Interface Surfaces for Protein-Protein Complexes

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(RECOMB 2004)

OUTLINE

- Motivation
- Prior Work
- Concepts
- Procedure
- Analysis
- Comments

MOTIVATION

- definition of **protein interface surface** as a descriptor for the protein-protein interaction
- to allow for **visualization**, **characterization** and **classification**
- **geometric approach** based on the local shape of proteins

PRIOR WORK

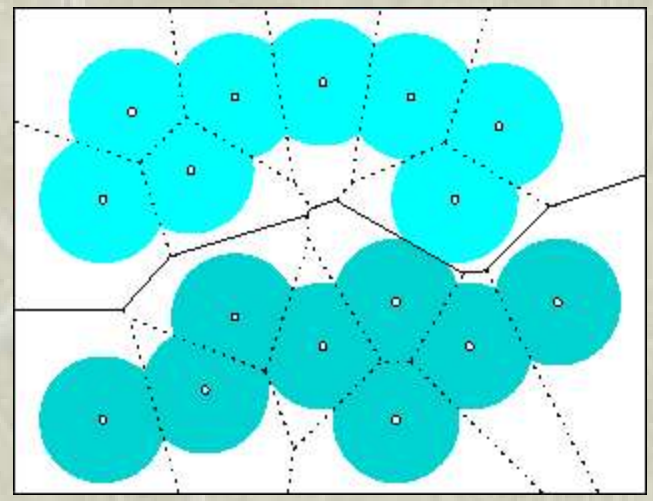
- experimental approach
  - **hot spot** theory
  - electrostatic steering
- computational approach
  - physical model
    - force-field model (Kortemme and Baker [14])
  - **geometric model**
    - power diagram approximation (Varshney et al. [23])

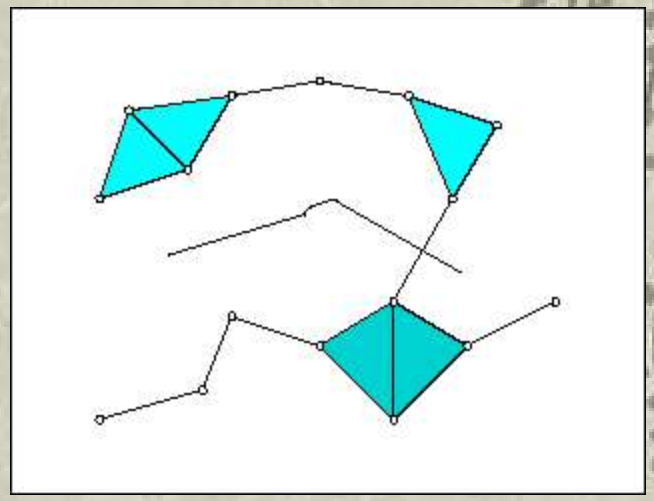
CONCEPTS

- **Voronoi diagram** & **Delaunay complex**
- **alpha shape** representation [10]
- **discrete flow** on the Delaunay simplices based on **Morse theory** [7][8]
- **persistence** to assess the importance of topological features [9]

CONCEPTS (cont'd)

