Global Optimization:
For Some Problems, There’s HOPE

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Outline

• Problem and Existing Methods
• Homotopy Optimization Methods
• Protein Structure Prediction Problem
• Numerical Experiments
• Conclusions/Future Directions
Problem

• Solve the unconstrained minimization problem

\[ f(x^*) = \min_{x \in \mathbb{R}^n} f(x) \quad (f : \mathbb{R}^n \rightarrow \mathbb{R}) \]

• Function Characteristics
  – Solution exists, smooth \((f \in C^2(\mathbb{R}^n, \mathbb{R}))\)
  – Complicated (multiple minima, deep local minima)
  – Good starting points unknown/difficult to compute

• Challenges
  – Finding solution in reasonable amount of time
  – Knowing when solution has been found
Some Existing Methods

• Exhaustive/enumerative search
• Stochastic search [Spall, 2003]; adaptive [Zabinsky, 2003]
• “Globalized” local search [Pinter, 1996]
• Branch and bound [Horst and Tuy, 1996]
• Genetic/evolutionary [Voss, 1999]

• Smoothing methods [Piela, 2002]
• Simulated annealing [Salamon, et al., 2002]
• Homotopy/continuation methods [Watson, 2000]
Outline

• Problem and Existing Methods
• **Homotopy Optimization Methods**
• Protein Structure Prediction Problem
• Numerical Experiments
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Homotopy Methods for Solving Nonlinear Equations

• Goal
  – Solve complicated nonlinear target system
    \[ f_1(x) = 0, \quad (f_1 : \mathbb{R}^n \rightarrow \mathbb{R}^n) \]

• Steps to solution
  – Easy template system: \( f_0(x^0) = 0 \) \( (x^0 \text{ known}) \)
  – Define a continuous homotopy function:
    \[ h(x, \lambda) = \begin{cases} f_0(x), & \text{if } \lambda = 0 \\ f_1(x), & \text{if } \lambda = 1 \end{cases} \]
    • Example (convex): \( h(x, \lambda) = (1 - \lambda)f_0(x) + \lambda f_1(x) \)
  – Trace path of \( h(x, \lambda) = 0 \) from \( \lambda = 0 \) to \( \lambda = 1 \)
Homotopy Optimization Methods (HOM)

• Goal
  – Minimize complicated nonlinear target function
  \[ \min_{x \in \mathbb{R}^n} f_1(x), \quad (f_1 : \mathbb{R}^n \rightarrow \mathbb{R}) \]

• Steps to solution
  – Easy template function: \( f_0(x^0) = \min_{x \in \mathbb{R}^n} f_0(x) \)
  – Define a continuous homotopy function:
    \[ h(x, \lambda) = \begin{cases} 
    f_0(x), & \text{if } \lambda = 0 \\
    f_1(x), & \text{if } \lambda = 1 
    \end{cases} \]
    • Example (convex): \( h(x, \lambda) = (1 - \lambda)f_0(x) + \lambda f_1(x) \)
  – Produce sequence of minimizers of \( h(x, \lambda) \) w.r.t. \( x \)
    starting at \( \lambda = 0 \) and ending at \( \lambda = 1 \)
Illustration of HOM

\[ x^* = \min_{x \in \mathbb{R}} f_1(x) \quad h(x, \lambda) = (1 - \lambda) f_0(x) + \lambda f_1(x) \]

\[ \nabla_x h = 0 ; \quad \nabla^2_x h > 0 \]
Homotopy Optimization using Perturbations & Ensembles (HOPE)

• Improvements over HOM
  – Produces ensemble of sequences of local minimizers of $h(x, \lambda)$ by perturbing intermediate results
  – Increases likelihood of predicting global minimizer

• Algorithmic considerations
  – Maximum ensemble size
  – Determining ensemble members
Illustration of HOPE

