Efficient use of semidefinite programming for selection of rotamers in protein conformations

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Motivation: Side Chain Positioning, SCP/using Semidefinite Programming, SDP, Relaxations

- Model the NP-hard SCP problem using

  QQP: quadratic (objective) -quadratic (constraints) program

- - approximate/relax using SDP relaxation
  - But, Slater's CQ fails for SDP relaxation; Preprocess/regularize using facial reduction
  - strengthen solutions using cutting plane techniques
- upper/lower bounds: we follow/improve SDP relax. approaches in:

  Chazelle, Kingsford, and Singh for SCP, 2004 and in Qing, Karish, Rendl, Wolkowicz for QAP, 1998.

Biological Preamble

Side Chain Positioning, SCP

- Given: constituent atoms of a protein; hard problem of predicting protein's three dimensional structure is often broken down into multiple subproblems, one of which is:

  side chain positioning, (SCP) problem

- For us: a protein macromolecule is a chain of amino acids, also called *residues*.
- An amino acid consists of an "alpha" carbon atom (-C_α-) and three components attached to it: an amino group (H_2N-), a carboxyl group (-COOH) and an atom group called a side chain. The amino acid is characterized by the composition of the side chain.

famous protein folding problem

Outline:

requires accurate prediction of all atomic positions for folded minimal energy conformation of such a chain of amino acids, e.g., solve two subproblems:

- calculate positions of atoms in backbone;
- given the positions of backbone atoms, calculate the conformations of all side chains. to minimize potential energy of protein

Background/Notation

$\mathcal{G} = (\mathcal{V}, \mathcal{E}, E)$ weighted, undirected graph

- node set $\mathcal{V} = \bigcup_{\mathbf{i}=\mathbf{1}}^{\mathbf{p}} \mathcal{V}_{\mathbf{i}}$; $\mathcal{V}_{\mathbf{i}}$ subset of *rotamers* for **i**-th amino acid/residue side chain; **p** number of residues.
- edge set $\mathcal{E}$; weights (energy) $\mathbf{E_{uv}}$ for edge $\mathbf{uv} \cong (\mathbf{u}, \mathbf{v}) \in \mathcal{E}$

Further ...

- $\mathcal{S}^{\mathbf{t}}$, $\mathbf{t} \times \mathbf{t}$ real symmetric matrices, with trace inner-product $\langle \mathbf{S}, \mathbf{T} \rangle = \text{trace}\, \mathbf{ST}$ and *Löwner partial order* $\mathbf{S} \succeq \mathbf{T}$, $(\mathbf{S} \succ \mathbf{T})$
- $\text{Diag}\,(\mathbf{v}) \in \mathcal{S}^{\mathbf{s}}$ diagonal matrix; adjoint is $\text{Diag}^{*}(\mathbf{S}) = \text{diag}\,(\mathbf{S}) \in \mathbb{R}^{\mathbf{s}}$
- $\bar{e} = \bar{e}_p \in \mathbb{R}^p$ vectors of ones; $\bar{E}_k = \bar{e}_k \bar{e}_k^T$; $\mathbf{x} \circ \mathbf{y}$ Hadamard (elementwise) product

Equivalent View of Stable Linearization

Find **global minimum-energy conformation, GMEC**

- minimize sum of weights/energies on edges in $\mathbf{E}$; choose exactly one rotamer from each set $\mathcal{V}_{\mathbf{i}}$
- off-diagonal edge weights $\mathbf{E_{uv}}, \mathbf{u} \neq \mathbf{v}$, are pairwise interaction energy between pairs of rotamers $\mathbf{u}, \mathbf{v}$; diagonal weight $\mathbf{E_{uu}}$ is energy from interaction between backbone and chosen rotamer $\mathbf{u}$.

