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Comparative Visualization of Molecular Surfaces Using Deformable Models

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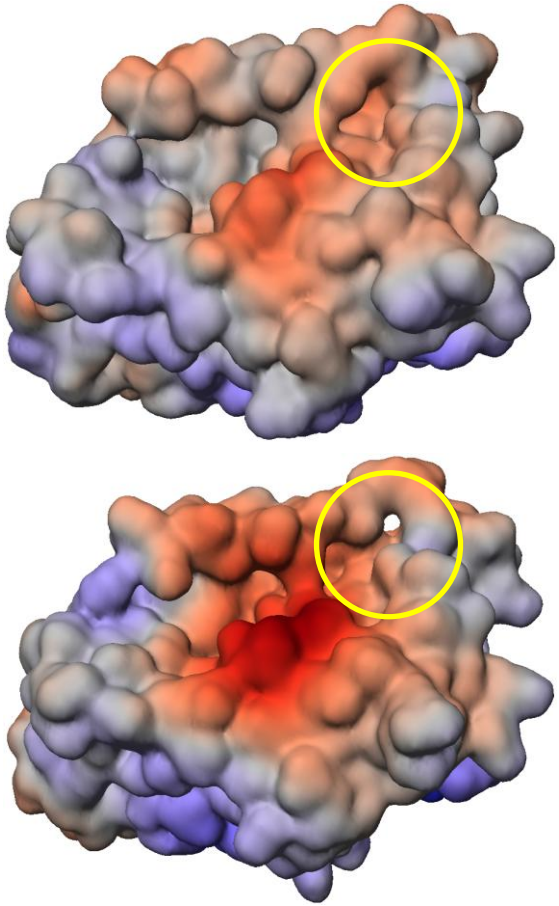
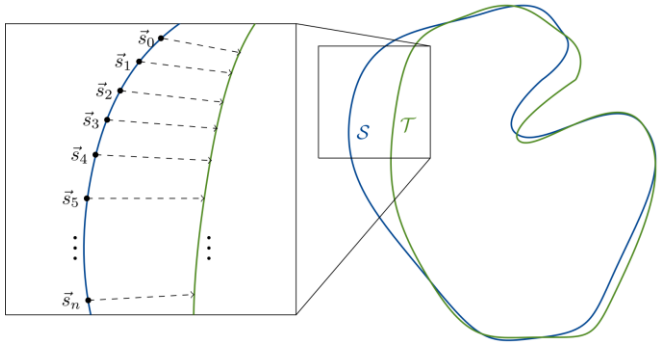
Motivation

- Simulations of same molecule under different conditions (solvent, mutations) → ensemble
  - Potentially changes functionality
  - Goal: direct comparison of surface attributes (electrostatics, hydrophilicity/hydrophobicity)
  - Requires point-to-point mapping
- Local and global comparison
- Challenges
  - Surfaces with high frequency details
  - Different genus (holes, tunnels)
  - Dynamic behavior (folding, bending)
  - Parts of the surfaces might not be comparable in a meaningful way



