Protein Shape Descriptors

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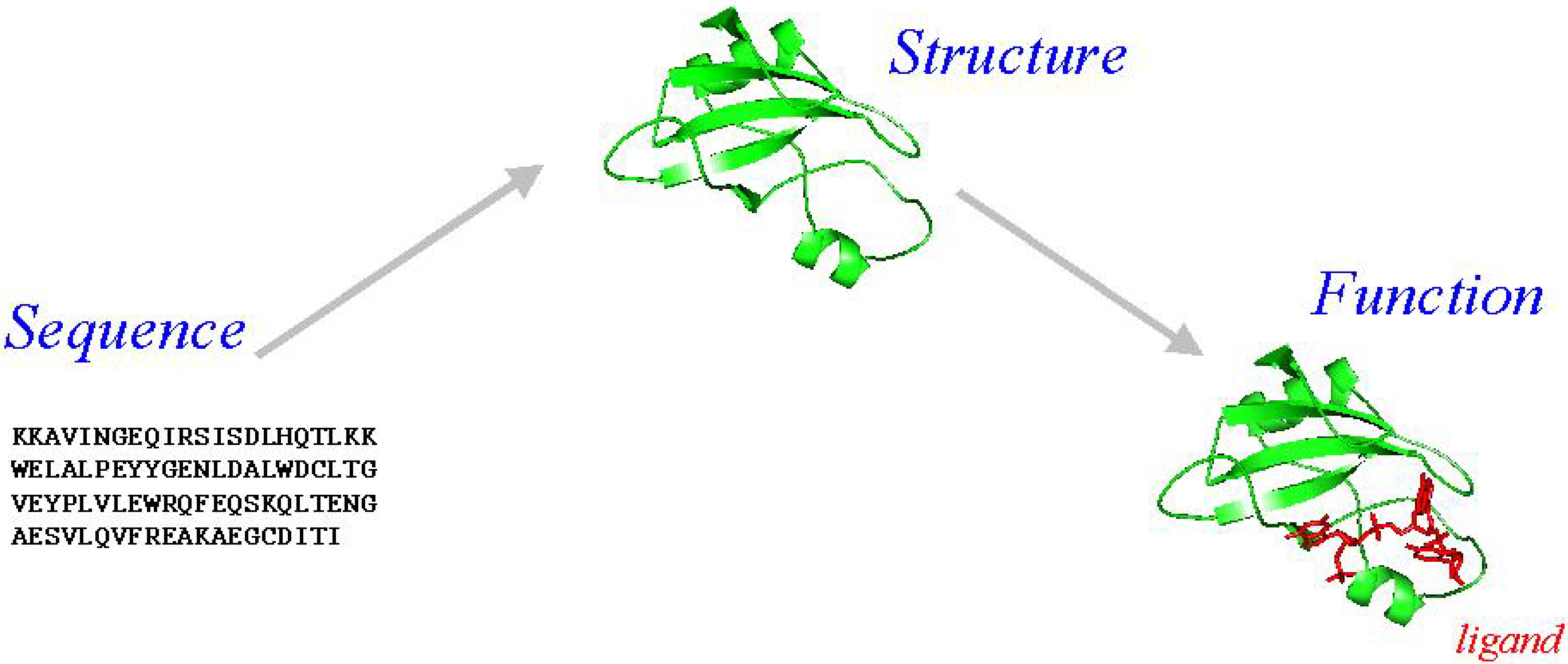
Stanford University

http://csb.stanford.edu/koehl/

From Sequence to Function and Back…



Sequence

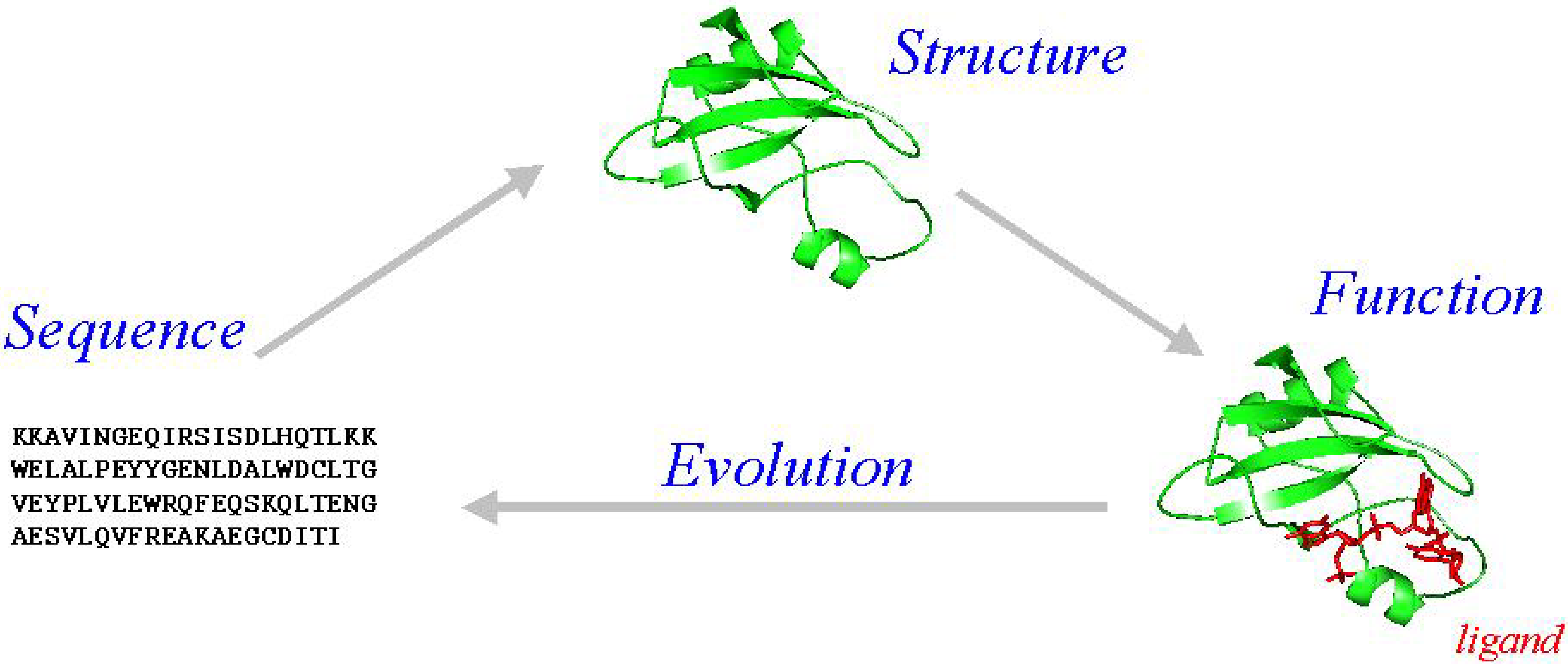
KKAVINGEQIRSISDLHQTLKK
WELALPEYYGENLDALWDCLTG
VEYPLVLEWRQFEQSKQLTENG
AESVLQVFREAKAEGCDITI

Structure

Function

ligand

From Sequence to Function and Back…



Structure

Sequence

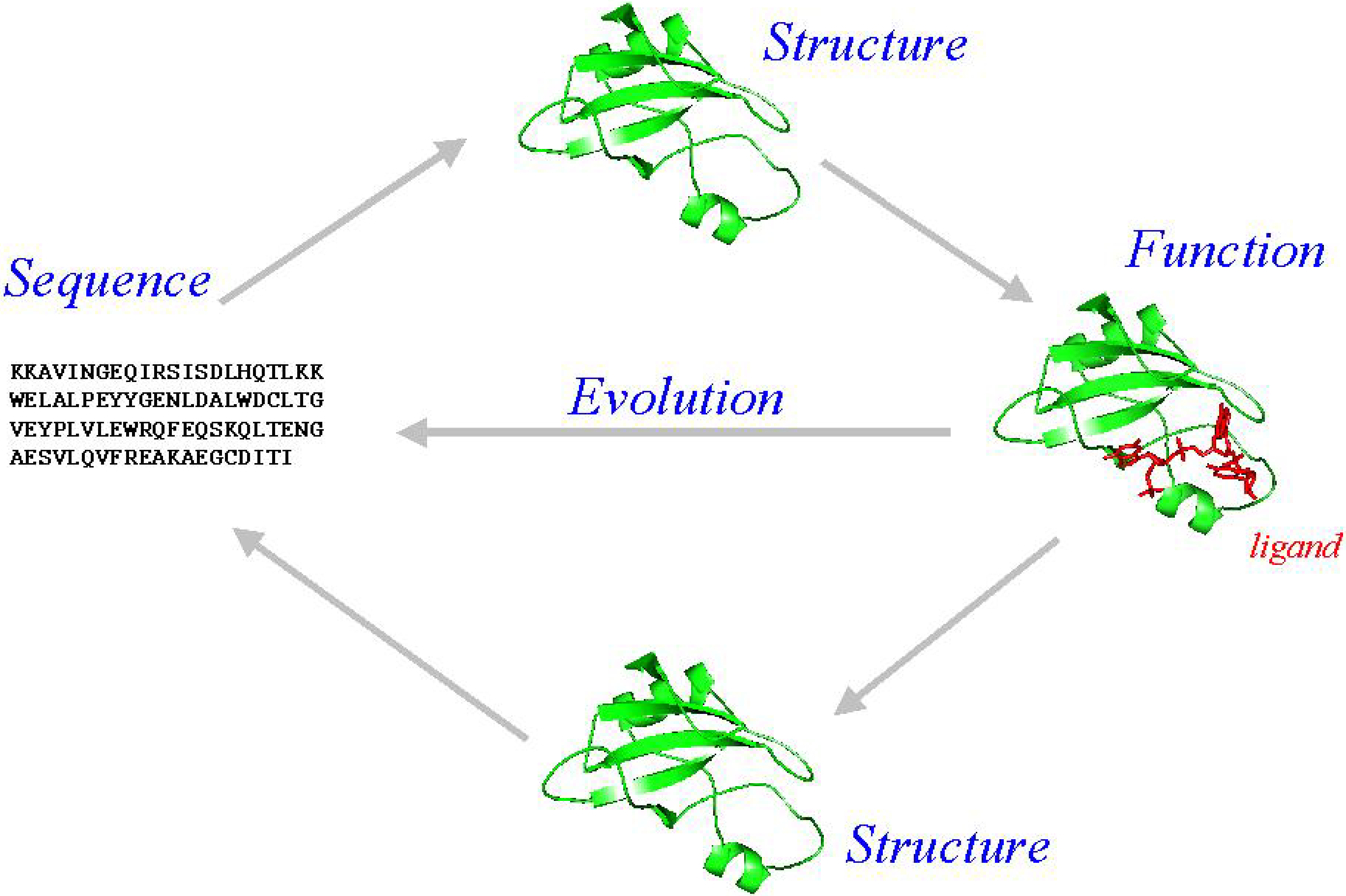
```
KKAVINGEQIRSISDLHQTLKK
WELALPEYYGENLDALWDCLTG
VEYPLVLEWRQFEQSKQLTENG
AESVLQVFREAKAEGCDITI
```

Function

Evolution

ligand

From Sequence to Function and Back…



Structure

Sequence

```
KKAVINGEQIRSISDLHQTLKK
WELALPEYYGENLDALWDCLTG
VEYPLVLEWRQFEQSKQLTENG
AESVLQVFREAKAEGCDITI
```

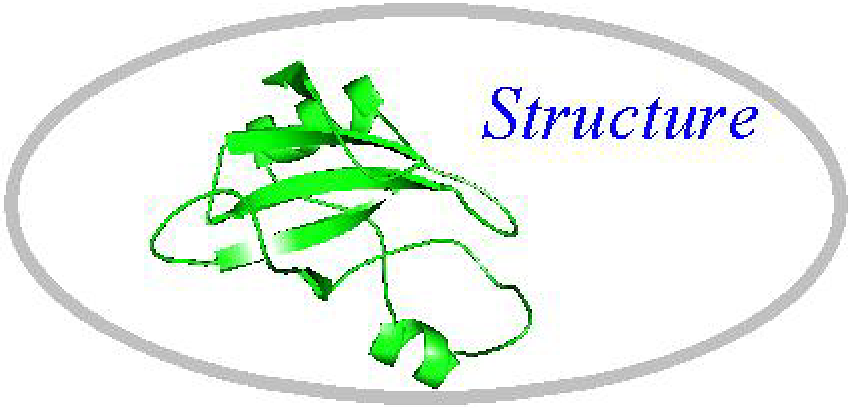
Function

ligand

Evolution

Structure

From Sequence to Function and Back…



Sequence

KQLAVIMGKQIRSISDLHQILKK
WETLRLDEYYCGEHLDALWDCLTG
VRYPLVLRWSQFEQSIQLTENG
AESVLQVFREAERAEGCDITI

Function

Outline

- Introduction

  What is a Protein?

- Protein Energy Functions

  Computational Geometry Tools

- Classifying Proteins

  The Shapes of Protein Structures

Outline

- Introduction
  - *What is a Protein?*
- Protein Energy Functions
  - *Computational Geometry Tools*
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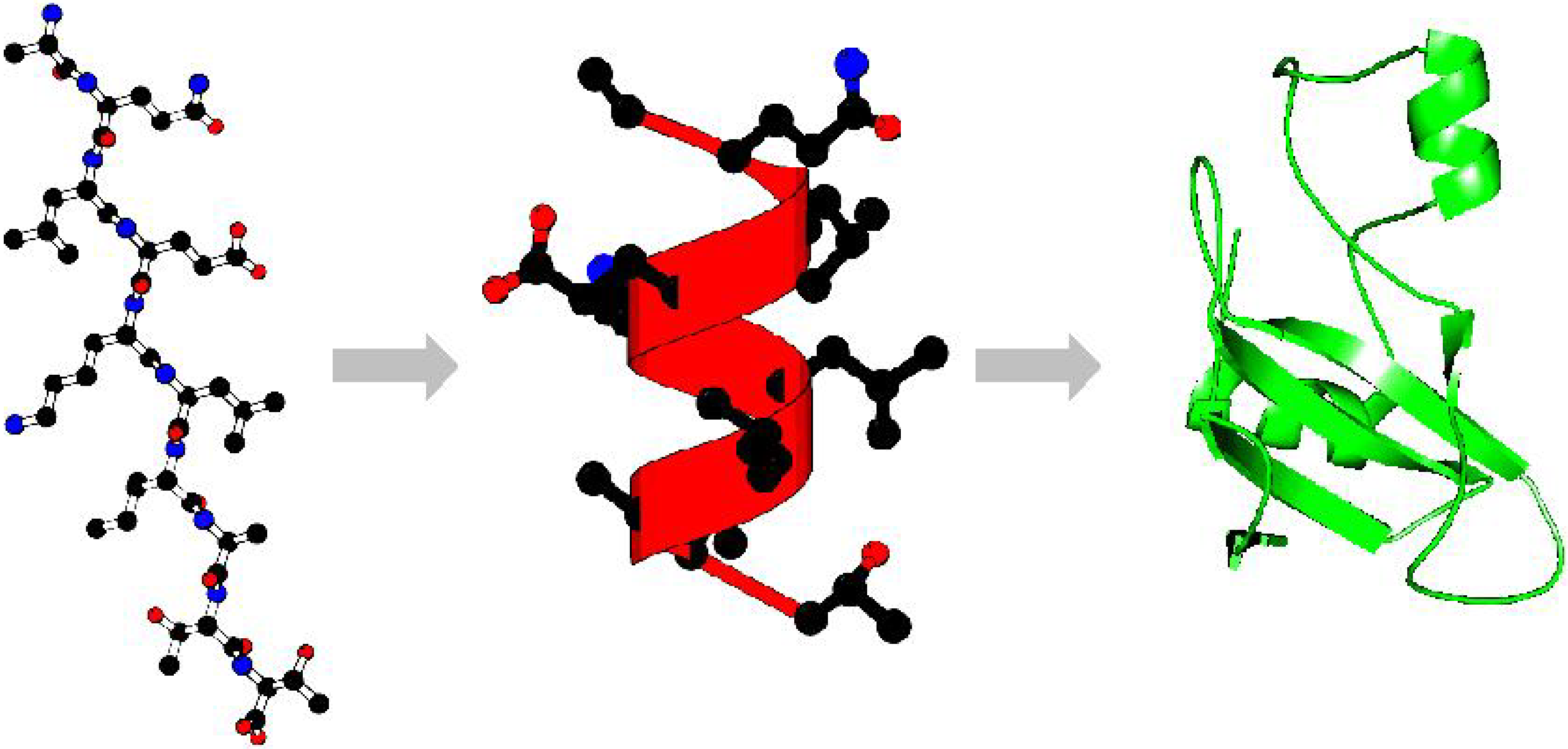
  - *The Shapes of Protein Structures*

What is a Protein ?

