequence
Database Search
FOLD ASSIGNMENT
Sequence Homologs
Templates
Sequence Multiple Alignment
Structural Multiple Alignment
SCR*
SVR*
HMM profile
TEMPLATES SELECTION
Target-Templates Alignment
SCR
SVR
Loops Database
ab initio

2. Schema of the method

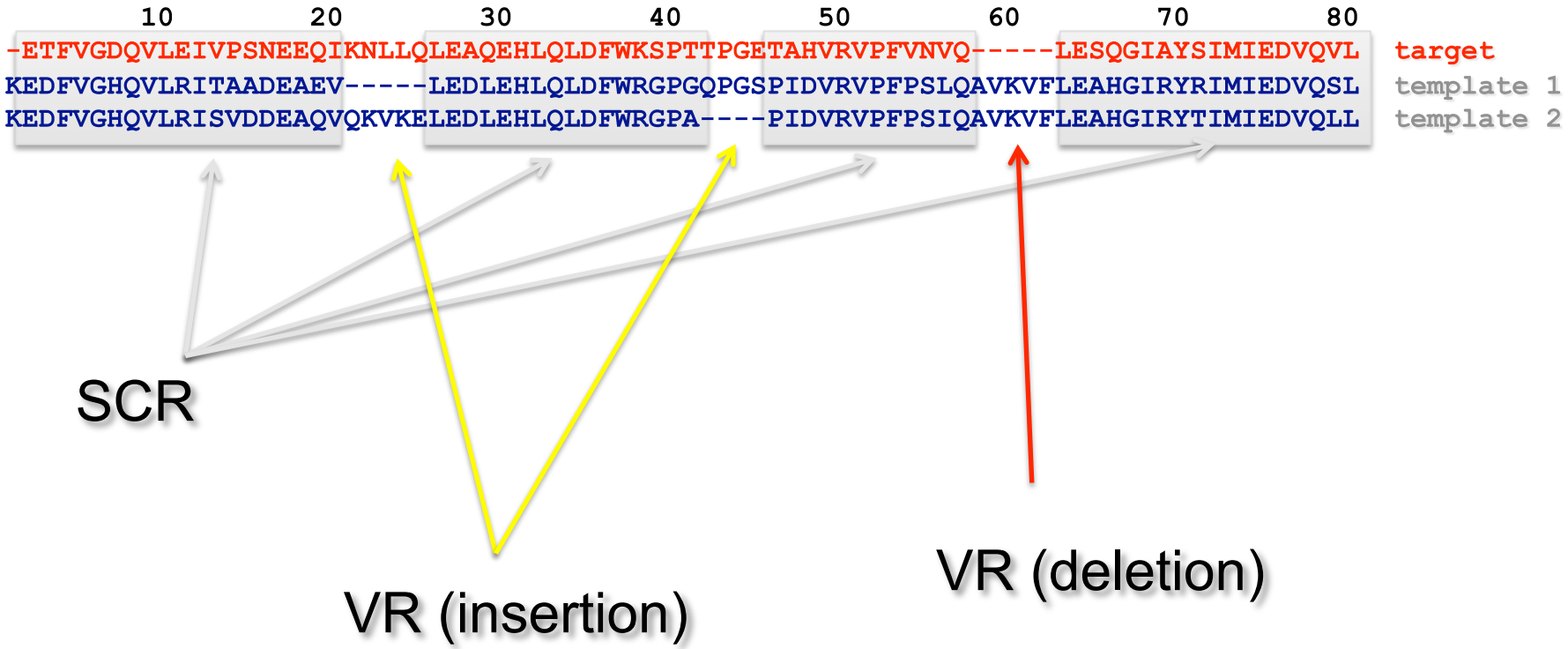
2. Template selection

Selecting the best target-alignment template

1. The template(s) should be the closest homolog(s) to the target
2. Small number of templates to avoid stress on model building
3. Multi-domain proteins require the use of at least one template with the largest coverage of sequence (containing the largest number of domains)
4. Structural alignment of homologs gives the information on position-specific substitutions
5. Detection of structurally conserved regions (SCR) and variable regions (VR)
6. Aligning the target sequence and template sequences using a multiple sequence profile helps to avoid misalignments
7. Methods (see practice)
    1. ClustalW
    2. T-coffee
    3. HMMER
        1. alignment with a known family profile (PFAM)
        2. Alignment with a profile built with the structure of homologs

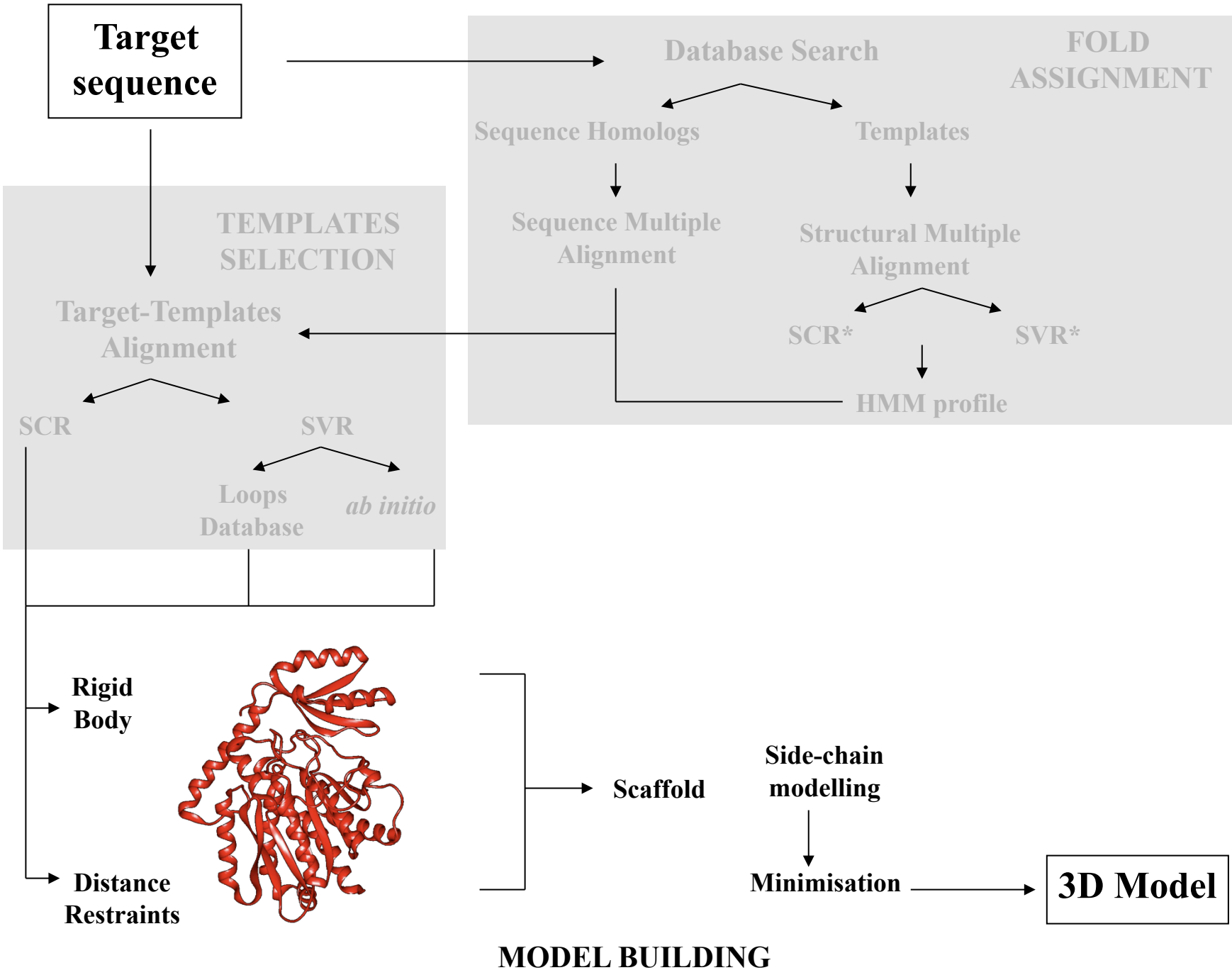
2. Schema of the method

2. Template selection



2. Schema of the method

2. Template selection


Target sequence
Database Search
FOLD ASSIGNMENT
Sequence Homologs
Templates
Sequence Multiple Alignment
Structural Multiple Alignment
TEMPLATES SELECTION
Target-Templates Alignment
SCR*
SVR*
HMM profile
SCR
SVR
Loops Database
ab initio
Rigid Body
Distance Restraints
Scaffold
Side-chain modelling
Minimisation
3D Model
MODEL BUILDING

2. Schema of the method

3. Model building

1. Rigid Body Assembly
    1. Core framework (SCR)
    2. Loop modeling (VR)
    3. Energy minimization
2. Spatial restraints
    1. Probability Density Functions (PDF)
    2. Distance restraints
    3. Simulated Annealing
    4. Loop modeling
3. Side-chain modeling
    1. Back-bone dependent rotamer libraries
    2. Energetic and packing criteria

2. Schema of the method

3. Model building: Rigid Body Assembling (core framework)

- Averaging core template backbone atoms

  (weighted by local sequence similarity with the target sequence)

- Leave non-conserved regions (loops) for later ….

2. Schema of the method

3. Model building: Rigid Body Assembling (loop modeling)

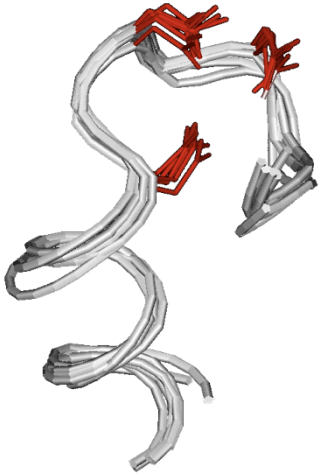
1. Use the “spare part” algorithm to find compatible fragments in a Loop-Database

2. “*ab-initio*” rebuilding of loops (Monte Carlo, molecular dynamics, genetic algorithms, etc.)

2. Schema of the method

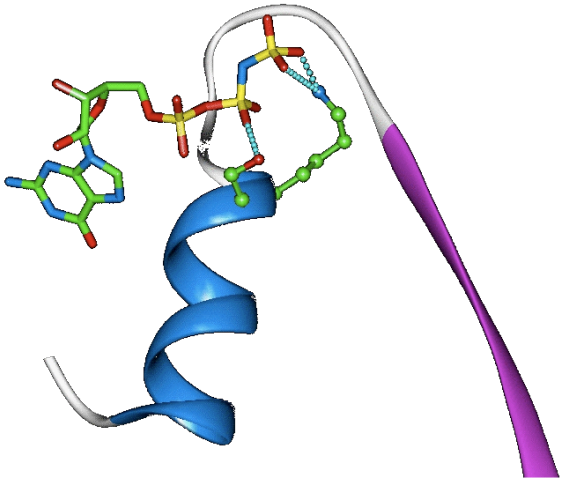
3. Model building: Rigid Body Assembling (loop modeling)

1. Use the “spare part” algorithm to find compatible fragments in a Loop-Database



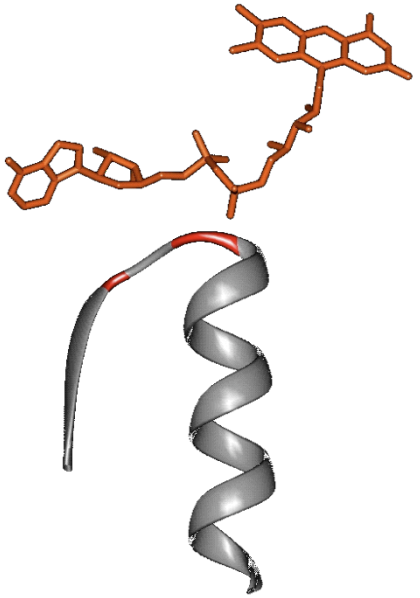
EF-Hand Calcium binding

```
aa{baalal}bb
Xh{DXDpDG}Xh
```