Defining a mapping relation

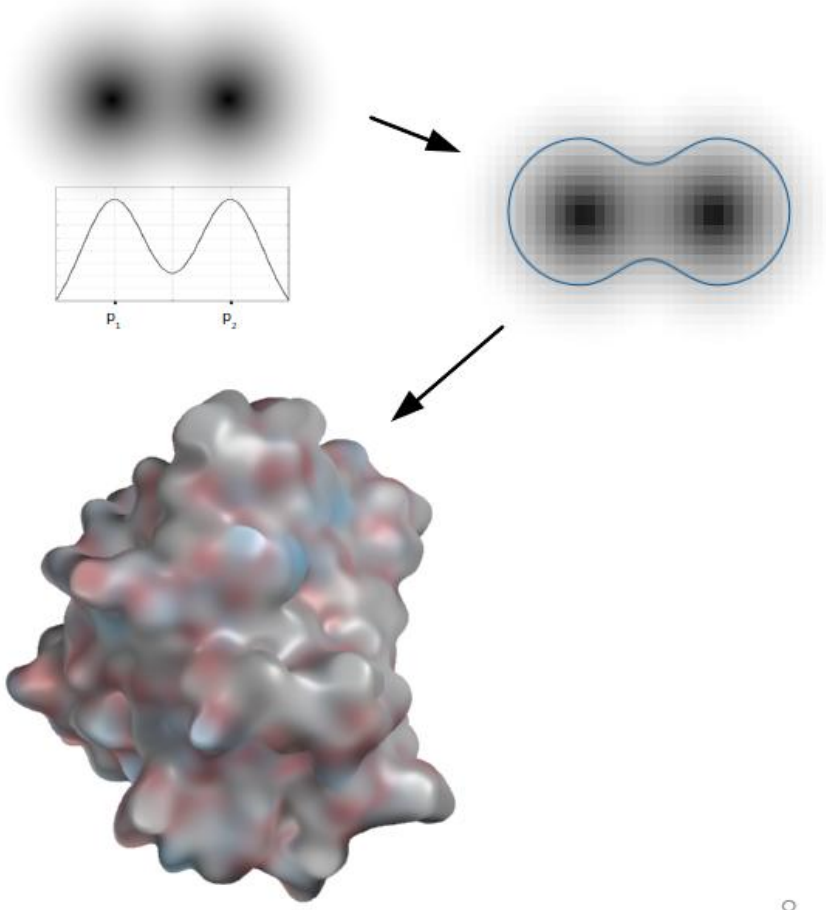
- Find mapping between points on surfaces S and T
  - Pairs of correlating vertex positions can be used to sample attributes of both molecular surfaces



- Algorithm
  - Represent S by a triangle mesh
  - Apply rigid alignment
  - Deform the triangle mesh of S until it fits T
  - Vertices on original mesh and deformed one define mapping

1. Initial surface triangulation
2. Rigid alignmment
3. Mapping deformation
4. Computation of heuristics

Surface representation



- *Metaballs*: Approximation for molecular surface (Blinn, 1982)
  - Each particle is associated with density distribution

$$\rho_i(x) = e^{\frac{-\|x-p_i\|}{2\alpha^2}}$$

  - Surface implicitly defined by level set
- We use Marching Tetrahedra to obtain a triangle mesh

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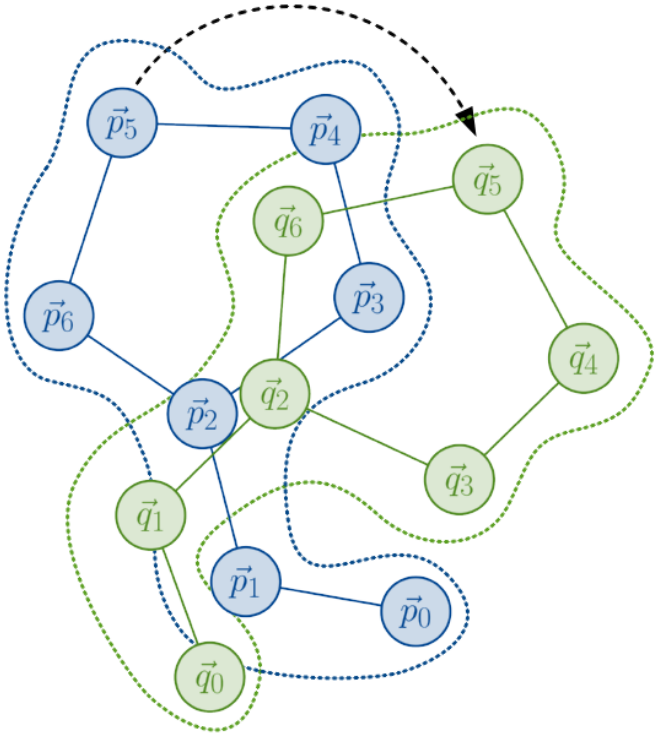
Rigid alignment

- Proteins have arbitrary orientations/positions
  - Rigid alignment necessary for meaningful mapping
  - Molecular surface is implicitly defined by particles
  - Standard technique in computational chemistry: RMSD (Root Mean Square Deviation)

$$RMSD(P,Q) = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\|p_i - q_i\|^2}$$

