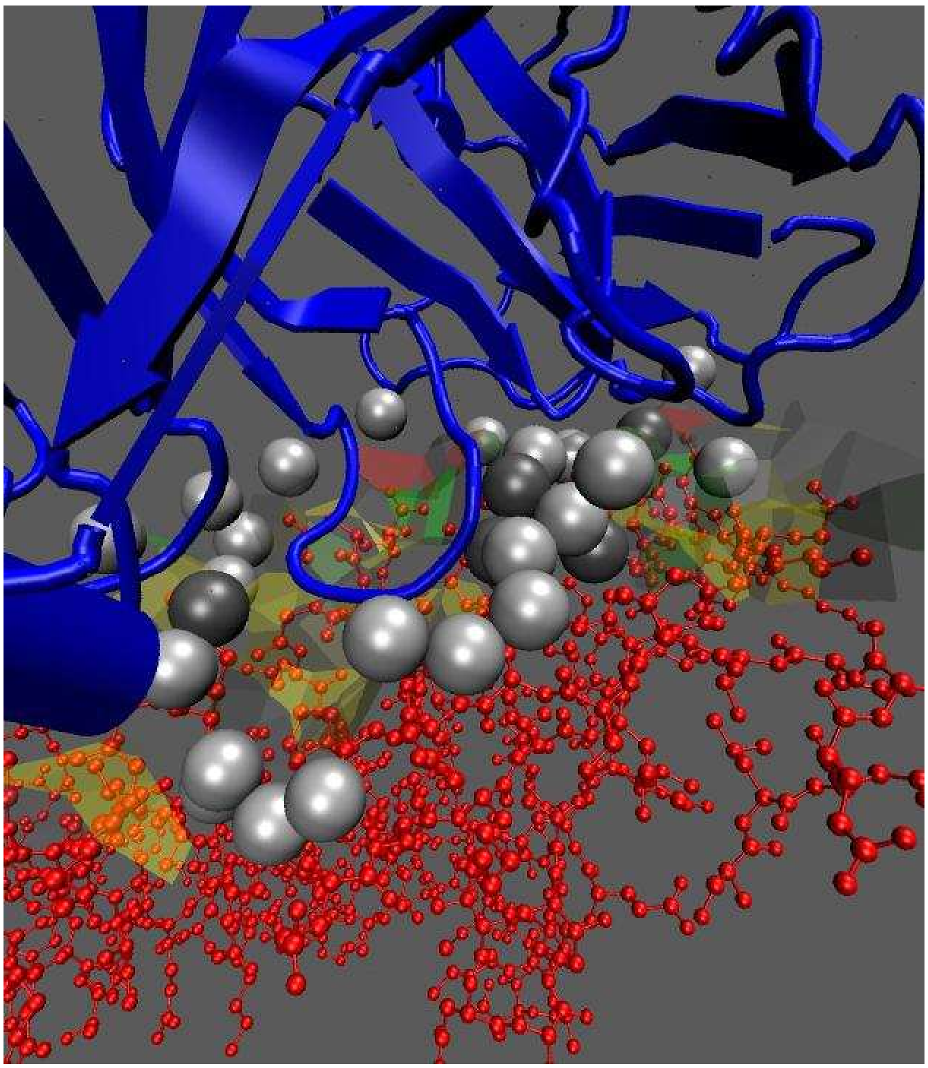
Revisiting the description of Protein-Protein interfaces.



F. Cazals, INRIA Sophia-Antipolis
J. Janin, CNRS / Univ. Orsay; Applications
F. Proust, INRIA Sophia-Antipolis; Visualization

Modeling interfaces and Non-Covalent contacts

▷ Crystals and interfaces

⇒ specific vs (non) specific (crystals) contacts
Monomeric/Multimeric (homo, hetero) status
⇒ Permanent vs Transient [e.g. Enz. Inh. vs Enz. Subs.]
⇒ Evolution (conserved residues, hot spots)

▷ Interfaces: General principles?

What is necessary to build a stable protein interface?
What part of a protein may form an interface?

▷ Analytical view

Calibrating statistical potentials
Docking / Folding (Flexibility, (De)-Solvation,. . .)
Defining patches for docking
Protein engineering
Deriving structures
(NMR, Crystallography, Homology modeling)

Previous work

▷ Parameters (J. Janin, J. Thornton, S. Wodak, . . .):

Buried SAS area BSA
Counts: #atoms, #residues, #pairs
Planarity, Geometry of the core/rim
Packing properties (buried atoms!!!)
Patches: number, geometry
Chemical composition (atoms / residues)

▷ Interface and accessibility

Interface: atoms loosing accessibility in $A \cup B$
Buried Surf. Area:
$BSA = SAS(A) + SAS(B) - SAS(A \cup B)$

Interface and contacts
pairs of atoms within a threshold

▷ Methodological contributions

R. Wade (96)
Herbert E. (04)

▷ Contributions:

Reconciling all these notions using a single DS
Providing new (local/global insights)

Interfaces: coherent description?

- ▷ atoms loosing SAS vs atoms' pairs?
- ▷ connected or not? simply connected?
- ▷ flat or curvy?
- ▷ role of structural water?