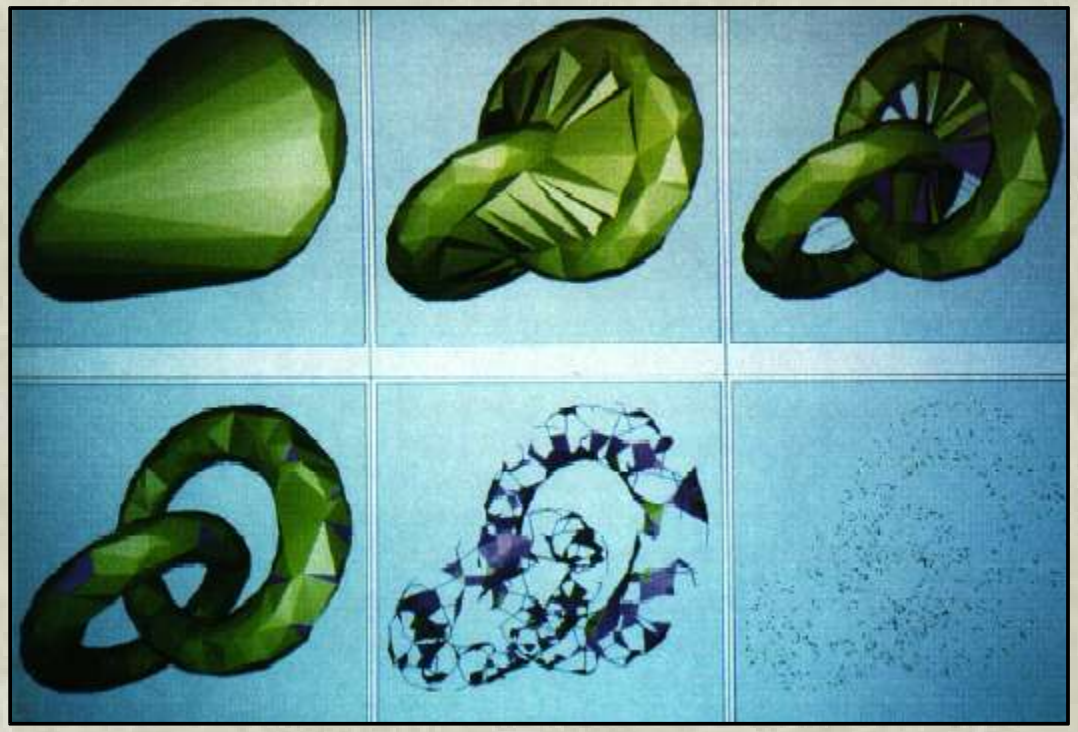
- Voronoi diagram & Delaunay triangulation
  - interface surface without boundary
- space-filling diragram & simplicial complex





CONCEPTS (cont'd)

- alpha shape representation [10]



PROCEDURE

1. constructs **Delaunay triangulation** with ordering of simplices by **filtration**
2. shrinks the complex keeping **homotopy type** by **retraction** and **removals**
3. the **interface surface** consists of all **multi-chromatic** Voronoi polygons, segments and points

FILTRATION

- sequence of nested dual complexes of growing space-filling diagram
- grows from empty complex to Delaunay triangulation
- alpha shape with increasing α value
- **critical** events & **regular** events

RETRACTION

- maximal sequence of **collapses**
- keeps **homotopy type**
- **independent of the sequence** in which the collapses are performed

REMOVAL

- regards a pair of critical events with small **persistence** as a regular events
- **seal value** of a pair of simplices (σ,υ):

$$f(s,u)=\frac{s}{u-s}$$

- **threshold** C_0

ANALYSIS

- visualization
- hot-spots in **protected regions**
- classification by **global measures**
  - **topological**: genus, total angle difficiency, wrinkledness
  - **geometric**

