

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

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# Daniel M. Dunlavy

Applied Mathematics and Scientific Computation

**Advisor: Dianne O'Leary**

Department of Computer Science

Institute for Advanced Computer Studies (UMIACS)

**Thanks: Ron Unger**

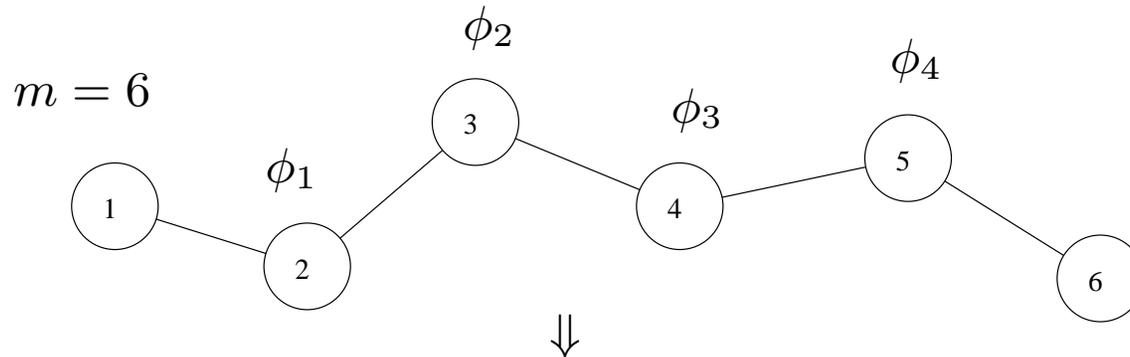
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# Introduction

- **Protein Folding**
  - Sequence of amino acids → three-dimensional structure
  - Minimum potential energy assumed for native structure
- **Difficult Goal**
  - Find structure with minimum potential energy
  - Computationally intractable for large proteins
- **Simple Model**
  - Chain of charged particles in a two dimensional space
  - Simple energy model
  - Find structure with minimum potential energy

# Formulation of the Problem

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



van der Waals Potential

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

Optimization Problem

$$\min E(\phi)$$

$$\text{s.t. } 0 \leq \phi_i \leq 2\pi, \quad (i = 1, \dots, m - 2)$$

# 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:**

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

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

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

**Homotopy:**

$$\begin{aligned} H(\phi, \lambda) &= \nabla \left( \sum_{i=1}^{m-2} \sum_{j=i+2}^m \left[ \frac{q_i(\lambda)q_j(\lambda)}{R_{ij}} + \varepsilon_{ij} \left( \left( \frac{\sigma_{ij}}{R_{ij}} \right)^{12} - 2 \left( \frac{\sigma_{ij}}{R_{ij}} \right)^6 \right) \right] \right) \\ &= \begin{cases} \nabla E^0(\phi), & \lambda = 0 \\ \nabla E^*(\phi), & \lambda = 1 \end{cases} \end{aligned}$$