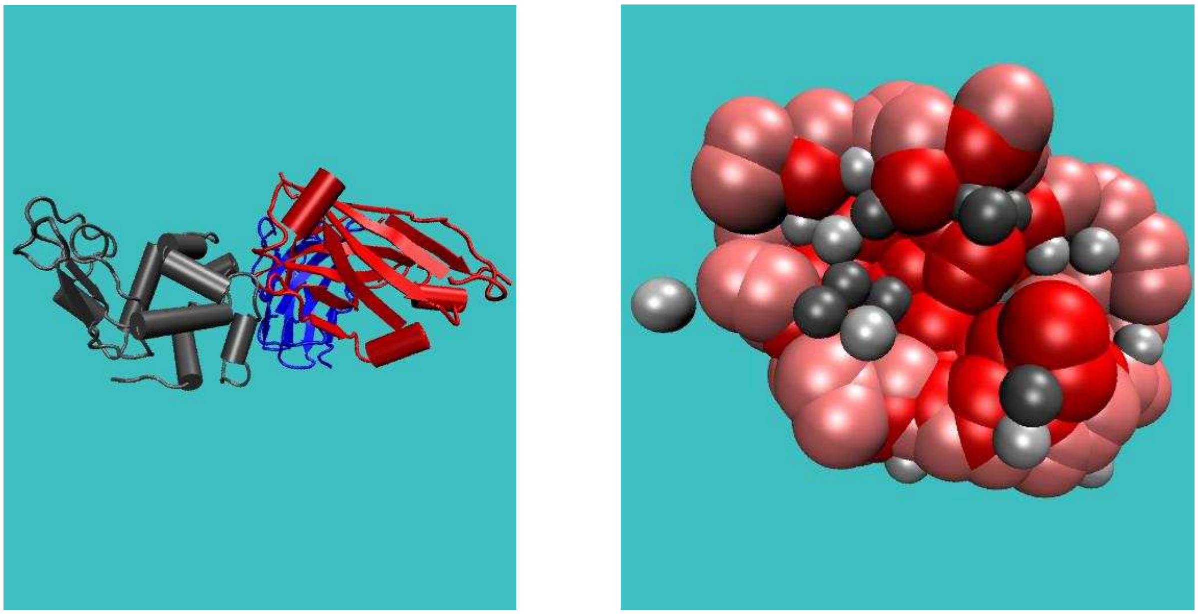
Partial answers from the α-complex!

- ▷ Voronoi Geometry/Topology of interfaces
- ▷ Key illustrations
  96 complexes, 30 at res. $< 2\AA$
  5 groups:
    - Proteases - Inhibitor (PI)
    - Enzyme - substrate / Inhibitor (ESI)
    - Antibody - Antigen (AA)
    - Signal Transduction & Cell cycle (ST)
    - Misc. (M)
- ▷ Demo.

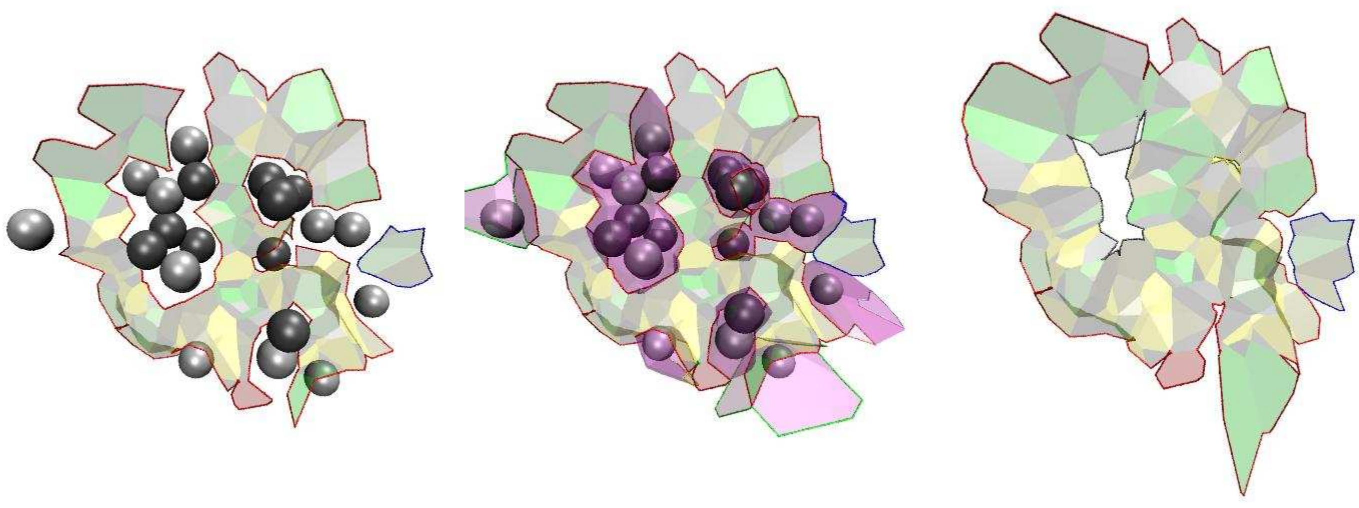
Application: Not covered

- ▷ Specific vs non specific contacts
- ▷ Statistical potentials
- ▷ ...