P-loop GTP binding

```
bb{eppgag}aa
hh{GhXXpG}Kp
```



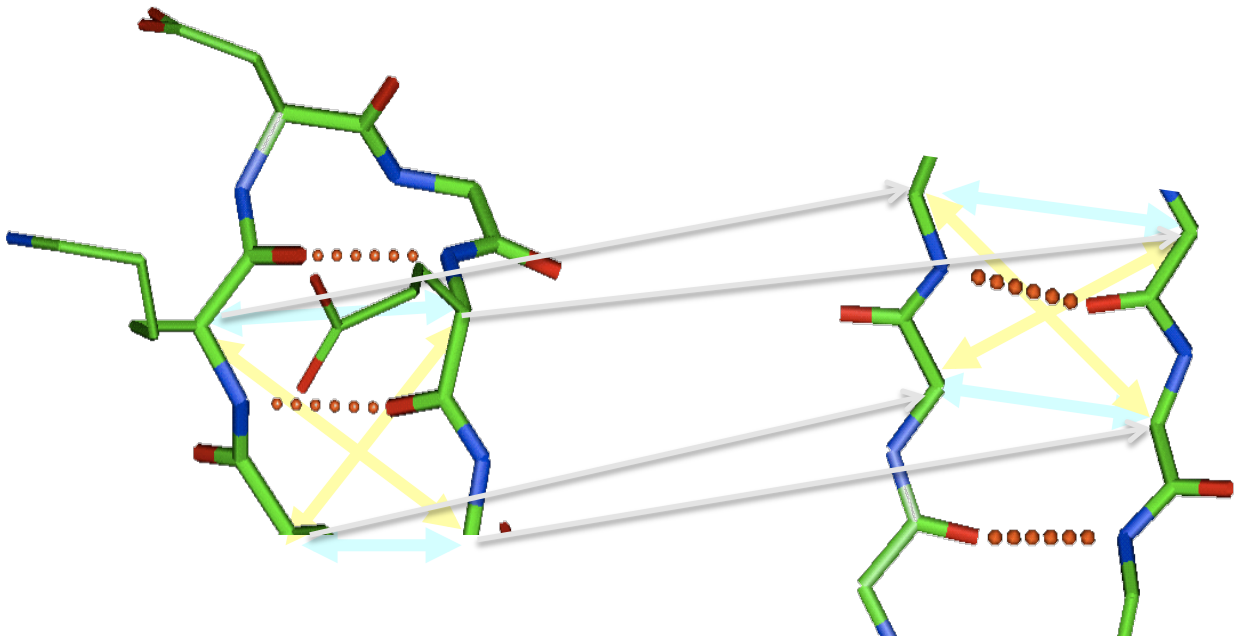
NAD(P)/FAD binding

```
bb{eab}aa
hh{GhG}hX
```

2. Schema of the method

3. Model building: Rigid Body Assembling (loop modeling)

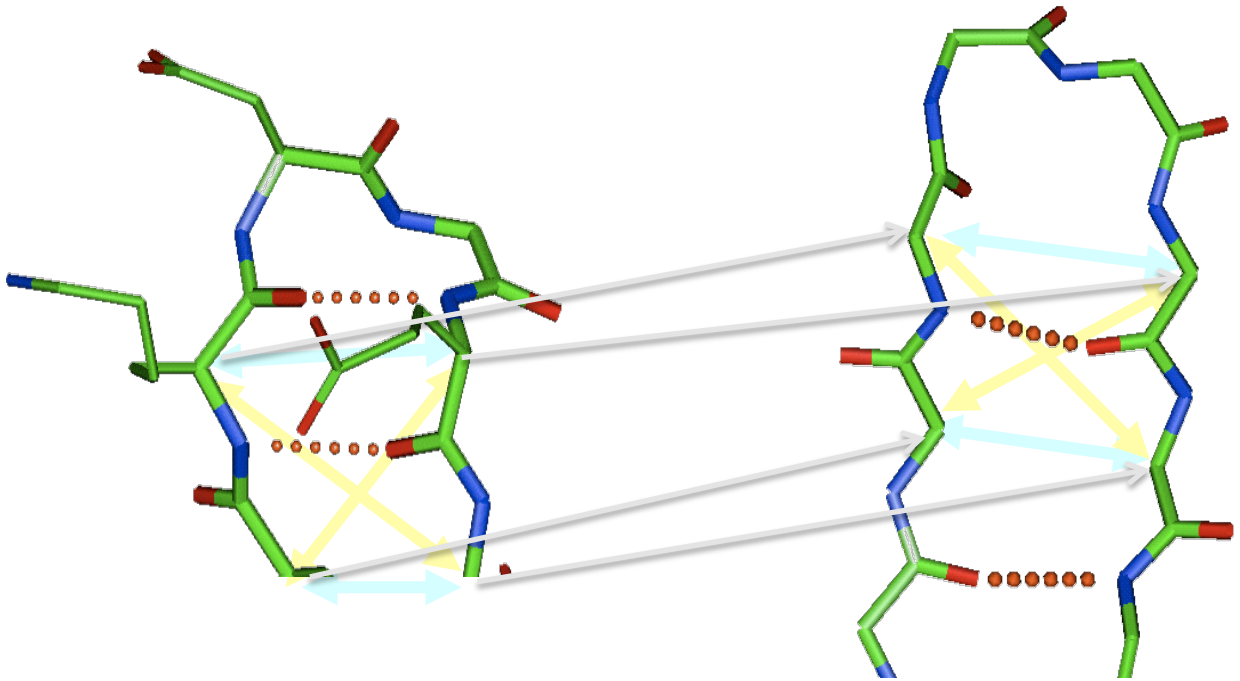
1. Use the “spare part” algorithm to find compatible fragments in a Loop-Database



2. Schema of the method

3. Model building: Rigid Body Assembling (loop modeling)

1. Use the “spare part” algorithm to find compatible fragments in a Loop-Database



2. Schema of the method

3. Model building: Rigid Body Assembling (Energy minimization)

$$E_{bonding} = \sum_{bonds} \frac{1}{2} k_i \left(d_i - d_i^0\right)^2 + \sum_{angles} \frac{1}{2} k_j \left(\alpha_j - \alpha_j^0\right)^2 + \sum_{\substack{improper \\ dihedral}} \frac{1}{2} k_n \left(\omega_n - \omega_n^0\right)^2 + \sum_{angles} E_m Cos\left(\omega_m \phi_m + \varphi_m\right)^2$$

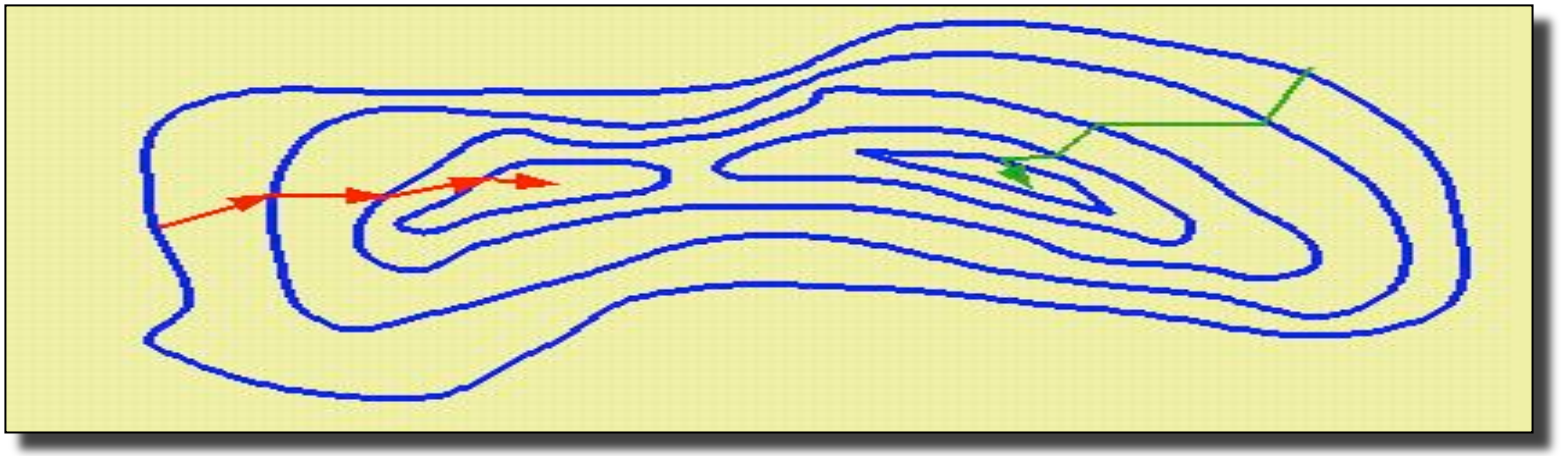
$$E_{non-bonding} = \frac{1}{4\pi\varepsilon_0} \sum_i \sum_{j>i} \frac{q_i q_j}{r_{ij}} + \sum_i \sum_{j>i} \frac{C_6^{ij}}{r_{ij}^6} - \frac{C_{12}^{ij}}{r_{ij}^{12}}$$

$$E = E_{bonding} + E_{non-bonding}$$

- modeling will produce unfavorable contacts and bonds: idealization of local bond and angle geometry
- extensive energy minimization will move coordinates away: keep it to a minimum
- Methods: Newton Rapson; Steepest Descent; Conjugate Gradient

2. Schema of the method

3. Model building: Rigid Body Assembling (Energy minimization)



$$x_{i+1} = x_i + \lambda \nabla E$$

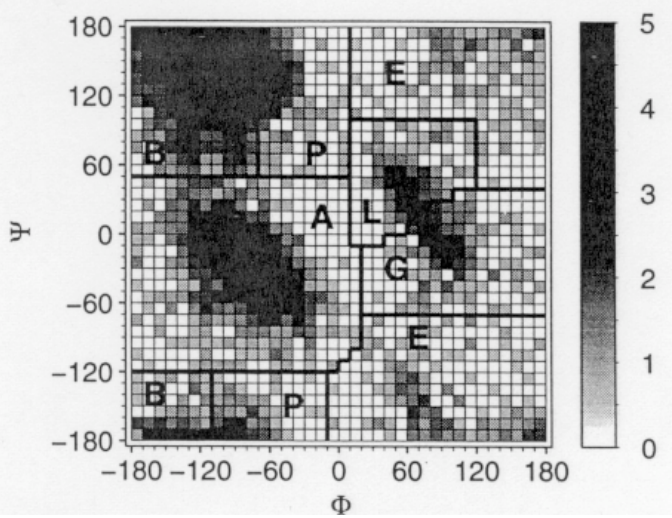
$$\lambda = \begin{cases} E(x_{i+1}) < E(x_i) \Rightarrow \lambda = \lambda + \varepsilon \\ E(x_{i+1}) > E(x_i) \Rightarrow \lambda = \lambda / 2 \\ \lambda < \lambda_{\max} \\ E(x_{i+1}) \approx E(x_i) \Rightarrow STOP \end{cases}$$

2. Schema of the method

3. Model building: Spatial restraints (Probability Density Functions)

Feature properties can be associated with

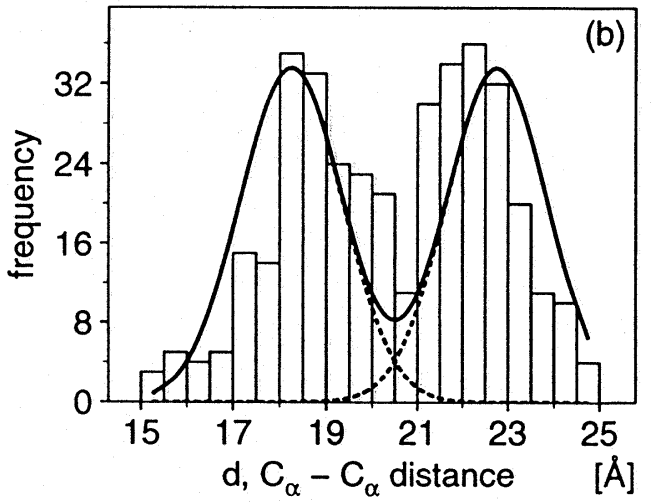
- a protein (e.g. X-ray resolution)
- residues (e.g. solvent accessibility)
- pairs of residues (e.g. C_a - C_a distance)
- other features (e.g. main chain classes)



Example: Ramachandran Plot
Distribution of (ϕ,ψ) angles

2. Schema of the method

3. Model building: Spatial restraints (Probability Density Functions)



Example:
Distribution of Cα−Cα distances

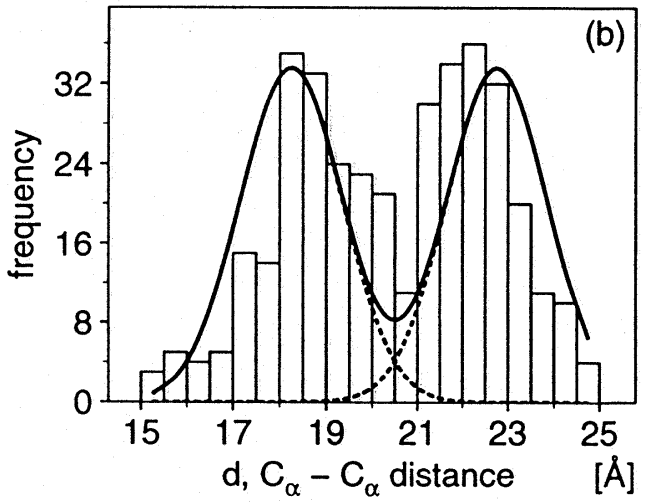
How can we derive modeling restraints from this data?