Further notation

- $\mathbf{m_k} := |\mathcal{V}_{\mathbf{k}}| \geq \mathbf{1}, \ \forall \mathbf{k}$, size of the subsets; $\mathbf{m} := \begin{pmatrix} m_1 & \dots & m_p \end{pmatrix}^{\mathbf{T}}$ vector of cardinalities;
- $\mathbf{n_0} = |\mathcal{V}| \left(= \sum_{\mathbf{k}} \mathbf{m_k}\right)$, total number of rotamers; $\mathbf{n} := \mathbf{n_0} + \mathbf{1}$ size of matrices in SDP relaxation

Quadratic integer programming model

Finding GMEC is equivalent to solving

$$
\text{(IQP)} \qquad
\begin{aligned}
val_{IQP} = \quad & \min_{x} \quad \sum_{(u,v)\in\mathcal{E}} E_{uv} x_u x_v \\
& \text{s.t.} \quad \sum_{u\in\mathcal{V}_k} x_u = 1, \qquad \forall\, k = 1, \ldots, p, \\
& \qquad\quad x_u \in \{0,1\}, \qquad \forall u \in \mathcal{V}\,,
\end{aligned}
$$

$$
\mathbf{x_u} = \begin{cases} 1 & \text{if rotamer } u \text{ is chosen} \\ 0 & \text{otherwise} \end{cases} .
$$

IQP in Matrix Notation

relabel the n_0 nodes in $\mathcal{V}$; complete E

$$\mathcal{V}_1 \cong \{1, \ldots, m_1\}, \mathcal{V}_2 \cong \{m_1 + 1, \ldots, m_1 + m_2\}, \ldots,$$
$$\mathcal{V}_p \cong \left\{ \left(\sum_{k=1}^{p-1} m_k \right) + 1, \ldots, n_0 \right\}.$$

and complete definition $E_{uv} = 0$ if $(u, v) \notin \mathcal{E}$

Define assignment type $A \in \{0, 1\}^{p \times n_0}$ matrix

$$A := \begin{bmatrix} \bar{e}_{m_1}^T & 0 & 0 & \cdots & 0 \\ 0 & \bar{e}_{m_2}^T & 0 & \cdots & 0 \\ 0 & 0 & \bar{e}_{m_3}^T & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & \bar{e}_{m_p}^T \end{bmatrix}; A^T A = \begin{bmatrix} \bar{E}_{m_1} & 0 & 0 & \cdots & 0 \\ 0 & \bar{E}_{m_2} & 0 & \cdots & 0 \\ 0 & 0 & \bar{E}_{m_3} & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & \bar{E}_{m_p} \end{bmatrix}$$

IQP in matrix notation

Using A

$$
\text{(IQP)} \qquad
\begin{aligned}
val_{IQP} = \min_{x} \quad & x^T E x \\
\text{s.t.} \quad & Ax - \bar{e}_p = 0 \in \mathbb{R}^p \\
& x = \begin{bmatrix} v_1^T & v_2^T & \cdots & v_p^T \end{bmatrix}^T \in \{0,1\}^{n_0} \\
& v_k \in \{0,1\}^{m_k}, \ \forall\, k = 1, \ldots, p.
\end{aligned}
$$

IQP as QQP and redundant constraints within brackets $\{\}$

$$
\text{(QQP)} \qquad
\begin{aligned}
val_{IQP} = val_{QQP} = \min_{x} \quad & x^T E x \\
\text{s.t.} \quad & \|\bar{e}_p - Ax\|^2 = 0 \\
& x \circ x - x = 0 \\
& \left\{ \begin{array}{l} (A^T A - I) \circ (xx^T) = 0 \\ (xx^T)_{ij} \geq 0, \ \forall\, (i,j) \in \mathcal{I} \end{array} \right\},
\end{aligned}
$$

$\mathcal{I} \subseteq \{(\mathbf{i}, \mathbf{j}) : \mathbf{1} \leq \mathbf{i} < \mathbf{j} \leq \mathbf{n_0}\}$ valid inequalities for cutting planes.

Forming the SDP relaxation

Start with QQP model; apply recipe

1. form the Lagrangian relaxation;
2. apply homogenization;
3. simplify to obtain the dual and an equivalent SDP;
4. take dual of dual; obtain SDP relaxation of original IQP
5. remove any redundant (linearly dependent) constraints.