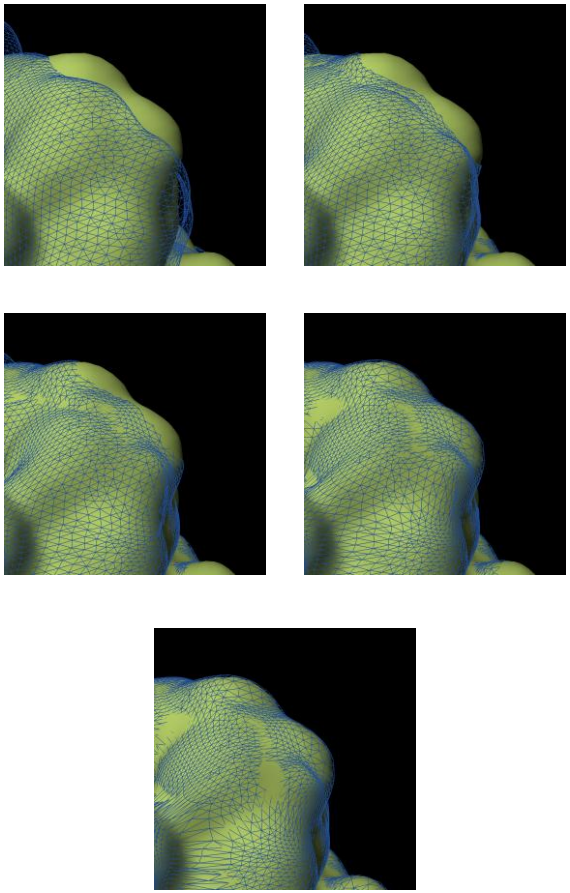
  - Find rotation/translation that minimizes RMSD (Kabsch, 1976)
- Molecular surface will be extracted from rotated/translated structure



Deformable models

- Originally for image segmentation and shape registration (Kass et al., 1988)
  - Shape is represented by an elastic model
  - Deformation is based on internal and external forces
- Internal forces F_{int}: maintain a smooth grid, prevent self-intersection
- External forces F_{ext}: pull the source shape towards the target shape
- Update position iteratively until net force is zero

$$s(t+1) = s(t) + (1-\mu)F_{int}(t) + \mu F_{ext}$$



Internal forces

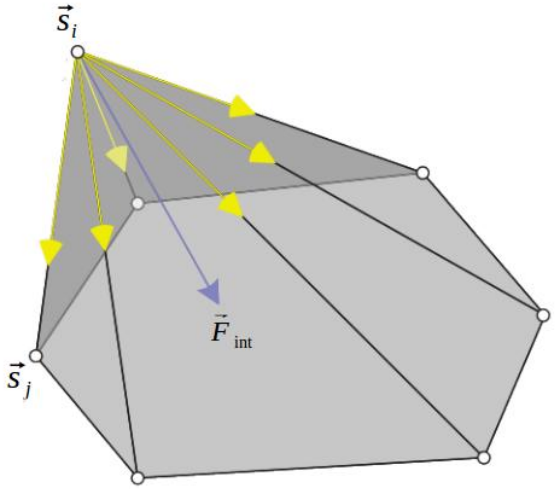
- Tension term: seeks to minimize surface area
- Rigidity term: emulates thin-plate behavior
- Approximation for the Laplacian in triangle meshes (Reuter, 2009): sum of all vectors from a point to its direct neighbors

$$F_{int} = \underbrace{(1-\rho)\Delta s}_{\text{tension}} - \underbrace{\rho\Delta^2 s}_{\text{rigidity}}$$

with

$$\Delta s = \frac{1}{n}\sum(s_i - s_j)$$

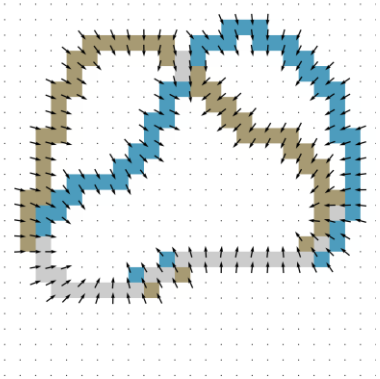
$$\Delta^2 s = \frac{1}{n}\sum(\Delta s_i - \Delta s_j)$$



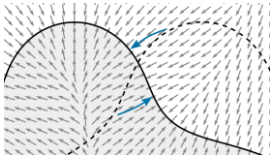
(Shen et al. 2011)