A restraint is defined as probability density function (*pdf*), p(x):

$$p(x1 \le x < x2) = \int_{x2}^{x1} p(x)dx \qquad \text{with} \qquad \int p(x)dx = 1 \qquad p(x) > 0$$

2. Schema of the method

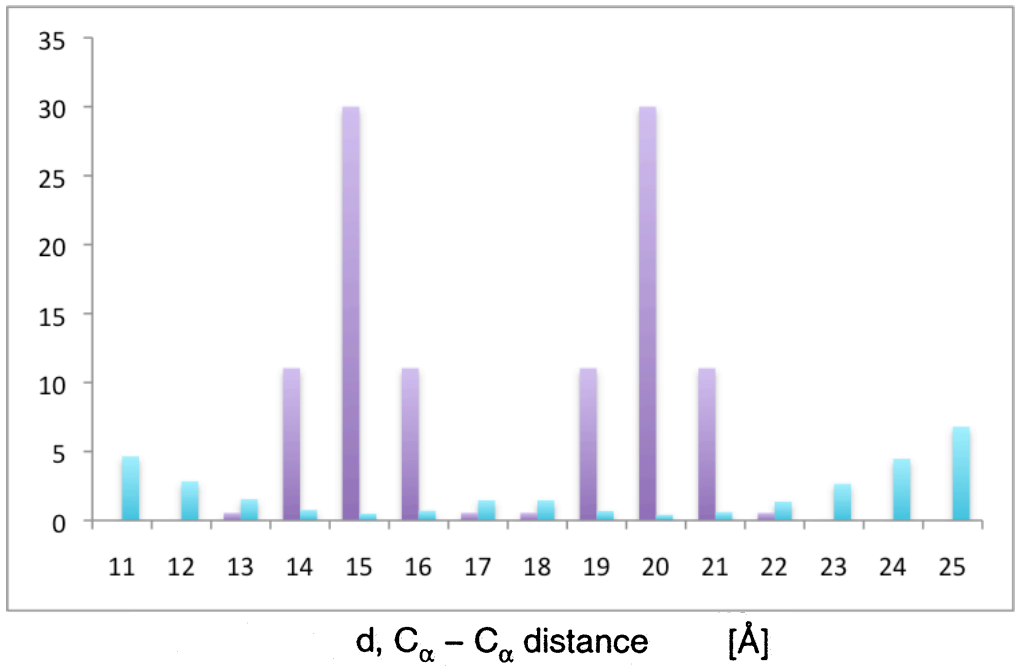
3. Model building: Spatial restraints (Probability Density Functions)



Example:
Distribution of Cα–Cα distances

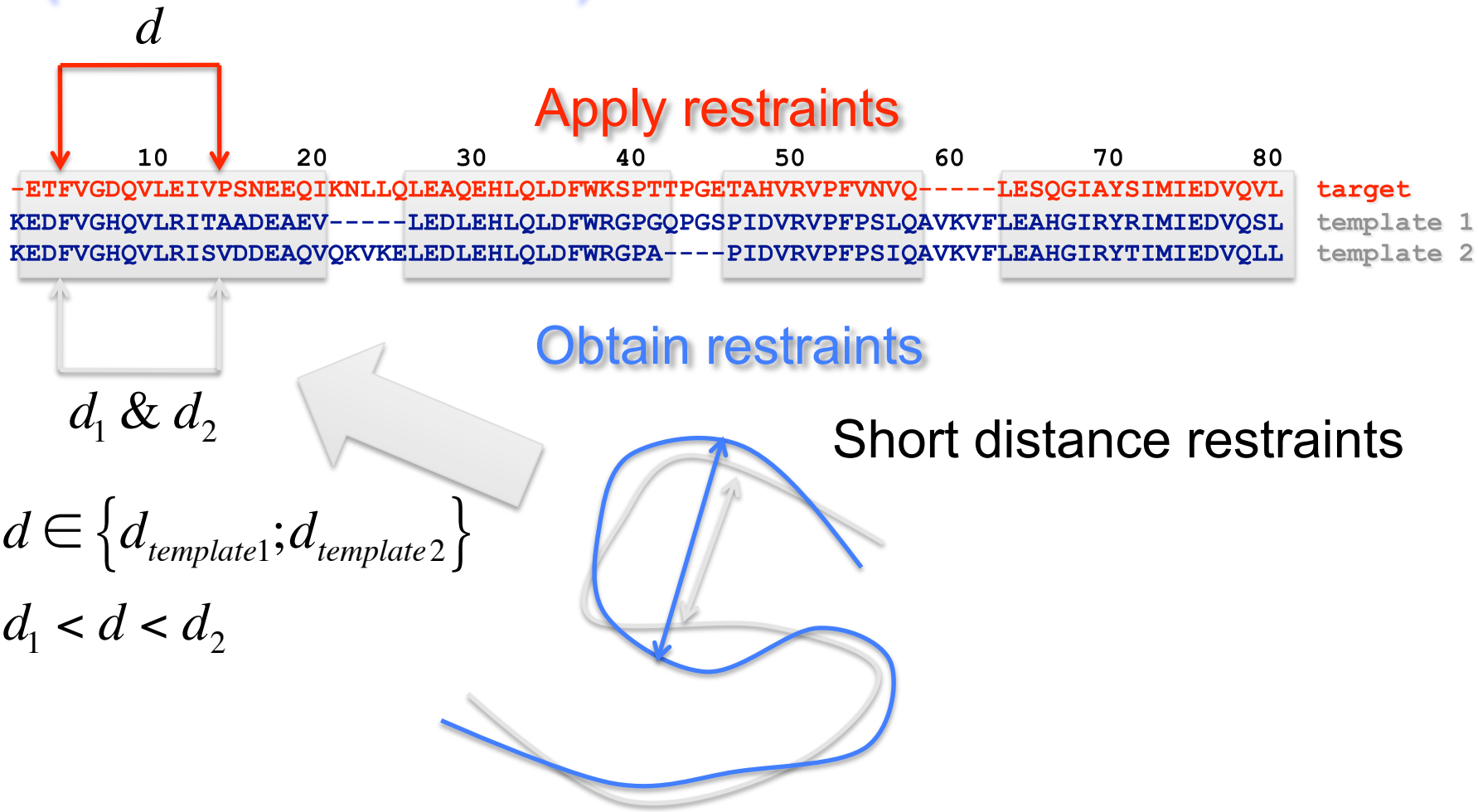
How can we derive modeling restraints from this data?

$$E_{pdf}(x) = -RT\log(p(x))$$



2. Schema of the method

3. Model building: Spatial restraints (Distance restraints)

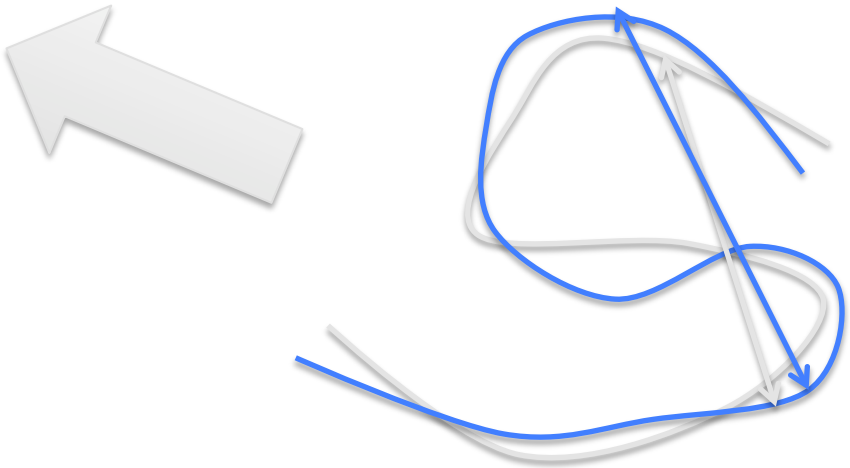


2. Schema of the method

3. Model building: Spatial restraints (Distance restraints)

$$d \in \{d_{template1}; d_{template2}\}$$

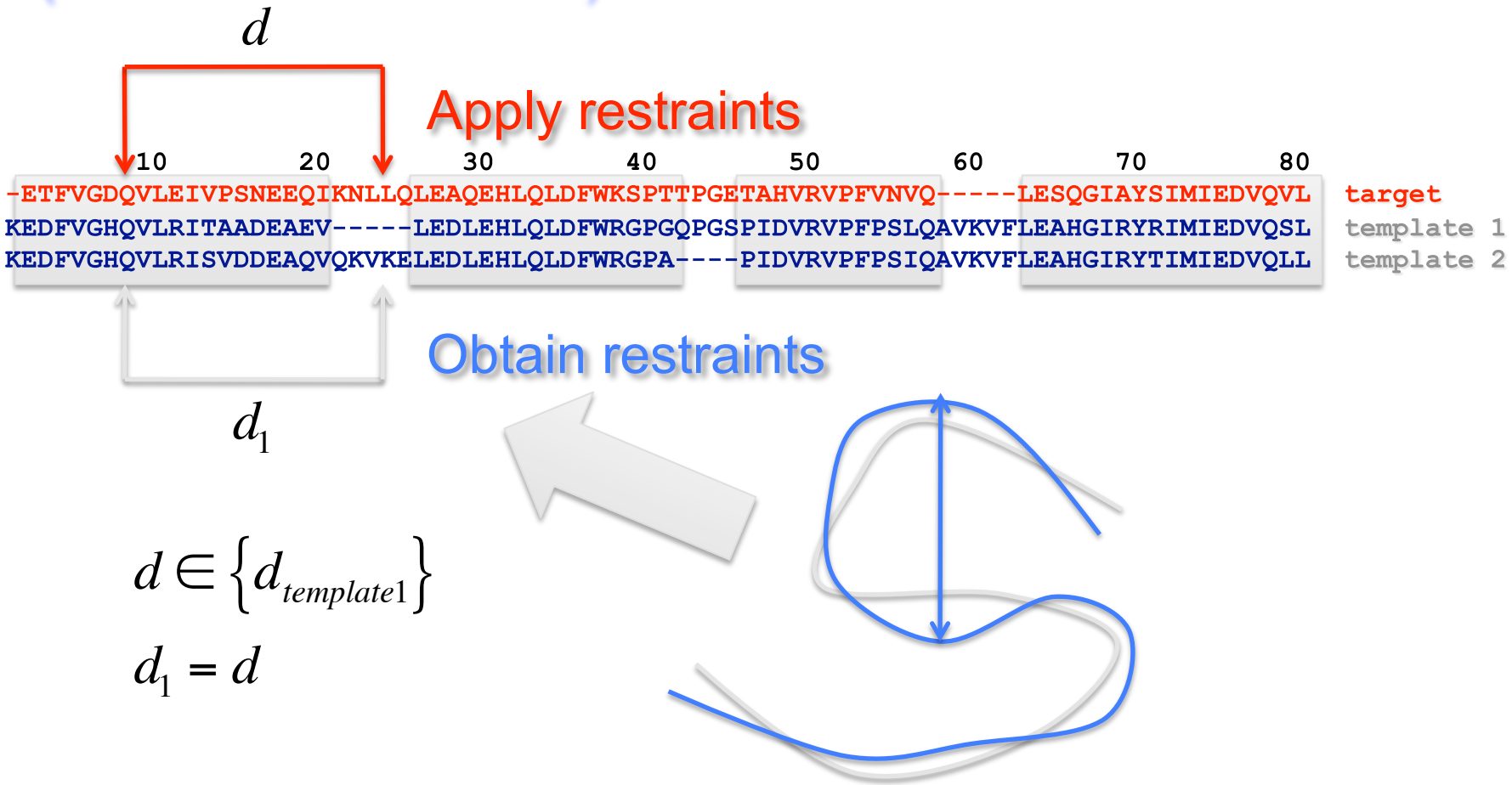
$$d_1 < d < d_2$$



Long distance restraints

2. Schema of the method

3. Model building: Spatial restraints (Distance restraints)



Distance restraints between Aa in SCR & VR
(required to locate the conformation of the VR)

2. Schema of the method

3. Model building: Spatial restraints (Distance restraints)

$$d \in \{d_{template1}\}$$

$$d_1 = d$$

Distance restraints between Aa in VR & VR
(required to obtain the conformation of the VR)

2. Schema of the method

3. Model building: Spatial restraints (Simulated annealing)

Optimizing a target function:

1. Start with e.g. a random conformation model and use only local restraints
2. Minimize some steps using a conjugate gradient optimization and molecular dynamics steps
3. Repeat, introducing more and more long range restraints until all restraints are used

$$E_{bonding} = \sum_{bonds} \frac{1}{2} k_i \left(d_i - d_i^0\right)^2 + \sum_{angles} \frac{1}{2} k_j \left(\alpha_j - \alpha_j^0\right)^2 + \sum_{\substack{improper \\ dihedral}} \frac{1}{2} k_n \left(\omega_n - \omega_n^0\right)^2 + \sum_{angles} E_m Cos\left(\omega_m \phi_m + \varphi_m\right)^2$$