Interfaces, Structural Water (res. $< 2\AA$)



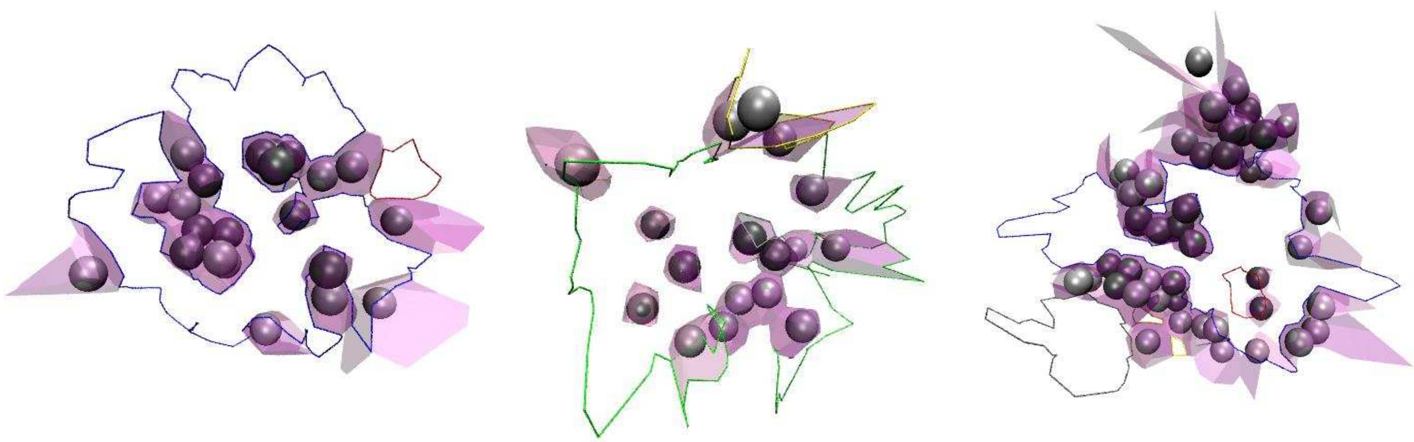
Complex 1vfb (a)Chains: Lysozyme (Grey), antibody Fv fragments (Blue, Red) (b)Interface atoms of the Lysozyme



Complex 1vfb (a)Creeks at the interface filled by water molecules (b)Facets of the AW-BW interface shown in purple (c)The interface without water molecules

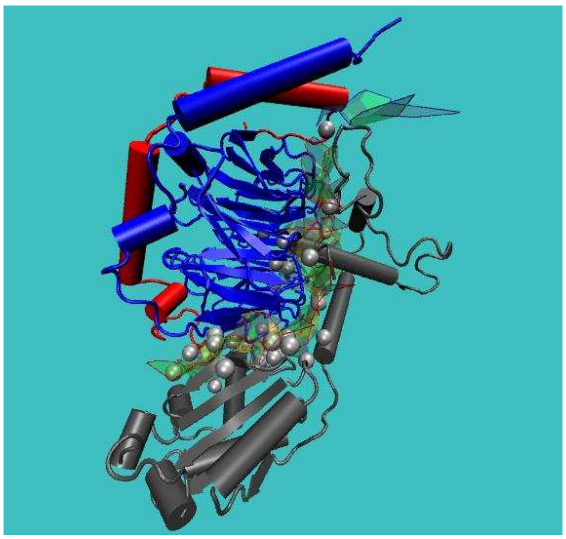
Hydration patterns

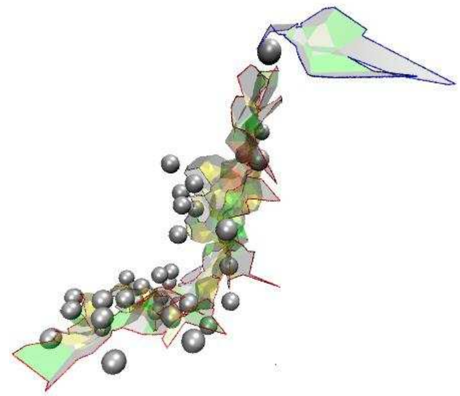
(Cooperative Hydrophobic effect)