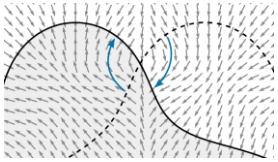
External forces

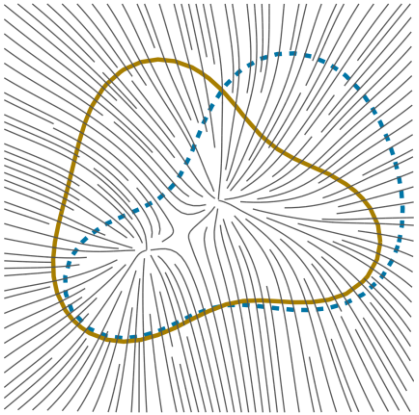
- Gradient Vector Flow (Xu 1998)
  - Initialize field at target borders
  - Essentially applies diffusion to individual vector field components
  - Smooth transition between target and source



- We use a modification:
  - Initialize field both at source and target surfaces
  - Symmetrical outcome
  - Takes surface orientation into account
  - Solve for all three vector components of v, respectively



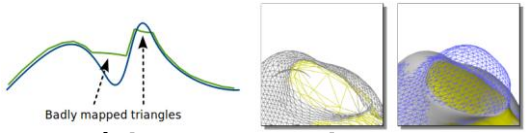




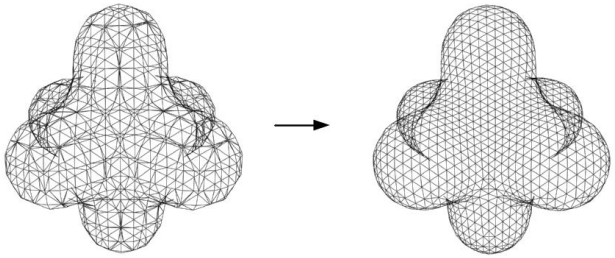
$$\underbrace{(1 - \|F_{ext}\|)\Delta v}_{\text{Diffusion}} - \underbrace{\|F_{ext}\|(v - F_{ext})}_{\text{Borders}} = 0$$

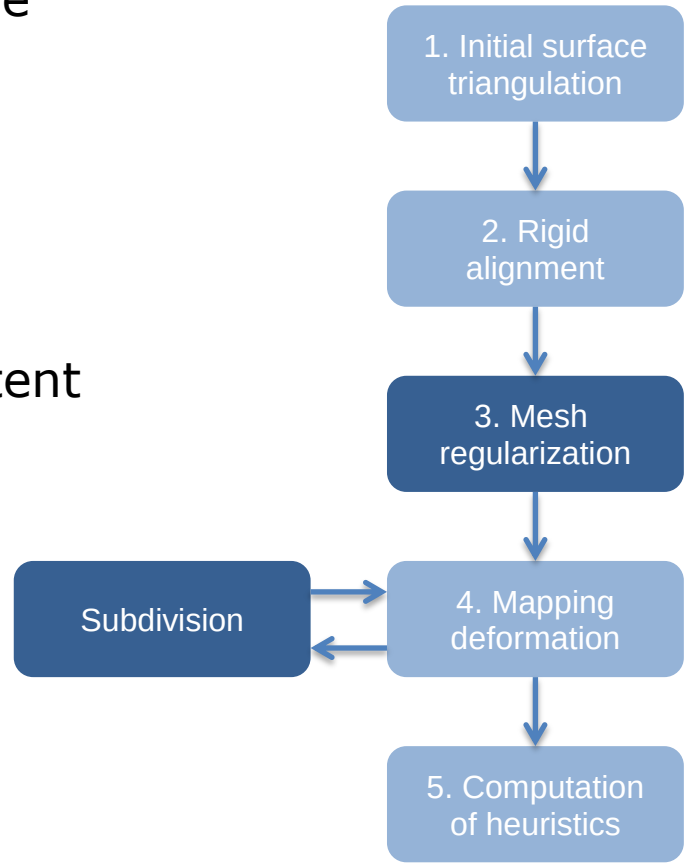
Mesh quality

- Problem: limited resolution leads to artifacts when mapping surface parts of different size



  - How to achieve consistent sampling
  - Start with mostly regular vertex distribution
- Additional subdivision step for more consistent sampling
- Prior mesh regularization



