Facial reduction for semidefinite programming and its application for the selection of rotamers in protein conformations

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Outline: Modeling/Degeneracy in SDP Relaxation

- Model the NP-hard side chain positioning problem using a QQP: quadratic (objective) - quadratic (constraints) program
- Find the standard semidefinite (SDP) relaxation for the QQP
- show: SDP relaxation is degenerate (not strictly feasible) (causes problems in theory and numerics)
- Preprocess/regularize using **facial reduction**
  - -two types of facial reduction
  - -facial reduction improves/strengthens numerics
- strengthen solutions using redundant quadratic constraints in model and using cutting plane techniques

We follow/improve/strengthen SDP relaxation approaches in:
-Chazelle, Kingsford, Singh for SCP, 2004
-Qing, Karish, Rendl, W. for QAP, 1998.

Biological Preamble I

Side chain positioning (SCP)

- Given: constituent atoms of a protein macromolecule:
  the side chain positioning (SCP) problem
  is one of the multiple subproblems of the hard problem of predicting a protein's three dimensional stable/folding structure.
- Our protein macromolecule is a chain of amino acid residues.

Each amino acid characterized by composition of its side chain

- amino acid consists of an "alpha" carbon atom (-C_α-), and three components attached to it:
  -(i) amino group ($(H_2N$-);
  -(ii) carboxyl group (-COOH);
  -(iii) atom group called a side chain

Biological Preamble II

Backbone of the protein

- Atoms in the *backbone* of the protein form a repetitive sequence of triplets: $\cdots \mathrm{NC_\alpha C} \quad \mathrm{NC_\alpha C} \quad \mathrm{NC_\alpha C} \quad \mathrm{NC_\alpha C} \cdots$ with each CN bonding being the result of a condensation reaction.
- Protein chain is a repetitive sequence of atoms with side chain groups sprouting from the alpha carbon atoms.

Famous protein folding problem

For tractability, subdivide into two problems:

accurate prediction of all atomic positions for folded minimal energy conformation typically uses:

1. calculate the positions of atoms in the backbone (e.g., homology modeling; fold recognition techniques)
2. given the positions of backbone atoms, calculate the conformations of all side chains, SCP.

Rotamericity/discretization of side chain conformations

- side chain typically adopts a conformation close to one of finitely many possible dihedral angles; each of the finite number of three dimensional conformations is called a rotamer.
- In this work: our more complicated side chains have rotamer sets with as many as 81 members for the twenty amino acids that make up proteins. (up to 81^{20} choices)

Mathematical MODELLING

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

- node set $\mathcal{V} = \bigcup_{i=1}^{p} \mathcal{V}_i$, $\mathcal{V}_i$ subset of rotamers for i-th amino acid side chain/residue position, ($|\mathcal{V}_i| \leq 81, i = 1, \ldots, p$) p is the number of residues.
- edge set $\mathcal{E}$; weights (energy between rotamers) E_{uv} for edge $uv \cong (u, v) \in \mathcal{E}$; E_{uu} is energy between backbone and chosen rotamer u. (ref. Kingsford thesis)

Further: SDP notation

- $\mathcal{S}^t$, $t \times t$ real symmetric matrices, trace inner-product $\langle S, T \rangle = \text{trace}\, ST$; Löwner partial order $S \succeq T$, $S \succ T$.
- for $v \in \mathbb{R}^s$, corresp. diagonal matrix is $\text{Diag}\,(v) \in \mathcal{S}^s$ adjoint linear transformation is $\text{Diag}^*(S) = \text{diag}\,(S) \in \mathbb{R}^s$ the adjoint satisfies $\langle \text{diag}\,(S), v \rangle = \langle S, \text{Diag}\,(v) \rangle$
- $\bar{e} = \bar{e}_p$ ones vector; $\bar{E} = \bar{E}_k = \bar{e}_k \bar{e}_k^T$ ones matrix

Model details

global minimum-energy conformation (GMEC)

Choose one rotamer from each set $\mathcal{V}_i$; minimize sum of weights/energies on edges in E.

