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

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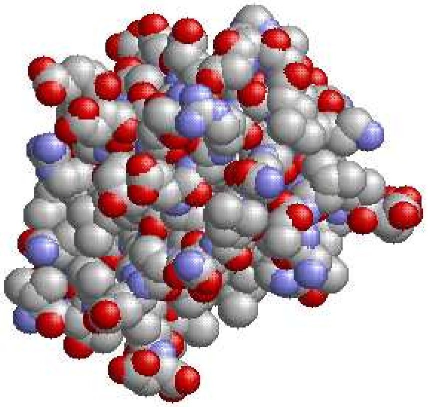
# Introduction

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

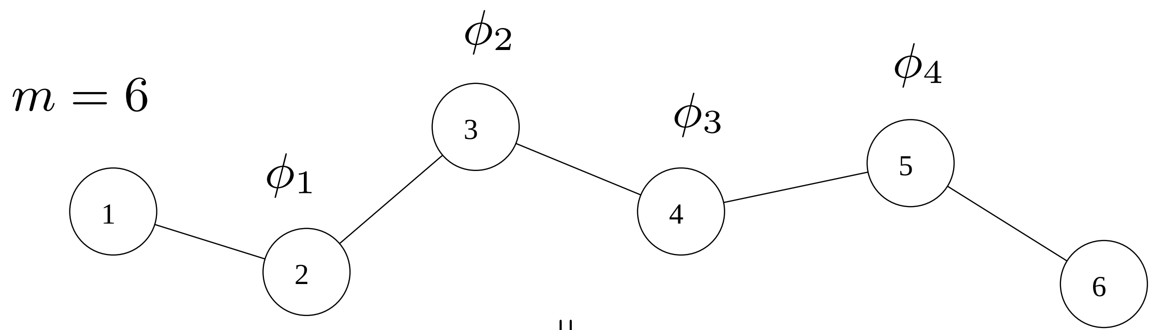

$\Longrightarrow$



- **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)




$\Downarrow$

van der Waals Potential

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

$\Downarrow$

Optimization Problem

$$\begin{aligned} &\min \quad E(\phi) \\ &\text{s.t.} \;\; 0 \le \phi_i \le 2\pi, \quad (i = 1, \ldots, m-2) \end{aligned}$$

# 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:**

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

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

$$\begin{array}{l} \min \; E^*(\phi) \\ \text{s.t. } \; 0 \leq \phi \leq 2\pi \end{array} \iff \left\{ \begin{array}{ll} \text{find} & \phi^* \\ \text{s.t.} & \nabla E^*(\phi^*) = 0 \\ & \nabla^2 E^*(\phi^*) > 0 \\ & 0 \leq \phi^* \leq 2\pi \end{array} \right.$$

**Homotopy:**

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

$$= \left\{ \begin{array}{ll} \nabla E^0(\phi) \, , & \lambda = 0 \\ \nabla E^*(\phi) \, , & \lambda = 1 \end{array} \right.$$

# General Homotopy Method

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

$$f(x) = 0, \qquad (f : \mathbb{R}^n \to \mathbb{R}^n).$$

**Steps to Solution:**

Easy system: $e(x^0) = 0 \qquad (x^0 \ \ known)$

Homotopy: $$h(x, \lambda) = \begin{cases} e(x)\ , & \lambda = 0 \\ f(x)\ , & \lambda = 1 \end{cases}$$