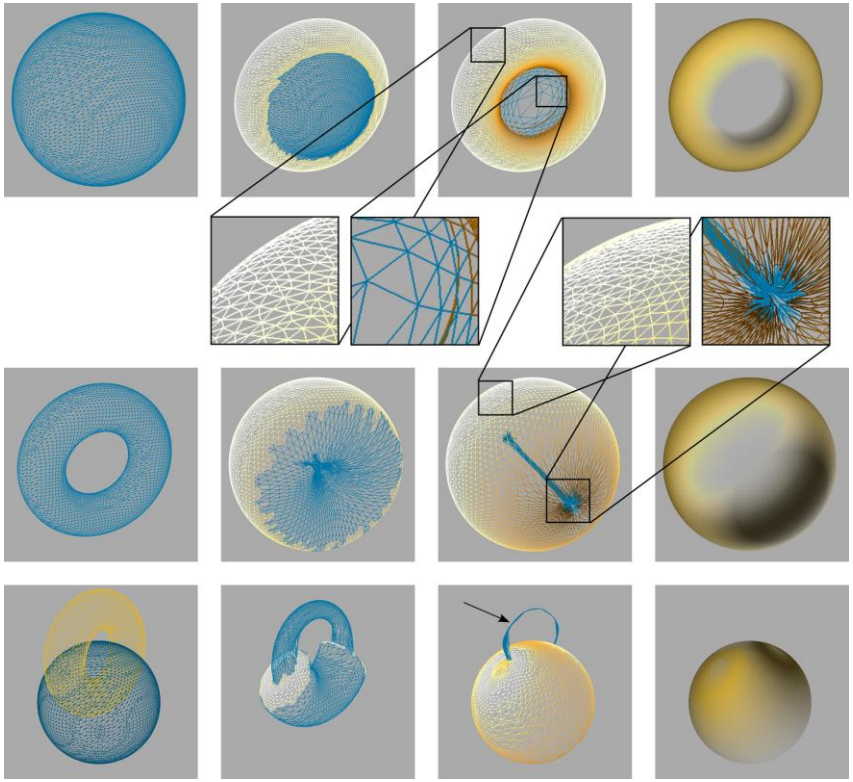


Measuring differences

- Absolute difference of the surface potential
- Sign difference
- Geometry: path length for the vertices
  - Surfaces are less comparable if strong deformation is necessary for mapping
    - Local deformation can be seen as criterion for uncertainty
    - Quantified e.g. by vertex path length
- For global value: integrate over mapped target surface area
  - Local → 3D Rendering
  - Global: Integrate value over target surface area 2D plot for an overview