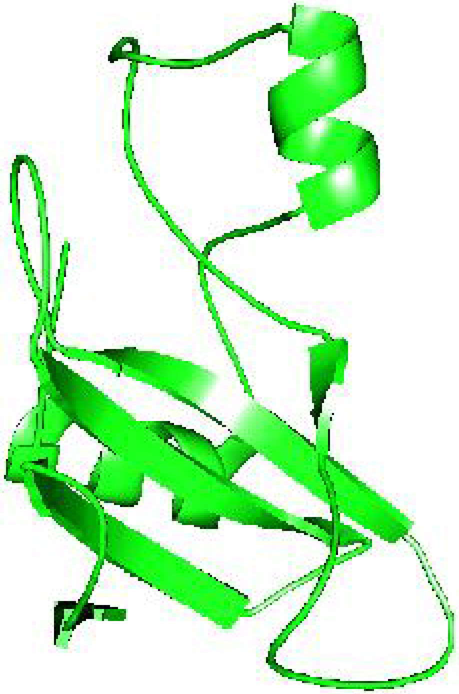
Primary Structure *Secondary Structure* *Tertiary Structure*



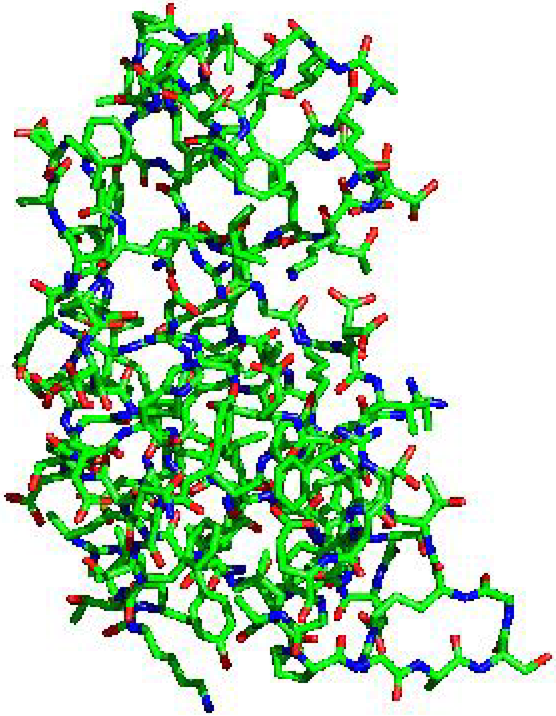
Sequence of amino acids

Native protein

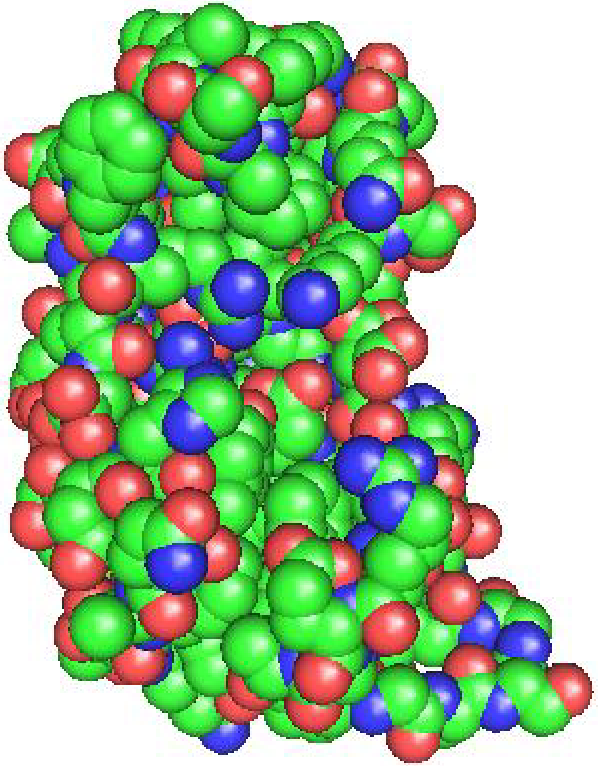
Protein Representations



Cartoon



Stick



Space-filling Model

Outline

- Introduction
  - *What is a Protein?*
- Protein Energy Functions
  - *Computational Geometry Tools*
- Classifying Proteins
  - *The Shapes of Protein Structures*

Energy of a Protein

Bonded Interactions

Bonds, Angles, Dihedral angles

Non Bonded Interactions

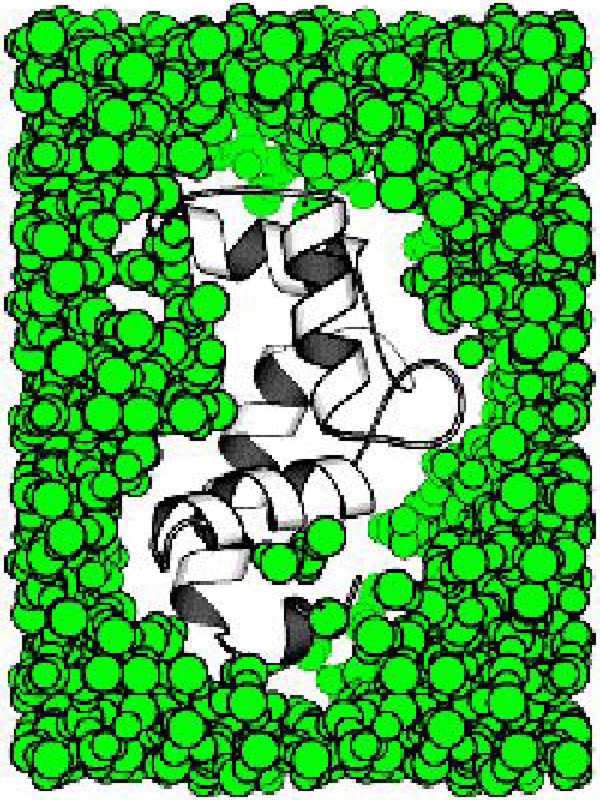
van der Waals interactions, Electrostatics

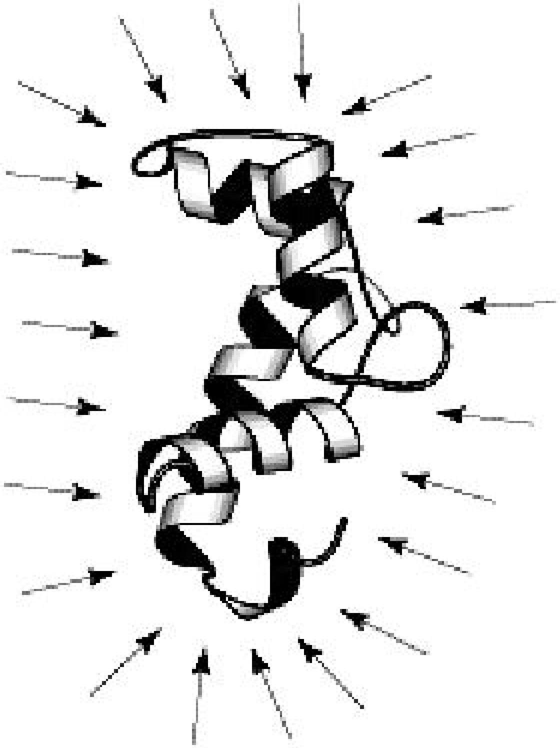
Solvent

Most difficult

Solvent

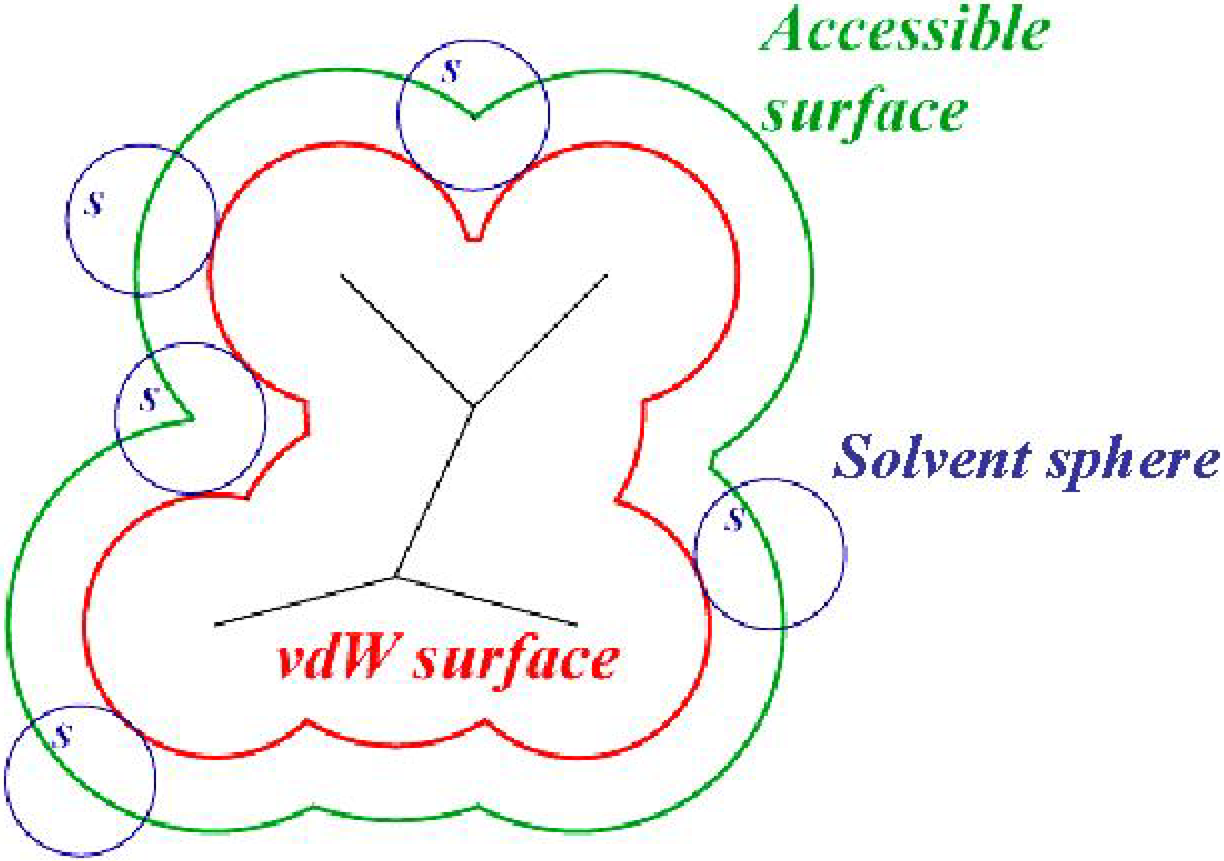
Explicit or Implicit ?





$$G_{sol} = G_{pol} + G_{cav} + G_{vdW}$$

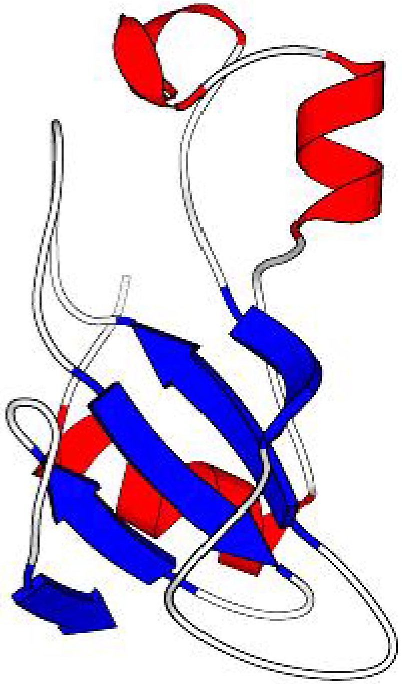
Solvation Potential



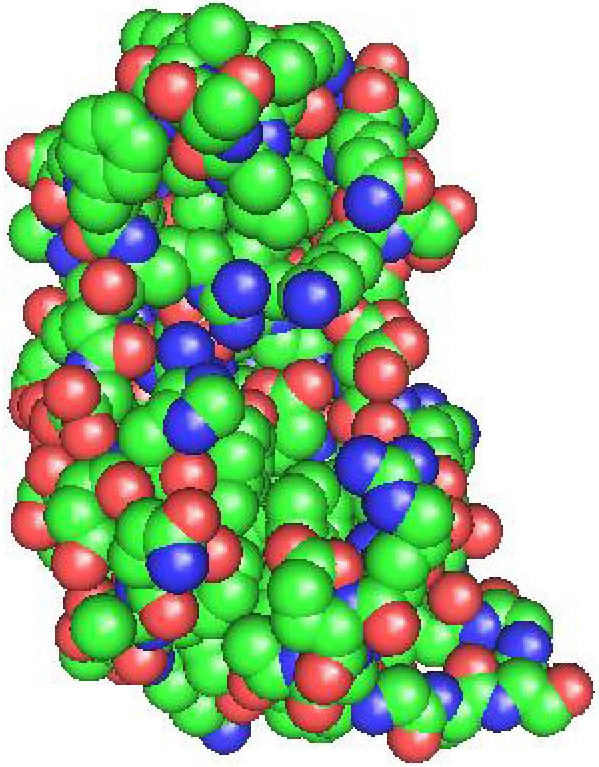
$$G_{cav} + G_{vdW} = \sum_{k=1}^{N} \sigma_k SA_k$$

