Modeling Proteins Using the SE(3) Group and Analyzing Cell Motion

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Part I

Modeling Proteins Using the SE(3) Group
Conformation Switching Behavior

Starting Point: Work by Igor Mezić

- Backbone with charges on rigid rods
- Global Morse potential produced by second backbone
- Torsion linkage between rods via backbone
- Perturbation can cause conformation switch
Conformation Switching Behavior

Modifications to Model

- Add torsion and freedom of motion in second angular direction
- Conformation switching behavior is retained
Modeling Proteins Using the SE(3) Group

Conformation Switching Simulations
Helical Structures and SE(3)
Charges on Elastic Rods

Time Evolution into Helices

Modifications to Model

- Add inter-particle interactions (Coulomb potential)
- Add opposing positive/negative charges
- Add friction dissipation
- Generates Helix-like structures; helicity is not constant
Let $g(t) \in SE(3)$ be given by

$$g(t) = \begin{bmatrix} \Lambda(t) & r(t) \\ 0 & 1 \end{bmatrix}, \quad \Lambda(t) \in SO(3), \quad r(t) \in \mathbb{R}^3$$

Then

$$g^{-1}(t) = \begin{bmatrix} \Lambda^{-1}(t) & -\Lambda^{-1}(t)r(t) \\ 0 & 1 \end{bmatrix}, \quad \dot{g}(t) = \begin{bmatrix} \dot{\Lambda}(t) & \dot{r}(t) \\ 0 & 0 \end{bmatrix}$$

$$g^{-1}(t)\dot{g}(t) = \begin{bmatrix} \Lambda^{-1}(t)\dot{\Lambda}(t) & \Lambda^{-1}(t)\dot{r}(t) \\ 0 & 0 \end{bmatrix} =: \begin{bmatrix} \hat{\Omega}(t) & \hat{\Gamma}(t) \\ 0 & 0 \end{bmatrix}$$
Now we demand $\hat{\Omega}$ and $\Gamma$ are $t$-invariant.

Choose coordinates so the angular velocity $\Omega$ points along the $z$ axis:

$$\hat{\Omega} = \begin{bmatrix} 0 & -\omega & 0 \\ \omega & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

Then:

$$\Lambda(t) = \begin{bmatrix} \cos(\omega t) & -\sin(\omega t) & 0 \\ \sin(\omega t) & \cos(\omega t) & 0 \\ 0 & 0 & 1 \end{bmatrix}$$
Finally, $\Lambda^{-1}(t)\dot{r}(t) = \text{constant}$ and choosing orientation of $x, y$ axes gives

$$r(t) = \begin{bmatrix} \frac{R}{\omega} \sin(\omega t) \\ \frac{R}{\omega} (\cos(\omega t) - 1) \\ Vt \end{bmatrix} + r(0)$$

So given any fixed $\left(\hat{\Omega}, \Gamma\right) \in TSE(3)$, the set

$$\{ u \in \mathbb{R}^3 \mid u = r(t), t \in \mathbb{R} \}$$

is a helix, and the corresponding $(\Lambda(t), r(t)) \in SE(3)$ gives the body frame transformations of the points of the helix.
Helices as solutions to charges on an elastic rod

**Continuous case**
- Continuous charge distribution along infinite elastic rod
- Stationary solution is helix due to invariance argument
- Two solutions may exist, different helicity

**Discrete case**
- Molecular model: few charges per helix period
- Similar argument, but invariance under discrete transformations
Search for stationary solutions in discrete case

Question

Given a charge bouquet configuration, elastic properties of the rod, and how far apart the bouquets are attached, what are the stationary solutions for the rod conformation?
Search for stationary solutions in discrete case

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**Solution**

- Find force/torques corresponding to a given helix
Search for stationary solutions in discrete case

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**Solution**
- Find force/torques corresponding to a given helix
- Find helix corresponding to a given periodic force/torque
Search for stationary solutions in discrete case

**Question**

Given a charge bouquet configuration, elastic properties of the rod, and how far apart the bouquets are attached, what are the stationary solutions for the rod conformation?

**Solution**

- Find force/torques corresponding to a given helix
- Find helix corresponding to a given periodic force/torque
- Find solutions where correspondences match
Derivation of force and torque

Orient coordinates so reference bouquet \((n = 0)\) has transformation

\[
g_0 = \begin{bmatrix} l & r_0 \\ 0 & 1 \end{bmatrix}
\]

Bouquet \(n\) as seen in body frame of bouquet 0:

\[
h_n = g_0^{-1} g_n = \begin{bmatrix} l & -r_0 \\ 0 & 1 \end{bmatrix} \begin{bmatrix} \Lambda_n & r_n \\ 0 & 1 \end{bmatrix} = \begin{bmatrix} \Lambda_n & r_n - r_0 \\ 0 & 1 \end{bmatrix}
\]

Vector from charge \(q_k\) at point \(x_k\) in reference bouquet to charge \(q_j\) at point \(x_j\) in the bouquet at the \(n^{th}\) position along the helix:

\[
v_{njk} = h_n x_j - x_k = \Lambda_n x_j - x_k + r_n - r_0
\]
Derivation of force and torque