Lagrange multipliers

$\lambda \in \mathbb{R}, \mathbf{w} \in \mathbb{R}^{\mathbf{n_0}}, \Lambda \in \mathcal{S}^{n_0}, \eta \in \mathbb{R}^{|\mathcal{I}|}$;
need the projection $\overline{\mathcal{P}}_{\mathcal{I}} : \mathcal{S}^{\mathbf{n_0}} \to \mathbb{R}^{|\mathcal{I}|} : \mathbf{X} \mapsto [\mathbf{X_{ij}}]_{(\mathbf{i},\mathbf{j})\in\mathcal{I}}$.

Lagrangian for QQP

$$
\begin{aligned}
L(x,\lambda,w,\Lambda,\eta) &= x^T E x + \lambda \|\bar{e}_p - Ax\|^2 + w^T(x\circ x - x) \\
&\quad + \langle \Lambda, (A^TA - I)\circ(xx^T)\rangle - \textstyle\sum_{(i,j)\in\mathcal{I}} \eta_{ij}(xx^T)_{ij} \\
&= \begin{cases} x^T E x + \lambda x^T A^T A x + w^T(x\circ x) & \\ \qquad + \langle \Lambda, (A^TA - I)\circ(xx^T)\rangle - \langle \eta, \overline{\mathcal{P}}_{\mathcal{I}}(xx^T)\rangle & \underline{\text{quadr}} \\ -2\lambda \bar{e}_p^T A x - w^T x & \underline{\text{lin}} \\ +\lambda p, & \underline{\text{const}} \end{cases}
\end{aligned}
$$

Lagrangian relaxation with homogenization

We use a homogenizing variable $x_0 \in \mathbb{R}$ and an additional Lagrange multiplier $t \in \mathbb{R}$.

$$
\begin{aligned}
d_{\mathcal{I}}^* &= \max_{\lambda,w,\Lambda,\eta\geq 0} \left\{ \min_x L(x,\lambda,w,\Lambda) \right\} \\
&= \max_{\lambda,w,\Lambda,\eta\geq 0,t} \left\{ \min_{x,x_0} x^T E x + \lambda x^T A^T A x + w^T(x\circ x) \right. \\
&\qquad + \langle \Lambda, (A^TA - I)\circ(xx^T)\rangle - \langle \overline{\mathcal{P}}_{\mathcal{I}}^*(\eta), xx^T\rangle \\
&\qquad \left. -2\lambda x_0 \bar{e}_{n_0}^T x - x_0 w^T x + \lambda p + t(1 - x_0^2) \right\}.
\end{aligned}
$$

First SDP (SDP-1)

(SDP-1)

$$\mathbf{d}_{\mathcal{I}}^{*} = \max_{\lambda,\mathbf{t},\mathbf{w},\tilde{},\eta} \mathbf{t} + \mathbf{p}\lambda$$

subject to the constraints:

$$LHS := \begin{bmatrix} t & \left(\lambda \bar{e}_{n_0}^T + \frac{1}{2} w^T\right) \\ \left(\lambda \bar{e}_{n_0} + \frac{1}{2} w\right) & \left(-\lambda A^T A - \mathrm{Diag}\,(w) - \Lambda \circ (A^T A - I) + \overline{\mathcal{P}}_{\mathcal{I}}^{*}(\eta)\right) \end{bmatrix} \preceq \begin{bmatrix} 0 & 0 \\ 0 & E \end{bmatrix}$$

$$\eta \geq 0$$

$$\lambda, t \in \mathbb{R}, w \in \mathbb{R}^{n_0}, \Lambda \in \mathcal{S}^{n_0}, \eta \in \mathbb{R}^{|\mathcal{I}|}.$$

