A Peaceman-Rachford Splitting Method for the Protein Side-Chain Positioning Problem

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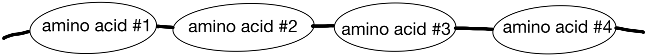
What is the Protein Side-Chain Positioning Problem?

What is a Protein?

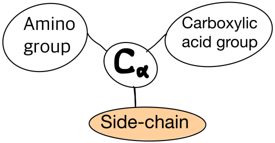
A protein

A collection of chains of amino acids

- **Chain**:
  a sequence of amino acids



- **Amino acid**:
  building blocks of a protein
  consists of $\{C, H, O, N\}$



Protein Side-Chain Positioning Problem (**SCP**)

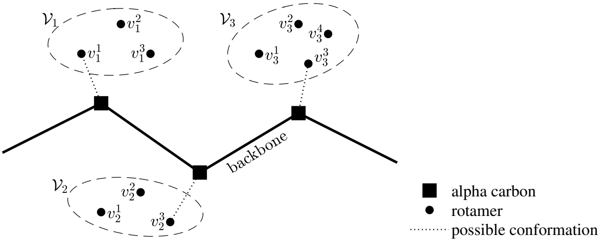
Task

Given

- a collection of sets of candidates for each side-chain of an amino acid
- pair-wise energy values between all candidates

Do

- Pick exactly ONE candidate from each set
- while yielding the minimum energy



Applications & Roadmap

Applications

- One of the most important subproblems of the protein structure prediction problem.
- Examples: ligand binding, protein-protein docking, etc

Roadmap

1. Formulate as a quadratic integer program
2. Obtain **SDP** (semidefinite) relaxation
3. Apply facial reduction (**FR**)
4. Obtain **DNN**(doubly nonnegative) relaxation
5. Solve the model using splitting method; Peaceman-Rachford

Problem Formulation

Problem Formulation as **IQP**

Given a collection of disjoint sets $\mathcal{V}_i, i \in [p]$. $|\mathcal{V}_i| = m_i$,
$n_0 = \sum_{i=1}^{p} m_i$ and $\mathcal{V} = \cup_{i=1}^{p} \mathcal{V}_i$.
$\mathcal{V}_i$: rotamer set, elements in $\mathcal{V}_i$ rotamers.

Goal

1. Select *exactly one* rotamer v_i from each set $\mathcal{V}_i$,
2. Minimize the sum of
   1. the weights (energy) on the edges between chosen rotamers, and
   2. the energy between each chosen rotamer and the backbone

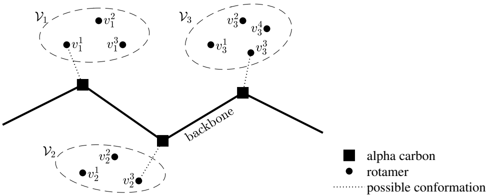


Figure: A Diagram of the Protein Side-Chain Positioning Problem

Problem Formulation as **IQP**

$$\begin{array}{rll} p^*_{\mathbf{IQP}} := & \min & \sum_{u,v} E_{uv} x_u x_v \\ & \text{s.t.} & \sum_{u \in \mathcal{V}_k} x_u = 1, \quad k = 1, \ldots, p \\ & & x = (x_u) \in \{0,1\}^{n_0}. \end{array}$$

Equivalently,

$$(\mathbf{IQP}) \qquad \begin{array}{rll} p^*_{\mathbf{IQP}} := & \min & x^T E x \\ & \text{s.t.} & Ax = \bar{e}_p \\ & & x = \begin{bmatrix} v_1^T & v_2^T & \ldots & v_p^T \end{bmatrix}^T \in \{0,1\}^{n_0} \\ & & v_i \in \{0,1\}^{m_i}, \; i = 1, \ldots, p, \end{array}$$

where

$$A := \operatorname{blkdiag}(\bar{e}^T_{m_1}, \bar{e}^T_{m_2}, \cdots, \bar{e}^T_{m_p}) \in \mathbb{R}^{p \times n_0},$$

Strategy

The **SCP** problem is NP-hard $\rightarrow$ Work with **SDP** relaxation

Model Formulation (Relaxation)