- Assume a central potential \( u(|v_{njk}|) \)
- Force is \( F_{njk} = -\nabla u(|v_{njk}|) \)
- Force acts along vector between particles
- We can write force as \( F_{njk} = G_{njk}v_{njk} \), \( G_{njk} \) a scalar function

Linear force given by

\[
F^\parallel_{njk} = (F_{njk} \cdot \hat{x}_k) \hat{x}_k \quad \text{where} \quad \hat{x}_k = \frac{x_k}{|x_k|}
\]

Torque given by

\[
\tau_{njk} = x_k \times F_{njk}
\]
Total force and torque acting on the helix at the reference position due to inter-particle potential is:

\[ \mathbf{F}_{\text{charge}} = \sum_{n=-\infty}^{\infty} \sum_{n \neq 0}^{J} G_{njk} (\mathbf{v}_{njk} \cdot \mathbf{\hat{x}}_k) \mathbf{\hat{x}}_k \]

\[ \mathbf{\tau}_{\text{charge}} = \sum_{n=-\infty}^{\infty} \sum_{n \neq 0}^{J} G_{njk} (\mathbf{x}_k \times \mathbf{v}_{njk}) \]
Considering the previous expressions under exchange of indices and reflection about the origin, we obtain two symmetries:

\[ \mathbf{v}_{njk} = -\Lambda_n \mathbf{v}_{-nkj} \]

\[ G_{njk} = G_{-nkj} \]
Given a particular periodic force and torque, we can derive the helix that corresponds to it.

- Use constant tensors to represent material elastic properties.
- Compute deformation of elastic rod due to point force/torques.

Result is a correspondence between helix parameters $\omega$, $V$, $R$ and the force/torque expressions from prior work.
This is where I am working right now, and what the next steps are:

Next steps:

- Six equations in three unknowns - solve (numerically?)
- Given tensors, find helix corresponding to torque/force
- Use optimization routine to find stationary solutions
- Look for multiple solutions with different helicities
Future Work

More realistic molecular models

- Repeating patterns of charge bouquets
- Solutions with multiple periods
- Bouquets of bouquets
- Helix of helix
Part II

Analyzing Cell Motion
Description of the Problem

Experimental Data

Hypothesis
- Cell motion is inversely related to local GABA concentration.

Goals of Analysis
- Extract cell velocities
- Infer local GABA concentration
- Deduce global GABA concentration
- Estimate reliability
Deriving Global Concentration from Local Measurements

**Discrete Source Model**
- Model GABA at boundary as set of discrete point sources
- Number of sources must be smaller than number of samples

- Point sources distributed on boundary $\partial\Omega$.
- Concentration in $\Omega$ is
  \[ G(r) = \sum_k a_k K_1\left(\frac{|r-r_k|}{\lambda}\right) \]
- $K_1(x)$ is the modified Bessel function
We derive a system of the form

\[ \mathbf{v} = A\mathbf{s} \]

where \( \mathbf{v} \) are the velocities at the sample points, \( \mathbf{s} \) are the source amplitudes, and \( A \) is a matrix containing the distances from each sample to each source point, scaled by the Bessel function \( K_1 \).

Matrix \( A \) is not square, so we find a least-squares solution. In MATLAB, this is done with

\[ \mathbf{s} = A\backslash\mathbf{v} \]
Analyzing Cell Motion

Description of the Problem
Inverse Problem
Regularization
Extracting gradient information from data
Random walk analysis

Ill-Conditioned System and Regularization

Problem with this approach
- A is frequently nearly singular
- Small variation in data \( \Rightarrow \) large variation in solution

To address this, we employ Tikhonov regularization:
- Begin with estimate \( \bar{s} \) of \( s \)
- Create error function \( P^\lambda(s, v) = \|As - v\|^2 + \lambda\|s - \bar{s}\|^2 \)
- Find \( s \) that minimizes \( P^\lambda(s, v) \)
- Result is \( s = (A^T A + \lambda I)^{-1} (A^T v - \lambda \bar{s}) \)
- Choice of \( \lambda \) is largely empirical
Recovering source amplitudes using regularized system:
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![Graph showing 50 sources, 200 samples, 25% noise]
Recovering source amplitudes using regularized system:
Using experimental data

- Deltas between observed cell points give velocities
- Recover source strengths
- Use source strengths to project concentrations in domain
Extracting Data Directly from Movies

Data Extraction

- Extracting frames from movie

Example
Analyzing Cell Motion

Extracting Data Directly from Movies

Data Extraction
- Extracting frames from movie
- Frame Smoothing

Example
Extracting Data Directly from Movies

**Data Extraction**
- Extracting frames from movie
- Frame Smoothing
- Identification of Cells

**Example**

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Data Extraction
- Extracting frames from movie
- Frame Smoothing
- Identification of Cells
- Motion Extraction

Example
Extracting Data Directly from Movies

Data Extraction
- Extracting frames from movie
- Frame Smoothing
- Identification of Cells
- Motion Extraction
- Trajectory Extraction

Example
Hypothesis

- Hard to get consistent velocity data from trajectories
- Trajectories resemble random walks
- Hypothesis: Random walks + “drift”
Random-Walk Analysis and Results

![Cell motion graph](image)

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Future Work

- Include more empirical data in analysis
- Extract drifts as averages over trajectories
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