Need Surface and Volume

Geometry of Protein Structure

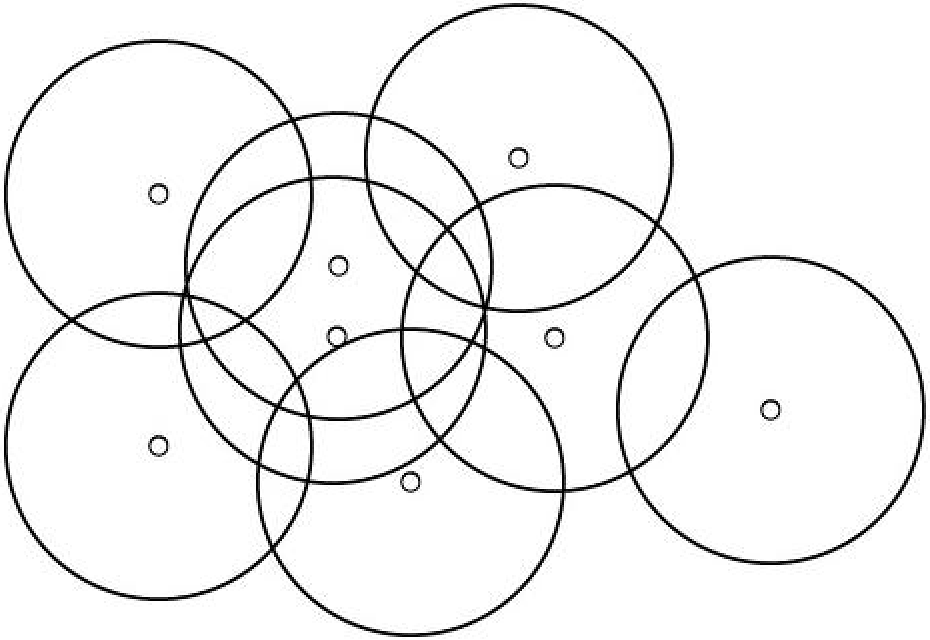


Cartoon



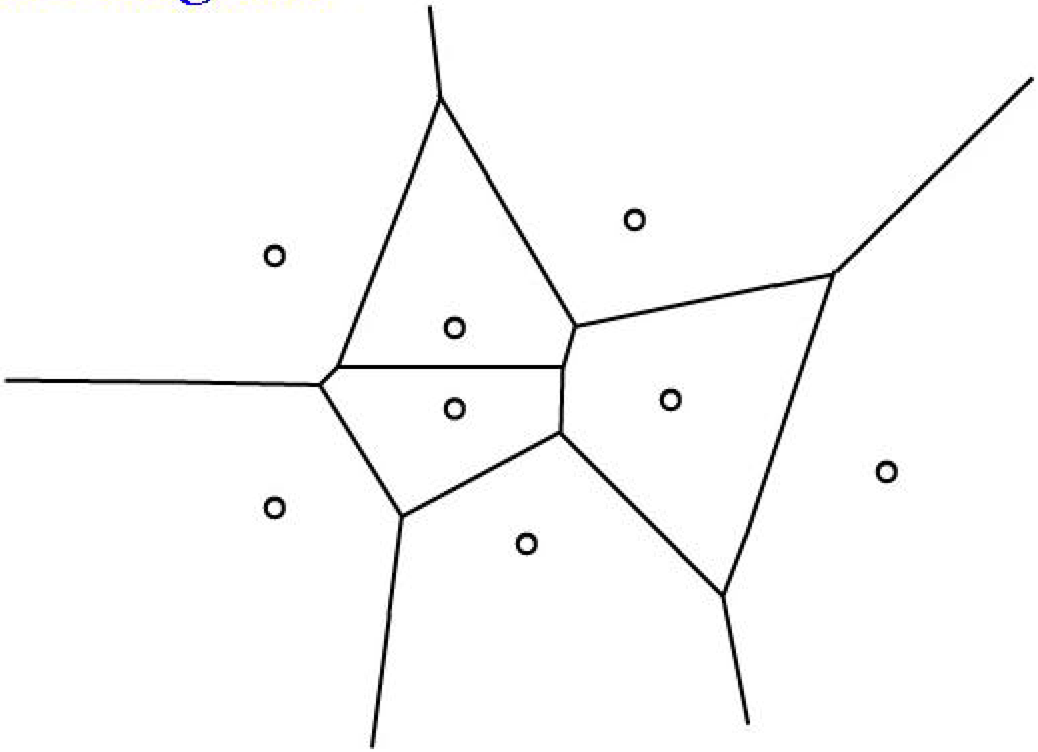
Space-filling Model

Computing the Surface Area and Volume of a Union of Balls



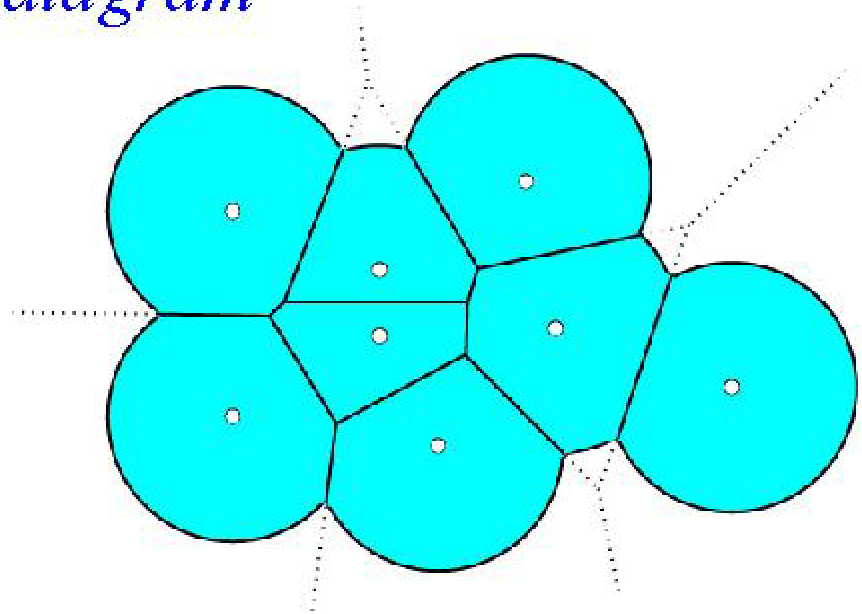
Computing the Surface Area and Volume of a Union of Balls

Power Diagram

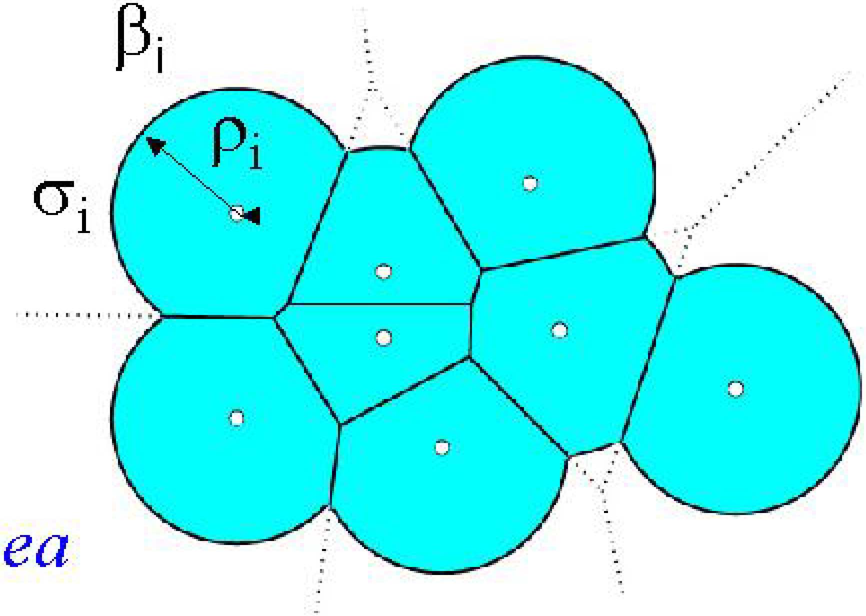


Computing the Surface Area and Volume of a Union of Balls

Decomposition of the Space-filling diagram



Computing the Surface Area and Volume of a Union of Balls



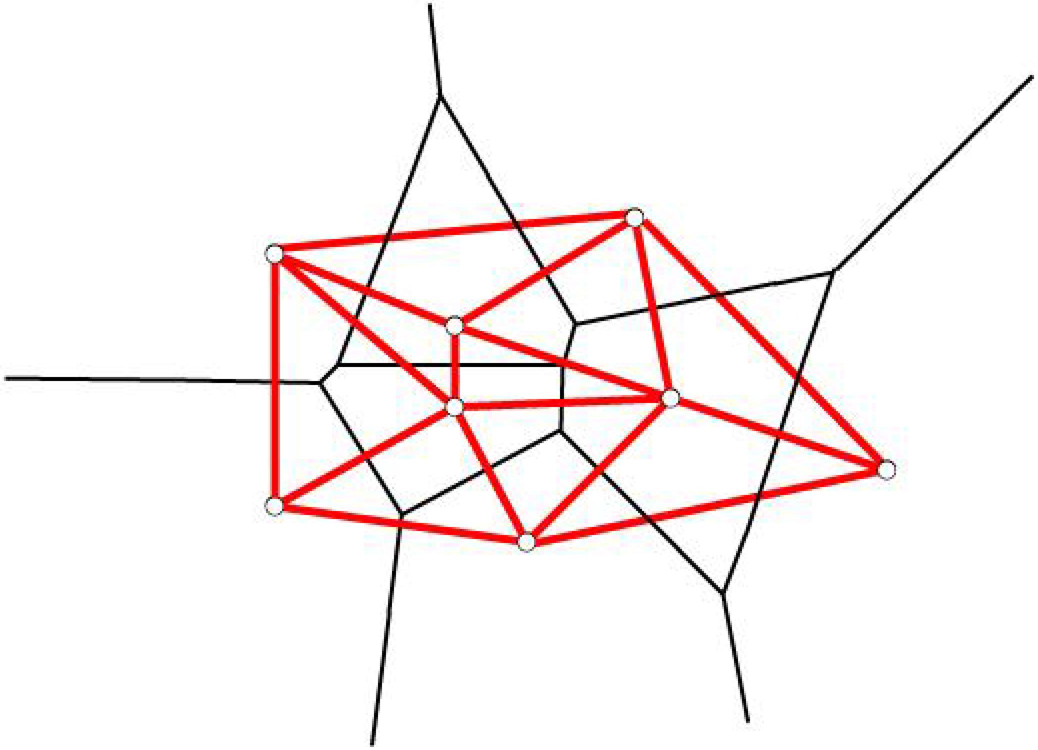
Surface Area

$$A = 4\pi \sum_{i=1}^{N} \rho_i^2 \sigma_i$$

Volume

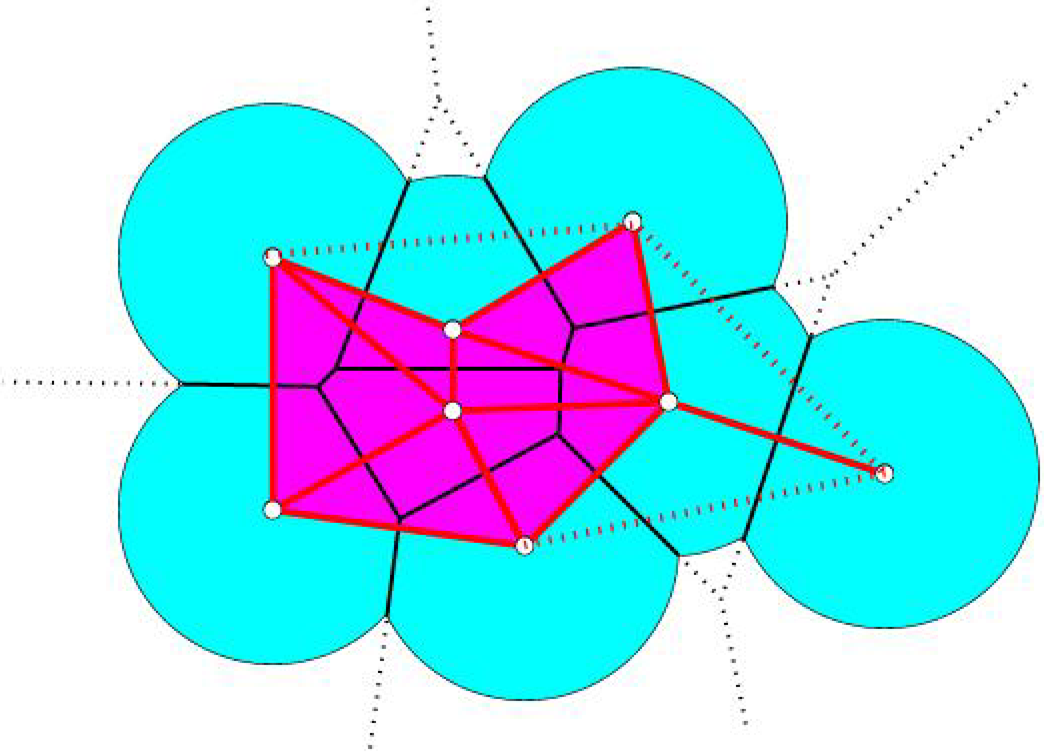
$$V = \frac{4\pi}{3} \sum_{i=1}^{N} \rho_i^3 \beta_i$$

Computing the Surface Area and Volume of a Union of Balls



The weighted Delaunay triangulation is the dual of the power diagram

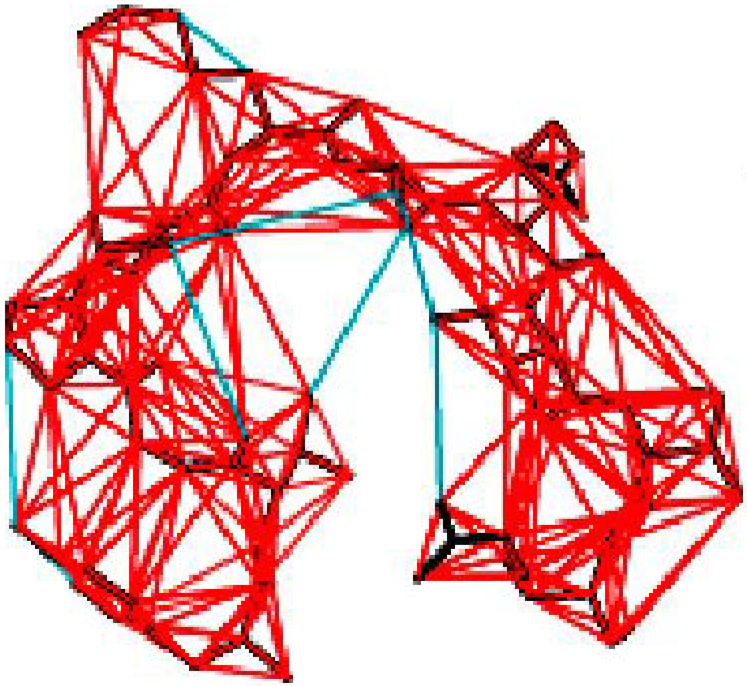
Computing the Surface Area and Volume of a Union of Balls