Linear transformations defined implicitly

$$LHS =: {}^{1}\mathcal{O}(t) + {}^{\mathrm{e}}\mathrm{BDiag}(\lambda) - \mathrm{Arrow}(w) - {}^{\mathrm{d}}\mathrm{BDiag}(\Lambda) + \mathcal{P}_{\mathcal{I}}^{*}(\eta)$$

partition $\mathbf{Y} = \begin{bmatrix} Y_{00} & y^T \\ y & \bar{Y} \end{bmatrix} \in \mathcal{S}^{\mathbf{n}}, \bar{Y} \in \mathcal{S}^{n_0}$

and define $\mathcal{P}_{\mathcal{I}}(Y) = \overline{\mathcal{P}}_{\mathcal{I}}(\bar{Y})$

Derive the Adjoints

1. ${}^{1}\mathcal{O}^{*}(\mathbf{Y}) = \mathbf{Y_{00}}$
2. ${}^{e}\text{bdiag}(Y) := {}^{e}\text{BDiag}^{*}(Y) = -\langle \bar{Y}, A^{T}A \rangle + 2\bar{e}_{n_0}^{T} y$
3. $\text{arrow}(Y) := \text{Arrow}^{*}(Y) = \text{diag}\,(\bar{Y}) - y$
4. ${}^{d}\text{bdiag}(Y) := {}^{d}\text{BDiag}^{*}(Y) = \bar{Y} \circ (A^{T}A - I)$

gangster operator

operator in Item 4 (when set to $= \mathbf{0}$ is *gangster operator* - *shoots holes/zeros* in the matrix $\bar{Y}$; guarantees that diagonal blocks are diagonal matrices. (strong cuts)

SDP relaxation from dual of Lagrangian relaxation

Recall: Dual is (SDP-1)

$$
\begin{aligned}
d_{\mathcal{I}}^{*} = \quad & \max_{\lambda,t,w,\Lambda,\eta} \quad t + p\lambda \\
& \text{s.t.} \quad {}^{1}\mathcal{O}(t) + {}^{e}\mathrm{BDiag}(\lambda) - \mathrm{Arrow}(w) - {}^{d}\mathrm{BDiag}(\Lambda) + \mathcal{P}_{\mathcal{I}}^{*}(\eta) \preceq \begin{bmatrix} 0 & 0 \\ 0 & E \end{bmatrix} \\
& \qquad \eta \geq 0 \\
& \qquad \lambda, t \in \mathbb{R}, w \in \mathbb{R}^{n_0}, \Lambda \in \mathcal{S}^{n_0}, \eta \in \mathbb{R}^{|\mathcal{I}|}.
\end{aligned}
$$

Lagrangian dual of SDP-1 is SDP relaxation of QQP

(DSDP-1)

$$
\begin{aligned}
d_{\mathcal{I}}^{**} := \quad & \min_{Y} \quad \left\langle \begin{bmatrix} 0 & 0 \\ 0 & E \end{bmatrix}, Y \right\rangle = \langle E, \bar{Y} \rangle \\
& \text{s.t.} \quad Y_{00} = 1 \\
& \qquad {}^{e}\mathrm{bdiag}(Y) = p \\
& \qquad \mathrm{arrow}(Y) = 0 \\
& \qquad {}^{d}\mathrm{bdiag}(Y) = 0 \\
& \qquad \mathcal{P}_{\mathcal{I}}(Y) \geq 0; Y = \begin{bmatrix} Y_{00} & y^{T} \\ y & \bar{Y} \end{bmatrix} \succeq 0.
\end{aligned}
$$

Strong Duality for SDP-1

PROP: $\mathbf{d}_{\mathcal{I}}^{*} = \mathbf{d}_{\mathcal{I}}^{**}$ and $\mathbf{d}_{\mathcal{I}}^{**}$ is attained.

Proof.

Proof. The results follow since the Slater constraint qualification, SCQ, (strict feasibility) holds for SDP-1 as both $\mathbf{w}, \mathbf{t}$ are free variables. □ □

On the other hand, we show that the SCQ fails for DSDP-1!