Constraint: ensemble size \( \equiv |\mathbb{E}| \leq 2 \)

\[
x^* = \min_{x \in \mathbb{R}} f_1(x) \quad h(x, \lambda) = (1-\lambda)f_0(x) + \lambda f_1(x)
\]

\[\nabla_x h = 0 ; \nabla^2_x h > 0\]
Convergence of HOPE

Goal: \( m \in \mathbb{Z}^+ \) s.t. \( \mathcal{P}(\exists x \in E_m \mid x \in S_N) > \rho \)

\[ T_{x^*}(\lambda) \]

\[ S_N(\lambda) \]

\[ S_i(\lambda) \]

\[ S_1(\lambda) \]

0 \( \Delta \lambda = 1/m \)

\[ \lambda \]

1
Convergence of HOPE

\[
\alpha = \min_{\lambda \in [0,1]} \{ T_x^*(\lambda) \} \quad P = \begin{bmatrix}
1 - 2\alpha & \alpha & \alpha \\
\alpha & 1 - 2\alpha & \alpha \\
\vdots & \vdots & \ddots \\
\alpha & 1 - 2\alpha & \alpha \\
\alpha & \alpha & 1 - 2\alpha
\end{bmatrix}
\]

No constraints on ensemble size: \( |\mathbb{E}_m| = 2^m \)

\[\mathbb{E}_0 = \{ x^0 \} \; ; \; \mathbb{E}_k = \mathbb{E}_{k-1} \cup \{ \text{perturbed versions of } \mathbb{E}_{k-1} \}\]

\[\mathcal{P}(\exists x \in \mathbb{E}_m : x \in S_N) = 1 - \prod_{k=0}^m \left( 1 - e_i^T P^k e_N \right)^{\binom{m}{k}} \]

\[\geq 1 - \prod_{k=\kappa}^m \left( 1 - P^{k}_{N/2,N} \right)^{\binom{m}{k}} \quad (\kappa = \min\{i, N - i\})\]

\[= 1 - \prod_{k=\kappa}^m \left( 1 - \frac{1}{N} \sum_{l=0}^{N-1} (-1)^l \left( 1 - 2\alpha + 2\alpha \cos \left( \frac{2\pi l}{N} \right) \right)^k \right)\]
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• Problem and Existing Methods
• Homotopy Optimization Methods
• **Protein Structure Prediction Problem**
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• Conclusions/Future Directions
Protein Structure Prediction

Amino Acid Sequence  Proteinc Structure

Given the amino acid sequence of a protein (1D), is it possible to predict its native structure (3D)?
Protein Structure Prediction

• **Given:**
  – Protein model
    • Molecular properties
    • Potential energy function (force field)

• **Goal:**
  – Predict lowest energy conformation
    • Native structure [Anfinsen, 1973]
  – Develop hybrid method, combining:
    • Energy minimization [numerical optimization]
    • Comparative modeling [bioinformatics]
      – Use template (known structure) to predict target structure
Protein Model: Particle Properties

• Backbone model
  – Single chain of particles with residue attributes
  – Particles model $C_\alpha$ atoms in proteins

• Properties of particles
  – Hydrophobic, Hydrophilic, Neutral
  – Diverse hydrophobic-hydrophobic interactions

[Veitshans, Klimov, and Thirumalai. Protein Folding Kinetics, 1996.]
Protein Model: Energy Function

\[ E(X) = E_{bl}(X) + E_{ba}(X) + E_{dih}(X) + E_{non}(X) \]

\[ E_{bl}(X) = \sum_{i=1}^{n-1} \frac{k_r}{2} \left( r_{i,i+1} - \bar{r} \right)^2 \]

\[ E_{ba}(X) = \sum_{i=1}^{n-2} \frac{k_\theta}{2} \left( \theta_i - \bar{\theta} \right)^2 \]

\[ E_{dih}(X) = \sum_{i=1}^{n-3} \left[ A_i (1 + \cos \phi_i) + B_i (1 + \cos 3\phi_i) \right] \]

\[ E_{non}(X) = \sum_{i=1}^{n-3} \sum_{j=i+3}^{n} \gamma_{ij} \left\{ \alpha_{ij} \left( \frac{\bar{r}}{r_{ij}} \right)^{12} - \beta_{ij} \left( \frac{\bar{r}}{r_{ij}} \right)^6 \right\} \]
Homotopy Optimization Method for Proteins