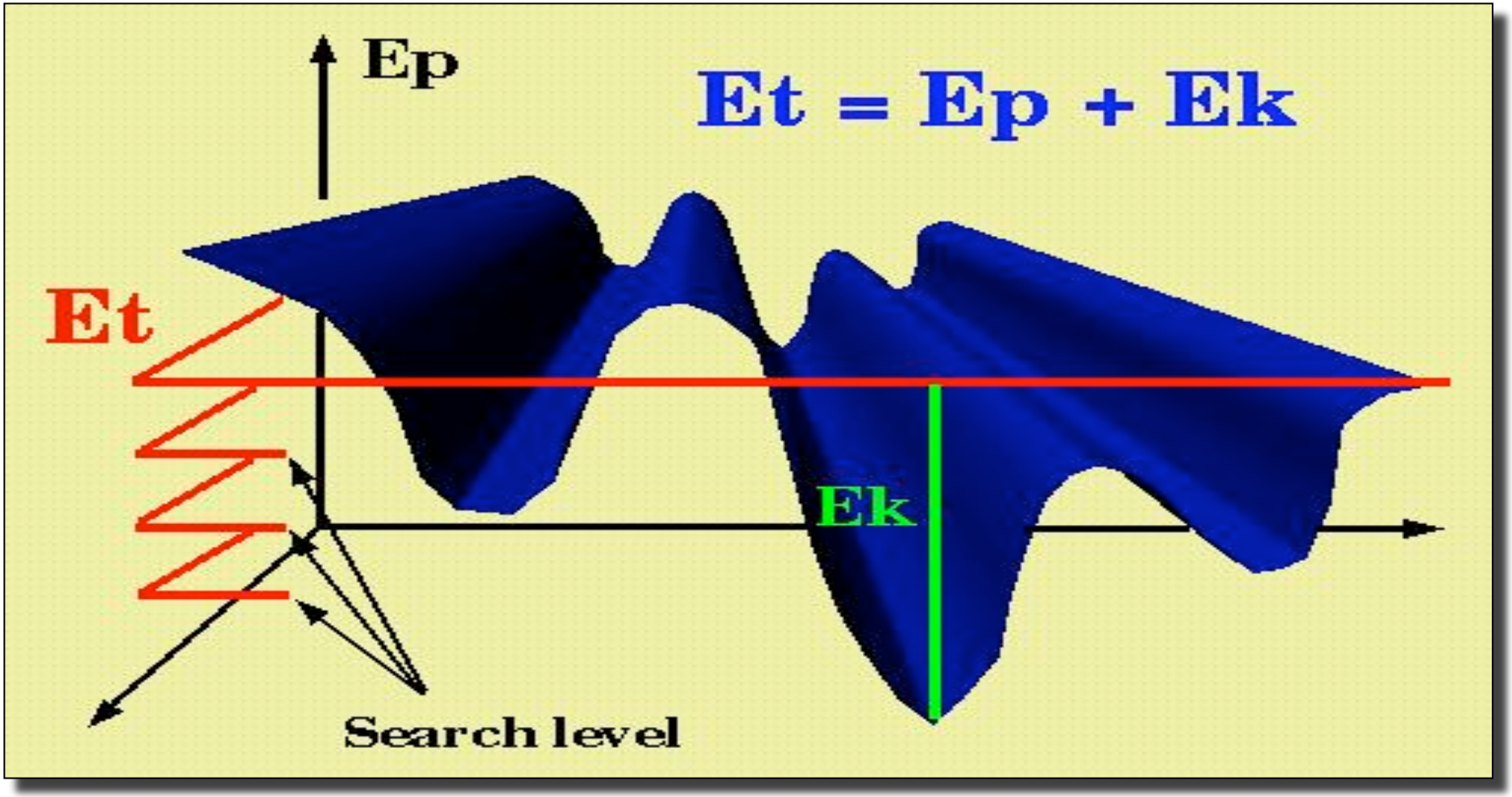
$$E_{non-bonding} = \frac{1}{4\pi\varepsilon_0} \sum_i \sum_{j>i} \frac{q_i q_j}{r_{ij}} + \sum_i \sum_{j>i} \frac{C_6^{ij}}{r_{ij}^6} - \frac{C_{12}^{ij}}{r_{ij}^{12}}$$

$$E_{dist} = \sum_{rest} \frac{1}{2} k_r \left(d_r - \left\langle d_r^0 \right\rangle\right)^2$$

$$E = E_{bonding} + E_{non-bonding} + E_{pdf} + E_{dist}$$

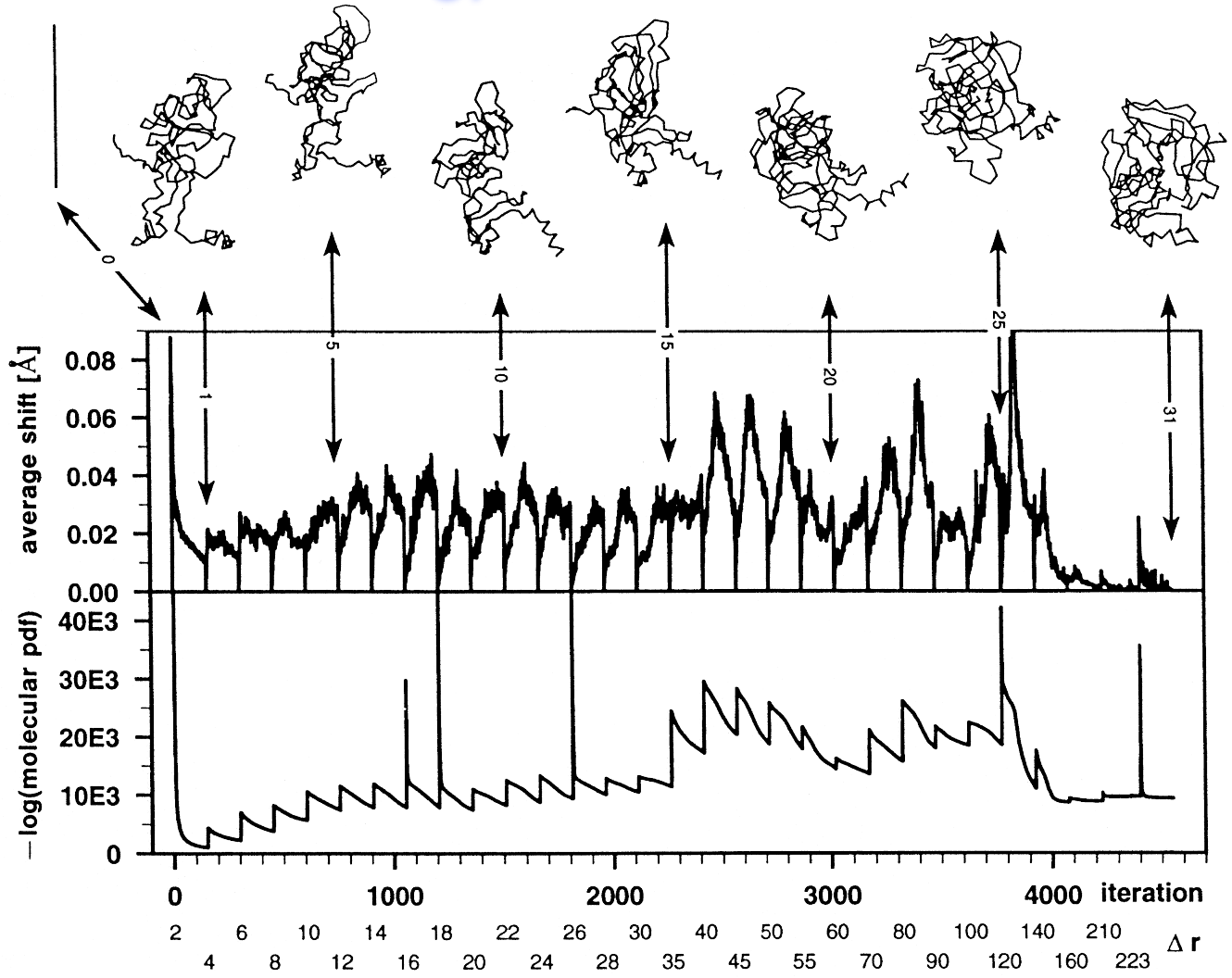
2. Schema of the method

3. Model building: Spatial restraints (Simulated annealing)



2. Schema of the method

3. Model building: Spatial restraints (Simulated annealing)



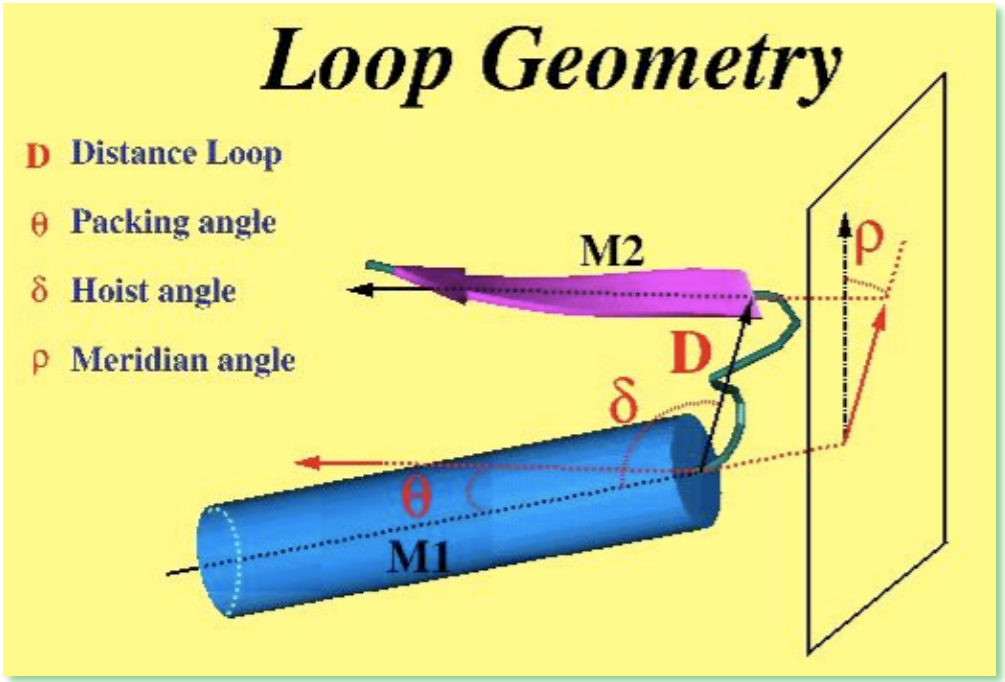
2. Schema of the method

3. Model building: Spatial restraints (Loop modeling using a database of loops)

Apply restraints

```
        10        20        30        40        50        60        70        80
-ETFVGDQVLEIVPSNEEQIKNLLQLEAQEHLQLDFWKSPTTPGETAHVRVPFVNVQ-----LESQGIAYSIMIEDVQVL  target
KEDFVGHQVLRITAADEAEV-----LEDLEHLQLDFWRGPGQPGSPIDVRVPFPSLQAVKVFLEAHGIRYRIMIEDVQSL  template 1
-------------VDDEAQVQKVKELEDLEH-------------------------------------------------  template 2
```

Obtain restraints



2. Schema of the method

3. Model building: Spatial restraints (Loop modeling using a database of loops)

Using the structure of a known loop:

1. The C-tail and N-tail of the loop (template 2) when superposed with the core of the main template (template 1) produce a low RMSD
2. The selection of the loop follow two criteria: similar sequence profile with the target and similar anchoring geometry of the loop with the main template

2. Schema of the method

3. Model building: Spatial restraints (Loop modeling *ab initio*)

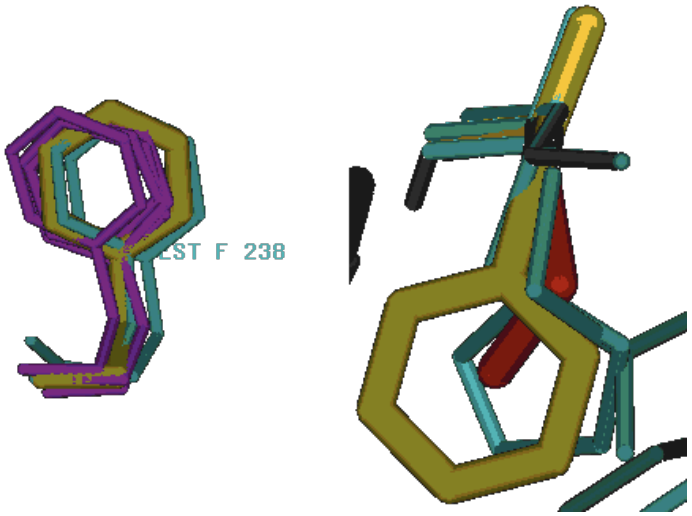
Using PDF of loops and minimization methods:

1. Calculate specific PDF residue properties of loops
2. Minimize by simulated annealing the loops
3. Extract main motion from normal modes on templates and apply them as restrictions on the conformational changes of the model
4. Methods:
    1. Loop-model from MODELLER
    2. ArchPred
    3. Rosetta