Equivalent Matrix Form of DSDP-1

$$
\begin{array}{rll}
d_{\mathcal{I}}^{**} = & \min\limits_{Y} & \left\langle \begin{bmatrix} 0 & 0 \\ 0 & E \end{bmatrix}, Y \right\rangle \\
& \text{s.t.} & \langle A_t, Y \rangle = 1, \quad Y_{00} = 1 \\
& & \langle A_\lambda, Y \rangle = p \\
& & \langle A_j, Y \rangle = 0, \forall j \quad \text{els diag blocks sum to els col 1} \\
& & \bar{Y} \circ (A^T A - I) = 0, \text{ diag blks are diagonal} \\
& & \bar{Y}_{ij} \geq 0, \ \forall (i,j) \in \mathcal{I} \\
& & Y = \begin{bmatrix} Y_{00} & y^T \\ y & \bar{Y} \end{bmatrix} \succeq 0.
\end{array}
$$

$$
\mathbf{A_t} = \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix}; \ \mathbf{A}_\lambda = \begin{bmatrix} 0 & \bar{e}_{n_0}^T \\ \bar{e}_{n_0} & -A^T A \end{bmatrix}; \ \mathbf{A_j} = \begin{bmatrix} 0 & \frac{1}{2} e_j^T \\ \frac{1}{2} e_j & -\mathrm{Diag}\,(e_j) \end{bmatrix}
$$

Loss of Slater/strict feasibility, Y DSDP-1 feasible

$$
\mathbf{0} \neq \mathbf{A}_{\mathbf{p},\lambda} := \begin{bmatrix} p & 0 \\ 0 & 0 \end{bmatrix} - \mathbf{A}_\lambda = \begin{bmatrix} p & -\bar{e}_{n_0}^T \\ -\bar{e}_{n_0} & A^T A \end{bmatrix} \succeq \mathbf{0}
$$

$$
\langle \mathbf{A}_{\mathbf{p},\lambda}, \mathbf{Y} \rangle = \mathbf{p} \langle \mathbf{A_t}, \mathbf{Y} \rangle - \langle \mathbf{A}_\lambda, \mathbf{Y} \rangle = \mathbf{p} - \mathbf{p} = \mathbf{0}
$$

$$
\mathrm{Range}(\mathbf{Y}) \subseteq \mathrm{Kernel}(\mathbf{A}_{\mathbf{p},\lambda}) \subsetneq \mathcal{S}^{\mathbf{n}},
$$

$$
Y = U \bar{Y} U^T, \quad \mathrm{Range}(\mathbf{U}) = \mathrm{Kernel}(\mathbf{A}_{\mathbf{p},\lambda}) \text{ (facial reduction)}
$$

Smaller Facially Reduced Equivalent DSDP-1

$\mathbf{n} \times (\mathbf{n} - \mathbf{p})$ Block arrow matrix $\mathbf{W}$, $\mathrm{Range}(\mathbf{W}) = \mathrm{Kernel}(\mathbf{A}_{\mathbf{p},\lambda})$

$$\mathbf{W} = \begin{array}{c} \\ 1 \\ m_1 \\ m_2 \\ \\ m_p \end{array} \begin{array}{c} \begin{array}{ccccc} 1 & m_1-1 & m_2-1 & & m_p-1 \end{array} \\ \begin{bmatrix} 1 & 0 & 0 & \cdots & 0 \\ e_{m_1} & B_{m_1} & 0 & \cdots & 0 \\ e_{m_2} & 0 & B_{m_2} & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ e_{m_p} & 0 & 0 & \cdots & B_{m_p} \end{bmatrix} \end{array}$$

Smaller dimensional SDP, where $\hat{E} := W^T \begin{bmatrix} 0 & 0 \\ 0 & E \end{bmatrix} W$

$$\begin{array}{lll} d_{\mathcal{I}}^{**} = & \min\limits_{X} & \left\langle \hat{E}, X \right\rangle \\ & \text{s.t.} & \mathrm{arrow}(X) = 0, \\ & & {}^{\mathrm{d}}\mathrm{bdiag}(X) = 0, \\ & & X_{00} = 1, \\ & & X \succeq 0,\ X \in \mathcal{S}^{n-p}, \\ & & (WXW^T)_{ij} \geq 0, \quad \forall\, (i,j) \in \mathcal{I}, \end{array}$$