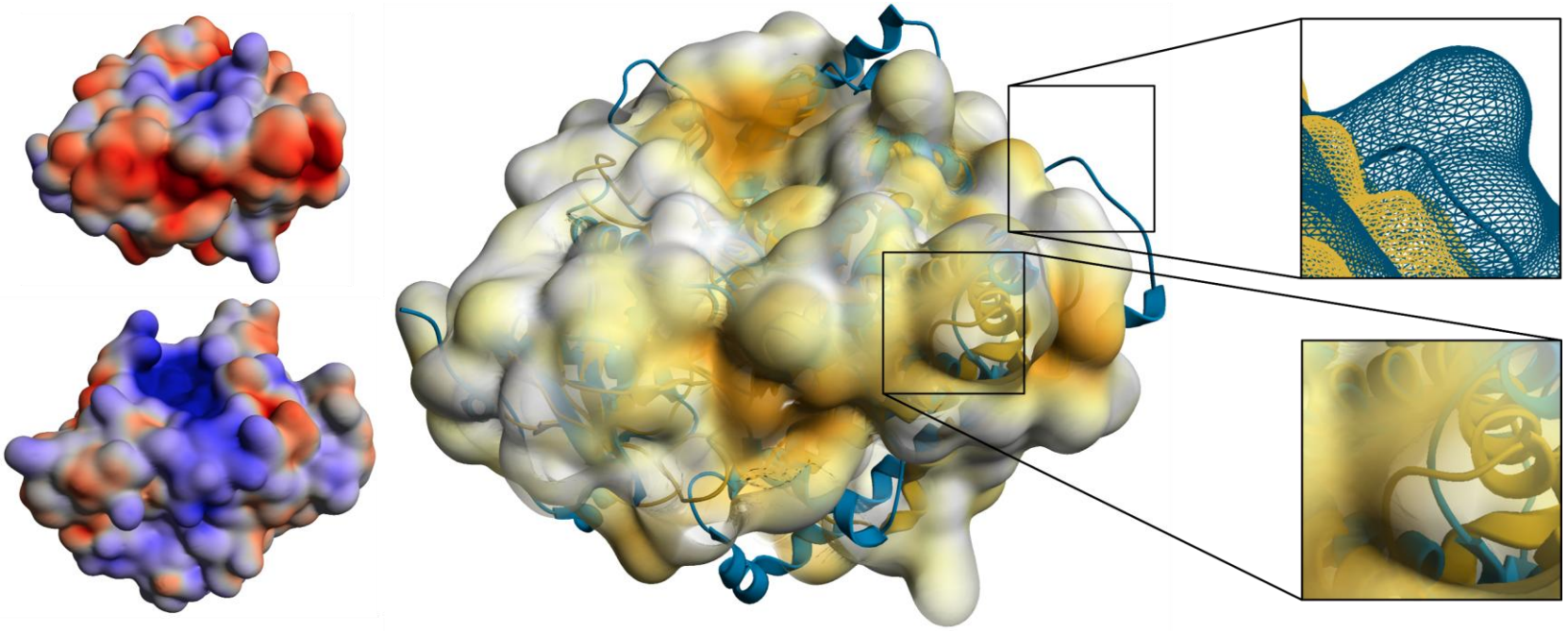
Results: local dissimilarity

- Method applied to synthetic data sets
- Non-mappable parts can be identified
- → Rendered transparently in our visualization



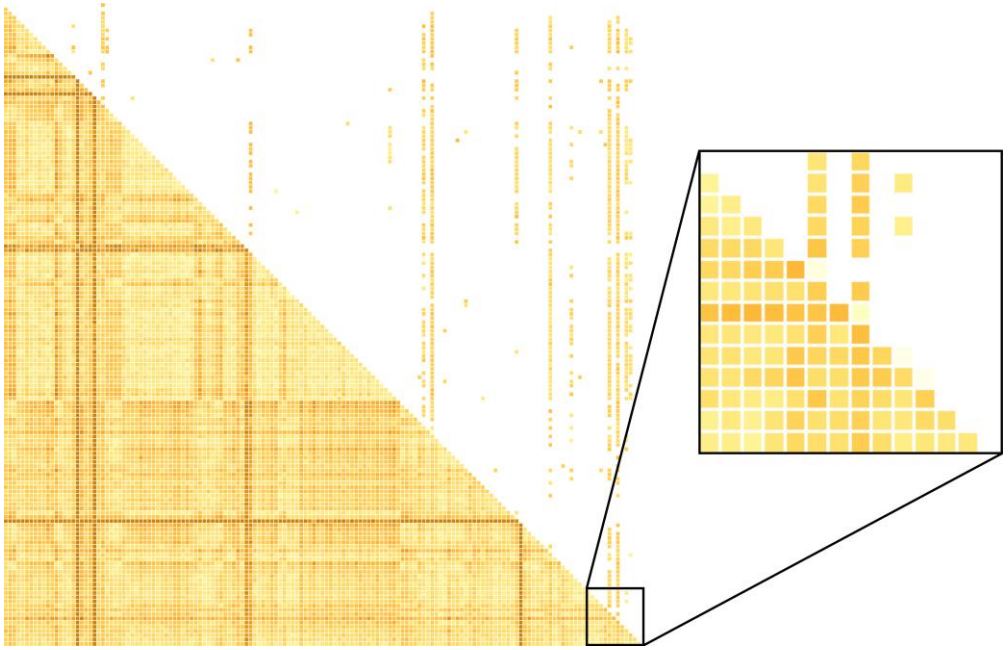
Results: local dissimilarity

- Comparative rendering of two molecular surfaces
  - Difference value of electrostatic potential is color coded
  - Different surface geometry is indicated by increased transparency