The dual complex K is the dual of the decomposition of the space-filling diagram

Computing the Surface Area and Volume of a Union of Balls

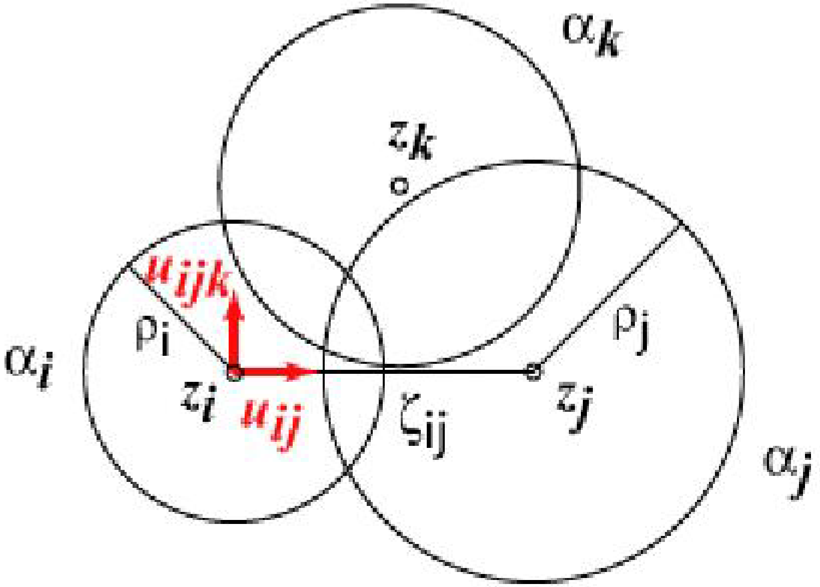
Inclusion-exclusion formulas for surface and volume



$$Area\left(\mathrm{Y}\,B\right) = \sum_{X \in K} (-1)^{\dim X}\, Area\left(\mathrm{I}\;\; X\right)$$

$$Vol\left(\mathrm{Y}\,B\right) = \sum_{X \in K} (-1)^{\dim X}\, Vol\left(\mathrm{I}\;\; X\right)$$

Weighted Area Derivative

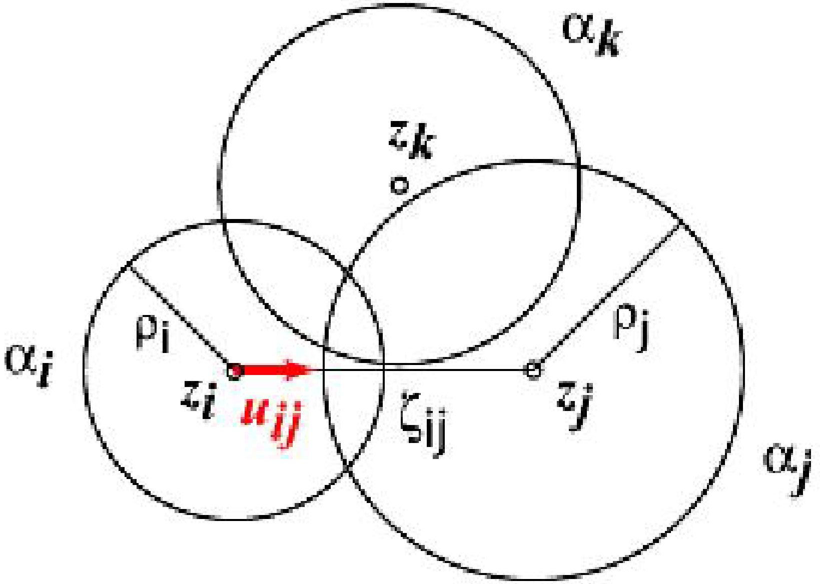


$$\begin{bmatrix} e_{3i-2} \\ e_{3i-1} \\ e_{3i} \end{bmatrix} = \sum_j \left(\sigma_{ij} \bullet e_{ij} + \sum_k \beta_{ijk} \bullet e_{ijk} \right)$$

$$e_{ij} = \pi \left[\left(\alpha_i \rho_i + \alpha_j \rho_j \right) - \left(\alpha_i \rho_i - \alpha_j \rho_j \right) \frac{\rho_i^2 - \rho_j^2}{\zeta_{ij}^2} \right] u_{ij}$$

$$e_{ijk} = 2 \rho_{ijk} \frac{\alpha_i \rho_i - \alpha_j \rho_j}{\zeta_{ij}} u_{ijk}$$

Weighted Volume Derivative



$$\begin{bmatrix} w_{3i-2} \\ w_{3i-1} \\ w_{3i} \end{bmatrix} = \sum_j S_{ij} \left(w_{ij} \bullet u_{ij} + x_{ij} \bullet v_{ij} \right)$$

$$w_{ij} = \left[\frac{\alpha_i + \alpha_j}{2} + \frac{(\alpha_i - \alpha_j)(\rho_i^2 - \rho_j^2)}{2\zeta_{ij}^2} \right]$$

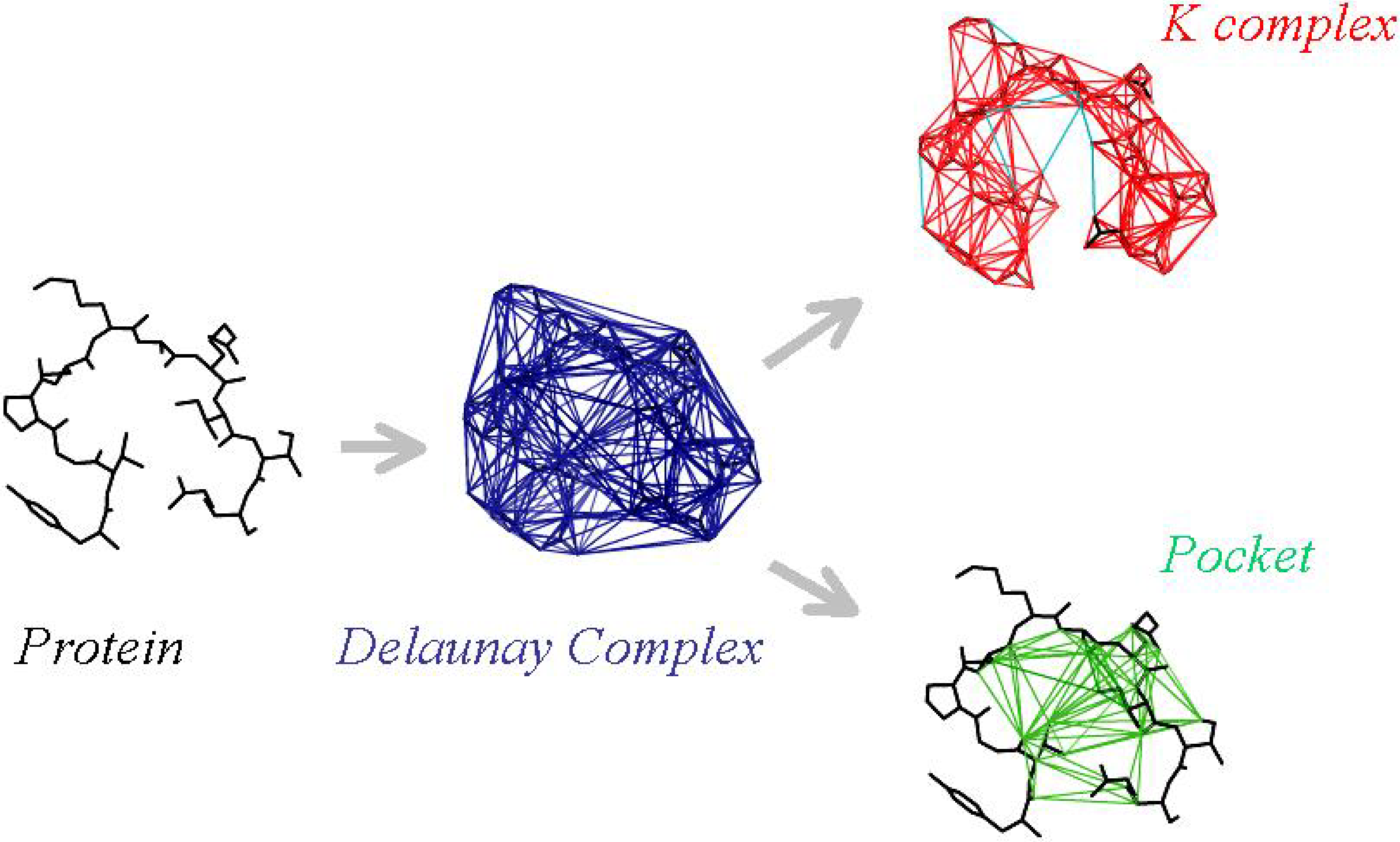
$$x_{ij} = \frac{2(\alpha_i - \alpha_j)}{3\zeta_{ij}}$$

S

S_{ij}: Area of facet (i,j)

V_{ij}: Average vector from center to boundary of facet (i,j)

Computing the Surface Area and Volume of a Protein



K complex

Protein

Delaunay Complex

Pocket

http://csb.stanford.edu/koehl/ProShape/download.php

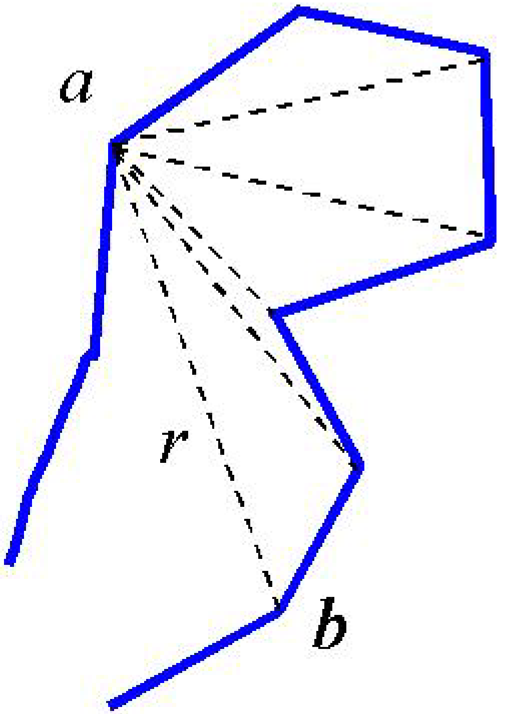
Software: ProGeom

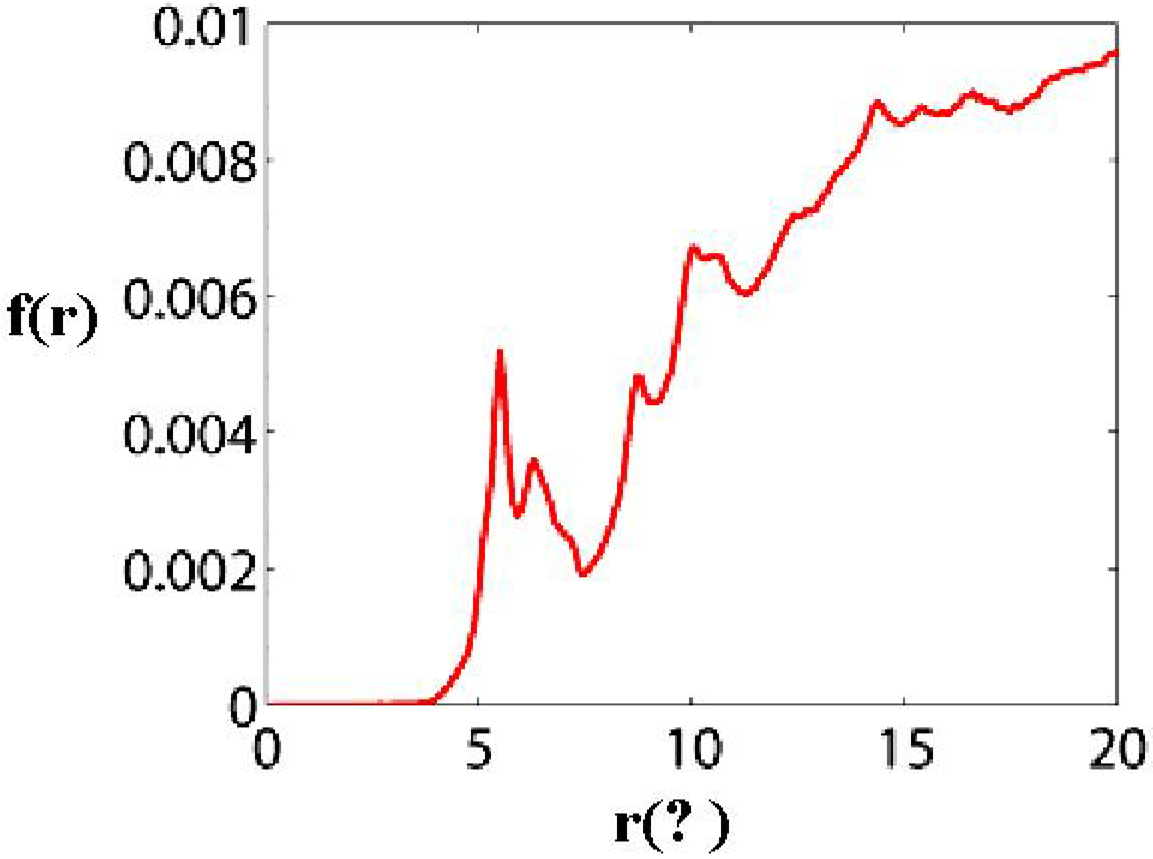
	Regular Triangulation	*Dual Complex*	*Inclusion-Exclusion*
Surface Area	0.19	0.06	0.05
Surface Area, Derivatives	0.19	0.06	0.08
Volume	0.19	0.06	0.18
Volume, Derivatives	0.19	0.06	0.29

System: 3740 balls (corresponding to a protein with 492 residues)
Computing time is seconds, on a Athlon 1.8 Ghz PC computer)

(http://csb.stanford.edu/koehl/ProShape/download.php)

