A Homotopy Method for Predicting the State of Minimal Energy for Chains of Charged Particles

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Introduction

- **Protein Folding**
  - Sequence of amino acids $\rightarrow$ three-dimensional structure
  - Minimum potential energy assumed for native structure

- **Difficult Goal**
  - Find structure with minimum potential energy
  - Computationally intractable for large proteins
Formulation of the Problem

Chain of $m$ charged particles with charges $q_i$ (2D space)

$$\begin{align*}
E(\phi) &= \sum_{i=1}^{m-2} \sum_{j=i+2}^{m} \left[ \frac{q_i q_j}{R_{ij}(\phi)} + \varepsilon_{ij} \left( \left( \frac{\sigma_{ij}}{R_{ij}(\phi)} \right)^{12} - 2 \left( \frac{\sigma_{ij}}{R_{ij}(\phi)} \right)^{6} \right) \right] \\
\text{min} & \quad E(\phi) \\
\text{s.t.} & \quad 0 \leq \phi_i \leq 2\pi, \ (i = 1, \ldots, m-2)
\end{align*}$$
Solving the Optimization Problem

- **Difficulty**
  - Many local minima
  - Number of minima increases exponentially

- **Classic Approach**
  - Gradient methods (e.g., steepest descent)
  - Good starting approximation needed
  - Converges to *local minimizer*

- **New Approach**
  - Homotopy method
  - Good starting approximation **not** needed
  - Improve likelihood of finding *global minimizer*
Potential Energy Homotopy

Goal:

\[ q^0 = [q_1^0, \ldots, q_m^0] \implies E^0(\phi) \]
\[ q^* = [q_1^*, \ldots, q_m^*] \implies E^*(\phi) \]

\[
\begin{aligned}
\min E^*(\phi) & \quad \text{s.t.} \quad 0 \leq \phi \leq 2\pi \\
& \quad \text{find} \quad \phi^* \\
& \quad \text{s.t.} \quad \nabla E^*(\phi^*) = 0 \\
& \quad \nabla^2 E^*(\phi^*) > 0 \\
& \quad 0 \leq \phi^* \leq 2\pi
\end{aligned}
\]

Homotopy:

\[
H(\phi, \lambda) = \nabla \left( \sum_{i=1}^{m-2} \sum_{j=i+2}^{m} \frac{q_i(\lambda)q_j(\lambda)}{R_{ij}} + \varepsilon_{ij} \left( \left( \frac{\sigma_{ij}}{R_{ij}} \right)^{12} - 2 \left( \frac{\sigma_{ij}}{R_{ij}} \right)^6 \right) \right)
\]

\[
= \begin{cases} 
\nabla E^0(\phi), & \lambda = 0 \\
\nabla E^*(\phi), & \lambda = 1 
\end{cases}
\]
General Homotopy Method

**Goal:** Solve complicated nonlinear system which may have multiple solutions

\[ f(x) = 0, \quad (f : \mathbb{R}^n \rightarrow \mathbb{R}^n). \]

**Steps to Solution:**

**Easy system:** \( e(x^0) = 0 \quad (x^0 \text{ known}) \)

**Homotopy:**

\[
\begin{align*}
  h(x, \lambda) &= \begin{cases} 
  e(x), & \lambda = 0 \\
  f(x), & \lambda = 1 
  \end{cases} \\
  \text{e.g.,} \quad h(x, \lambda) &= \lambda f(x) + (1 - \lambda) e(x)
\end{align*}
\]

**Trace Path:** Follow \( h(x, \lambda) = 0 \) from \( \lambda = 0 \) to \( \lambda = 1 \)
Tracing $H(\phi, \lambda) = 0$

**Predictor–Corrector Algorithm:**

$\phi^0 =$ global minimizer of $E^0(\phi)$

$\lambda_0 = 0$

$k = 0$

repeat until $\lambda_k = 1$

$k = k + 1$

$\lambda_k = \lambda_{k-1} + (\Delta \lambda)_k$

$\phi^k \leftarrow \begin{cases} \text{using } \phi^{k-1} \text{ as initial guess} \\ \text{solve } H(\phi, \lambda_k) = 0 \end{cases}$

end

$\phi^* = \phi^k \quad [H(\phi^k, 1) = \nabla E^*(\phi^k) \approx 0]$
Pairwise Energy for Charged Particles

(Carbon-like in atomic/van der Waal radius, monovalent in charge)

Energy in kcal/mol ($E$) vs Distance in Angstroms ($R_{ij}$)

- Blue line: Charges with same sign
- Red line: Charges with opposite sign

Spotlight on Graduate Research
Example 1 – Negligible Difference

\[ m = 20 \]

\[ q \in \{-1, +1\} \]

\[ E^0(\phi) = -22.9708 \]

6 changes in \( q \)

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Gradient Method

\[ E^*(\phi) = -22.4510 \]

Homotopy Method

\[ E^*(\phi) = -22.4511 \]
Example 2 – No Difference

\[ m = 20 \]
\[ q \in \{-1, +1\} \]
\[ E^0(\phi) = -22.9708 \]
\[ 10 \text{ changes in } q \]

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Gradient Method

\[ E^*(\phi) = -20.0044 \]

Homotopy Method

\[ E^*(\phi) = -20.0044 \]
Example 3 - Qualitative Difference

\[ m = 20 \]
\[ q \in \{-1, +1\} \]
\[ E^0(\phi) = -22.9708 \]
16 changes in \( q \)

Gradient Method

\[ E^*(\phi) = -18.8808 \]

Homotopy Method

\[ E^*(\phi) = -19.4268 \]
Conclusions

- **Homotopy Method**
  - Rivals gradient methods (GM) in accuracy
  - Outperforms GM when many charges change
  - More function evaluations than GM
Future Work

- **Simple Model**
  - Larger examples \((m > 100)\)
    - different evaluation methods
  - Simple model in 3D
    - Existing data for validation
  - Path existence proof

- **Proteins**
  - Predict tertiary structure of proteins
  - Utilize existing data/software
    - Protein Data Bank (solutions to \(E^0\))
    - AMBER (energy computation)
    - HOMPACK (homotopy)