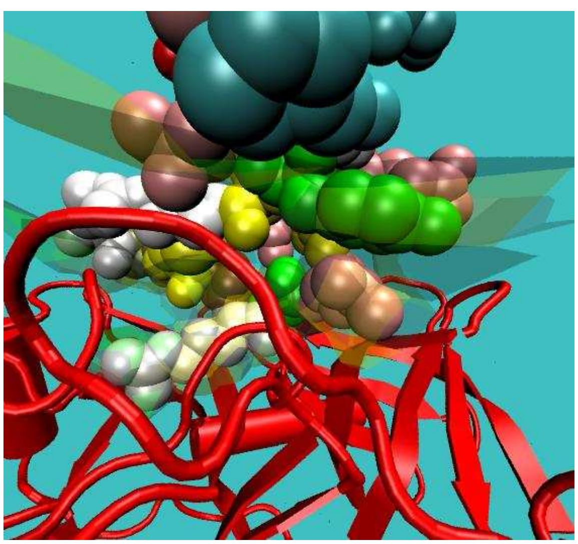
(a)IS: 1vfb (b)P: 1ppe (c)ST:1tx4

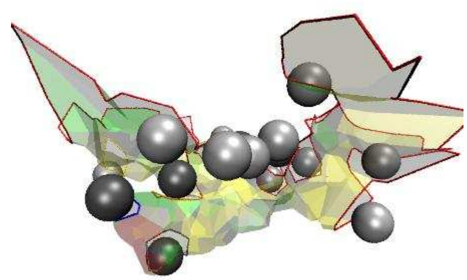
Planarity / Curvature





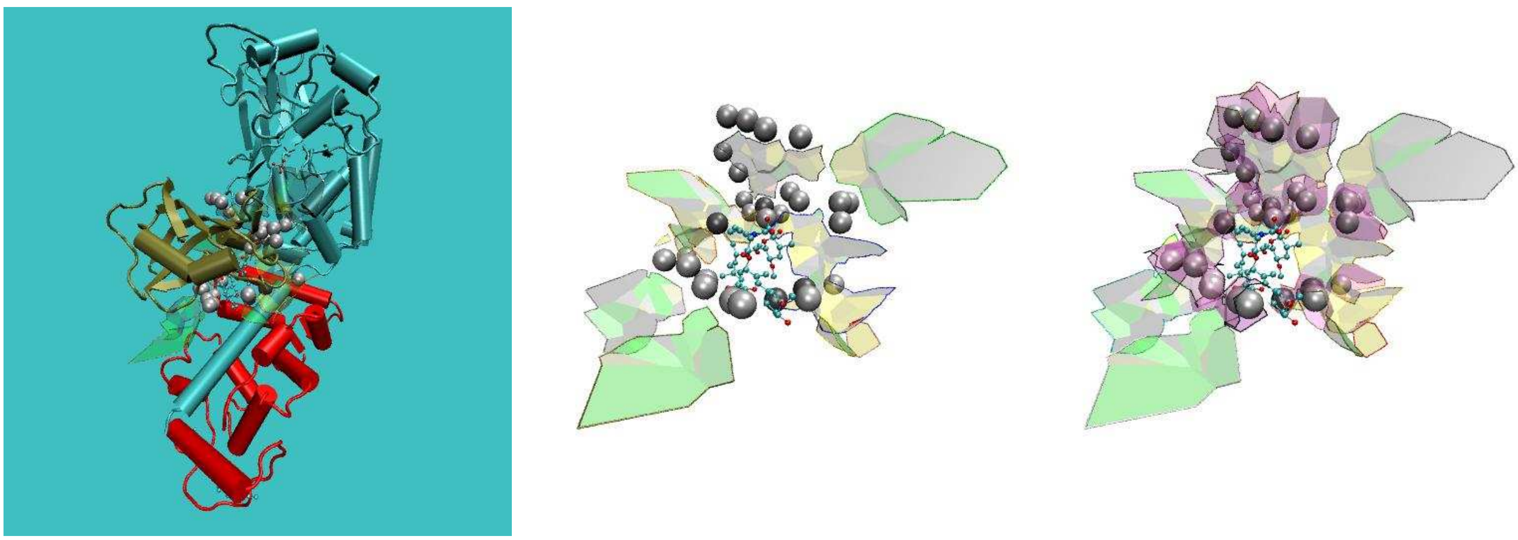
Complex 2trc (a)Chains: Transducin (Blue, Red), Phosducin (Grey) (b)Interface with a bend





Complex 1ppe (a)Chains: beta-trypsin (Red), Trypsin inhibitor (Colored by residue) (b)Interface with a deep pocket

Multi-patch structure



Complex 1tco (a)Chains: Calcineurin A (Cyan), Calcineurin B (Red), FKBP12 (Green), Immuno-suppressant drug FK506 (Van der Waals) (b,c)The AB interface has 5 significant cc, but water molecules bridge them into a single cc

Hilights without water (all complexes)

• 13% of interface atoms DO NOT LOOSE solvent accessibility. Mainly main chain atoms. Missed by previous studies.

• Protease-Inhibitor complexes have larger curvature than other families of complexes, a signature of their active site.

• In the AB model, the number of connected components varies in the range 1..6 with an average of 1.9 by complex.

Hilights with Water (res. $< 2\mathring{A}$)

• On average: nb. of interf. atoms increases of 45%
ratio of buried atom increases of 67%

• The relative numbers of scc in the AB and ABW models identifies the size and shape of packing defects