$$e.g.,\ h(x, \lambda) = \lambda\, f(x) + (1 - \lambda)\, e(x)$$

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

# Tracing $H(\phi, \lambda) = 0$

**Predictor–Corrector Algorithm:**

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

$$\lambda_0 = 0$$

$$k = 0$$

repeat until $\lambda_k = 1$

$$k = k + 1$$

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

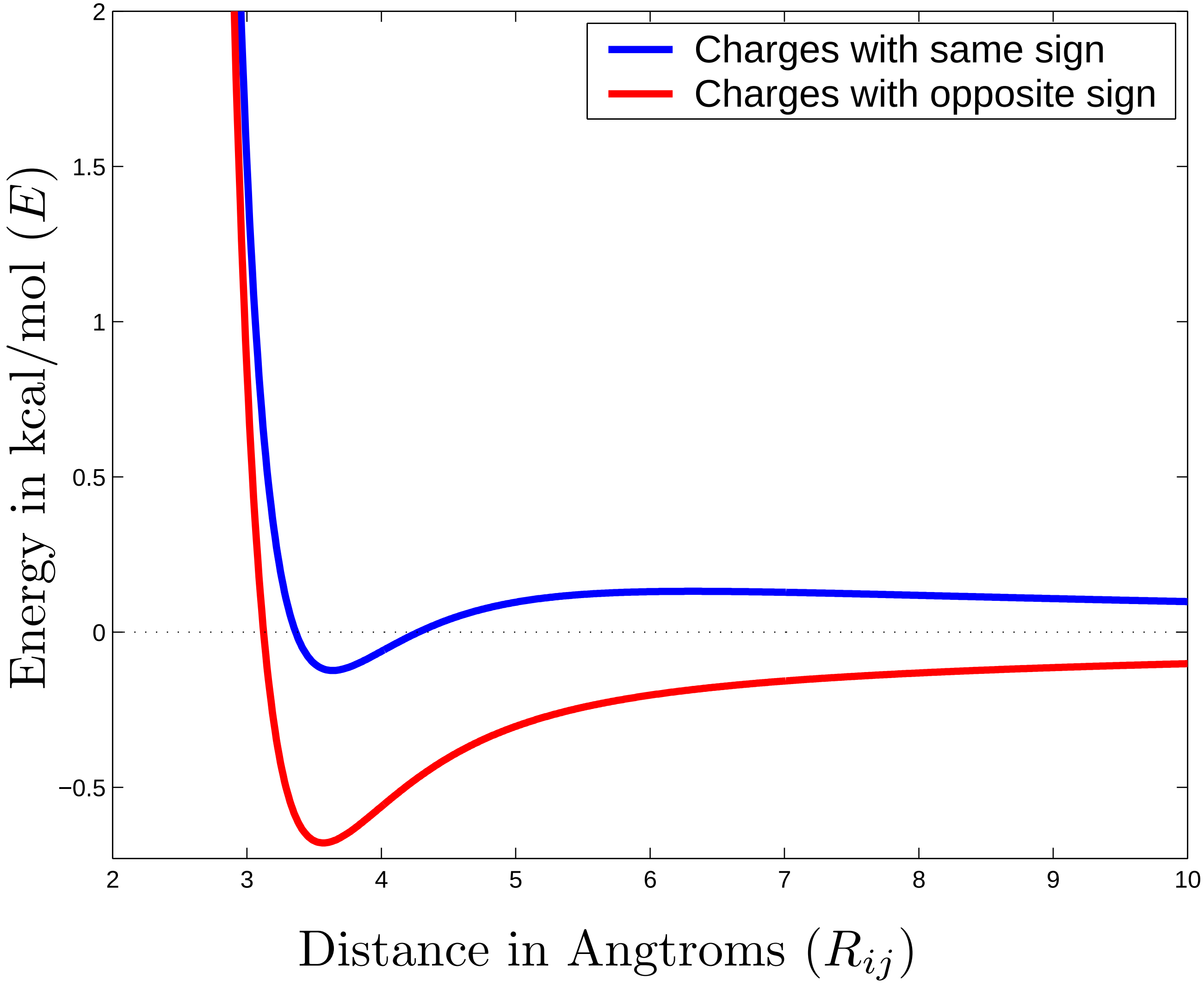
$$\phi^k \leftarrow \begin{cases} \text{using } \phi^{k-1} \text{ as initial guess} \\ \text{solve } H(\phi, \lambda_k) = 0 \end{cases}$$

end

$$\phi^* = \phi^k \quad \left[H(\phi^k, 1) = \nabla E^*(\phi^k) \approx 0\right]$$