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

## Algorithm:

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

$\lambda_0 = 0$

$k = 0$

repeat until  $\lambda_k = 1$

$k = k + 1$

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

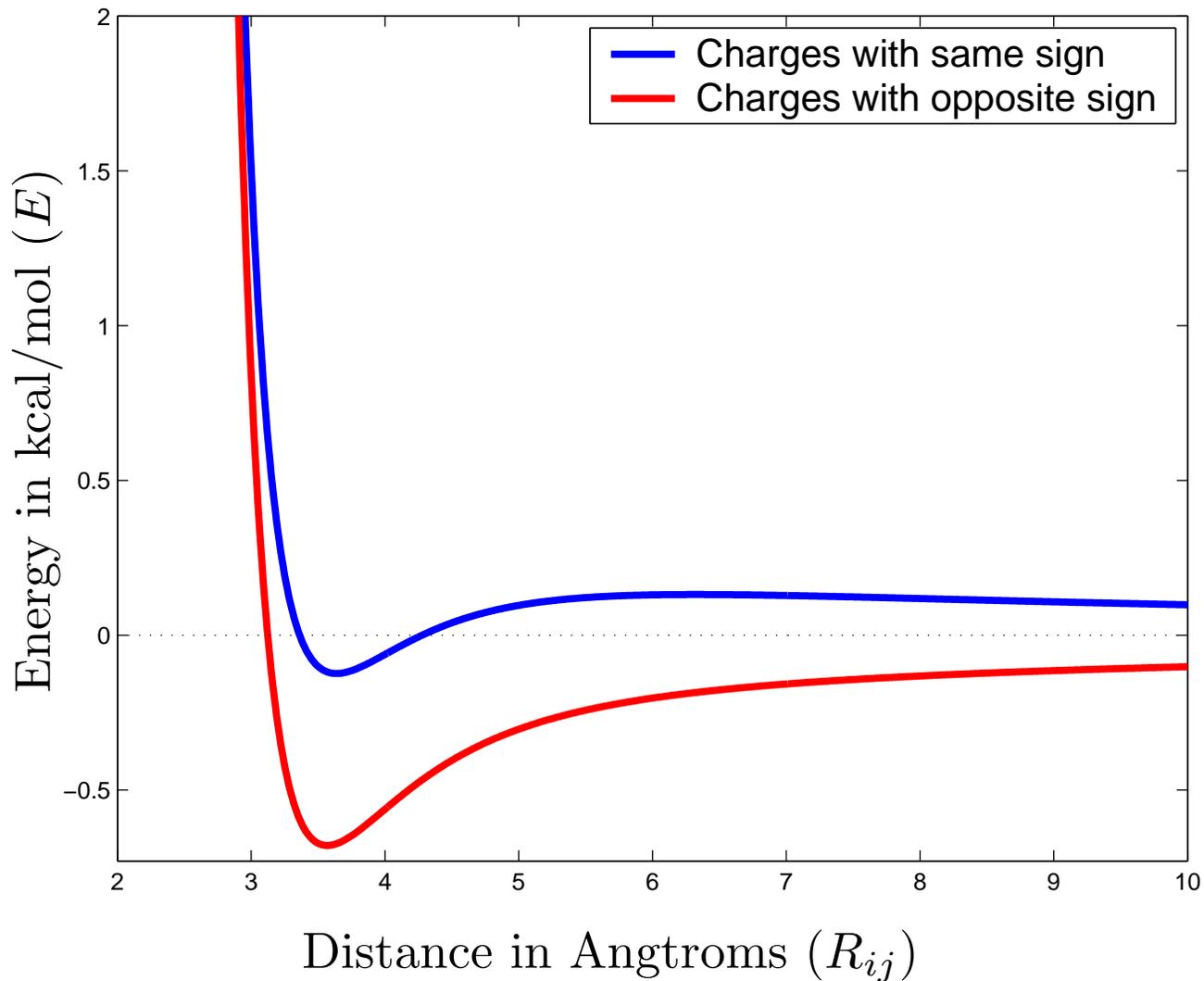
$\phi^k \leftarrow \begin{cases} \text{solve } H(\phi, \lambda_k) = 0 \\ \text{using } \phi^{k-1} \text{ as initial guess} \end{cases}$

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)