Reformulation; **SDP** Lifting

Step 1: Lift $x \in \mathbb{R}^{n_0}$ to symmetric matrix

$$Y_x := \begin{bmatrix} 1 \\ x \end{bmatrix} \begin{bmatrix} 1 \\ x \end{bmatrix}^T = \begin{bmatrix} 1 & x^T \\ x & xx^T \end{bmatrix} \in \mathbb{S}^{n_0+1}.$$

- Objective: $\hat{E} := \text{blkdiag}(0, E) \implies \langle x, Ex \rangle = \langle \hat{E}, Y_x \rangle$
- Constraint:

$$\begin{array}{rcl} Ax = e & \implies & A^T Ax = A^T e = e \\ & \implies & (A^T A - I)x = e - x \\ & \implies & (A^T A - I)xx^T = ex^T - xx^T \\ & \implies & \text{trace}(A^T A - I)xx^T = \text{trace}(ex^T - xx^T) = 0 \\ & \implies & (A^T A - I) \circ xx^T = 0 \\ & \implies & G_{\mathcal{J}}(Y_x) = E_{00} \quad \text{(Gangster constraint)} \end{array}$$

Step 2: drop the rank-1 restriction on Y_x

Reformulation; **SDP** Lifting

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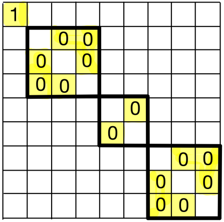


Step 2: drop the rank-1 restriction on Y_x

SDP Relaxation

$$\textbf{(IQP)} \qquad p^*_{\textbf{IQP}} := \min\{x^T E x \ : \ Ax = \bar{e}, \ x \in \{0,1\}^{n_0}\}$$

$$\Downarrow$$

$$p^*_{\textbf{IQP}} = \min_{Y_x} \left\{ \operatorname{trace}(\hat{E} Y_x) \ : \ G_{\mathcal{J}}(Y_x) = E_{00}, \, Y_x \succeq 0 \text{ AND } Y_x \text{ rank-1} \right\}$$

$$\Downarrow$$

$$p^* = \min_{Y \in \mathbb{S}^{n_0+1}} \left\{ \operatorname{trace}(\hat{E} Y) \ : \ G_{\mathcal{J}}(Y) = E_{00}, \, Y \succeq 0 \right\}$$

Advantage

1. convex

Disadvantage

1. potential loss in optimal value: $p^* \leq p^*_{\textbf{IQP}}$

Face of $\mathbb{S}^n_+$

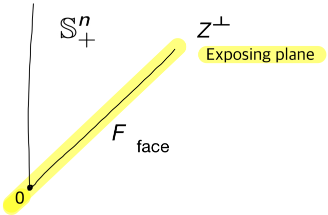
Face

A convex cone F is a face of $\mathbb{S}^n_+$ if,

for $X, Y \in \mathbb{S}^n_+$ with $\{\lambda X + (1-\lambda)Y : \lambda \in (0,1)\} \subseteq F$, we have $X, Y \in F$.

Every face F of $\mathbb{S}^n_+$ is exposed, i.e., $Z \in \mathbb{S}^n_+$, $V \in \mathbb{R}^{m \times r}$, $r \leq n$,

$$\boxed{F = \mathbb{S}^n_+ \cap Z^\perp = V \mathbb{S}^r_+ V^T}$$



Facial Reduction for **SCP**

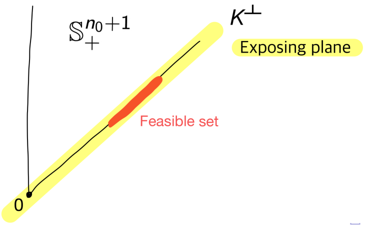
$$Ax = \bar{e}_p \implies \begin{bmatrix} 1 \\ x \end{bmatrix}^T \begin{bmatrix} -\bar{e}_p^T \\ A^T \end{bmatrix} = 0$$

$$\implies \begin{bmatrix} 1 \\ x \end{bmatrix} \begin{bmatrix} 1 \\ x \end{bmatrix}^T \begin{bmatrix} -\bar{e}_p^T \\ A^T \end{bmatrix} \begin{bmatrix} -\bar{e}_p^T \\ A^T \end{bmatrix}^T = 0$$