- $m := (m_1 \quad \dots \quad m_p)^T$ size of subsets $\mathcal{V}_i$.
- $n_0 = |\mathcal{V}| \, (= \sum_k m_k)$
- $n := n_0 + 1$ size of matrices in SDP relaxation.

Quadratic integer programming (QIP) model

Computing the GMEC; assignment type problem

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

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

Prepare model for lifting

Change to quadratic-quadratic; Lift and Relax

Let $x := (x_u)$ and $y = \begin{pmatrix} 1 \\ x \end{pmatrix}$.

Lift to symmetric matrix space with

$$Y = yy^T, \qquad (\succeq 0)$$

i.e., Y_{uv} represents product $x_u x_v$, Y_{u0} represents $x_u 1$

Relax: ignore the (hard) rank one constraint on Y.

Zero-one variables

Change to quadratic $x_u^2 - x_u = 0$. This translates to the arrow constraint

in the lifting to Y (row/column-0 equals diagonal)

Efficiency versus strength of relaxation

Few constraints or many?

Few constraints means fewer constraints in the SDP relaxation. But adding more redundant constraints in the model means a possibly strenghtened SDP relaxation.

SDP is the Dual of Lagrangian relaxation

- Minimizing a quadratic subject to quadratic constraints leads to a Lagrangian dual which is the $\max_\lambda \min_x L(x, \lambda)$, where L is quadratic in x.
  (Thus more constraints implies stronger relaxation.)
- This leads to the constraint that the Hessian of the Lagrangian is positive semidefinite, an SDP.
- Take dual again; yields an SDP relaxation of the original problem.

Matrix formulation for QIP

relabel the n_0 nodes in $\mathcal{V}$

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

complete definition $E_{uv} = 0$ if $(u, v) \notin \mathcal{E}$ (not an edge)

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

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

$\bar{e}_j$, $\bar{E}_j$, vector, matrix of ones, respectively.

QIP in matrix notation

Using A

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

QIP as QQP and redundant constraints within {}

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

where: $\circ$ is Hadamard/elementwise product (forces zeros in Y) and $\mathcal{I} \subseteq \{(i,j) : 1 \leq i < j \leq n_0\}$ are valid inequalities

Forming SDP relaxation; start with MANY constraints

Start with QQP model with many constraints; apply recipe

1. form the Lagrangian relaxation;
2. apply homogenization;
3. simplify to obtain the dual and an equivalent SDP;
4. take the dual of dual to obtain the SDP relaxation of the original QIP
5. if strict feasibility fails, then apply facial reduction;
   -find the minimal face; obtain smaller problem with substitution $Y = W\bar{Y}W^T, \quad W \in \mathbb{R}^{n_0 \times t}, t < n_0$.
6. remove any redundant (linearly dependent) constraints.

Facial reduction as preprocessing

Exploit $Ax - \bar{e}_p = 0 \in \mathbb{R}^p$ constraint

Equivalently:

$$\begin{aligned} 0 &= e_i^T(Ax - \bar{e}_p), \quad \forall i = 1, \ldots, p \\ &= x^T A^T e_i - 1, \quad \forall i = 1, \ldots, p \\ &= \begin{pmatrix} 1 \\ x \end{pmatrix}^T \begin{pmatrix} -1 \\ A^T e_i \end{pmatrix}, \quad \forall i = 1, \ldots, p \end{aligned}$$

Let $V = \begin{bmatrix} \begin{pmatrix} -1 \\ A^T e_1 \end{pmatrix} & \cdots & \begin{pmatrix} -1 \\ A^T e_p \end{pmatrix} \end{bmatrix}$. Then $y^T V = 0$. Therefore we can add the equivalent constraint to the SDP relaxation

$$Y(VV^T) = 0 \quad \text{equivalently} \quad \text{trace}(YVV^T) = 0$$

If range of W (full column rank) equals null space of V^T, then facial reduction (smaller $\bar{Y}$) is:

$$Y \leftarrow W\bar{Y}W^T.$$

Form of SDP relaxation? ($\langle \cdot, \cdot \rangle$ trace inner prod.)