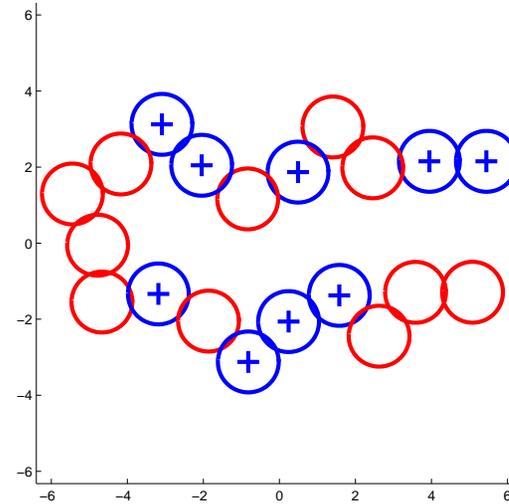
# Example 1 – Negligible Difference

$$m = 20$$

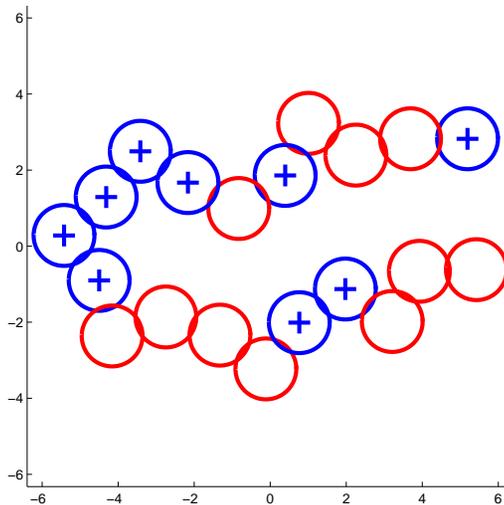
$$q \in \{-1, +1\}$$

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

6 changes in  $q$

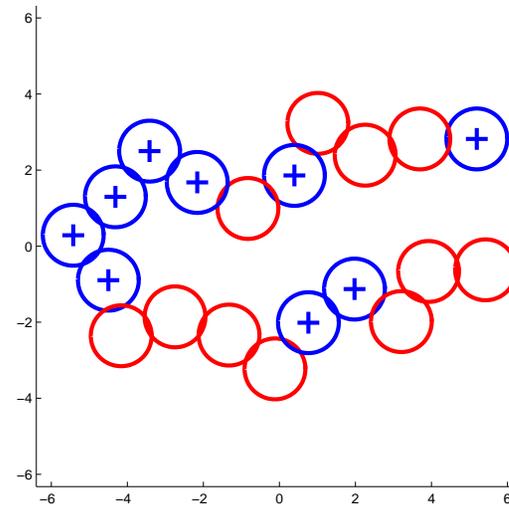


Gradient Method



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

Homotopy Method



$$E^*(\phi) = -22.4511$$

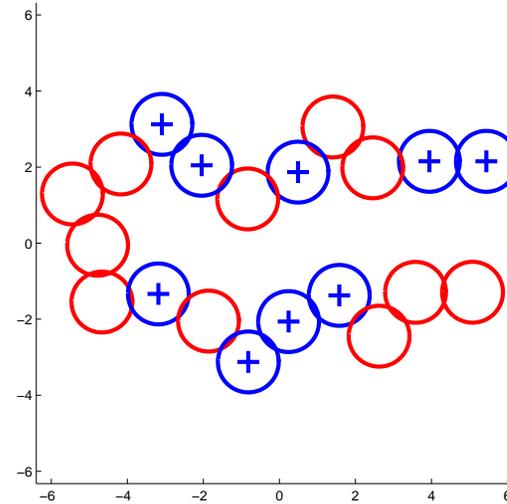
## Example 2 – No Difference

$$m = 20$$

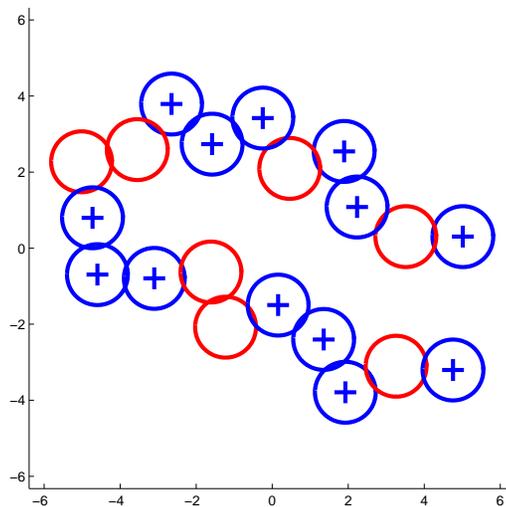
$$q \in \{-1, +1\}$$

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

10 changes in  $q$

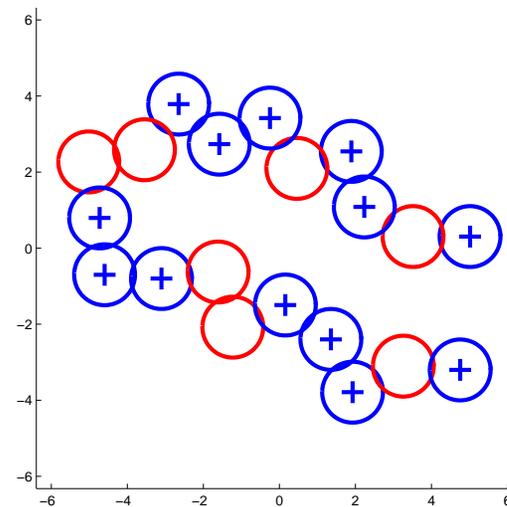


Gradient Method



$$E^*(\phi) = -20.0044$$

Homotopy Method



$$E^*(\phi) = -20.0044$$

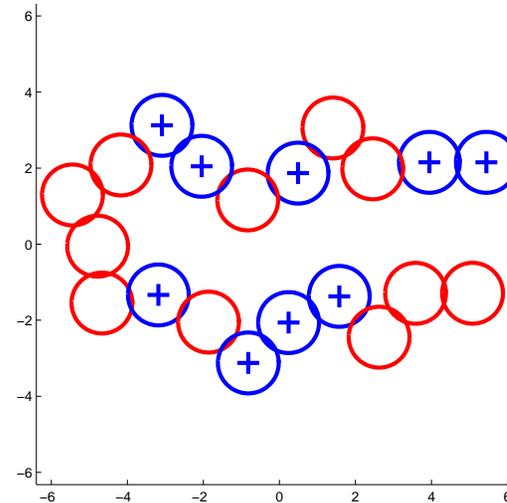
# Example 3 - Qualitative Difference

$$m = 20$$