VISUALIZATION

- interface surface between **Barnase** & **Barstar**

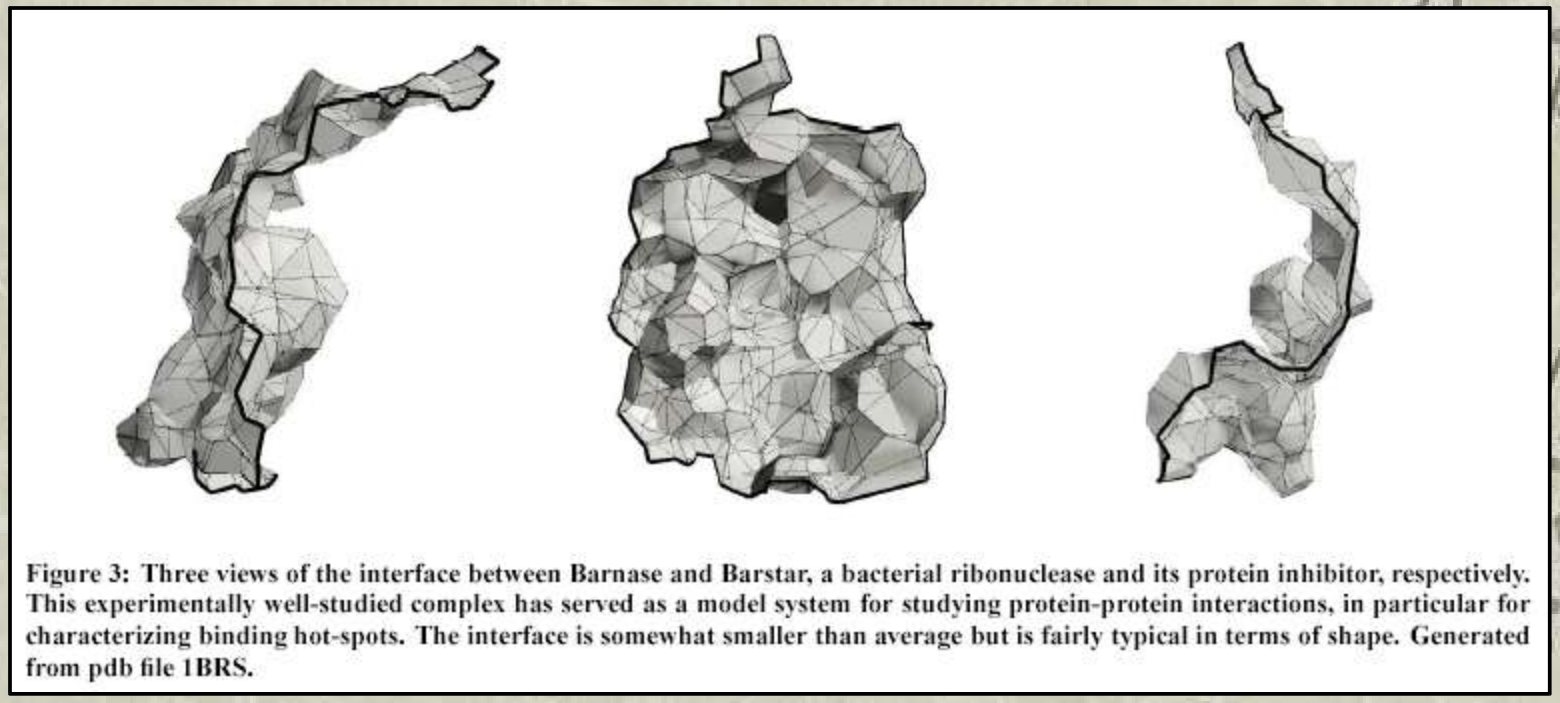


Figure 3: Three views of the interface between Barnase and Barstar, a bacterial ribonuclease and its protein inhibitor, respectively. This experimentally well-studied complex has served as a model system for studying protein-protein interactions, in particular for characterizing binding hot-spots. The interface is somewhat smaller than average but is fairly typical in terms of shape. Generated from pdb file 1BRS.

VISUALIZATION (cont'd)

- interface surface between **colicin E9 DNase & immunity protein IM9**

Figure 4: Two views of the interface between colicin E9 DNase and the immunity protein IM9, a toxin produced during cell stress and its inhibitor, respectively. The affinity in the E9-IM9 complex is extremely tight (sub-femtomolar). This interface is also smaller than average, but has a very prominent saddle shape. Generated from pdb file 1BXI.