$$
\begin{array}{rll}
d_{\mathcal{I}}^{**} := & \min\limits_{Y} & \left\langle \begin{bmatrix} 0 & 0 \\ 0 & E \end{bmatrix}, Y \right\rangle = \langle E, \bar{Y} \rangle \\
& \text{s.t.} & Y_{00} = 1 \\
& & {}^{e}\text{bdiag}(Y) = p \quad (\textit{exposing matrix}) \\
\text{(DSDP-1)} & & \text{arrow}(Y) = 0 \quad (\textit{zero} - \textit{one}) \\
& & {}^{d}\text{bdiag}(Y) = 0 \quad (\textit{gangster}) \\
& & \mathcal{P}_{\mathcal{I}}(Y) \geq 0 \quad (\textit{cutting planes}) \\
& & Y = \begin{bmatrix} Y_{00} & y^T \\ y & \bar{Y} \end{bmatrix} \succeq 0.
\end{array}
$$

Adding gangster/redundant Hadamard prod. constr.

shoots holes/zeros in the matrix Y; guarantees that the diagonal blocks are diagonal matrices.

Smaller primal-dual pair - satisfying strong p-d duality

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

and: $\hat{E} := W^T \begin{bmatrix} 0 & 0 \\ 0 & E \end{bmatrix} W$, $B_k := \begin{bmatrix} I_{k-1} \\ -\bar{e}_{k-1}^T \end{bmatrix} \in \mathbb{R}^{k \times (k-1)}$

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

Dual SDP

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

We have both primal and dual strong duality, e.g., for primal strong duality this means

a zero duality gap and dual attainment

Implementation/Heuristics I (cutting planes)

Cutting planes

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

Obtaining a good approximation for QIP from SDP

Perron-Frobenius rounding

normalized eigenvector (largest) of Y^*:
$u' := \frac{p}{u_2+\cdots+u_n}(u_2, \ldots, u_n) \in \mathbb{R}^{n_0}$ satisfies

$$Au' = \bar{e}_p \quad \text{and } u' \geq 0 \text{ if } Y^* \geq 0.$$

(Empirically true even without nonnegativity of Y^*.)
(We note that the Perron-Frobenius rounding is equivalent to the best rank-one approximation as given by the Eckart-Young Theorem.)

Projection rounding

Use diagonal $\begin{pmatrix} 1 \\ u'' \end{pmatrix}$ of the optimal solution Y^*. Again, u'' satisfies

$$Au'' = \bar{e}_p,\ u'' \geq 0.$$

Data set/Numerics

Four Methods

1. original SDP relaxation
2. SDP and facial reduction
3. SDP and cutting planes
4. SDP and facial reduction and cutting planes (SCPCP)

26 proteins; data from PDB of various sizes

`SCPCP` consistently produces

- shorter cpu time,
- higher accuracy of SDP solution, and
- importantly, better integer solutions from rounding (essentially optimal - close to dual optimal value)