# Pairwise Energy for Charged Particles

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



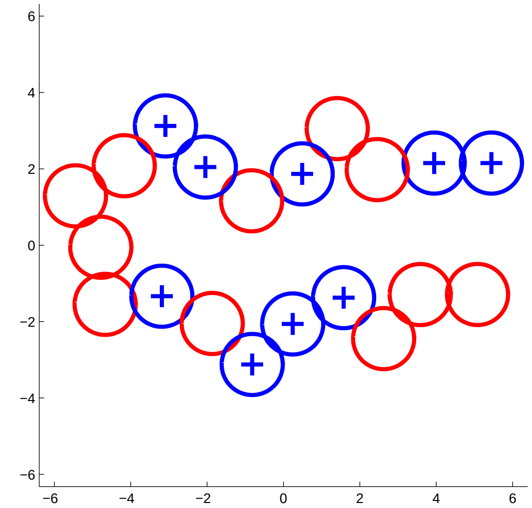
# Example 1 – Negligible Difference

$$m = 20$$

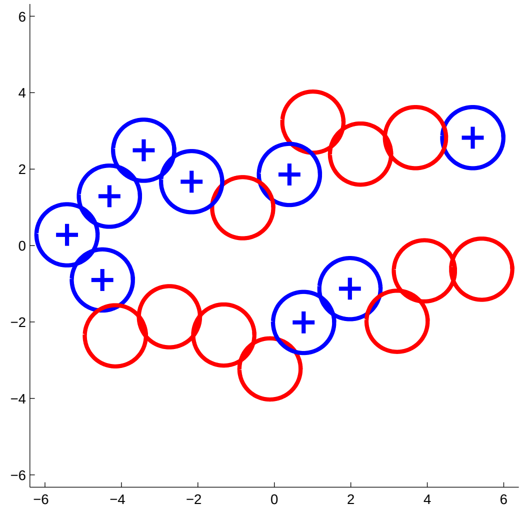
$$q \in \{-1, +1\}$$

$$E^0(\phi) = -22.9708$$

6 changes in $q$

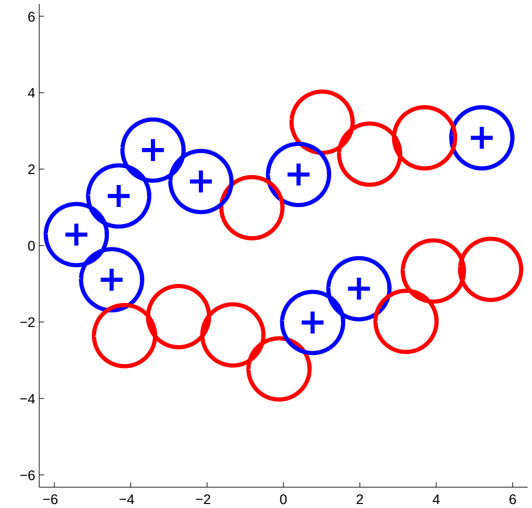


Gradient Method



$$E^*(\phi) = -22.4510$$

Homotopy Method



$$E^*(\phi) = \boxed{-22.4511}$$

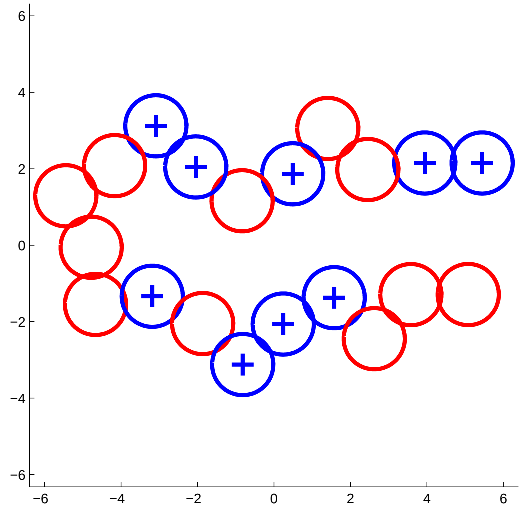
# Example 2 – No Difference

$$m = 20$$

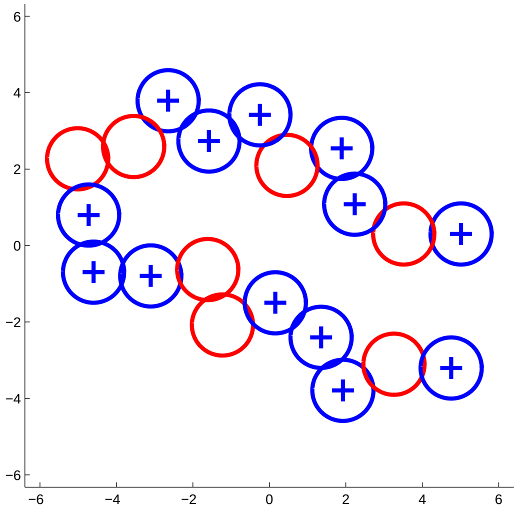