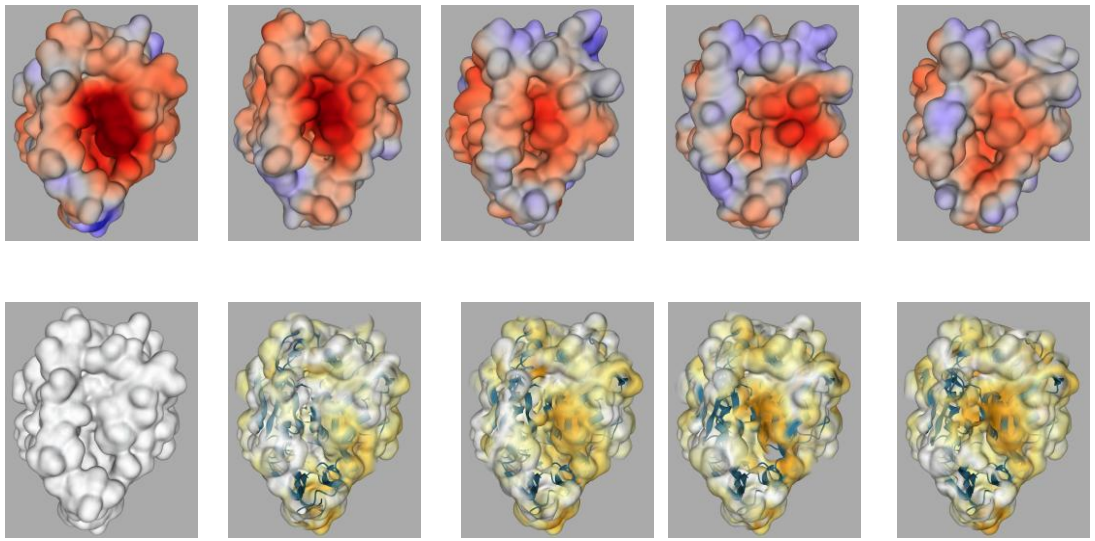
Results: global dissimilarity

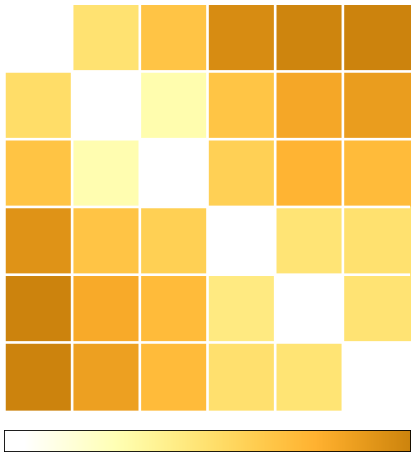
- Application to ensemble with 152 proteins in varying solvent
  - Difference in surface potential
- Global heuristics are overall symmetric
- Some cases of asymmetry in the geometrical comparison
  - Deformation process does not converge in some cases
  - leads to very long vertex paths



Application

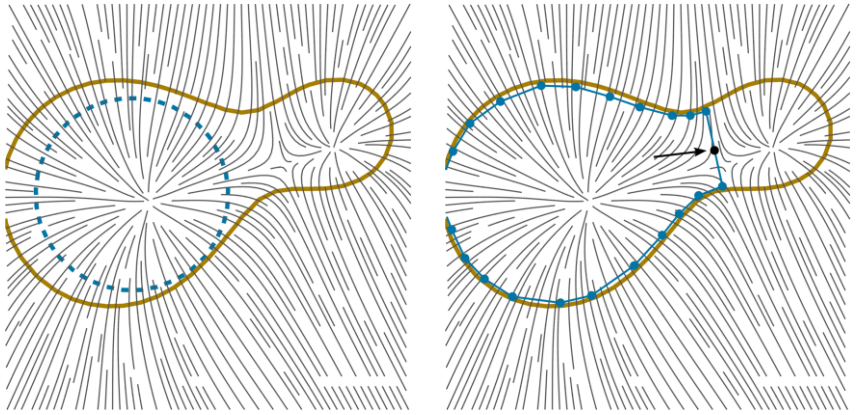
- Application to small ensemble of proteins (subset of the ones before)
- Joint work with domain scientists
- Subset with increasing MeOH activity → correlation to electrostatics





Limitations

- Limitations
  - Not meaningful for very different global geometry
  - Questionable to what point an additional global deformation step would make sense (since it could change the SAS)
  - Cannot guarantee handling of very complicated genus differences
  - Saddles in velocity field



Conclusion & future work

- Comparative visualization of molecular surface attributes
  - Partial shape matching of molecular surfaces by using deformable models
  - Rigid and non-rigid alignment
  - Local and global comparison
- Future work
  - Apply to docking/binding problems
  - Combine more than one conformer in ne visual representation
  - Use method to identify functional regions on protein surfaces

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