2. Schema of the method

3. Model building: Side-chains

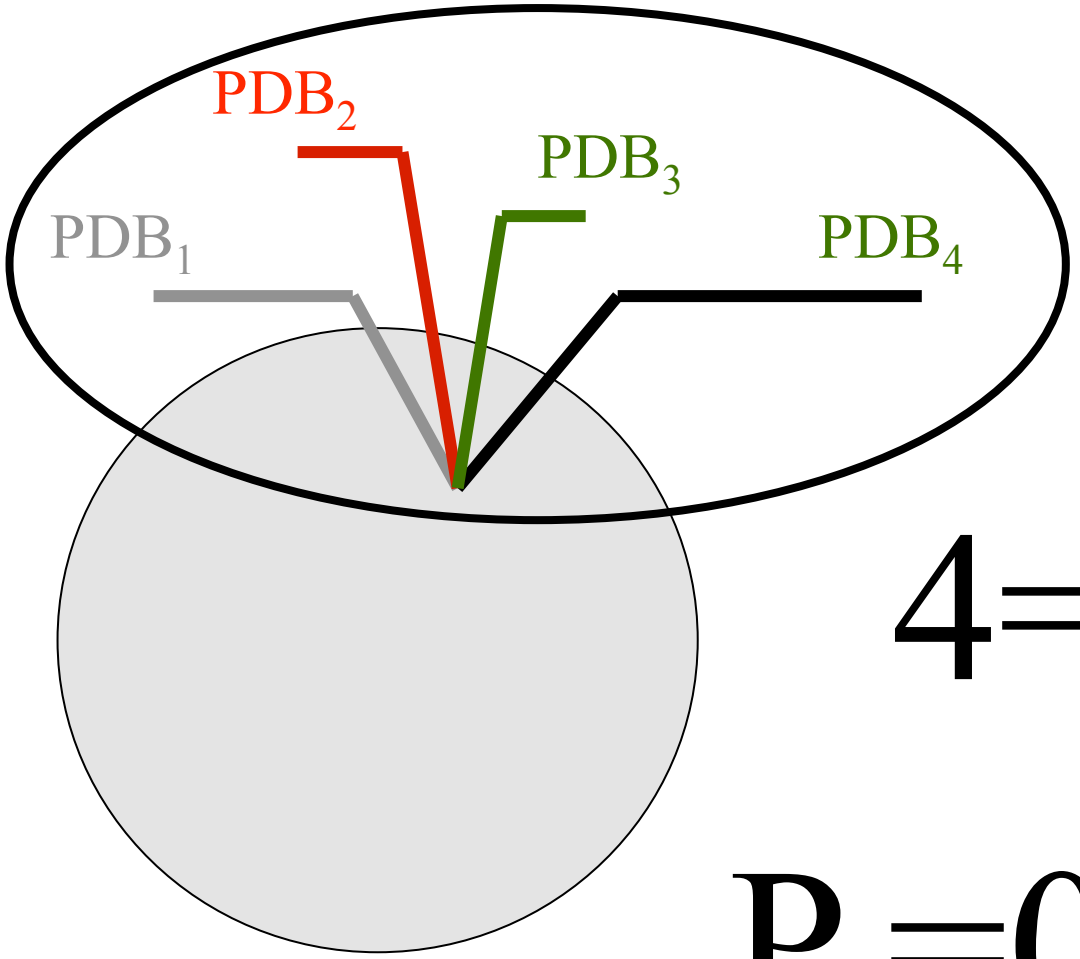
Let be a rotamer library, we define the probability of side-chain “i” in conformation “k” as **CM**(i,k).
Initially **CM**(i,k)=1/Ki, where Ki is the total of rotamers of residue “i”.



Multi-copy.
Koehl and Delarue *J.Mol. Biol.* (1994) **239**, 249-275

2. Schema of the method

3. Model building: Side-chains



$$4=K_i$$

$$P_i=0.25$$

2. Schema of the method

3. Model building: Side-chains

Given U the total potential energy of the protein and its environment, we define the effective potential of rotamer “k” of residue “i” as E(i,k), where:

$$E(i,k) = \int \rho(x) U(i,k,X) \mathrm{dX};$$

$$\mathrm{X} = (x_0, x_1, ..)$$

U is obtained with $E_{\text{non-bonding}}$, E_{bonding} on a system that includes the protein and water molecules

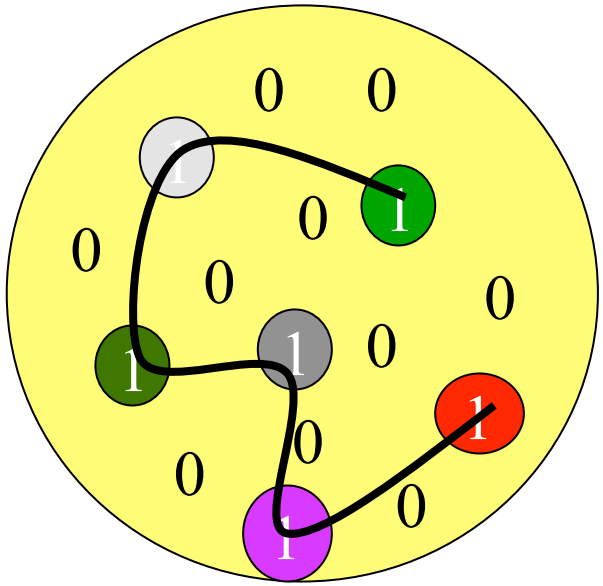
2. Schema of the method

3. Model building: Side-chains

$$\rho(x_0, x_1, ..) = \prod_{j=0}^{N} \rho(x_j);$$

$$\rho(x_0) = \delta(x_0 - xC_0);$$

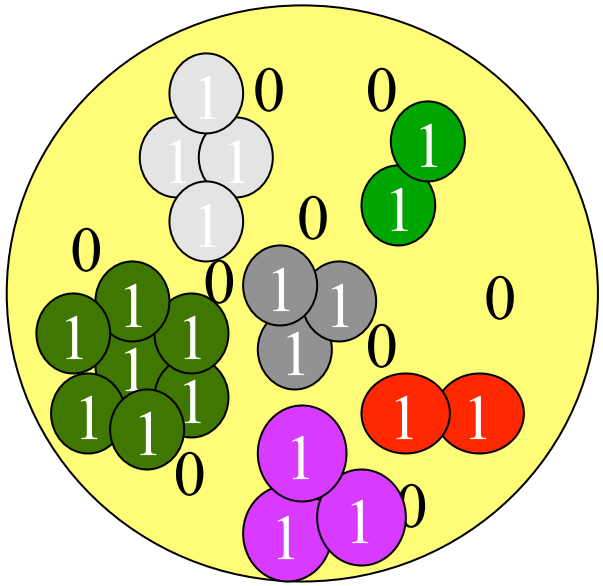
xC_0 backbone coordinates



2. Schema of the method

3. Model building: Side-chains

$$\rho(x_0, x_1, ..) = \prod_{j=0}^{N} \rho(x_j);$$



$$\rho(x_0) = \delta(x_0 - xC_0);$$

xC_0 backbone

$$\rho(x_i) = CM(i,k) * \delta(x_i - xC_i^k);$$

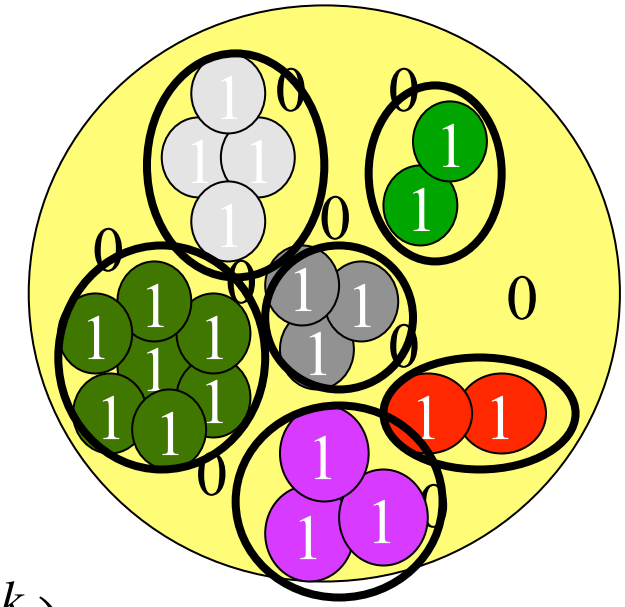
xC_i^k residue "i" coordinates

with conformation "k"

2. Schema of the method

3. Model building: Side-chains

$$\rho(x_0, x_1, ..) = \prod_{j=0}^{N} \rho(x_j);$$



$$\rho(x_j) = \sum_{k=1}^{K_j} CM(j,k)\delta(x_j - xC_j^k);$$

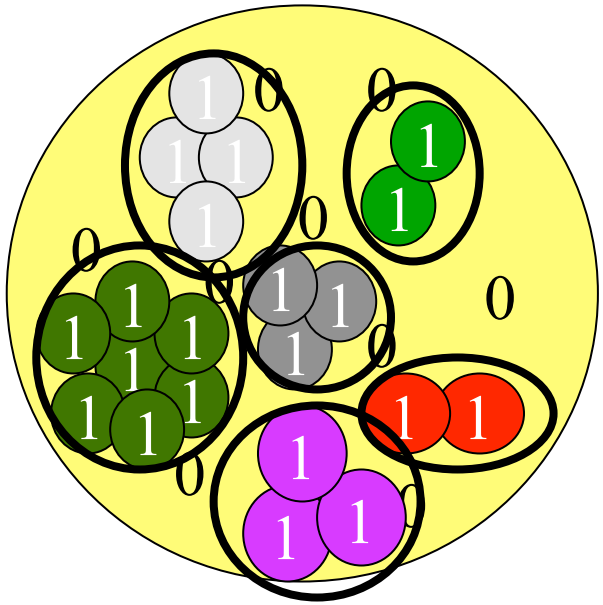
2. Schema of the method

3. Model building: Side-chains

$$\rho(x_j) = \sum_{l=1}^{K_j} CM(j,l)\delta(x_j - xC_j^l);$$

$$\rho(x_0, x_1, ..) = \prod_{j=0}^{N} \rho(x_j);$$

$$E(i,k) = \int \rho(x) U(i,k,X) \mathrm{d}X;$$



2. Schema of the method

3. Model building: Side-chains

By Statistical Mechanics we know that

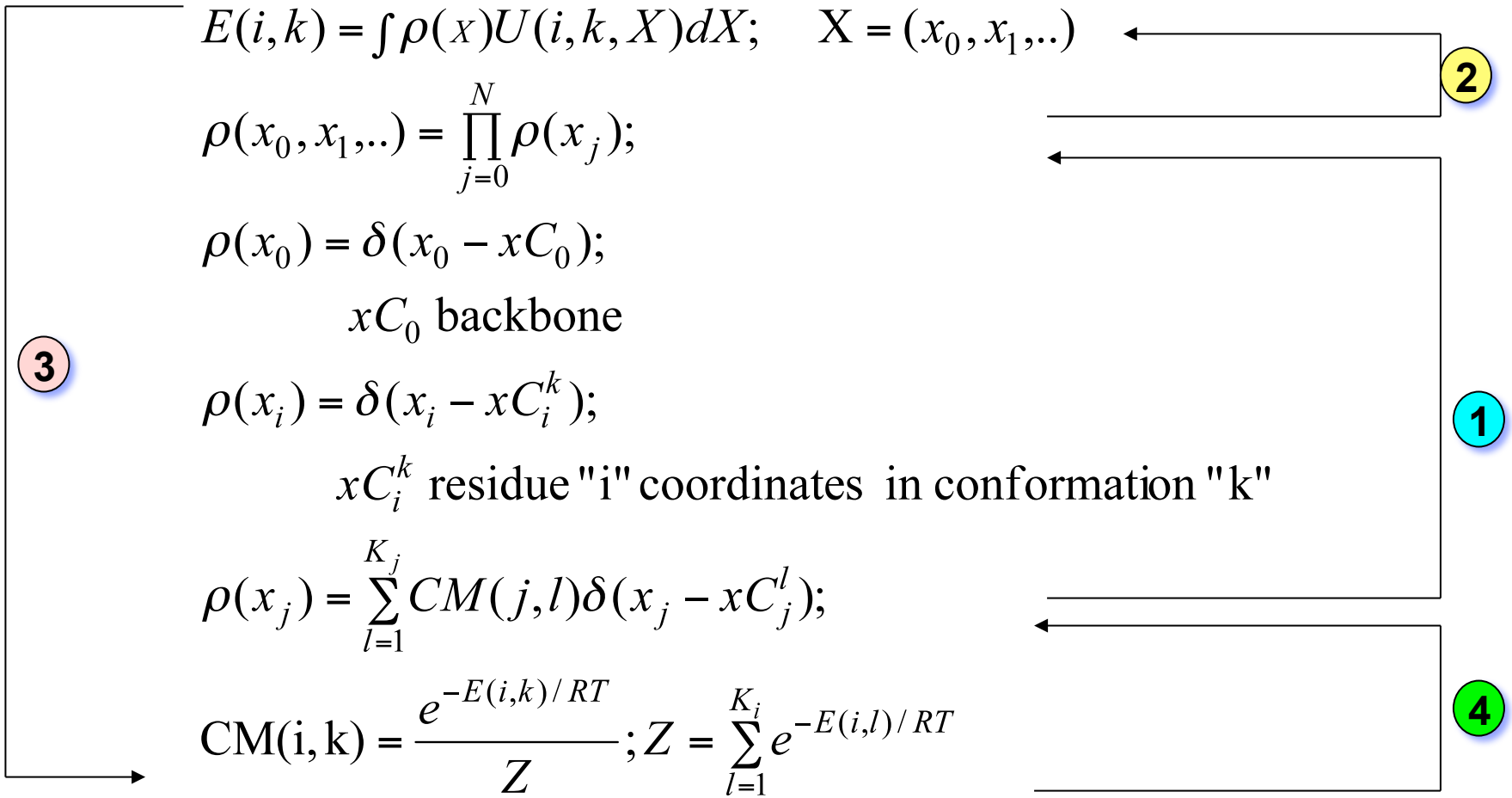
$$\mathrm{CM(i,k)} = \frac{e^{-E(i,k)/RT}}{Z};$$