$$\implies \left\langle \underbrace{\begin{bmatrix} 1 \\ x \end{bmatrix} \begin{bmatrix} 1 \\ x \end{bmatrix}^T}_{=:Y_x}, \underbrace{\begin{bmatrix} -\bar{e}_p^T \\ A^T \end{bmatrix} \begin{bmatrix} -\bar{e}_p^T \\ A^T \end{bmatrix}^T}_{=:K} \right\rangle = 0.$$

$$\boxed{Y_x, K \succeq 0 \implies KY_x = 0 \implies K \text{ is an } \textit{exposing vector}}$$

For all Y feasible point range$(Y) \subseteq$ null(K).



Facially Reduced Model

Find a full column rank matrix $V \in \mathbb{R}^{(n_0+1)\times(n_0+1-p)}$ such that $\operatorname{range}(V) = \operatorname{null}(K) = \operatorname{null}\left(\left[\bar{e}_p, A\right]\right)$:

$$\text{feasible set} \subseteq V\mathbb{S}_+^{n_0+1-p}V^T$$

$$\boxed{\min_{Y\in\mathbb{S}^{n_0+1}} \left\{\operatorname{trace}(\hat{E}Y) \ : \ G_{\mathcal{J}}(Y) = E_{00}, Y \succeq 0\right\}}$$

$\Downarrow$ Include $Y = VRV^T$

$$\boxed{\min_{Y,R} \left\{\operatorname{trace}(\hat{E}Y) \ : \ G_{\mathcal{J}}(Y) = E_{00}, Y = VRV^T, \ R \in \mathbb{S}_+^{n_0+1-p}\right\}}$$

- Nice environment for using a spitting scheme
- Slater condition holds

DNN Relaxation

Extra Properties

Let $Y \in \mathbb{S}^{n_0+1}$, $R \in \mathbb{S}_+^{n_0+1-p}$ with $Y = VRV^T$, $G_{\mathcal{J}}(Y) = E_{00}$.
Then the following hold.

1. $\operatorname{trace}(R) = p + 1$.
2. $0 \leq Y_{i,j} \leq 1, \ \forall i, j$.

We define the sets

$$\mathcal{Y} := \{Y \in \mathbb{S}^{n_0+1} : G_{\mathcal{J}}(Y) = E_{00}, \ 0 \leq Y \leq 1\},$$
$$\mathcal{R} := \{R \in \mathbb{S}^{n_0+1-p} : R \succeq 0, \ \operatorname{trace}(R) = p + 1\}.$$

Complete our model, **DNN** relaxation to (**IQP**)

$$(\mathbf{DNN}) \qquad \begin{array}{rl} p^*_{\mathbf{DNN}} = \min\limits_{R,Y} & \operatorname{trace}(\hat{E}Y) \\ & Y = VRV^T \\ & Y \in \mathcal{Y} \\ & R \in \mathcal{R}. \end{array}$$

Some Known Dual Multipliers

Some elements of the optimal dual multiplier Z^* are known.

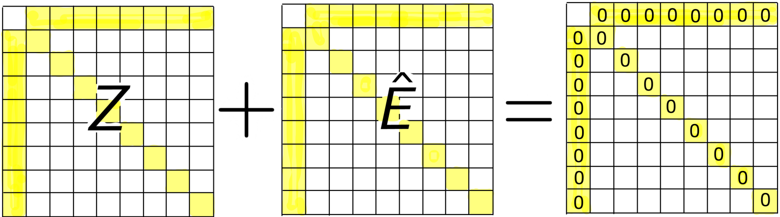
Theorem

Let (R^*, Y^*) be an optimal pair for and let Z be a Lagrange multiplier associated with the constraint $Y = VRV^T$. Define

$$\mathcal{Z}_A := \left\{ Z \in \mathbb{S}^{n_0+1} : Z_{i,i} = -(\hat{E})_{i,i},\ Z_{0,i} = Z_{i,0} = -(\hat{E})_{0,i},\ i = 1, \ldots, n_0 \right\}.$$

Then there exists $Z^* \in \mathcal{Z}_A$ such that (R^*, Y^*, Z^*) solves **DNN** *.*

We define the projection operator $\mathcal{P}_{\mathcal{Z}_A}(Z)$ onto the set $\mathcal{Z}_A$.