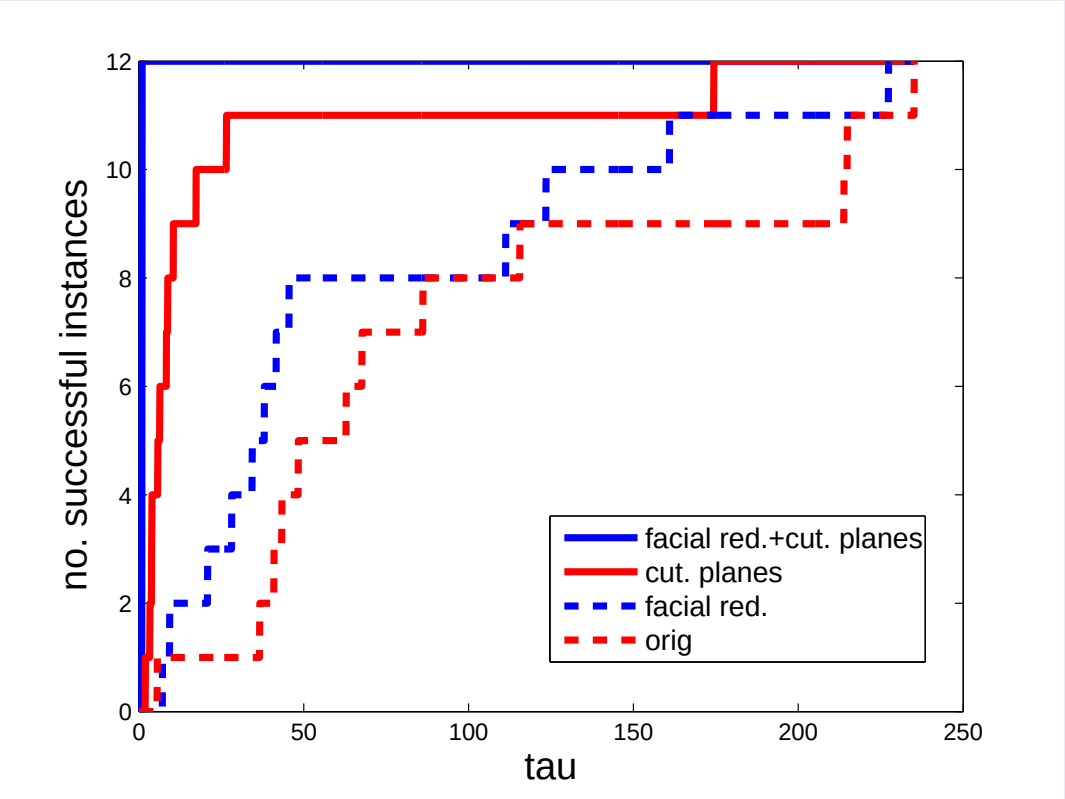
Performance Profile

$t_{i,j}$:= run time for QIP final solution, instance i method j

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

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

Figure: Performance profile comparing the four methods



Medium sized triose phosphate isomerase, 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 QIP	685.61	685.61	685.61
relative diff	5.81e-12	8.68e-12	4.62e-13

Results on small proteins

Table 3 Results on small proteins

Protein	n_0	p	run time (sec)		dual SDP optval		objval in IQP		relative diff		relative gap	
			SCPCP	[6]	SCPCP	[6]	SCPCP	[6]	SCPCP	[6]	SCPCP	[6]
1AAC	117	85	6.58	296.06	-206.33	-206.33	-206.33	-206.33	5.75E-11	1.72E-05	1.30E-09	4.21E-04
1AHO	108	54	7.97	364.73	33.53	33.53	33.53	33.53	8.44E-11	4.95E-05	2.45E-09	4.68E-04
1BRF	130	45	14.96	977.08	-31.11	-31.11	-31.11	-31.11	3.92E-11	2.27E-05	3.08E-09	1.24E-04
1CC7	160	66	28.60	1059.06	-63.76	-2.30E+07	-63.76	3.73E+04	1.13E-11	2.01	1.27E-09	1.11
1CKU	115	60	5.46	815.18	113.83	113.83	113.83	113.83	7.17E-11	4.79E-05	3.42E-09	1.13E-04
1CRN	65	37	12.76	46.42	-14.87	-14.87	-14.87	-14.87	1.64E-12	3.05E-05	2.20E-10	3.66E-04
1CTJ	153	61	16.15	777.31	-129.53	-6.69E+06	-129.53	174.65	2.98E-11	2.00	2.29E-09	1.07
1D4T	188	89	41.32	2775.34	-173.03	-2.96E+07	-173.03	291.13	3.88E-11	2.00	1.35E-09	1.20
1IGD	82	50	5.51	189.04	-69.25	-69.25	-69.25	-69.25	4.79E-10	2.74E-06	5.76E-09	3.39E-05
1PLC	129	82	14.32	1766.03	-1.50	-1.50	-1.50	-1.50	1.28E-11	7.28E-04	4.60E-10	1.09E-03
1VFY	134	63	23.49	1765.36	-90.09	-90.09	-90.09	-90.09	1.67E-11	-1.11E-05	9.15E-10	3.79E-05
4RXN	98	48	18.44	366.48	-21.65	-21.65	-21.65	-21.65	1.48E-11	2.62E-05	4.19E-10	6.67E-05