VISUALIZATION (cont'd)

- interface surface in **human hemoglobin**

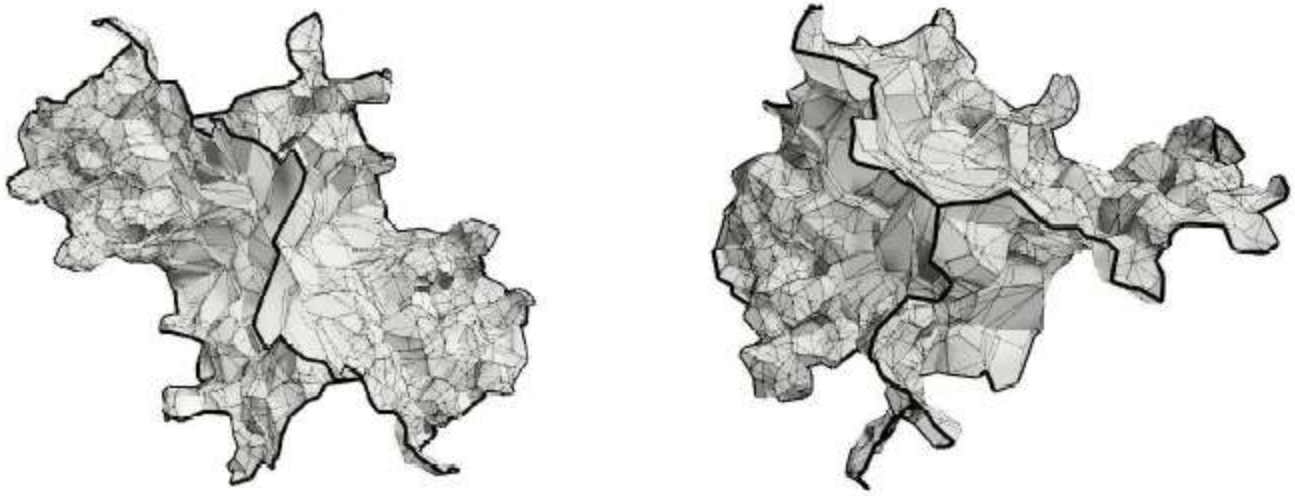


Figure 5: Two views of the interface in human hemoglobin that demonstrate the utility of these representations for multimeric complexes. Hemoglobin consists of four separate but identical chains and the resulting interface shows the more complicated nature of a multi-subunit interaction. Generated from pdb file 1A3N.

VISUALIZATION (cont'd)

- interface between **human angiogenin** & **placental ribonuclease inhibitor**

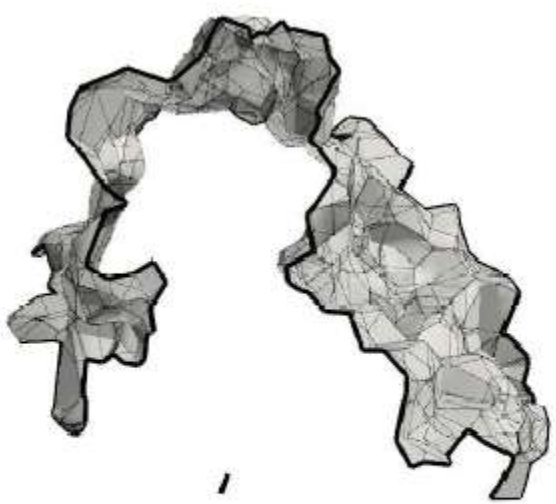


Figure 6: On the left, a view of the interface between human angiogenin and a placental ribonuclease inhibitor. The interaction between these proteins is extremely tight (femtomolar) and the interface exhibits both a very large surface area and an interesting overall bent shape. Generated from pdb file 1A4Y. On the right, a view of interface in the neurotoxic vipoxin complex from Western Sand Viper consisting of phospholipase A2 and its inhibitor. A rather unusual interface with genus 3. Generated from pdb file 1JLT.