Smaller primal-dual pair; Slater holds for both

$$
\begin{aligned}
\min_{X} \quad & \left\langle \hat{E}, X \right\rangle \\
\text{s.t.} \quad & \text{arrow}(X) = 0, \\
& {}^{\text{d}}\text{bdiag}(X) = 0, \\
& X_{00} = 1, \\
& X \succeq 0,\ X \in \mathcal{S}^{n-p},
\end{aligned}
$$

$$
\begin{aligned}
\max_{t,w,\Lambda} \quad & t \\
\text{s.t.} \quad & {}^{1}\mathcal{O}(t) + \text{Arrow}(w) + {}^{\text{d}}\text{BDiag}(\Lambda) \preceq \hat{E}.
\end{aligned}
$$

Smaller p-d pair with nonneg. constr; Slater's holds

$$
\begin{aligned}
\min_{X} \quad & \left\langle \hat{E}, X \right\rangle \\
\text{s.t.} \quad & \text{arrow}(X) = 0, \\
& {}^{\text{d}}\text{bdiag}(X) = 0, \\
& X_{00} = 1, \\
& X \succeq 0,\ X \in \mathcal{S}^{n-p}, \\
& (WXW^T)_{ij} \geq 0, \quad \forall\, (i,j) \in \mathcal{I},
\end{aligned}
$$

$$
\begin{aligned}
d_{\mathcal{I}}^{**} = \quad & \max_{t,w,\Lambda,\xi} \quad t \\
& \text{s.t.} \quad {}^{1}\mathcal{O}(t) + \text{Arrow}(w) + {}^{\text{d}}\text{BDiag}(\Lambda) \\
& \qquad\qquad + \textstyle\sum_{(i,j)\in\mathcal{I}} \xi_{ij} W^T (e_i e_j^T + e_j e_i^T) W \preceq \hat{E} \\
& \xi \geq 0,\ \xi \in \mathbb{R}^{|\mathcal{I}|}.
\end{aligned}
$$

Implementation/Heuristics

Cutting planes

- start with small initial set $\mathcal{I} \subset \mathcal{I}_{\geq \mathbf{0}}$; corresponding to largest entries in $\mathbf{E}$
- add *most violated* constraints; i.e., $\mathbf{Y_{ij}} = (\mathbf{WXW^T})_{\mathbf{ij}}$ is negative and $\mathbf{E_{ij}}(\mathbf{WXW^T})_{\mathbf{ij}}$ is very negative

Obtaining a good approximation for IQP from SDP

- Perron-Frobenius rounding: *normalized* eigenvector (largest) of $\mathbf{Y}$: $\mathbf{u'} := \frac{\mathbf{p}}{\mathbf{u_2}+\cdots+\mathbf{u_n}}(\mathbf{u_2}, \ldots, \mathbf{u_n}) \in \mathbb{R}^{\mathbf{n_0}}$ satisfies $Au' = \bar{e}_p$, and $\mathbf{u'} \geq \mathbf{0}$ if $\mathbf{Y}^* \geq \mathbf{0}$ (even without $\mathbf{Y} \geq \mathbf{0}$: $\mathbf{u}$ still empirically nonnegative.)
- Projection rounding: use diagonal $\begin{pmatrix} 1 \\ u'' \end{pmatrix}$ of optimal solution $\mathbf{Y}^*$. Again, $\mathbf{u''}$ satisfies $Au'' = \bar{e}_p$, $\mathbf{u''} \geq \mathbf{0}$.

Round to (nearest) integral solution using simple LP

PROP:

For any $c \in \mathbb{R}^{n_0}$, the integer program
$\min_x \|x - c\|$ s.t. $Ax = \bar{e}_p,\ x \in \{0,1\}^{n_0}$ is equivalent to an LP.