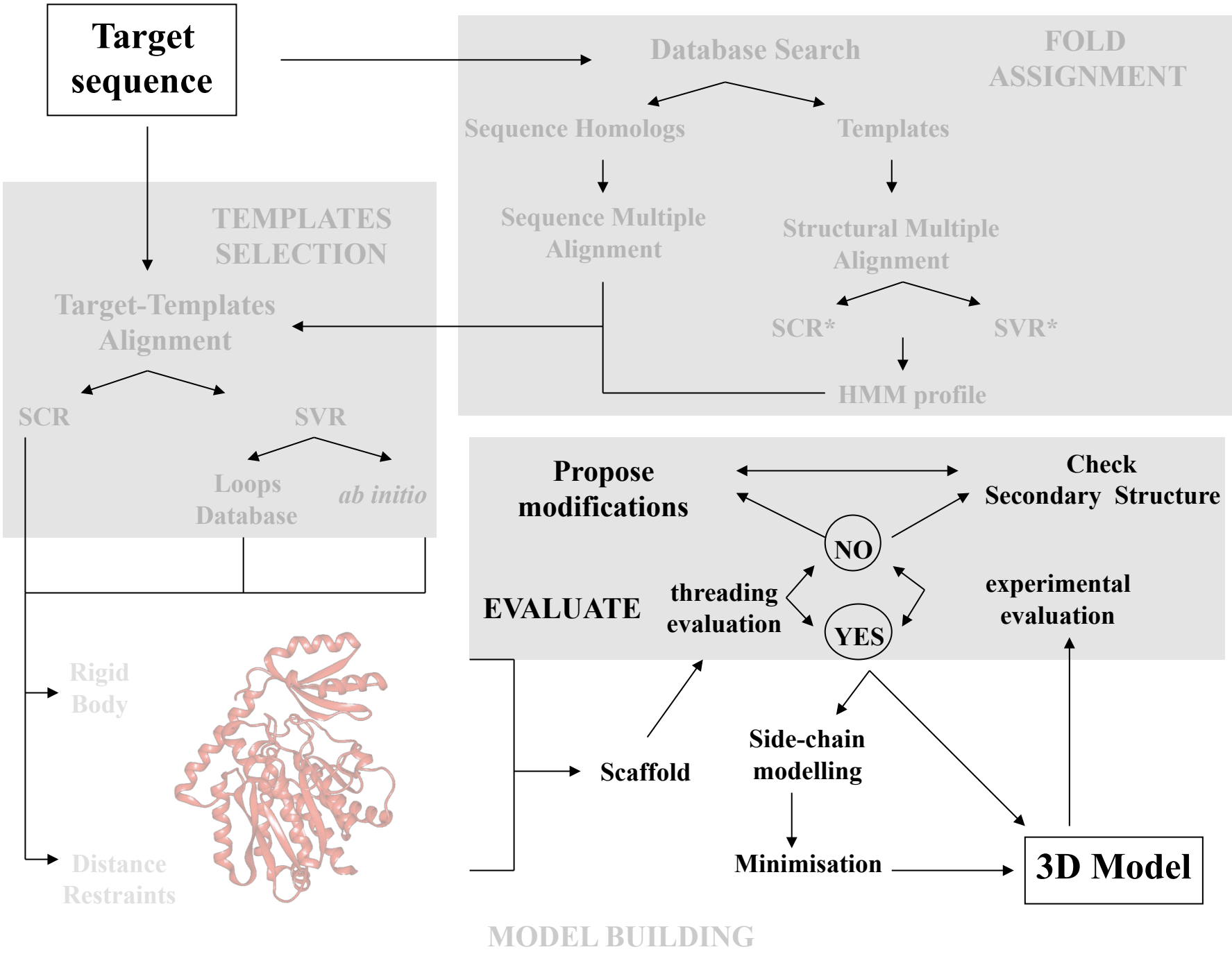
$$Z = \sum_{l=1}^{K_i} e^{-E(i,l)/RT}$$

2. Schema of the method

3. Model building: Side-chains

Iterative optimization




Target sequence
Database Search
FOLD ASSIGNMENT
Sequence Homologs
Templates
Sequence Multiple Alignment
Structural Multiple Alignment
SCR*
SVR*
HMM profile
TEMPLATES SELECTION
Target-Templates Alignment
SCR
SVR
Loops Database
ab initio
Propose modifications
Check Secondary Structure
NO
EVALUATE
threading evaluation
YES
experimental evaluation
Rigid Body
Distance Restraints
Scaffold
Side-chain modelling
Minimisation
3D Model
MODEL BUILDING

2. Schema of the method

4. Evaluation

Types of Errors

1. *Errors in side-chain packing .*
2. *Shifts of correctly aligned residues .*
3. *Regions without template .*
4. *Errors due to misalignments .*
5. *Errors produced by incorrect templates .*

2. Schema of the method

4. Evaluation

Shifts of correctly aligned residues

```
HHHHHHHH HHH .HHC
GARFIELD THE .CAT
GARFIELD THE CCAT
```

Solution

```
HHHHHHHH HHH HHC.
GARFIELD THE CAT.
GARFIELD THE CCAT
```

2. Schema of the method

4. Evaluation

Errors due to misalignments .

```
GARFIELD THE CAT ...
GARFIELD THE FAT CAT
```

Solution

```
GARFIELD THE ... CAT
GARFIELD THE FAT CAT
```

2. Schema of the method

4. Evaluation

How to test the model?

1. Compare the RMSD between the model and the real structure
2. Check that secondary structures are correctly aligned
3. Calculate the percentage of residues that are closer than a threshold after superposing the model and the real structure
4. Calculate the percentage of identical residues aligned when superposing the real structure and the model.
5. Check the energy of threading to compare the real structure and the model (see next chapter)

2. Schema of the method

4. Evaluation

Model Accuracy Evaluation

CASP

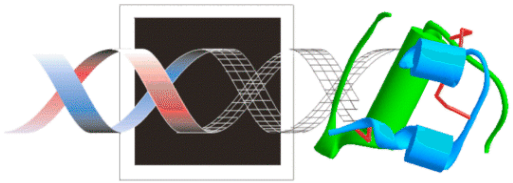
Community Wide Experiment on the Critical Assessment of Techniques for Protein Structure Prediction

http://PredictionCenter.llnl.gov/casp5/

EVA

Evaluation of Automatic protein structure prediction

[Burkhard Rost, Andrej Sali, http://maple.bioc.columbia.edu/eva/]



3D - Crunch

Very Large Scale Protein Modeling Project

http://www.expasy.org/swissmod/SM_LikelyPrecision.html

2. Schema of the method

5. Improvement

How to detect possible errors in the model if we don't know the solution?

1. Compare the model and all the templates
2. Check that secondary structures are not broken
3. Check if the prediction of secondary structure agrees with the secondary structure of the model
4. Check if the loops of the target are similar to some loops in the database of loops and they agree in sequence and anchoring geometry
5. Check the capping of helices
6. Check pseudo-energies of threading and compare the model with the templates.

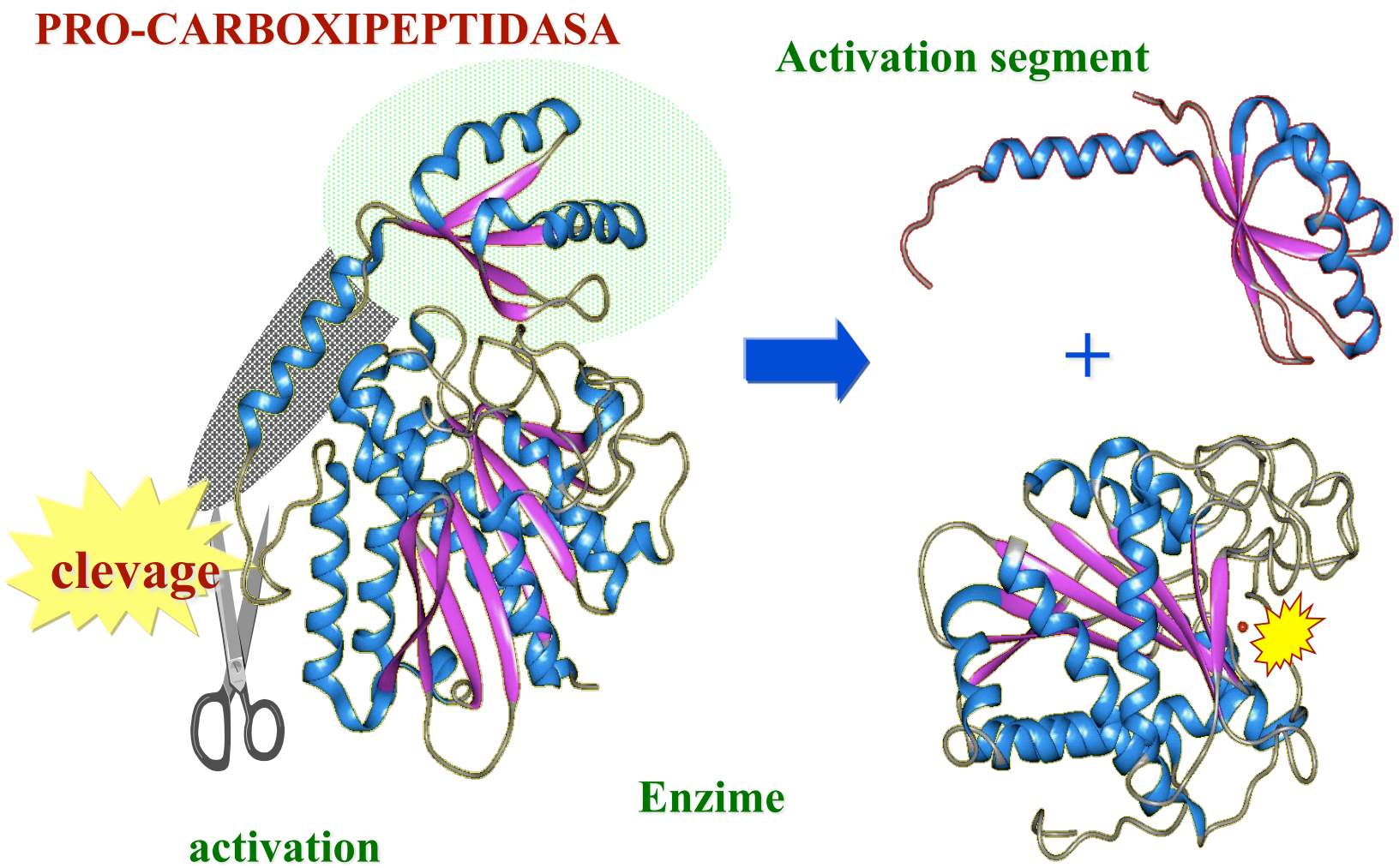
2. Schema of the method

5. Improvement

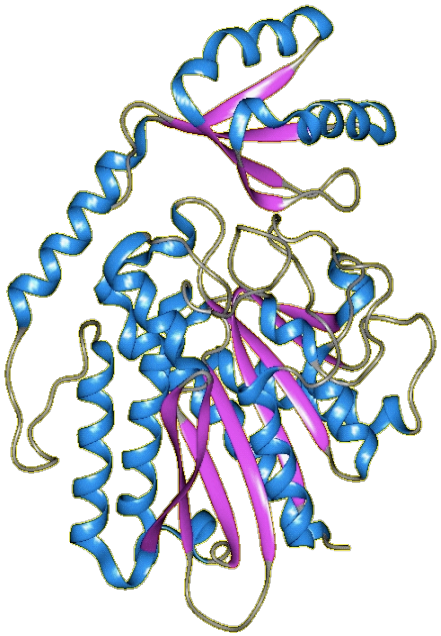
How to improve the model?