Statistical Potentials

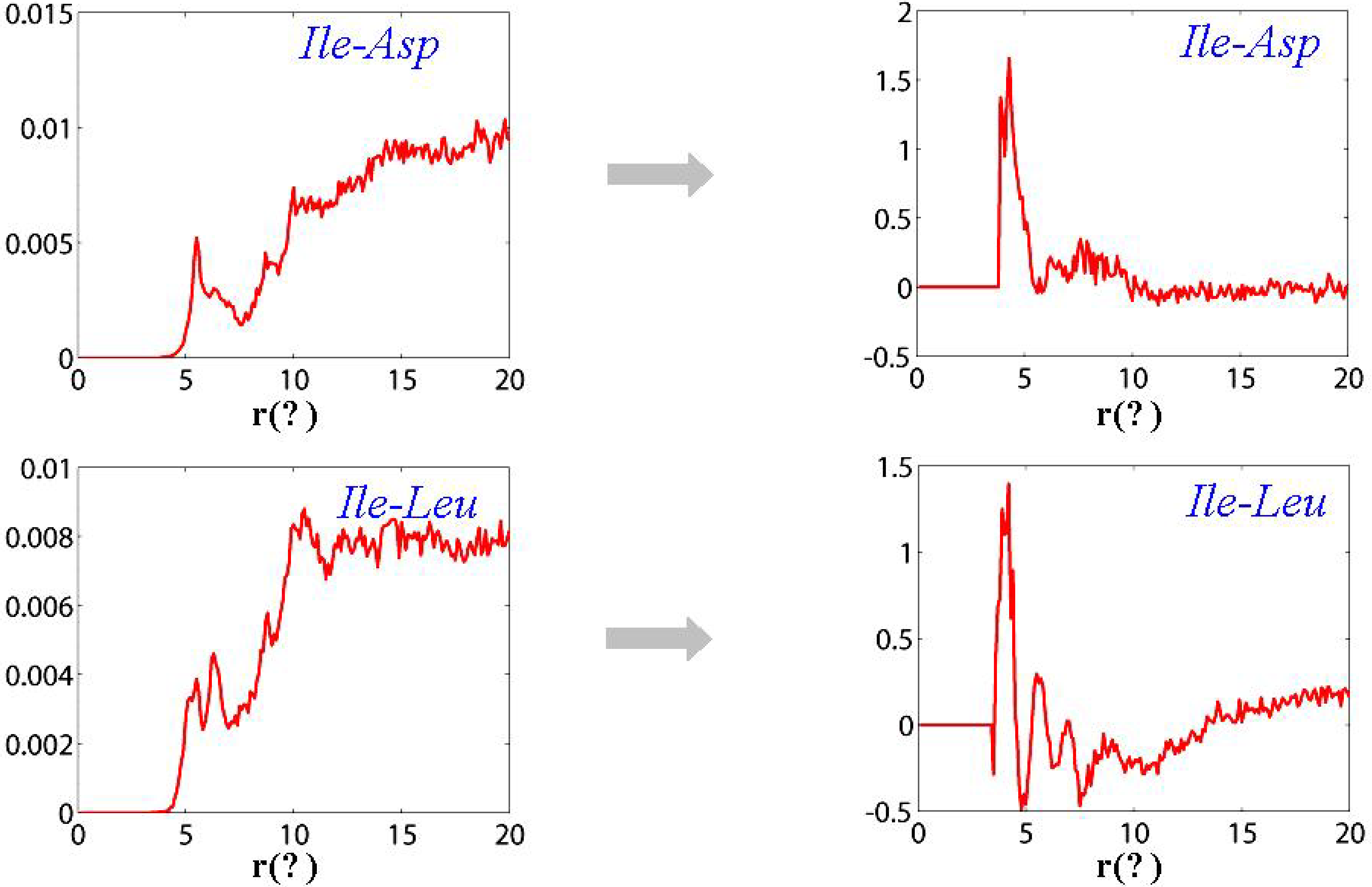




$$E(a,b,r) = -\ln\left(\frac{P_{(a,b)}(r)}{P(r)}\right)$$

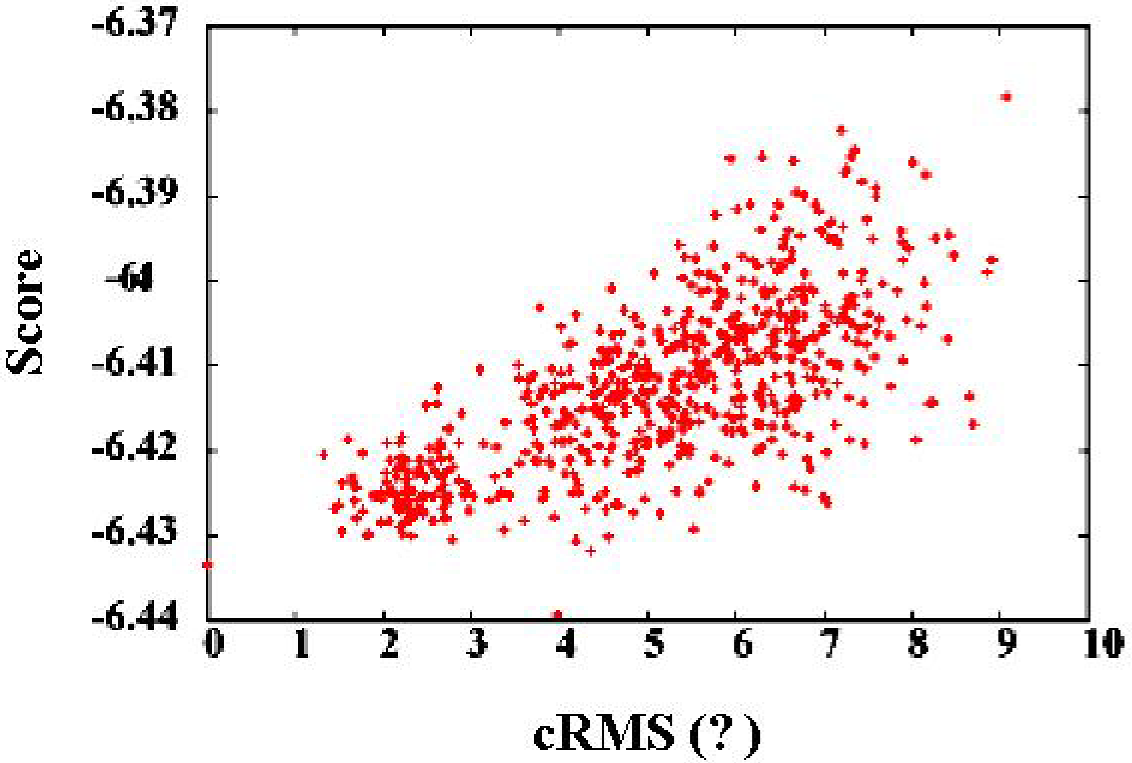
Counts

Energy



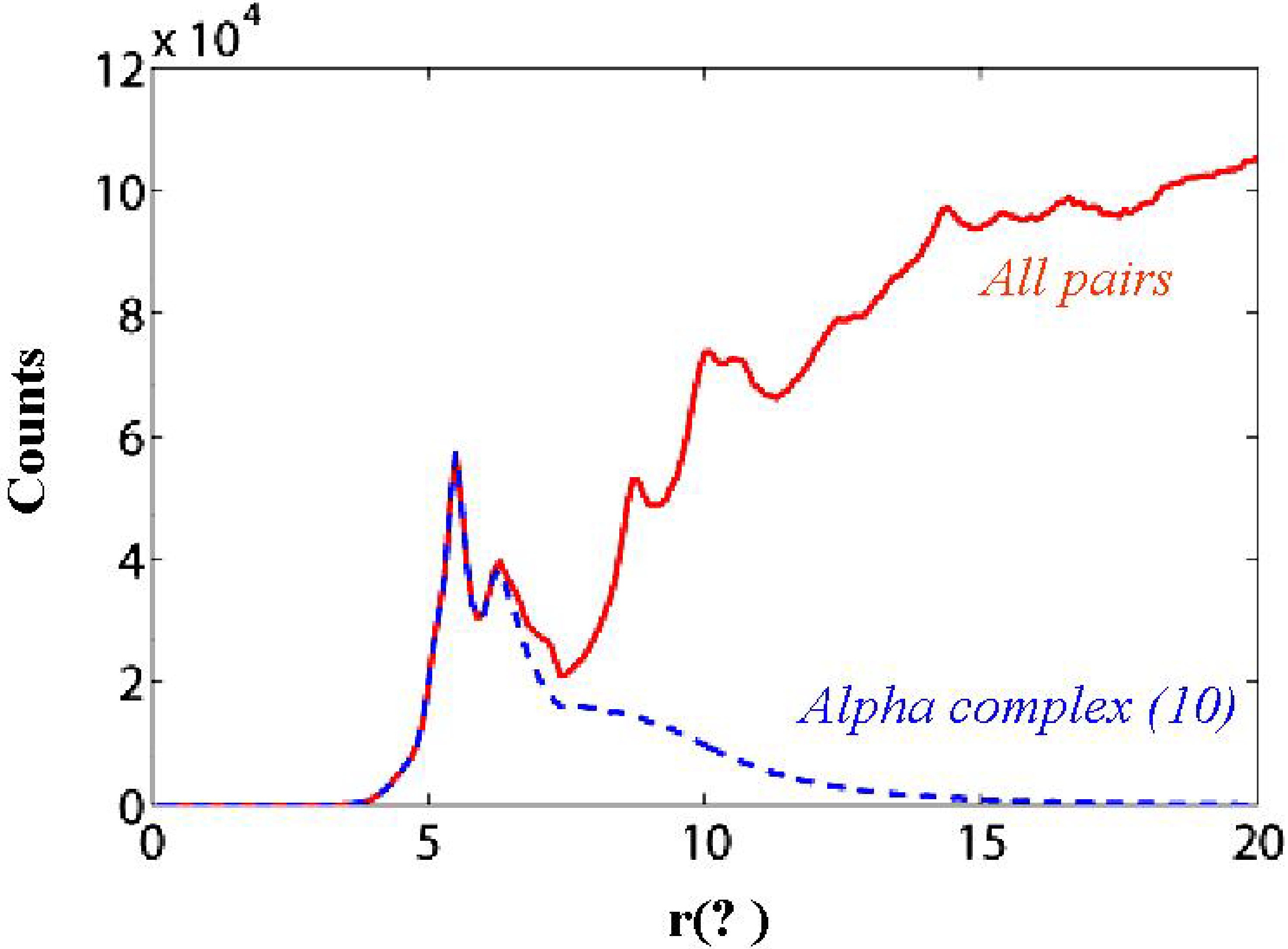
The Decoy Game
Finding near native conformations

1CTF

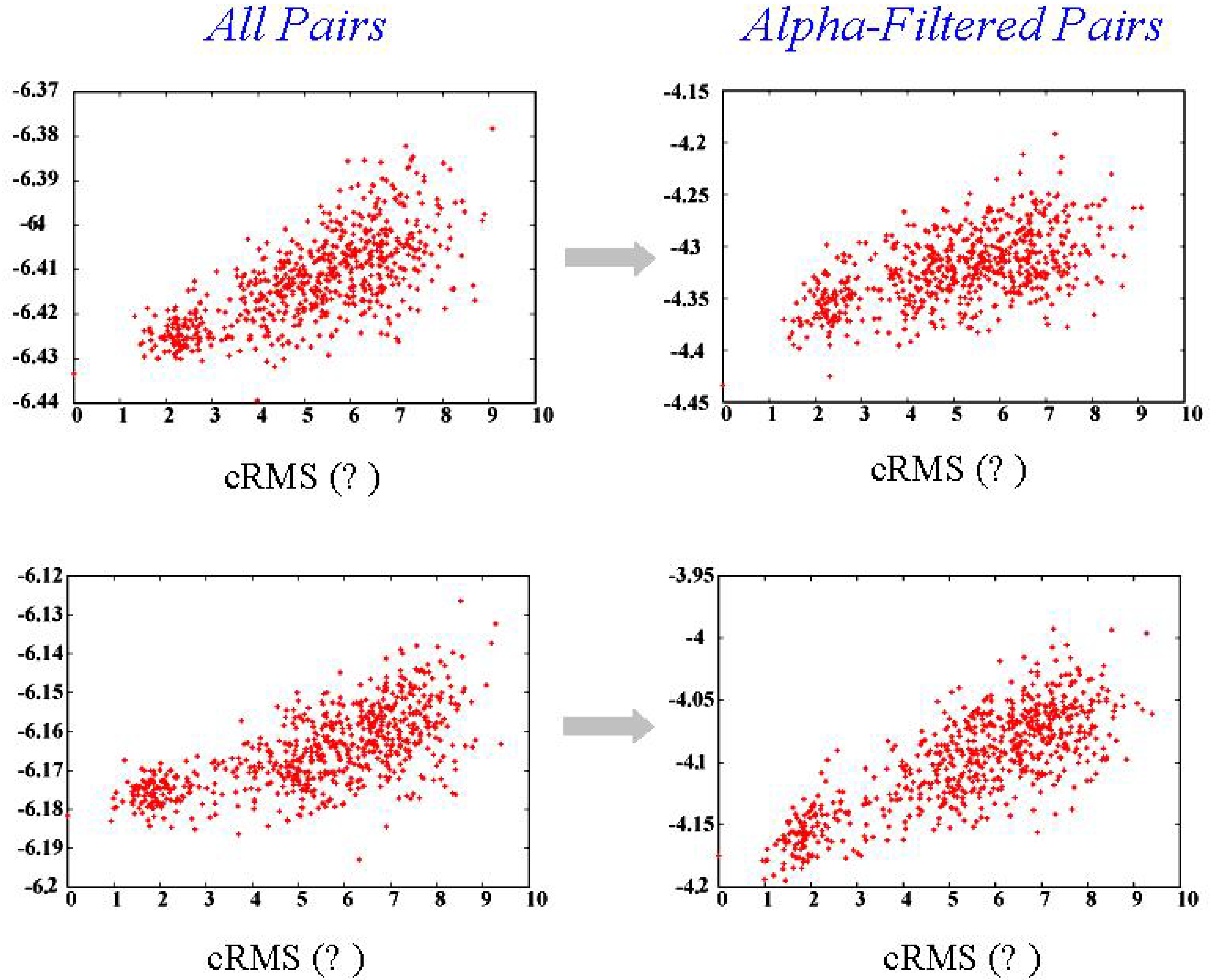


$$E = \sum_{i<j} E(i,j) = -\sum_{i<j} \ln\left(\frac{P(a_i,a_j,r_{ij})}{P(r_{ij})}\right)$$

Geometric Filtering of the Residue Pairs



Filtering Does Not Reduce Performance of PMF



Outline

- Introduction

  What is a Protein?