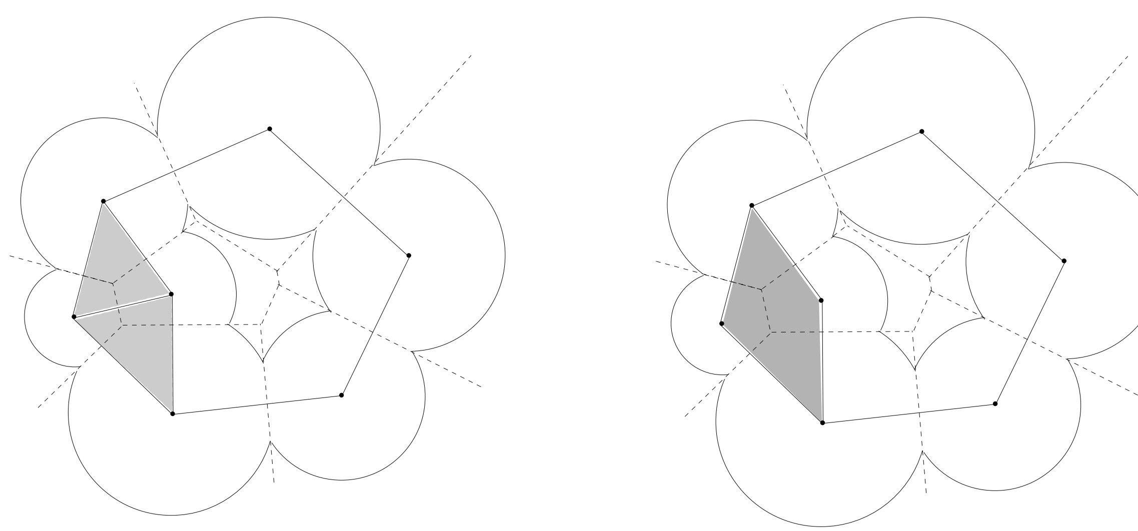
• In the Hydophobic / Polar model: distribution of interface pairs $\sim$ *random*

Weighted Delaunay / Voronoi
α-complex

▷ Ball restricted to Voronoi region $R_i = B_i \cap V_i$

▷ For a collection $R \subset \mathcal{R} = \{R_1, \ldots, R_n\}$ of restricted regions, define $\mathcal{K}$:

$$\Delta(R) \in \mathcal{K} \text{ iff } \bigcap_{R_i \in R} R_i \neq \emptyset.$$



(a)α-complex, $\alpha = 0$ (b)α-shape, $\alpha = 0$

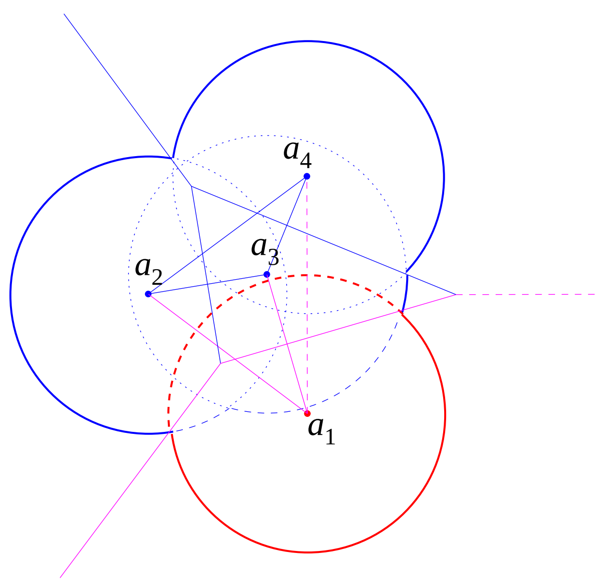
▷ α-complex: $\mathcal{K}(\alpha)$ for α-expanded balls

▷ Classification of simplices in the α-complex: singular, regular, interior

▷ Surfaces (VdW, SAS): directly from α-complex for $\alpha = 0$

▷ Performances using CGAL: 10^6 pts / minute (2GHz)

Balls and interface neighbors (I)



Intersecting balls. Del.edge, no interface edge: S_1 and S_4

Definition. 1

- *An AB interface edge is an edge of type AB in the α-complex of the balls $B_i(a_i, r_i + r_w)$, with $\alpha = 0$.*

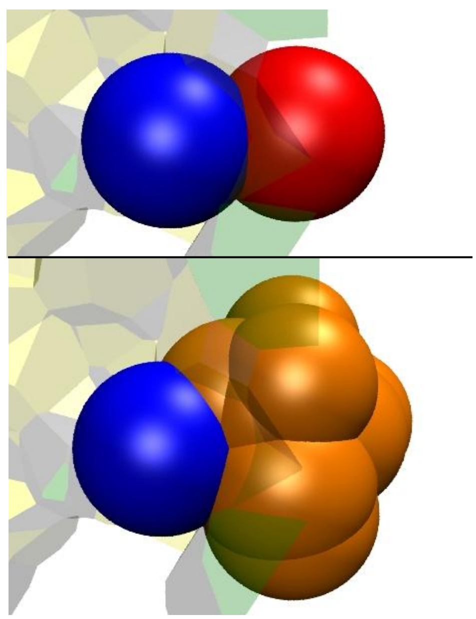
- *The interface neighbors of a sphere S_i: atomes connected through an interface edge.*

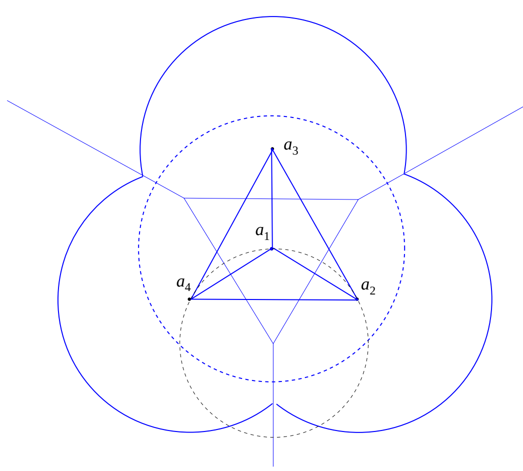
- *The AB interface: Voronoi facets dual of the AB interface edges.*