1. Decide the changes in the alignment according to the secondary structure prediction or the structure of the templates and recalculate the model
2. Change the main template and recalculate the model
3. Include new templates
4. Calculate the main motion of normal modes from the templates of the homologous family and optimize by molecular dynamics under motion restrictions the conformation
5. Recalculate the pseudo energy profile of the new model and compare with the original model to test the improvement

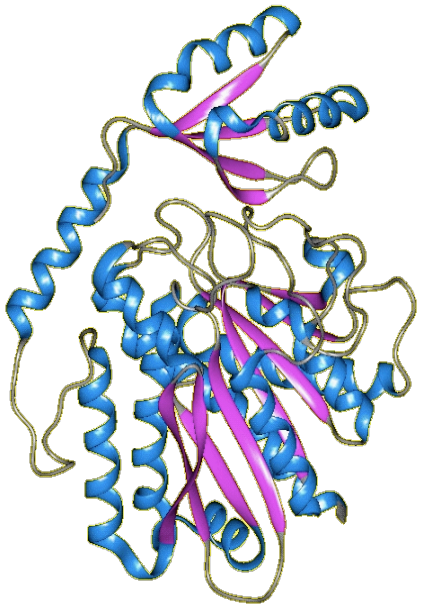
EXAMPLE


PRO-CARBOXIPEPTIDASA
Activation segment
clevage
+
activation
Enzime

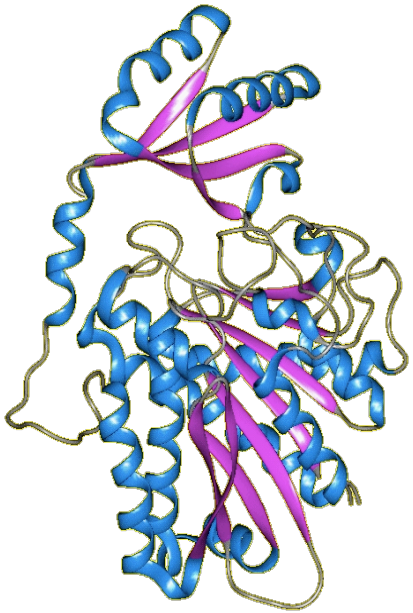
PRO-CARBOXYPEPTIDASES



Bovine
Pro Carboxypeptidase A1
PCPA1b



Porcine
Pro Carboxypeptidase A1
PCPA1p

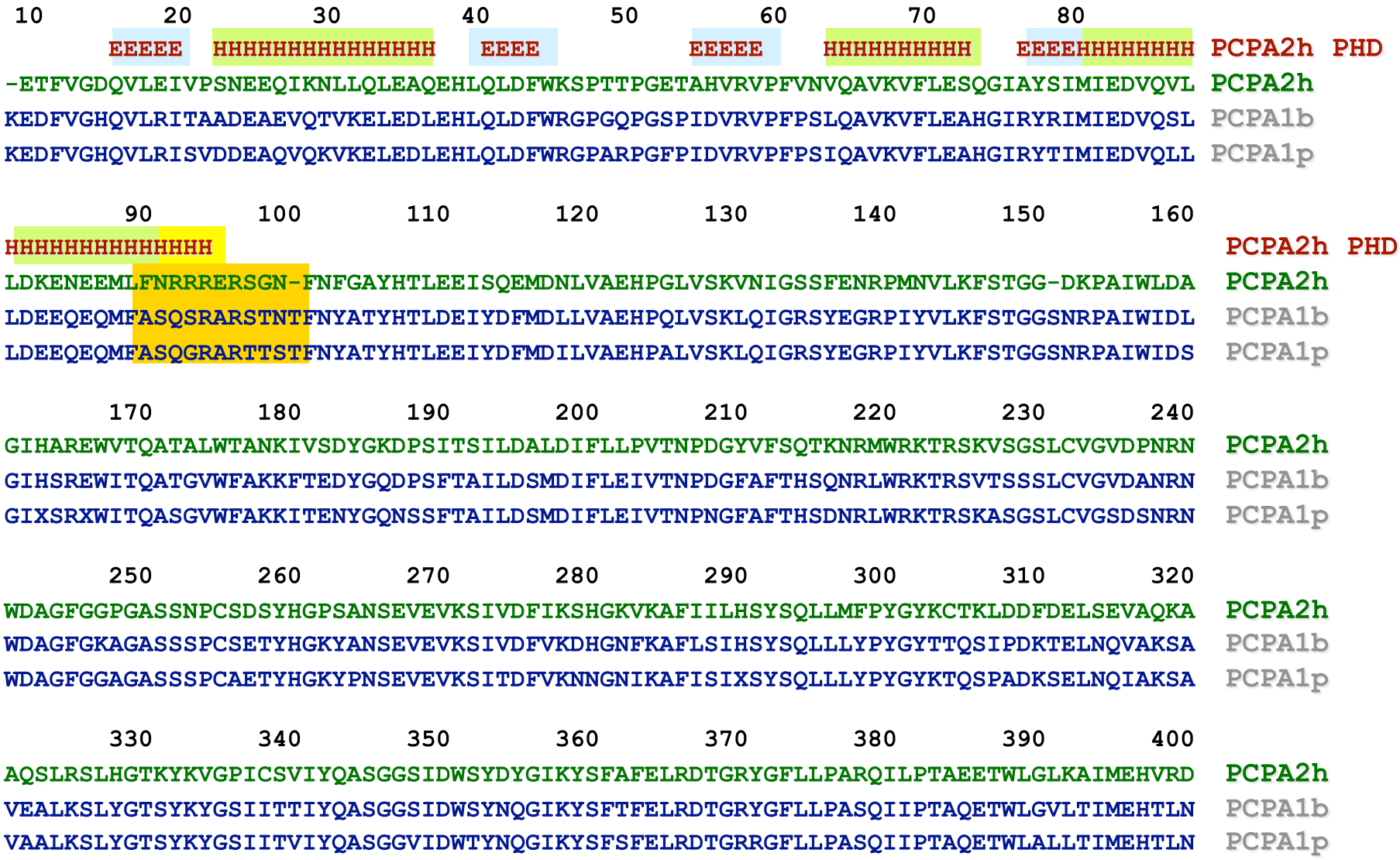


Porcine
Pro Carboxypeptidase B
PCPBp

SEQUENCE ALIGNMENT OF PRO-CARBOXYPEPTIDASES

```
 10        20        30        40        50        60        70        80
-ETFVGDQVLEIVPSNEEQIKNLLQLEAQEHLQLDFWKSPTTPGETAHVRVPFVNVQAVKVFLESQGIAYSIMIEDVQVL  PCPA2h
KEDFVGHQVLRITAADEAEVQTVKELEDLEHLQLDFWRGPGQPGSPIDVRVPFPSLQAVKVFLEAHGIRYRIMIEDVQSL  PCPA1b
KEDFVGHQVLRISVDDEAQVQKVKELEDLEHLQLDFWRGPARPGFPIDVRVPFPSIQAVKVFLEAHGIRYTIMIEDVQLL  PCPA1p

        90        100       110       120       130       140       150       160
LDKENEEMLFNRRRERSGN-FNFGAYHTLEEISQEMDNLVAEHPGLVSKVNIGSSFENRPMNVLKFSTGG-DKPAIWLDA  PCPA2h
LDEEQEQMFASQSRARSTNTFNYATYHTLDEIYDFMDLLVAEHPQLVSKLQIGRSYEGRPIYVLKFSTGGSNRPAIWIDL  PCPA1b
LDEEQEQMFASQGRARTTSTFNYATYHTLEEIYDFMDILVAEHPALVSKLQIGRSYEGRPIYVLKFSTGGSNRPAIWIDS  PCPA1p

       170       180       190       200       210       220       230       240
GIHAREWVTQATALWTANKIVSDYGKDPSITSILDALDIFLLPVTNPDGYVFSQTKNRMWRKTRSKVSGSLCVGVDPNRN  PCPA2h
GIHSREWITQATGVWFAKKFTEDYGQDPSFTAILDSMDIFLEIVTNPDGFAFTHSQNRLWRKTRSVTSSSLCVGVDANRN  PCPA1b
GIXSRXWITQASGVWFAKKITENYGQNSSFTAILDSMDIFLEIVTNPNGFAFTHSDNRLWRKTRSKASGSLCVGSDSNRN  PCPA1p

       250       260       270       280       290       300       310       320
WDAGFGGPGASSNPCSDSYHGPSANSEVEVKSIVDFIKSHGKVKAFIILHSYSQLLMFPYGYKCTKLDDFDELSEVAQKA  PCPA2h
WDAGFGKAGASSSPCSETYHGKYANSEVEVKSIVDFVKDHGNFKAFLSIHSYSQLLLYPYGYTTQSIPDKTELNQVAKSA  PCPA1b
WDAGFGGAGASSSPCAETYHGKYPNSEVEVKSITDFVKNNGNIKAFISIXSYSQLLLYPYGYKTQSPADKSELNQIAKSA  PCPA1p

       330       340       350       360       370       380       390       400
AQSLRSLHGTKYKVGPICSVIYQASGGSIDWSYDYGIKYSFAFELRDTGRYGFLLPARQILPTAEETWLGLKAIMEHVRD  PCPA2h
VEALKSLYGTSYKYGSIITTIYQASGGSIDWSYNQGIKYSFTFELRDTGRYGFLLPASQIIPTAQETWLGVLTIMEHTLN  PCPA1b
VAALKSLYGTSYKYGSIITVIYQASGGVIDWTYNQGIKYSFSFELRDTGRRGFLLPASQIIPTAQETWLALLTIMEHTLN  PCPA1p
```

Secondary Structure Prediction and Multiple Alignment of Pro-Carboxypeptidases



α-Helix C-cap
Schellman Motif

Schellman Motif Profile

C´´ » C3 / C´ Gly

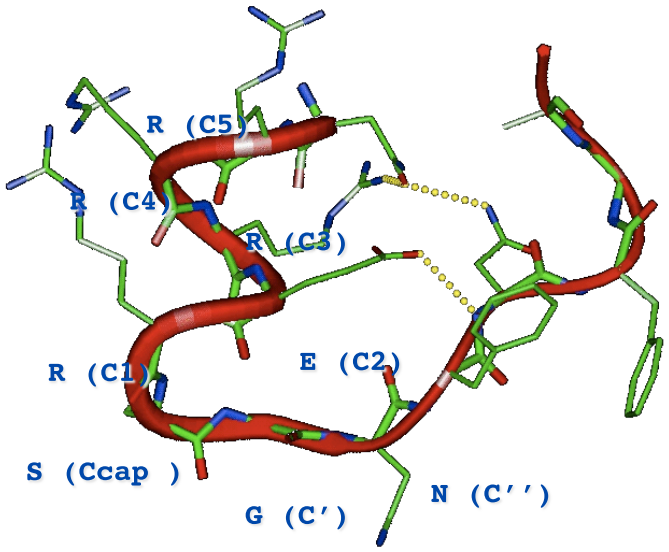
C3	C2	C1	Ccap	C′	C′′
L	Q	E	H	G	I
A	R	A	K	G	V
M	K	K	L	G	K