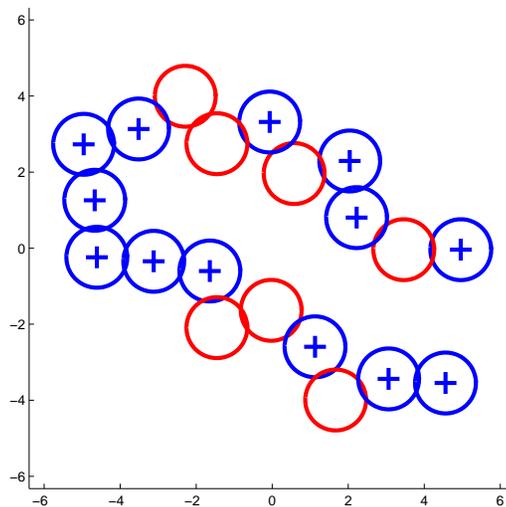
$$q \in \{-1, +1\}$$

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

16 changes in  $q$

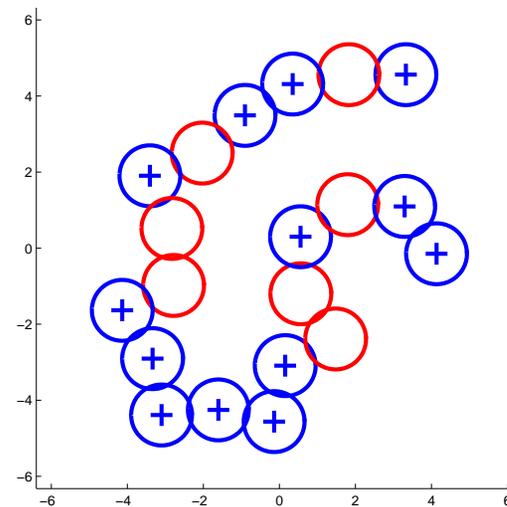


Gradient Method



$$E^*(\phi) = -18.8808$$

Homotopy Method



$$E^*(\phi) = -19.4268$$

# Conclusions and Future Work

- **Results Using Homotopy–Simple Model(2D)**
  - Rivals gradient methods (GM) in accuracy
  - Outperforms GM when many charges change
  - More function evaluations than GM
- **Goal Using Homotopy–Simple Model (3D)**
  - Produce results similar to 2D model
  - Validate against existing examples from community
- **Goal Using Homotopy–Protein Folding**
  - Predict tertiary structure of proteins
  - Utilize Protein Data Bank (PDB)
    - ◊ Homologues as starting points
  - Utilize Amber
    - ◊ Potential energy computation