PROOF:

For any feasible solution $\mathbf{x}$, the equality constraint $\mathbf{x^T x = p}$ is satisfied. So $\|\mathbf{x - c}\|^2 = -\mathbf{2c^T x} + (\|\mathbf{c}\|^2 + \mathbf{p})$. Hence we get the equivalent linear integer program

$$\min_x (-c)^T x \text{ s.t. } Ax = \bar{e}_p,\ x \in \{0,1\}^{n_0}.$$

Since columns of $\mathbf{A}$ are drawn from $\mathbf{I_p}$, $\mathbf{A}$ is totally unimodular. We get an equivalent linear program
$\min_x (-c)^T x$ s.t. $Ax = \bar{e}_p,\ x \in [0,1]^{n_0}$, which has an integral optimal solution. $\square$

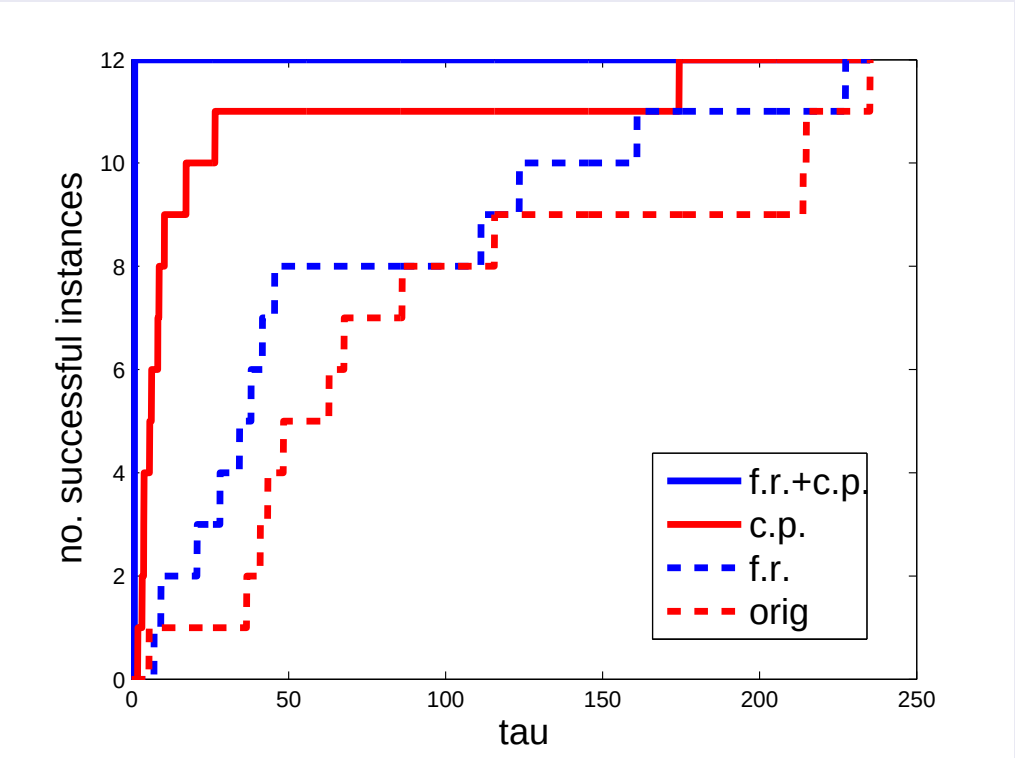
Performance Profile

$\mathbf{t_{i,j}}$:= run time for IQP final solution, instance **i** method **j**

$\mathbf{1 \leq r_{i,j}} := \dfrac{\mathbf{t_{i,j}}}{\min\{\mathbf{t_{i,j}}:\mathbf{j}=\mathbf{1},\mathbf{2},\mathbf{3},\mathbf{4}\}}$ *perform. ratio* method **j** on instance **i**