Table 4 Results on medium-sized proteins

Results on medium sized proteins

Table 4 **Results on medium-sized proteins**

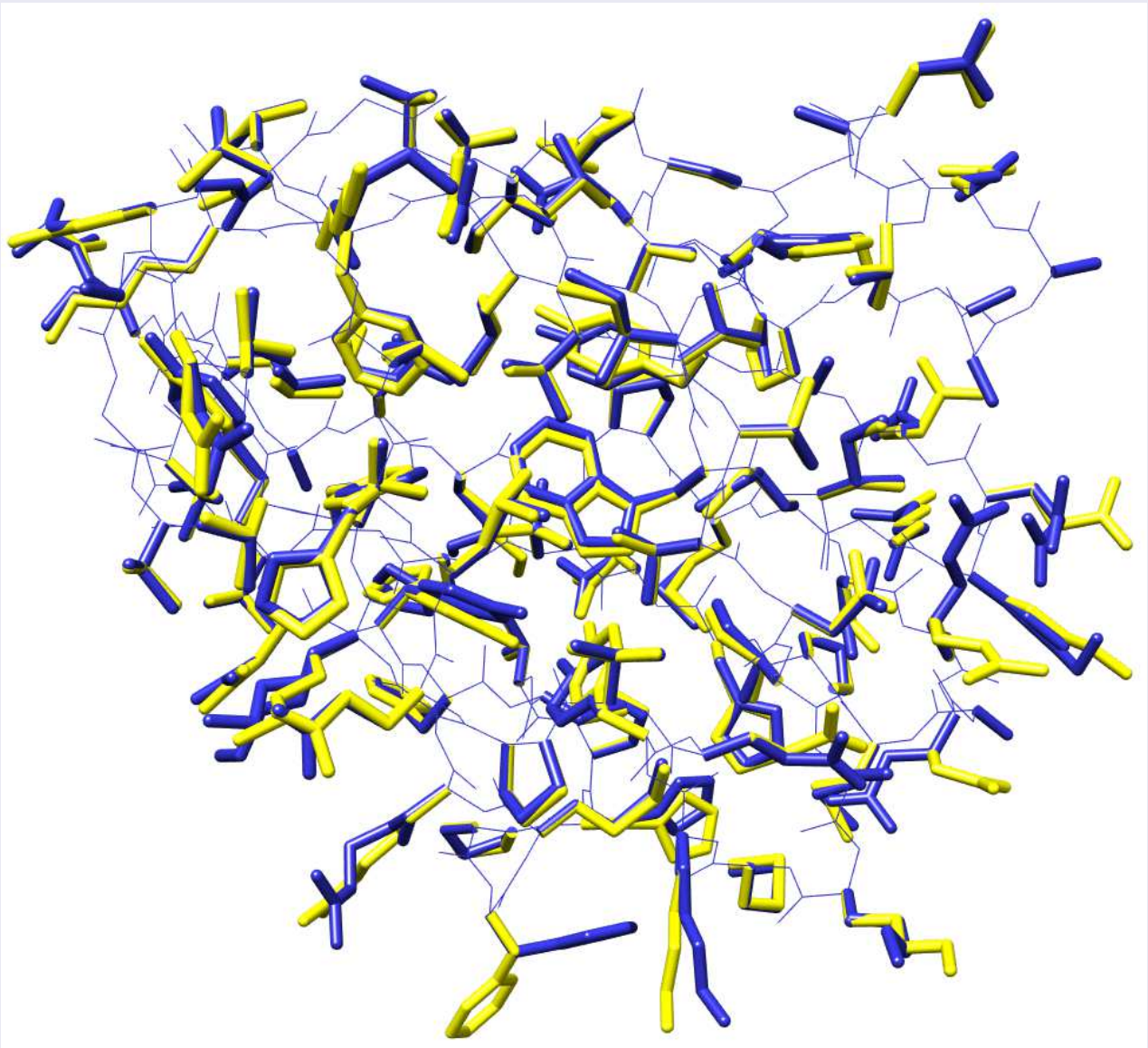
Protein	n_0	p	run time (min)		dual SDP optval		objval in IQP		relative diff		relative gap	
			SCPCP	[6]	SCPCP	[6]	SCPCP	[6]	SCPCP	[6]	SCPCP	[6]
1B9O	265	112	0.64	254.85	-140.24	-5.63E+07	-140.24	1.91E+06	1.19E-11	2.14	1.45E-09	1.24
1C5E	200	71	2.59	70.63	-131.75	-6.46E+04	-131.75	148.82	4.93E-11	2.01	5.02E-09	1.00
1C9O	207	53	2.15	66.50	-83.55	-1.88E+06	-83.55	1628.10	3.35E-12	2.00	2.77E-10	1.02
1CZP	237	83	1.90	143.95	-37.88	-2.26E+04	-37.88	1254.42	8.30E-11	2.24	1.03E-08	1.00
1MFM	216	118	0.19	102.11	-201.29	-7.36E+07	-201.29	1369.92	2.01E-11	2.00	1.24E-09	1.09
1QQ4	365	143	5.70	-	-102.40	-	-102.40	-	6.49E-11	-	2.27E-08	-
1QTN	302	134	5.04	-	-178.77	-	-178.77	-	2.24E-11	-	4.12E-09	-
1QU9	287	101	7.55	-	-124.96	-	-124.96	-	1.80E-11	-	5.52E-09	-