$$q \in \{-1, +1\}$$

$$E^0(\phi) = -22.9708$$

10 changes in $q$

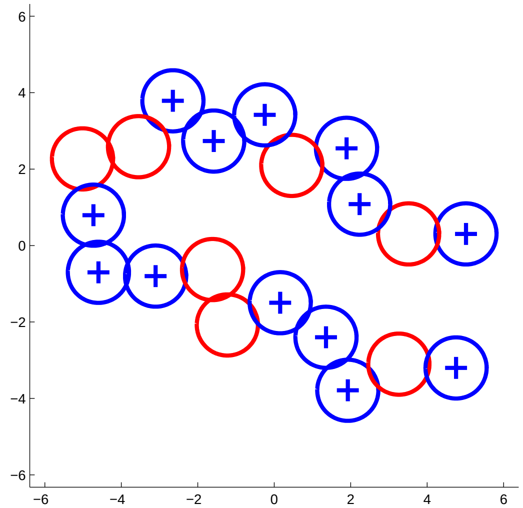


Gradient Method



$$E^*(\phi) = \boxed{-20.0044}$$

Homotopy Method



$$E^*(\phi) = \boxed{-20.0044}$$

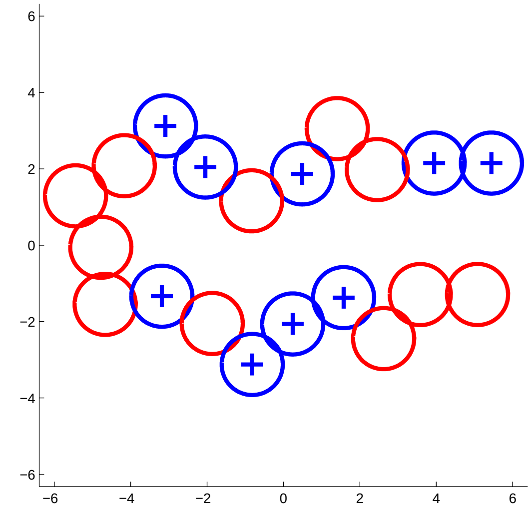
# Example 3 - Qualitative Difference

$$m = 20$$

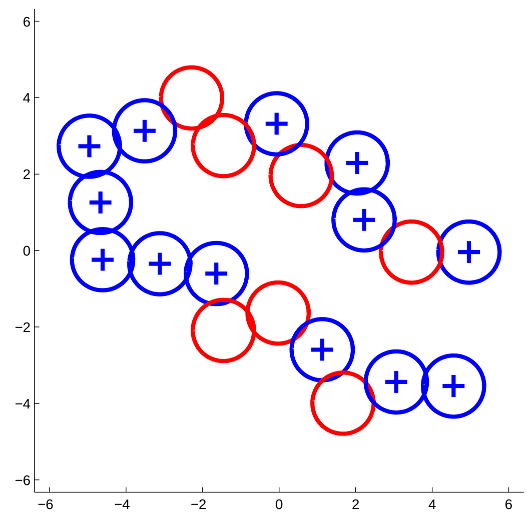
$$q \in \{-1, +1\}$$

$$E^0(\phi) = -22.9708$$

16 changes in $q$

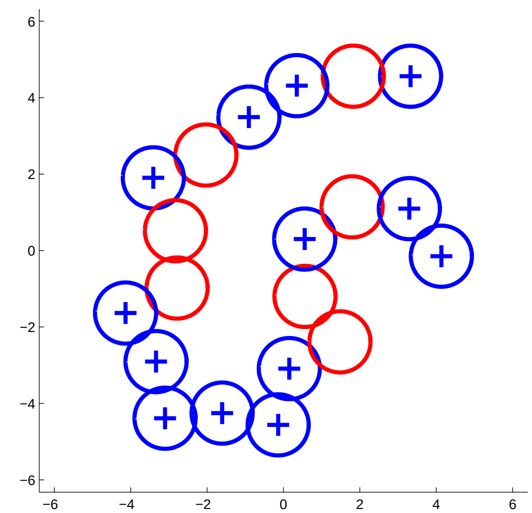


Gradient Method



$$E^*(\phi) = \boxed{-18.8808}$$

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)