$\rho_{\mathbf{j}}(\tau)$:= number of instances **i** such that $\mathbf{r_{i,j}} \leq \tau$

Figure: Performance profile comparing the four methods



Medium sized protein 1TIM

Table: Information on input data for 1TIM

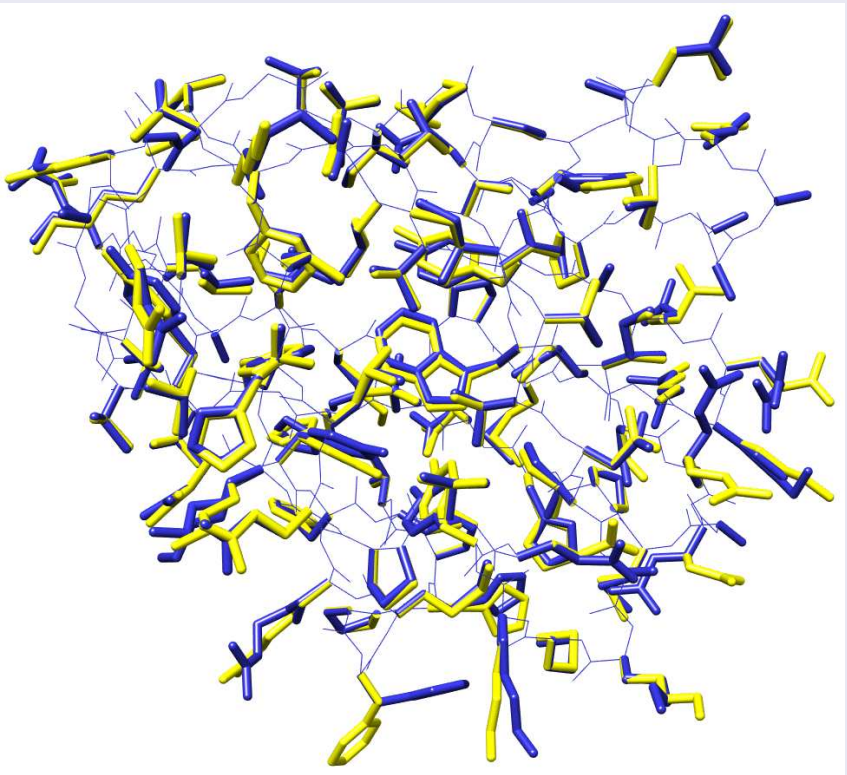
Total number of residues / partitions	249
Total number of rotamers / nodes	819
Number of energy values / edges	66520
$\max_{i,j} E_{i,j}$	5.80e+15
$\min_{i,j} E_{i,j}$	-7.7783
Number of valid nonnegativity constraints $\left(= \frac{1}{2}\left(n_0^2 - \sum_{k=1}^{p} m_k^2\right)\right)$	329760

Table: Information on output for 1TIM

Increments in cuts	**100**	**120**	**180**
Total time elapsed (hr)	2.51	2.16	1.36
Number of iterations	12	11	9
Final number of nonneg. constr.	2306	2247	2217
Percentage of valid nonneg. constr. used	0.70 %	0.68 %	0.67%
dual SDP optval	685.61	685.61	685.61
objval for IQP	685.61	685.61	685.61
relative diff	5.81e-12	8.68e-12	4.62e-13

SDPT3 4.0 with MATLAB R2012A; Linux 2.4 GHz/46.76GB

Superposition of reconstruction (light yellow) of protein 1AAC over crystallized form described in PDB (dark blue)



"For clarity: fixed backbone uses wire representation; while side chains use stick representation."

Summary

- Model protein design hard problems using IQP and quadratic-quadratic model
- Lagrangian Relaxation leads to an SDP problem and the dual is the SDP relaxation
- The Slater condition typically fails for SDP relaxations (facial reduction results in smaller/stable problem)
- Cutting planes help yield stronger approximate solutions.
- Empirical evidence shows efficiency and robustness of the approach.

Thanks for your attention! Questions?

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