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 alignment
3. Mapping deformation
4. Computation of heuristics
Surface representation

- **Metaballs**: Approximation for molecular surface (Blinn, 1982)
  - Each particle is associated with density distribution
    \[
    \rho_i(x) = e^{-\frac{\|x-p_i\|^2}{2\alpha^2}}
    \]
  - Surface implicitly defined by level set
- We use Marching Tetrahedra to obtain a triangle mesh
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

$$F_{int} = (1 - \rho) \Delta s - \rho \Delta^2 s$$

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 \( \mathbf{v} \), respectively

\[
(1 - \|F_{\text{ext}}\|) \Delta \mathbf{v} - \|F_{\text{ext}}\| (\mathbf{v} - F_{\text{ext}}) = 0
\]
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

1. Initial surface triangulation
2. Rigid alignment
3. Mesh regularization
4. Subdivision
5. Mappign deformation
6. Computation of heuristics
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 $\rightarrow$ 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 $\rightarrow$ correlation to electrostatics
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 new visual representation
  - Use method to identify functional regions on protein surfaces
References