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Protein Structure Space

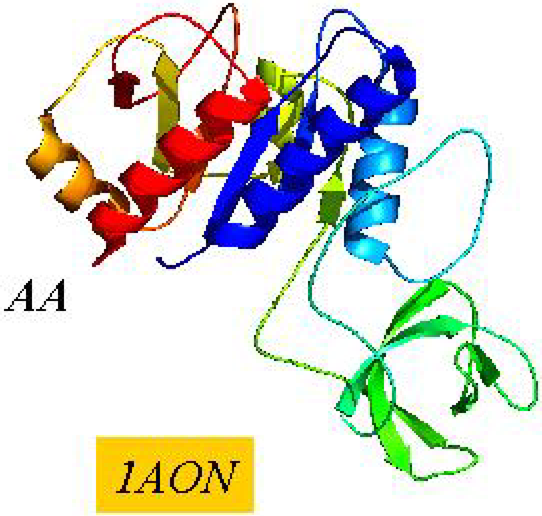
1CTF

68 AA

1TIM

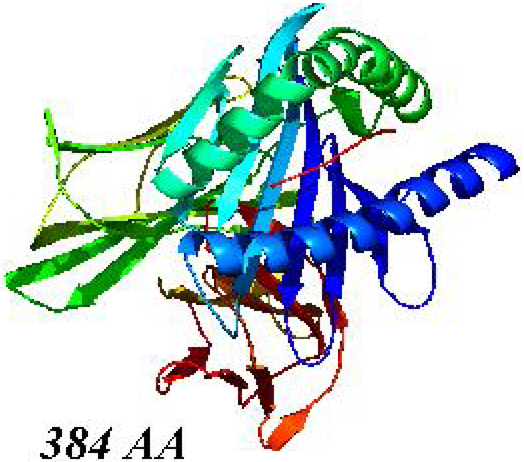
247 AA

1K3R



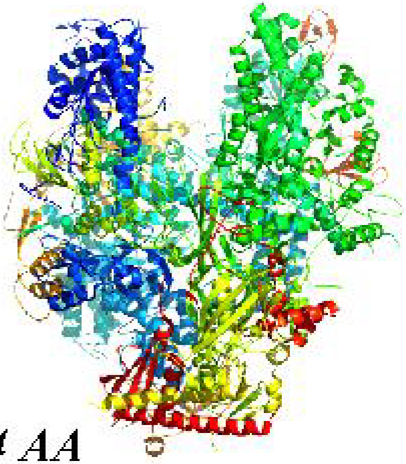
268 AA

1A1O



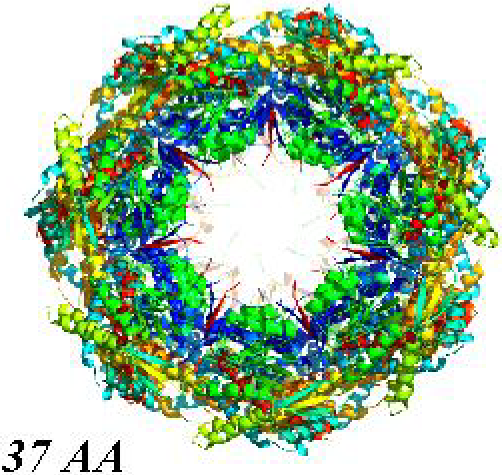
384 AA

1NIK



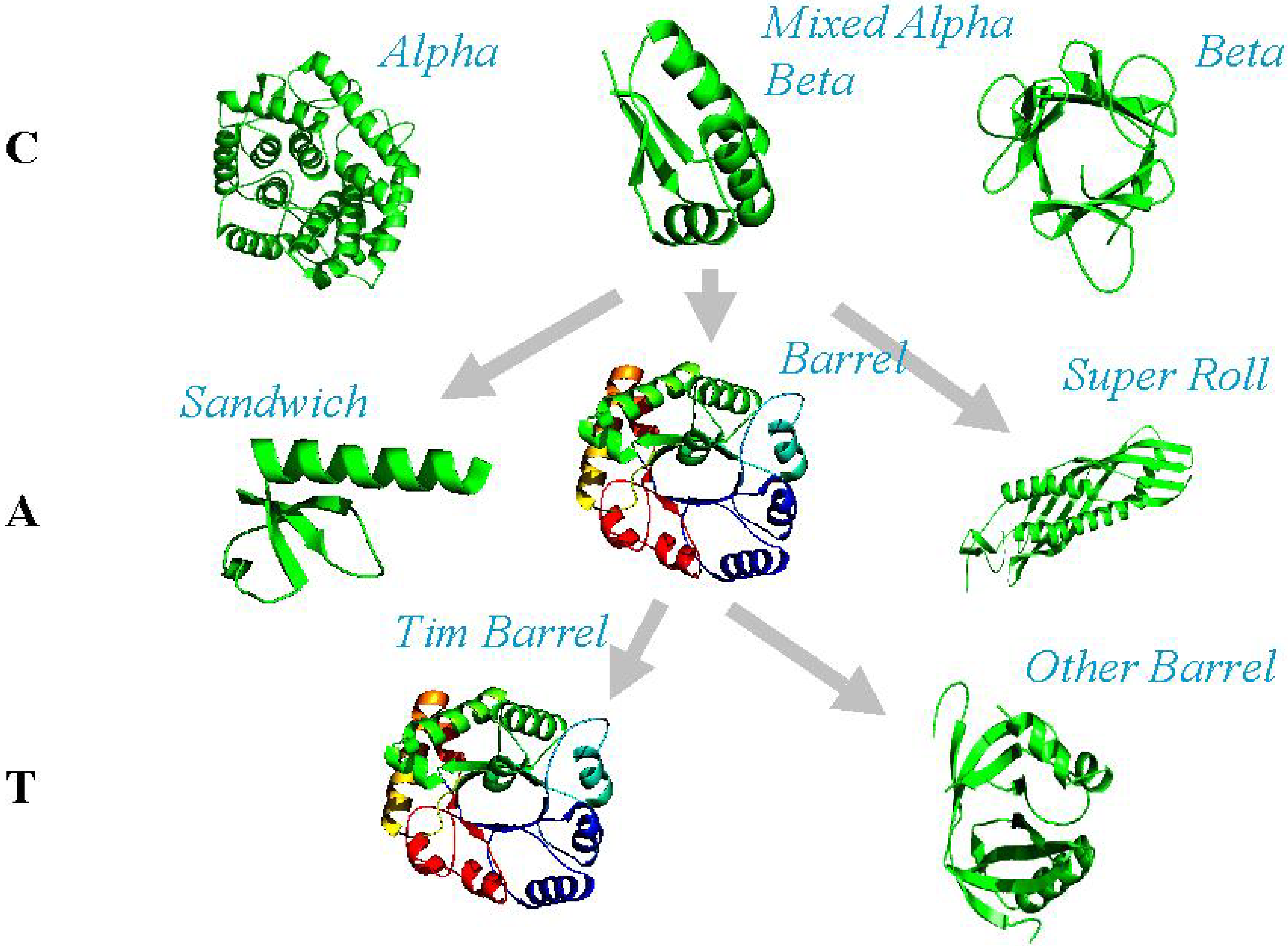
4504 AA

1AON



8337 AA

Classification of Protein Structure: CATH



C

Alpha

Mixed Alpha Beta

Beta

A

Sandwich

Barrel

Super Roll

T

Tim Barrel

Other Barrel

Protein Structure Similarity

Test set

2,930 proteins out of 23,000 proteins in PDB

No sequence similarity (Fasta E-value < e-4)

Reference structural similarity defined from CATH

769 folds

104,000 pairs of similar structures out of 4,600,000 pairs

Projecting Protein Structure Space

$$D = \begin{bmatrix} 0 & \dots & d_{1N} \\ \dots & 0 & \dots \\ d_{N1} & \dots & 0 \end{bmatrix} \longrightarrow G = X^T X \longrightarrow X$$

Distance Matrix

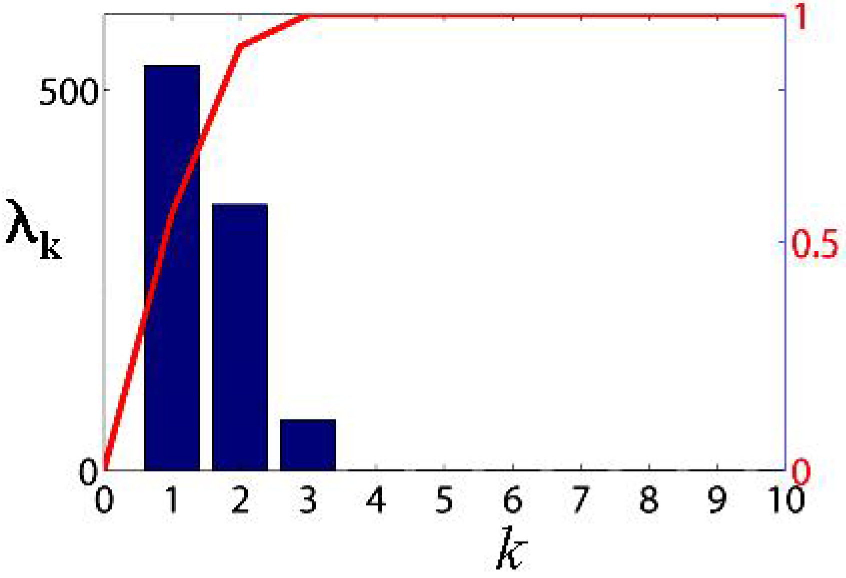
Metric Matrix

Points in Space

Projecting Protein Structure Space

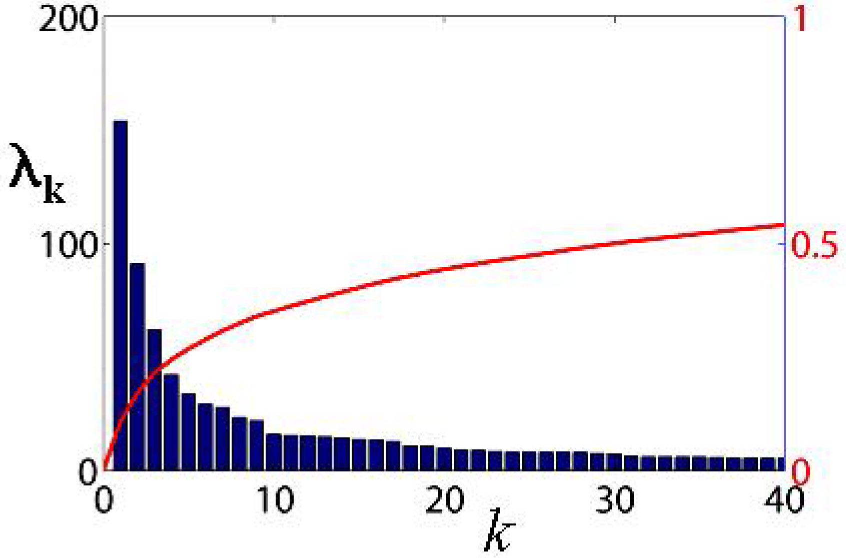
Class

$$D = \begin{bmatrix} 0 & 1 & 1 \\ 1 & 0 & \dots \\ 1 & \dots & 0 \end{bmatrix}$$



Fold

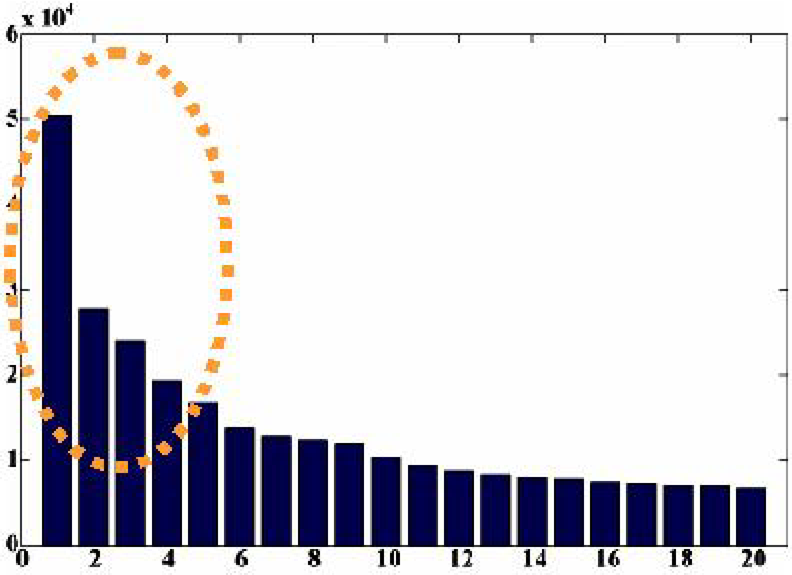
$$D = \begin{bmatrix} 0 & 1 & 0 \\ 1 & 0 & \dots \\ 0 & \dots & 0 \end{bmatrix}$$



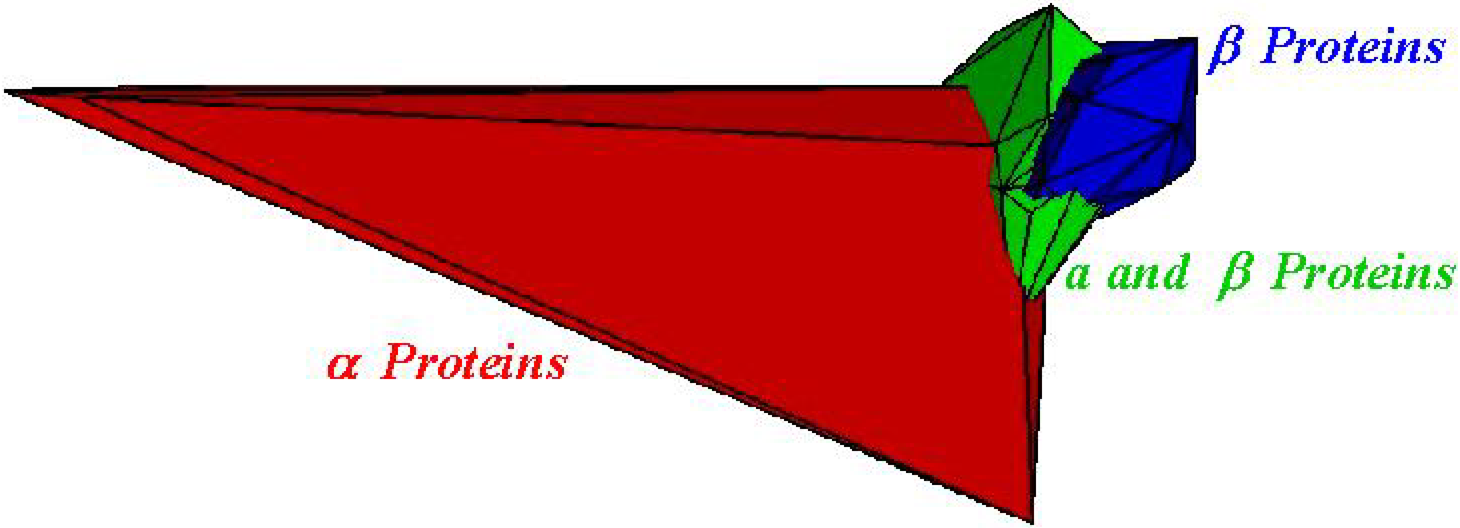
Protein Structure Classes

Measure of Structure Similarity: cRMS after Optimal Superposition (Structal)