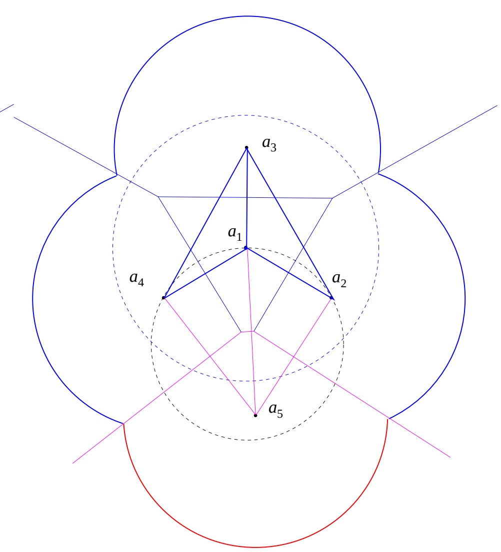
Interface neighborsand SAS

Observation. 1 *Any atom loosing accessibility is an interface atom.*

Converse is false (cf 13%):
interf. atoms may even be buried

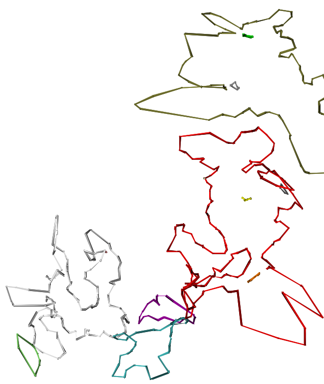




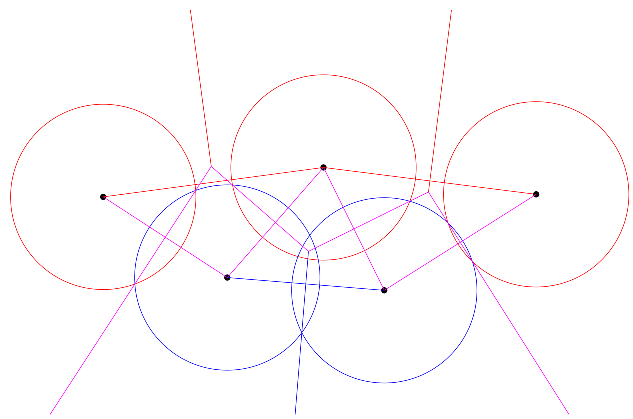


Topology of the interface

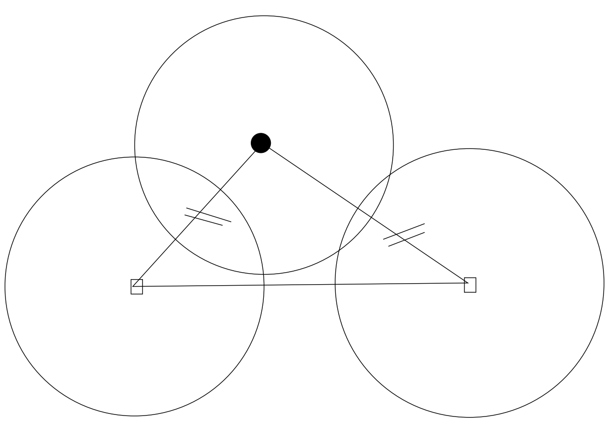
Interface connectivity

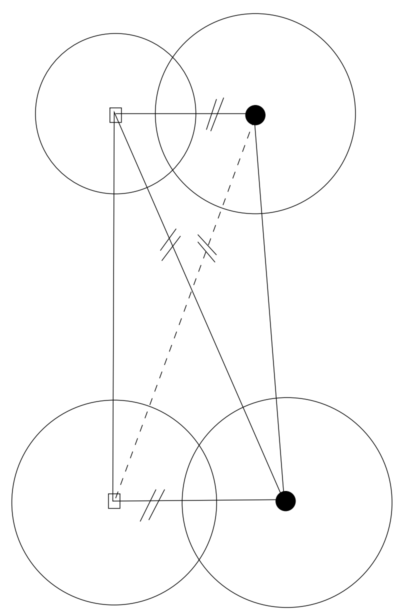


Three main connected ccs (1dan.pdb, AB model)



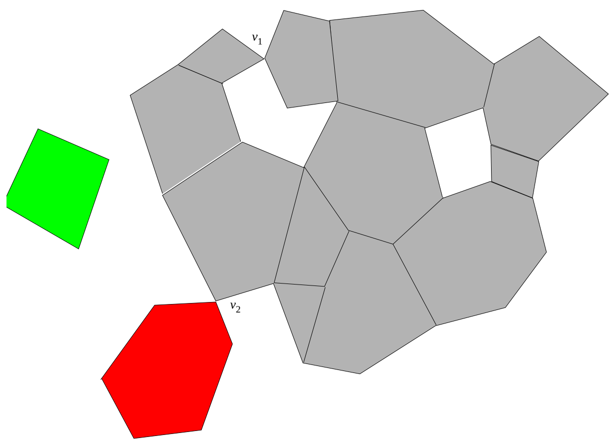
intuition: R B R B...