Hbond

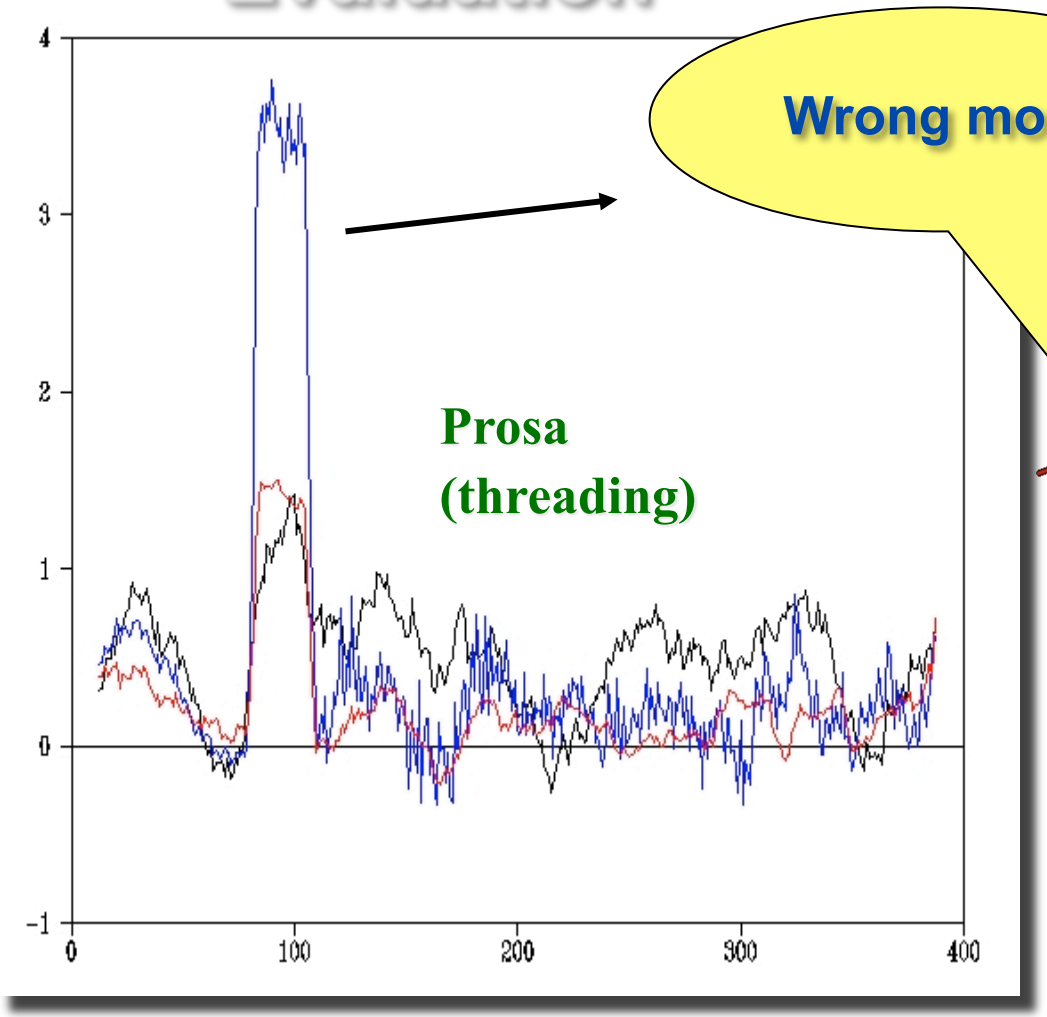
hydrophobic

C3					C	C′C′′			
N	R	R	R	E	R	S	G	N	F	N

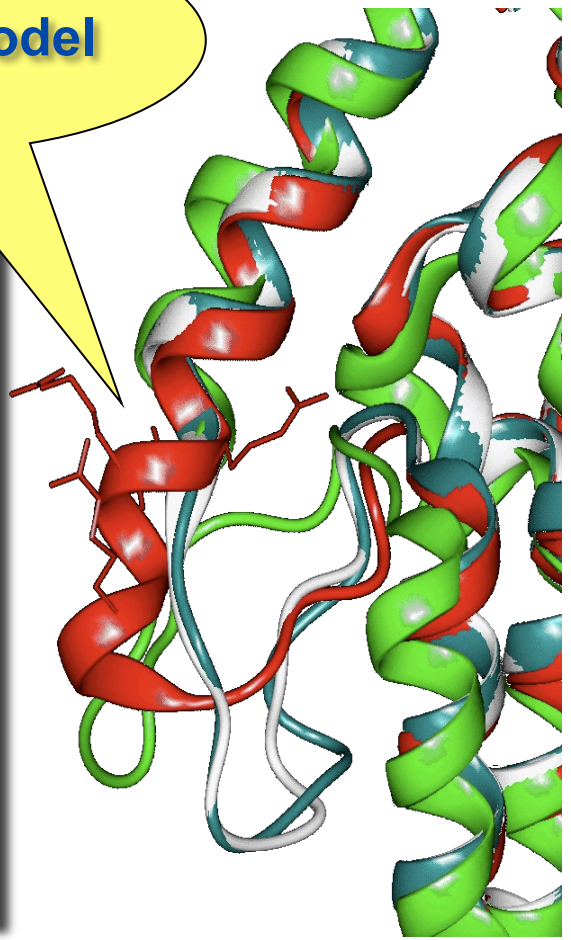
Hbond



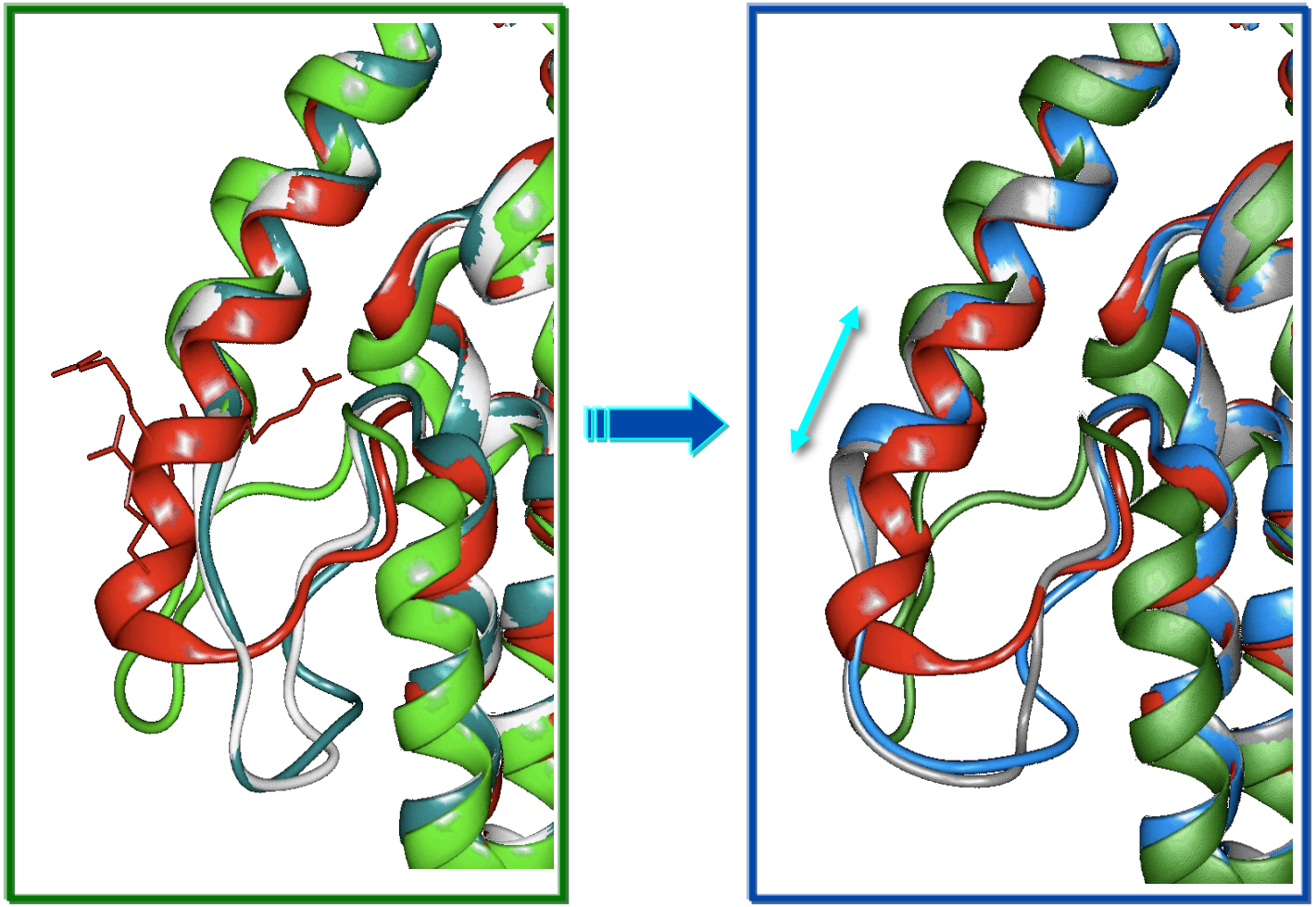
Evaluation

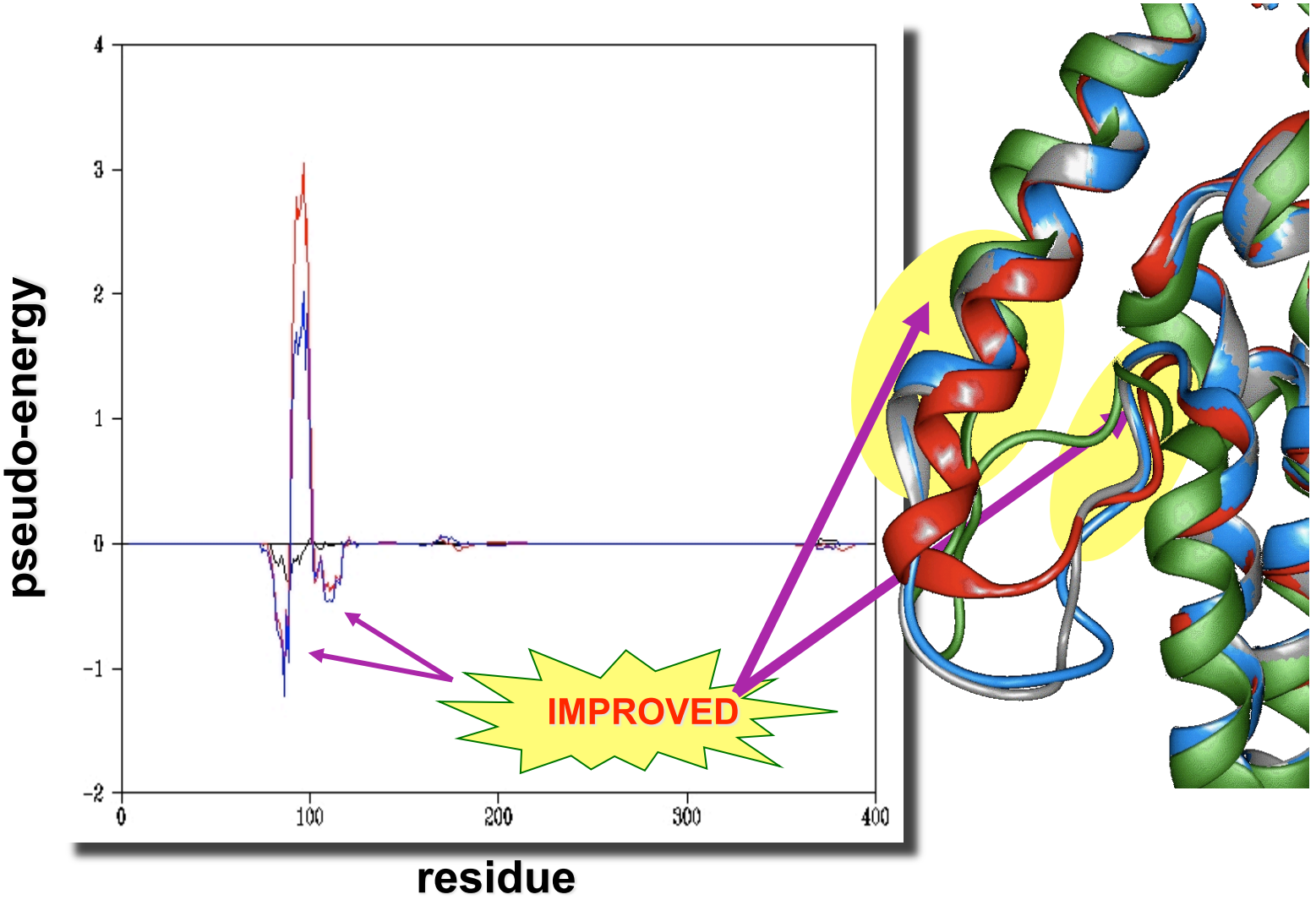


Wrong model



Refinement of the Model




pseudo-energy
residue
4
3
2
1
0
-1
-2
0
100
200
300
400
IMPROVED

Annex

Protein Structure Resources

PDB http://www.pdb.org
PDB – Protein Data Bank of experimentally solved structures (RCSB)

CATH http://www.biochem.ucl.ac.uk/bsm/cath/
Hierarchical classification of protein domain structures

SCOP http://scop.mrc-lmb.cam.ac.uk/scop/
Alexey Murzin's Structural Classification of proteins

DALI http://www2.ebi.ac.uk/dali/
Lisa Holm and Chris Sander's protein structure comparison server

SS-Prediction and Fold Recognition

PHD http://cubic.bioc.columbia.edu/predictprotein/
Burkhard Rost's Secondary Structure and Solvent Accessibility Prediction Server

3DPSSM http://www.sbg.bio.ic.ac.uk/~3dpssm/
Fold Recognition Server using 1D and 3D Sequence Profiles coupled with Secondary Structure and Solvation Potential Information.

Annex

Protein Homology Modeling Resources

SWISS MODEL: http://www.expasy.ch/swissmod/

Deep View - SPDBV:
homepage: http://www.expasy.ch/spdbv/
Tutorials http://www.usm.maine.edu/~rhodes/SPVTut/
http://www.bbsrc.ac.uk/molbiol/

WhatIf http://www.cmbi.kun.nl/whatif/
Gert Vriend's protein structure modeling analysis program WhatIf

Modeller: http://guitar.rockefeller.edu/modeller/
Andrej Sali's homology protein structure modelling by satisfaction of spatial restraints

FAMS: http://physchem.pharm.kitasato-u.ac.jp/FAMS/fams.html
Full Automatic Modelling System (FAMS); Kitasato University; Tokyo, Japan

3D-JIGSAW: http://www.bmm.icnet.uk/people/paulb/3dj/form.html
Comparative Modelling Server; Imperial Cancer Research Fund; London, UK

CPHmodels: http://www.cbs.dtu.dk/services/CPHmodels/
Centre for Biological Sequence Analysis; The Technical University of Denmark; Denmark

SDSC1: http://cl.sdsc.edu/hm.html
SDSC Structure Homology Modelling Server; San Diego Supercomputing Centre