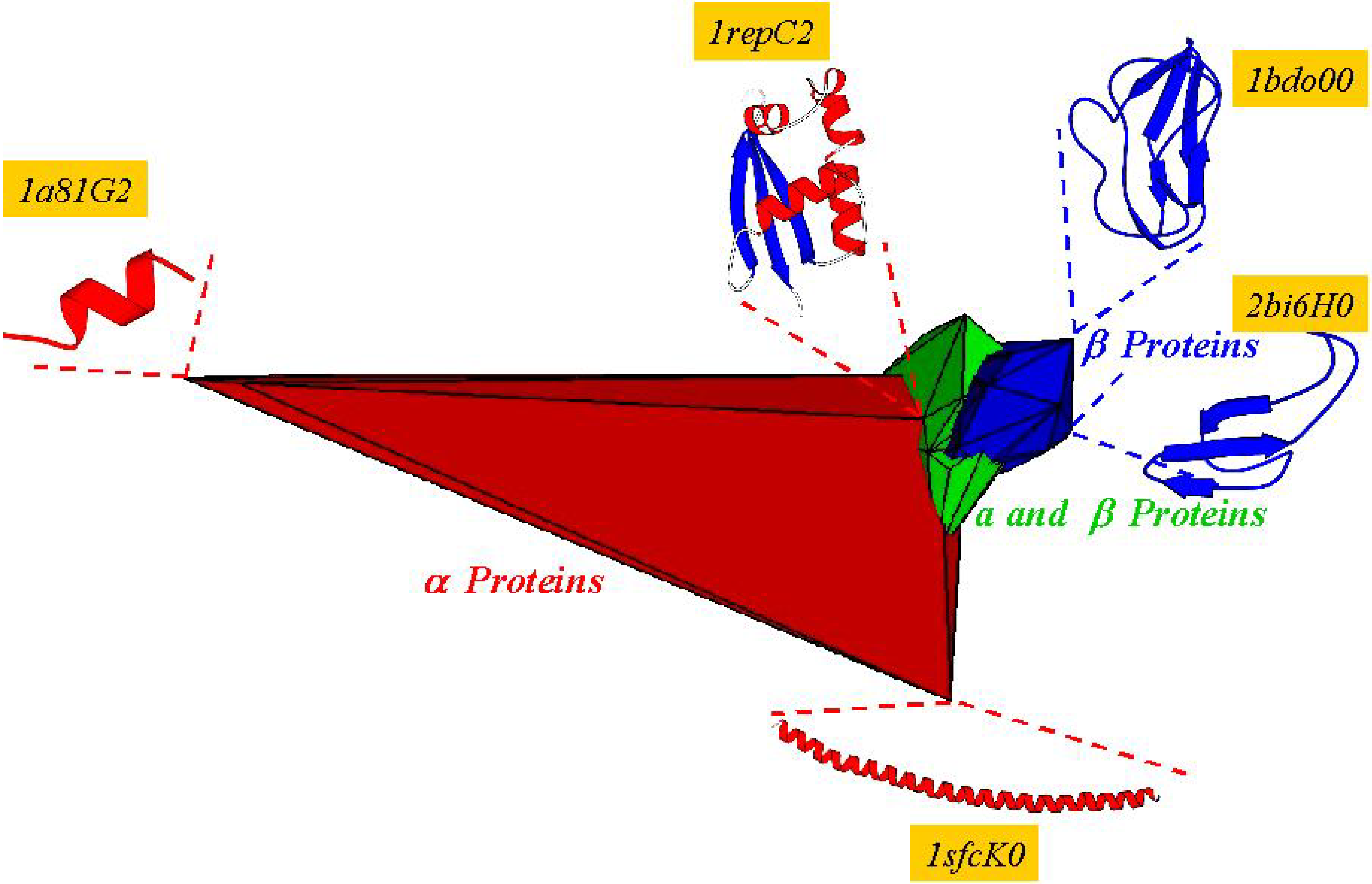
Eigenvalues of the Metric Matrix:



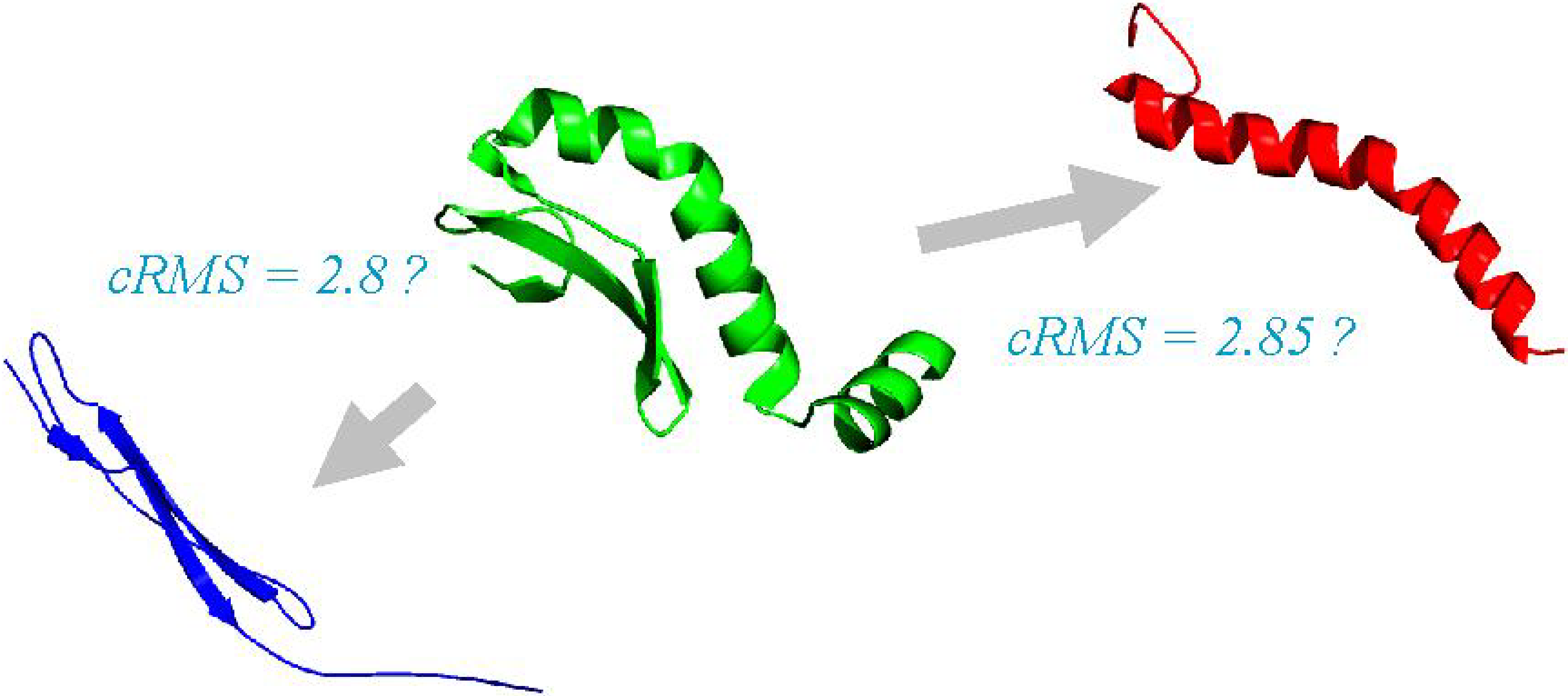
A Picture of the Protein Structure Space



A Picture of the Protein Structure Space



cRMS is not a Metric

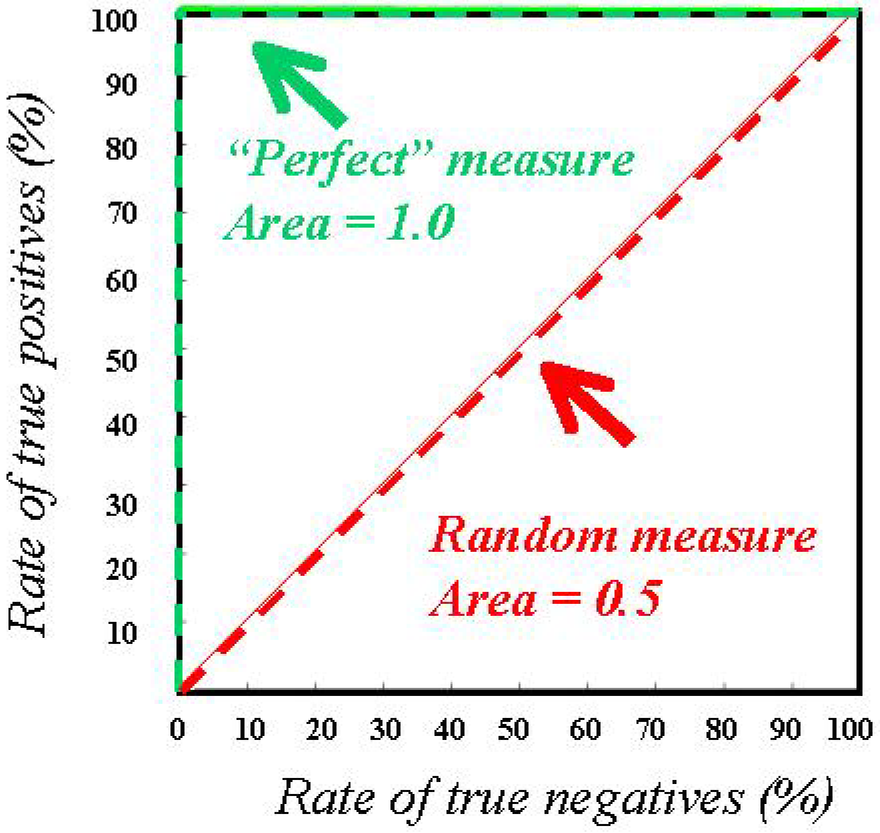


cRMS = 2.8 ?

cRMS = 2.85 ?

Protein Fold Space
ROC Analysis

(Receiver Operating Characteristic)



Protein Fold Space
ROC Analysis

(Receiver Operating Characteristic)

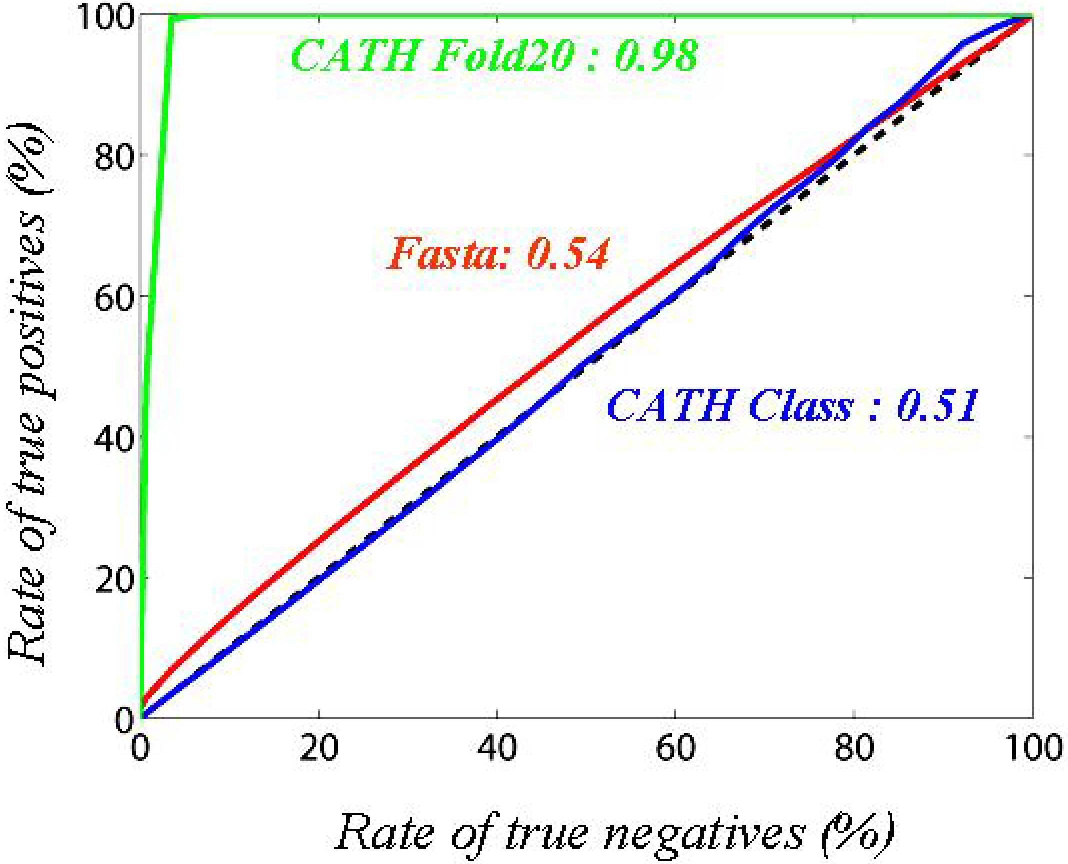
True positives

pairs of proteins that belong to the same T class of CATH

True negatives

pairs of proteins that belong to the same C class, but not the same T class.

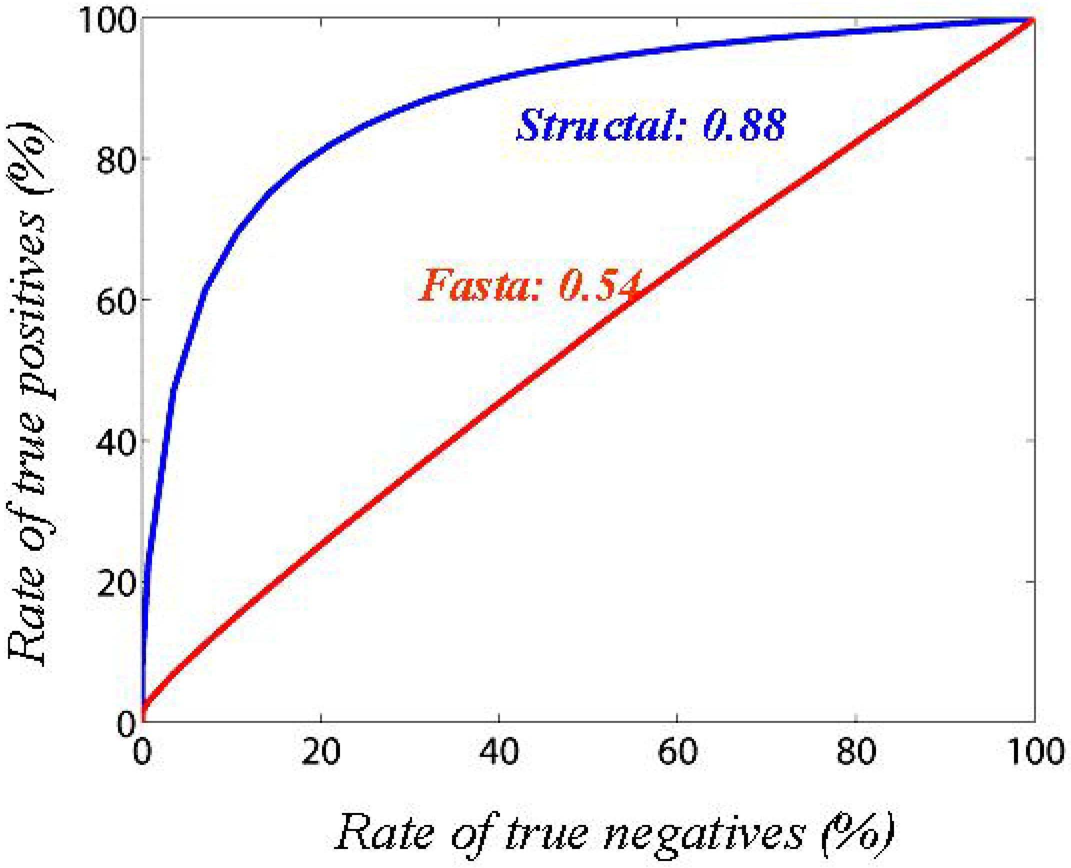
Protein Fold Space



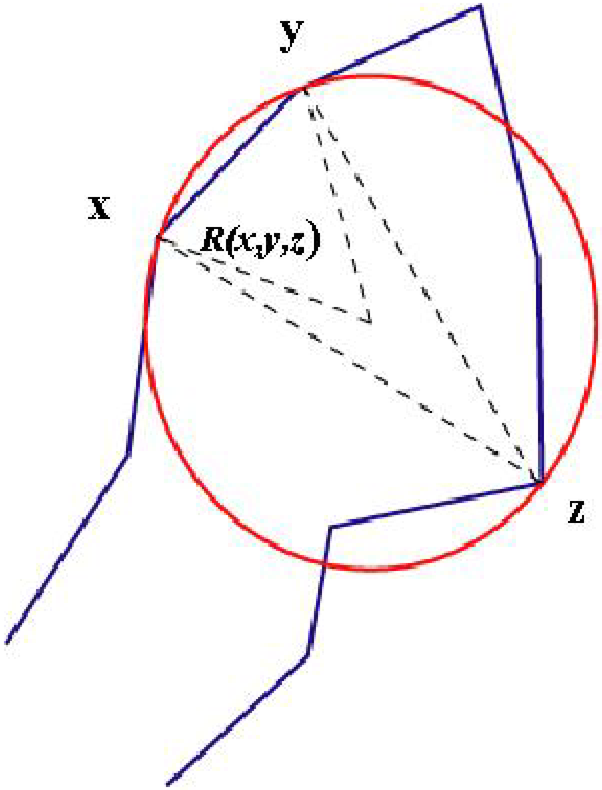
Fold20: first 20 coordinates derived from the CATH fold matrix