Topology of the interface (I)

Definition. 2 *Two Voronoi facets are called edge-connected if they share a Voronoi edge. An edge-connected component of the interface is a collection of edge-connected Voronoi facets.*



3 cc, 4 boundary loops

Observation. 2 *Topology of a bicolor interface:*

- *Vor. edges of a bicolor interface are manifold.*
- *The neighborhood of every Voronoi vertex is either a topological disk, a half-topological disk, or two half-topological disks pinched. together at the Voronoi vertex.*

Algorithms

▷ From the Delaunay triangulation:

- exploring a connected component
- reporting the boundaries

reduces to testing whether a given edge

- is bicolor
- is in the α-complex

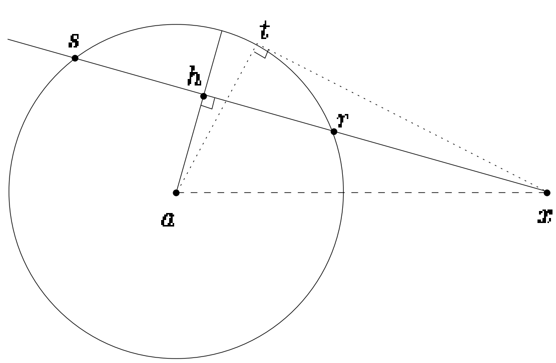
Interface facet $f_1 \Leftrightarrow$ Del. Edge e_1

Facet $f_2 \cap f_1 \neq \emptyset \Leftrightarrow f_2$ dual of e_2 with $e_1, e_1 \in$ Del. triangle

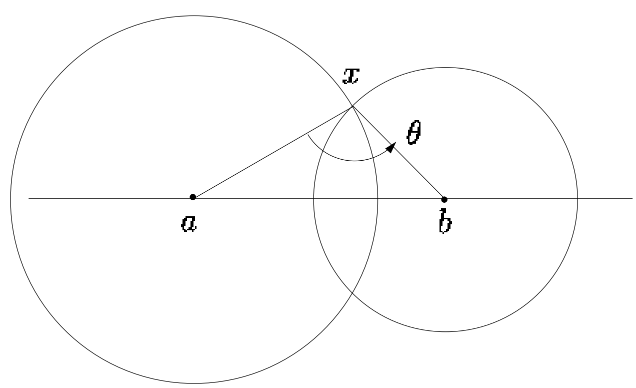
Weighted Delaunay / Voronoi (III)
Orthogonal spheres

- sphere: $S_i(a_i, w_i = r_i^2)$
- power of a point wrt sphere: $\pi(p, S_i) = a_i p^2 - w_i$
- power distance: $\pi(S_i, S_i) = a_i a_j^2 - w_i - w_j$
- orthogonal spheres: $\pi(S_i, S_j) = 0$
- Voronoi region

$$V_i = \{p \in \mathbb{R}^3 : \forall j \in \mathcal{S} \quad \pi(p, S_i) \leq \pi(p, S_j)\}.$$



Power of a point

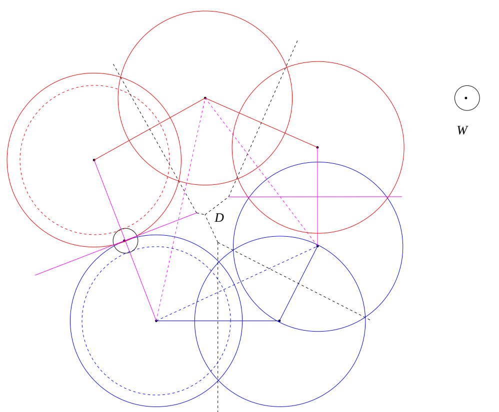


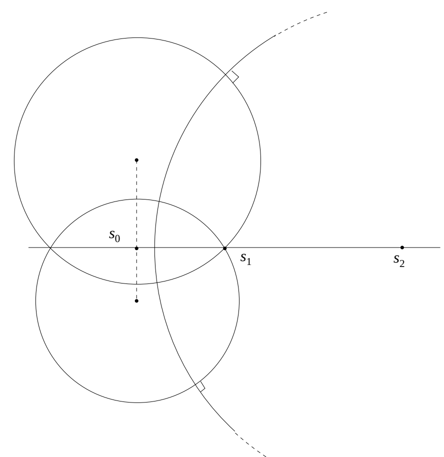
Angle between spheres

Geometry of the CCs:

Surface Area

▷ Surface Area





▷ Filtering criterion

$$\overline{\mu}/(min(w_i, w_j)) \geq M.\text{Practically: } M = 25.$$

▷ Filtering from the α-complex:

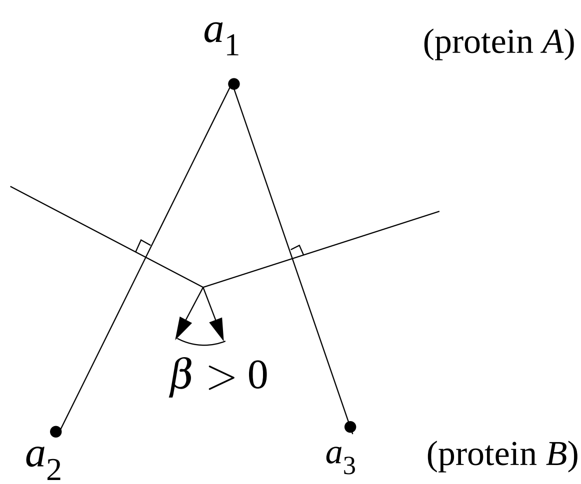
- largest ortho. sphere: $\overline{\mu}$ value (edge interior)

▷ Illustration —Geometry/Topology: 1ydr, 1tbq, 1cgi

Geometry of the CCs: Discrete Mean Curvature

▷ Local measure (Back to Steiner/Santalo/. . .)

$$h(e) = \beta(e) length(e)$$



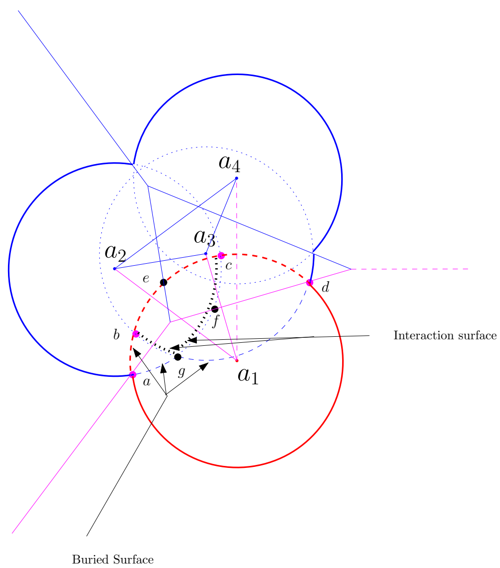
(a)Convex angle (b)Side view

▷ Global measure $s_H = \sum_{e \text{interior Voronoi edge}} | h(e) |$

▷ Rmk: dihedral angle $\sim$ triangle $\sim$ 3-1 d.o.f.

Interacting pairs vs interacting tuples

Buried | interaction surfaces



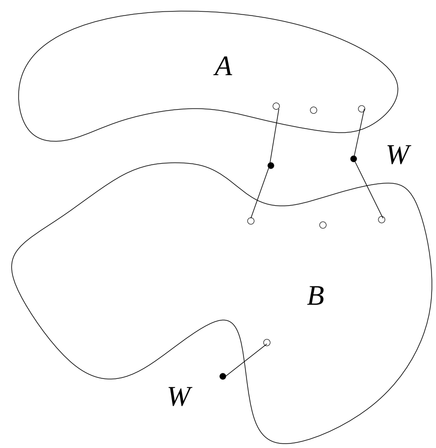
▷ Weighting the interface facets with coeffs. F_{ij}:

$$\sum_{(i,j)\in \text{IE}} F_{i,j}(BS) = \sum_{j=1}^{4} BSA(M_j, \mathcal{C}) = BSA$$

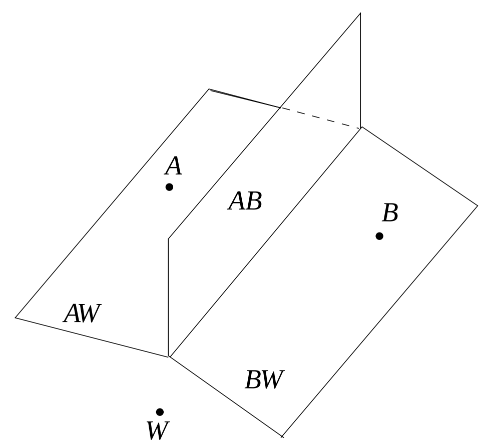
or

$$\sum_{(i,j)\in \text{IE}} F_{i,j}(IS) = \sum_{i=1}^{4} ISA(S_i, \mathcal{C}) = ISA$$

Tricolor interfaces



Top/bottom contacts: ok/ko



∂ ABW is not a one-manifold

Definition. 3 *An interface water: connected to A and B in the α-complex. An AW (or BW) interface edge is an edge of type of type AW (or BW), with W an interface water molecule.*

Definition. 4 *More interfaces:*
—$AW - BW$: facets dual of edges AW or BW
—ABW: union of AB and $AW - BW$ interfaces

Observation. 3 *Interfaces AB and $AW - BW$ have the same topology.*

▷ Algorithm:
—compute the AB and ABW interfaces independently
—merge the ccs and the ∂ by Union-Find

Key features

▷ coherence between interface / atoms loosing accessibility

▷ topology and geometry of interfaces

▷ interface weights and SASA

▷ accommodation of water molecules

▷ efficient $O(n \log n)$ algorithms

▷ possibility to encode finer properties (higher-order Voronoi)

▷ software / VMD plugin

References

- Revisiting the description of Protein-Protein interfaces. Part I: Algorithms, F. Cazals, F. Proust.

- Revisiting the description of Protein-Protein interfaces. Part II: Applications, F. Cazals, J. Janin, F. Proust.

- `http://bombyx.inria.fr/Intervor/intervor.html`

- `http://www-sop.inria.fr/geometrica/team/Frederic.Cazals/intervor`