Large Scale Case

Table 5 Results on large proteins (SCPCP only)

Protein	n_0	p	run time (hr)	dual SDP optval	Objval in IQP	rel. diff	rel. gap	numcut	# iter	Final # cuts
1CEX	435	146	0.08	140.20	140.20	1.26E-11	5.57E-09	40	9	485
1CZ9	615	111	3.96	497.46	497.46	2.98E-13	6.37E-10	60	25	1997
1QJ4	545	221	0.15	-286.83	-286.83	5.31E-12	1.14E-09	60	14	1027
1RCF	581	142	0.85	-191.54	-191.54	3.71E-12	1.15E-08	60	17	1305
2PTH	930	151	29.65	-159.41	-159.41	8.69E-09	7.63E-06	120	34	7247
5P21	464	144	0.31	-135.75	-135.75	1.39E-12	7.33E-10	40	16	822

Figure: Superposition of the reconstruction (light grey) of 1AAC over the crystallized form described in the PDB (dark grey)



Summary

- We model protein design using using a QIP and transform to a quadratic-quadratic model
- Lagrangian Relaxation leads to an SDP program and the dual is the SDP relaxation
- Adding redundant constraints strengthens the SDP relaxation
- The strict feasibility fails for SDP relaxation; but, it can be exploited using facial reduction to get a smaller/stable problem
- Cutting planes help yield stronger approximate solutions. Empirical evidence shows efficiency and robustness of adding redundant constraints and applying facial reduction.

Thanks for your attention!

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