CATH class: first 3 coordinates derived from the CATH class matrix

Protein Fold Space



Protein Structure Features



$$R(x,y,z) = \frac{d(x,y)}{2\left|\sin\left(\hat{z}\right)\right|}$$

Global radius of curvature:

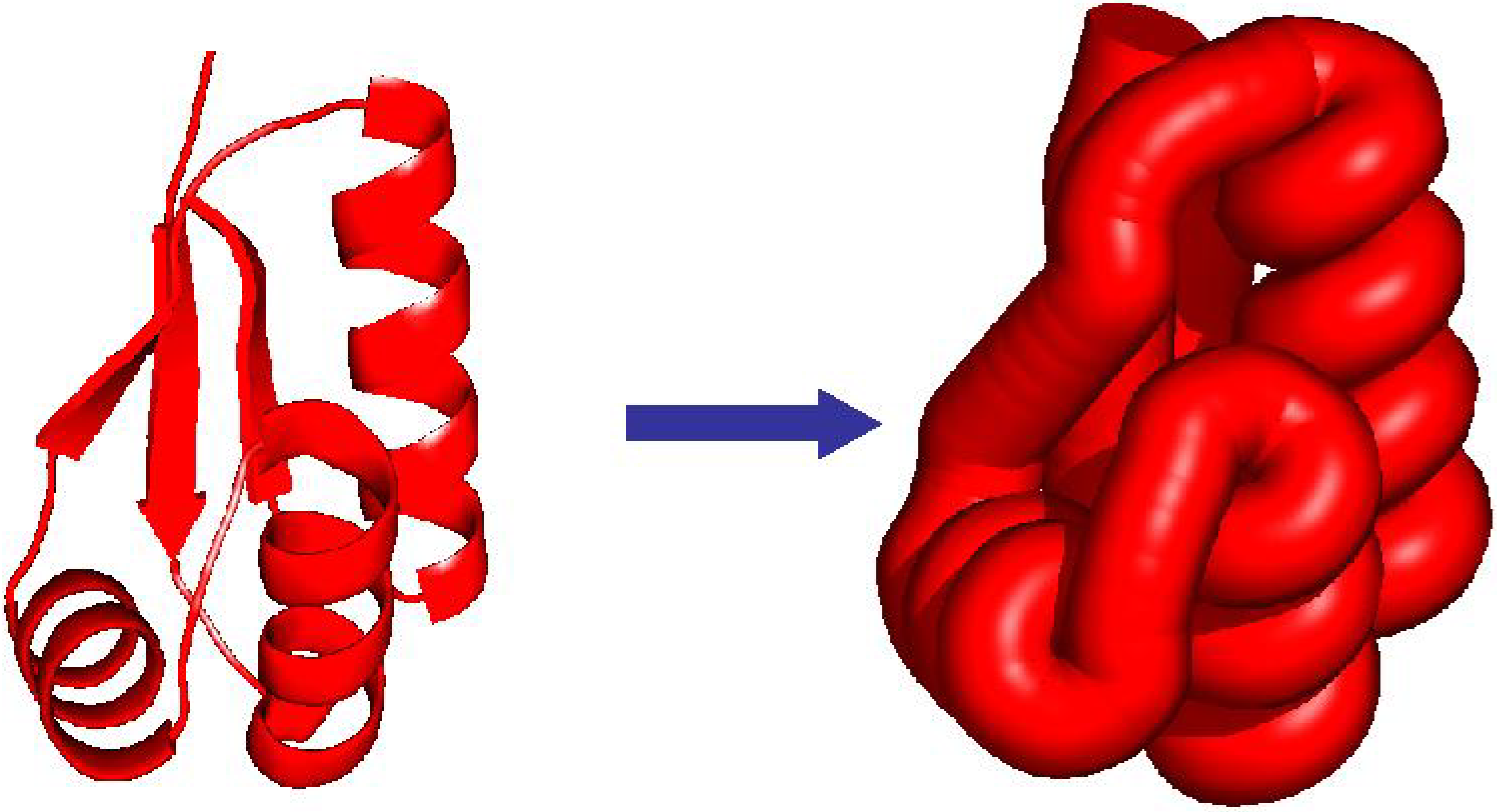
$$\boxed{\rho(x) = \min_{(y,z)}\left\{R(x,y,z)\right\}}$$

Thickness:

$$\boxed{\Delta = \min_{x}\left\{\rho(x)\right\}}$$

(Gonzalez & Maddocks, PNAS, 1999, 96:4769)

Thickness of a protein structure



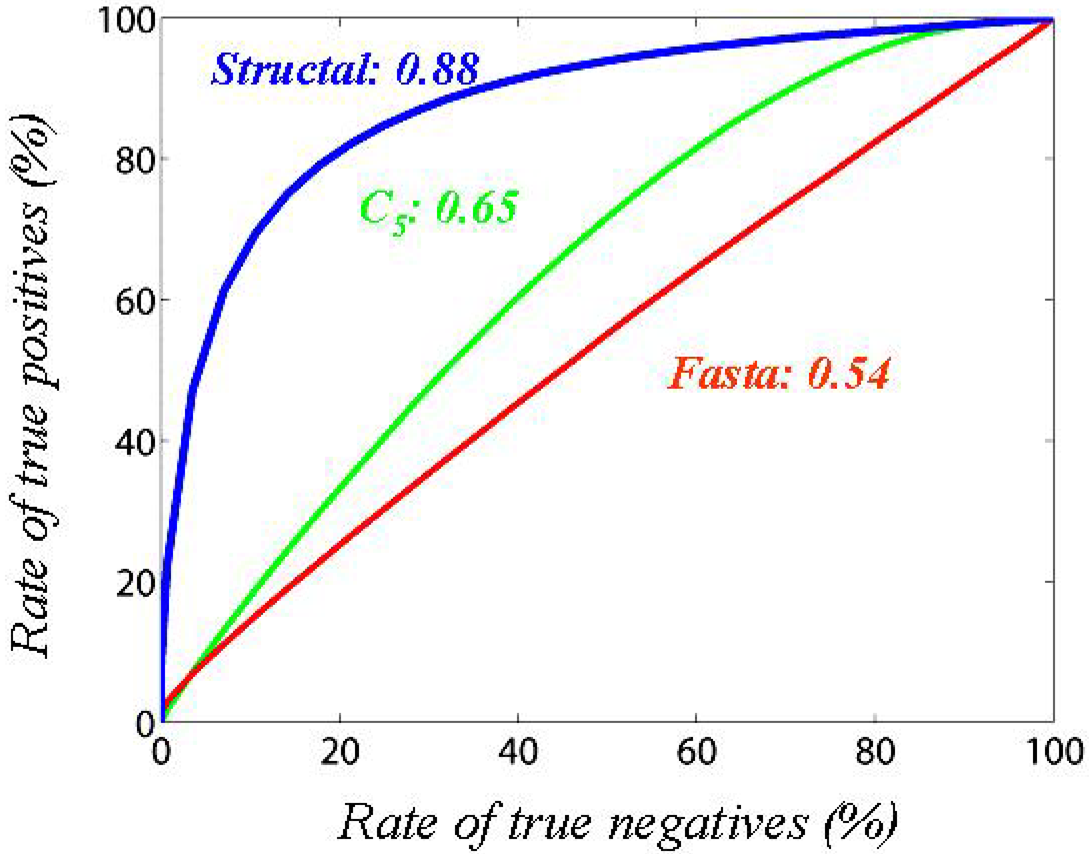
Δ= 2.60 ?

Curvature Feature Vector

$$U_p = \left(\iiint \frac{1}{R(x, y, z)^p} dC_x dC_y dC_z \right)^{1/p}$$

$$C_5 = \begin{bmatrix} U_1 & U_2 & U_3 & U_4 & U_5 \end{bmatrix}$$

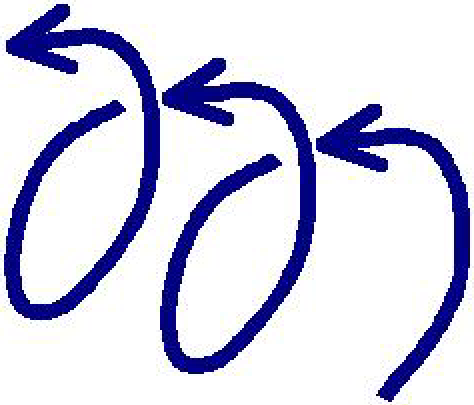
Performance of the Curvature Feature Vector



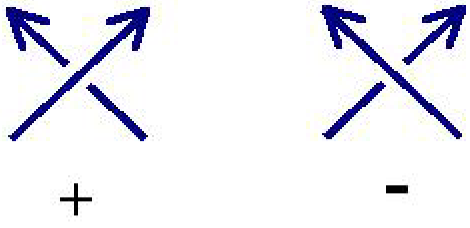
Curvature vector performs better than fasta.

Needs more features to match Structal.

Protein Structure Features: Writhing



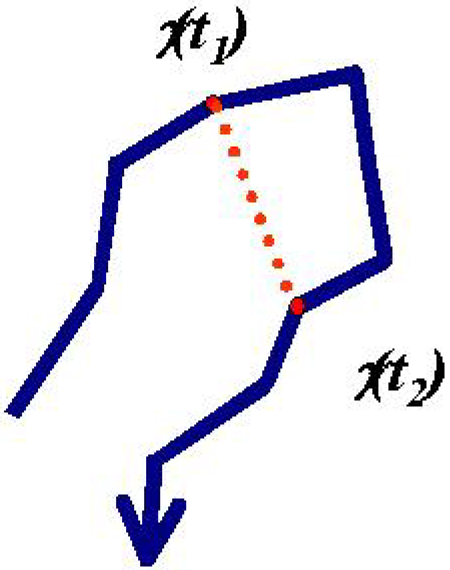
Sign of Crossing



Writhing Number

$$Wr_1 = \frac{1}{4\pi} \iint_{\Delta^2} \omega(t_1, t_2)\, dt_1 dt_2$$

$$\omega(t_1, t_2) = \frac{\det(\gamma'(t_1), \gamma(t_1) - \gamma(t_2), \gamma'(t_1))}{|\gamma(t_1) - \gamma(t_2)|^3}$$

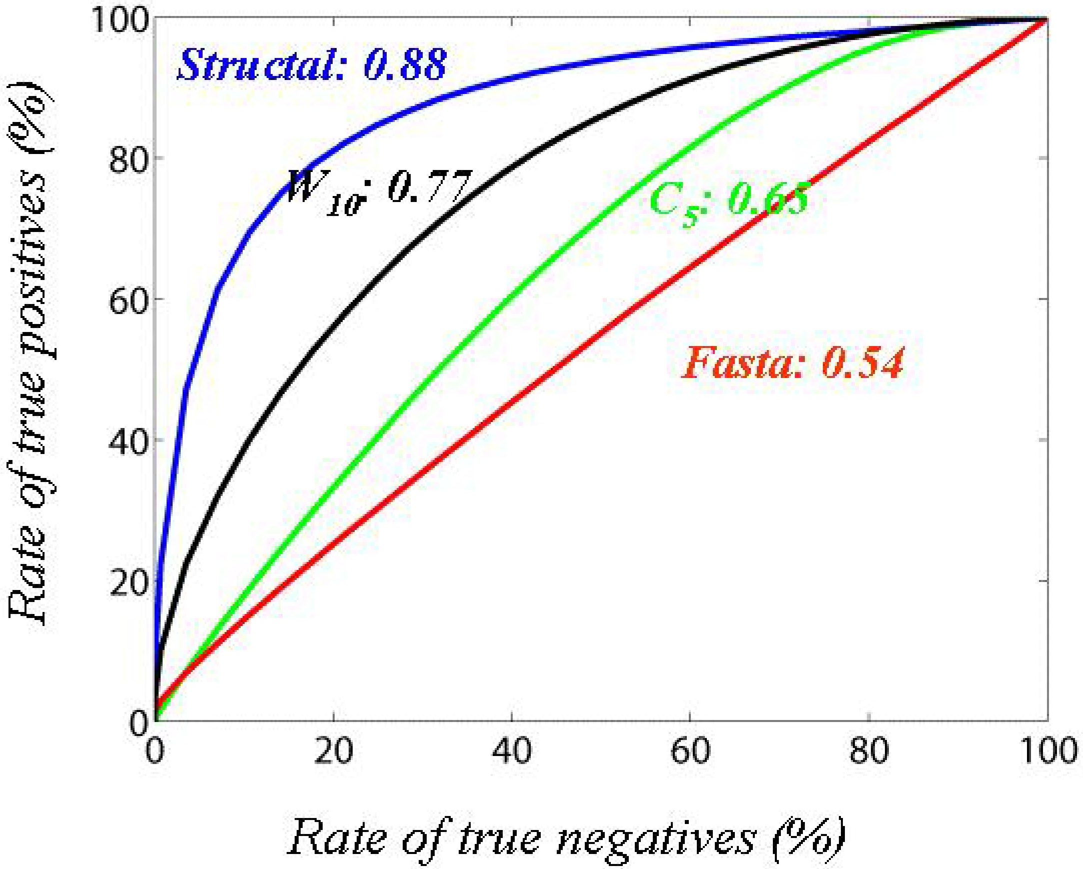


Writhe Feature Vector for Each Protein

$$W_{10} = [Wr_1 \quad |Wr_1| \quad Wr_{12} \quad |Wr_{12}| \qquad]$$

Fain and Røgen, PNAS, 100: 119 (2003)

Protein Structure Features: Writhing



W_{10} Writhe performs better than C_5 Curvature

Collaborators

- Leo Guibas
  Stanford University

- Herbert Edelsbrunner
  Duke University

- Michael Levitt
  Stanford University

- Afra Zomorodian
  Stanford University

- Rachel Kolodny
  Stanford University

Thank You