• Goal
  – Minimize energy function of target protein
    \[ \min_{X \in \mathbb{R}^{3n}} E^1(X), \quad (E^1 : \mathbb{R}^{3n} \to \mathbb{R}) \]

• Steps to solution
  – Energy of template protein: \( E^0(X^0) = \min_{X \in \mathbb{R}^{3n}} E^0(X) \)
  – Define a homotopy function:
    • \( H(X, \lambda) = \rho^0(\lambda) E^0(X) + \rho^1(\lambda) E^1(X) \)
    • Deforms template protein into target protein
  – Produce sequence of minimizers of \( H(X, \lambda) \)
    starting at \( \lambda = 0 \) and ending at \( \lambda = 1 \)
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Numerical Experiments

9 chains (22 particles) with known structure

Loop Region

Sequence Matching (%)

<table>
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<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
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Numerical Experiments
Numerical Experiments

• 62 template-target pairs
  – 10 pairs had identical native structures

• Methods
  – HOM vs. Newton’s method w/trust region (N-TR)
  – HOPE vs. simulated annealing (SA)
    • Different ensemble sizes (2, 4, 8, 16)
    • Averaged over 10 runs
    • Perturbations where sequences differ

• Measuring success
  – Structural overlap function: $0 \leq \chi \leq 1$
    • Percentage of interparticle distances off by more than 20% of the average bond length ($\bar{r}$)
  – Root mean-squared deviation (RMSD)
## Results

<table>
<thead>
<tr>
<th>Method</th>
<th>$\chi = 0$</th>
<th>Success</th>
<th>Mean $\chi$</th>
<th>Mean RMSD</th>
<th>Time (sec)</th>
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<tbody>
<tr>
<td>HOM</td>
<td>15</td>
<td>0.24</td>
<td>0.36</td>
<td>0.38</td>
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<td>N-TR</td>
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<td>0.55</td>
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<table>
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<th>Ensemble Size</th>
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<th>Mean $\chi$</th>
<th>Mean RMSD</th>
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<td>40.20</td>
<td>0.65</td>
<td>0.08</td>
<td>0.12</td>
<td>434</td>
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</tbody>
</table>
Results

Success of HOPE and SA with ensembles of size 16 for each template-target pair. The size of each circle represents the percentage of successful predictions over the 10 runs.
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Conclusions

• Homotopy optimization methods
  – More successful than standard minimizers

• HOPE
  – For problems with $f^0, x^0 (E^0, X^0)$ readily available
  – Solves protein structure prediction problem
  – Outperforms ensemble-based simulated annealing
    • No fine tuning of SA
HOPEful Directions

• Protein structure prediction
  – Protein Data Bank (templates), TINKER (energy)
  – Probabilistic convergence analysis (\( \mathbb{R}^n \))

• HOPE for large-scale problems
  – Inherently parallelizable
  – Communication: enforce maximum ensemble size

• Sandia
  – Protein structure prediction (Bundler)
  – LOCA, APPSPACK
  – SGOPT
Other Work/Interests

• Optimization
  – Surrogate models in APPSPACK (Sandia)

• Linear Algebra
  – Structure preserving eigensolvers
    • Quaternion-based Jacobi-like methods
  – RF circuit design – efficient DAE solvers
    • Preconditioners, harmonic-balance methods

• Information processing/extraction
  – Entity recognition/disambiguation
    • Persons, locations, organization
  – Querying, clustering and summarizing documents
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