VISUALIZATION (cont'd)

- interfaces in **HIV-1 protease**

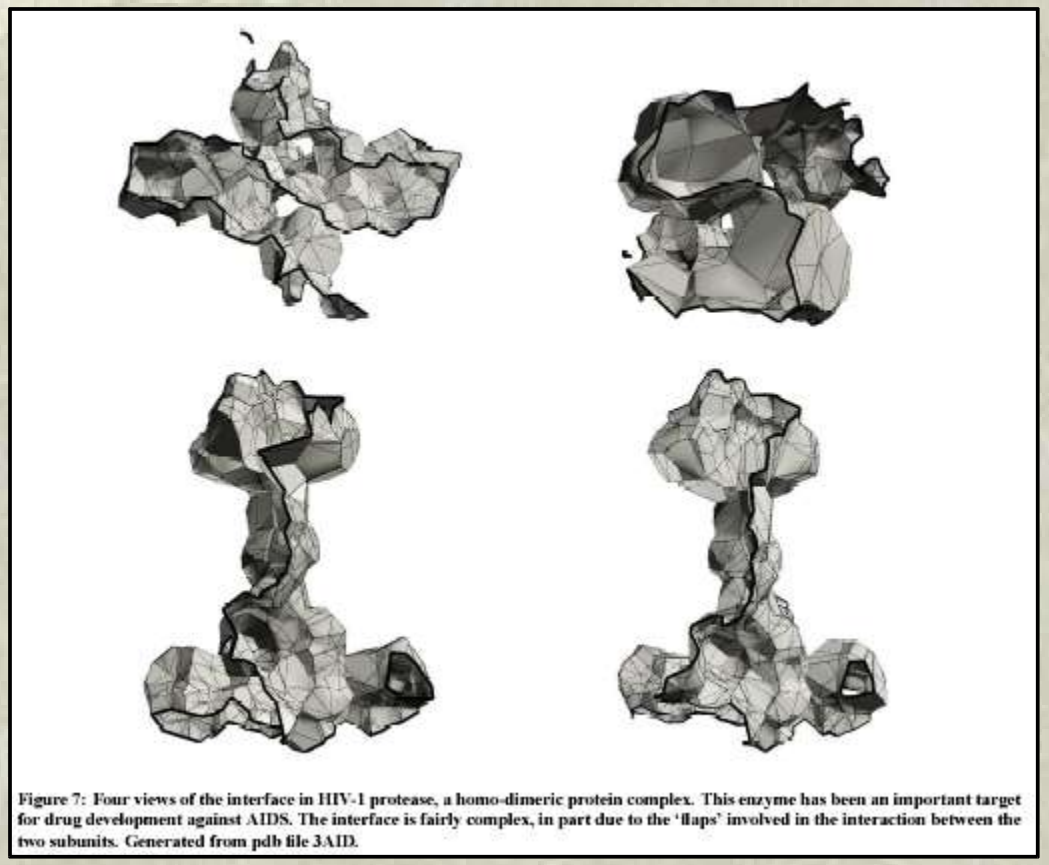


Figure 7: Four views of the interface in HIV-1 protease, a homo-dimeric protein complex. This enzyme has been an important target for drug development against AIDS. The interface is fairly complex, in part due to the 'flaps' involved in the interaction between the two subunits. Generated from pdb file 3AID.

PROTECTED REGION

- high correlation between the **protected regions** of the interface surfaces and the experimentally determined **hot-spot residues**
- residues which have atoms involved in the **late stages** of the hierarchy are somehow more critical for the interaction

PROTECTED REGION (cont'd)

- function to distinguish hot-spot from neutral residues in the interface

$$h(R) = \sum_{i=0}^{k} \text{area}(p_i) \frac{\text{area}_t(R)}{\text{area}_t(\boldsymbol{S})}$$

TOTAL ANGLE DIFFICIENCY

- **Gaussian curvature** for piecewise linear manifold
- defined at each vertex *u*

$$\theta_u = 2\pi - \sum \phi_j$$

- elliptic / flat / hyperbolic

WRINKLEDNESS

- root-mean-square variation of total angle difficiency

$$W = \sqrt{\frac{1}{m} \sum_{u \in U} (\theta_u - \frac{\theta}{m})^2}$$

COMMENTS

- poor explanation of level-of-focus hierarchy construction
- purely geometric approach
- poor understanding of the biochemical details captured in the hierarchy