Algorithm

Peaceman-Rachford Splitting Scheme

Define augmented Lagrangian

$$\mathcal{L}_A(R, Y, Z) := \langle \hat{E}, Y \rangle + \langle Z, Y - VRV^T \rangle + \frac{\beta}{2} \| Y - VRV^T \|_F^2.$$

We use a variation of the strictly contractive Peaceman-Rachford splitting method (PRSM) to solve the model.

Algorithm Splitting Method Scheme

1: **Initialize:** $Y^0 \in \mathbb{S}^{n_0+1}$, $Z^0 \in \mathcal{Z}_A$, $\beta \in [1, \infty), \gamma \in (0, 1)$
2: **while** stopping criteria not met **do**
3: $\quad R^{k+1} = \operatorname*{argmin}_{R \in \mathcal{R}} \mathcal{L}_A(R, Y^k, Z^k)$
4: $\quad Z^{k+\frac{1}{2}} = Z^k + \gamma\beta \cdot \mathcal{P}_{\mathcal{Z}_A}\left(Y^k - VR^{k+1}V^T\right)$
5: $\quad Y^{k+1} = \operatorname*{argmin}_{Y \in \mathcal{Y}} \mathcal{L}_A(R^{k+1}, Y, Z^{k+\frac{1}{2}})$
6: $\quad Z^{k+1} = Z^{k+\frac{1}{2}} + \gamma\beta \cdot \mathcal{P}_{\mathcal{Z}_A}\left(Y^{k+1} - VR^{k+1}V^T\right)$
7: **end while**

Subproblems

1. R-subproblem

$$\begin{aligned} R^{k+1} &= \operatorname*{argmin}_{R\in\mathcal{R}} \mathcal{L}_A(R, Y^k, Z^k) \\ &= \operatorname*{argmin}_{R\in\mathcal{R}} \left\| Y^k - VRV^T + \tfrac{1}{\beta} Z^k \right\|_F^2 \\ &= \operatorname*{argmin}_{R\in\mathcal{R}} \left\| R - V^T(Y^k + \tfrac{1}{\beta} Z^k) V \right\|_F^2 \\ &= \mathcal{P}_{\mathcal{R}} \left(V^T \left(Y^k + \tfrac{1}{\beta} Z^k \right) V \right). \end{aligned}$$

2. Y-subproblem

$$\begin{aligned} Y^{k+1} &= \operatorname*{argmin}_{Y\in\mathcal{Y}} \mathcal{L}_A(R^{k+1}, Y, Z^{k+\frac{1}{2}}) \\ &= \operatorname*{argmin}_{Y\in\mathcal{Y}} \left\| Y - \left(VR^{k+1}V^T - \tfrac{1}{\beta}(\hat{E} + Z^{k+\frac{1}{2}}) \right) \right\|_F^2 \\ &= \mathcal{P}_{0\leq Y\leq 1} \left(G_{\mathcal{J}^c} \left(VR^{k+1}V^T - \tfrac{1}{\beta}(\hat{E} + Z^{k+\frac{1}{2}}) \right) \right). \end{aligned}$$

Lower Bound

Dual functional $g : \mathbb{S}^{n_0+1} \to \mathbb{R}$

$$g(Z) := \min_{R \in \mathcal{R}, Y \in \mathcal{Y}} \langle \hat{E}, Y \rangle + \langle Z, Y - VRV^T \rangle.$$

Lower bound via Lagangian dual

$$\begin{aligned} p^*_{\mathbf{DNN}} &= \max_Z \min_{R \in \mathcal{R}, Y \in \mathcal{Y}} \langle \hat{E}, Y \rangle + \langle Z, Y - VRV^T \rangle \\ &\geq \min_{R \in \mathcal{R}, Y \in \mathcal{Y}} \langle \hat{E}, Y \rangle + \langle Z, Y - VRV^T \rangle \\ &= \min_{Y \in \mathcal{Y}} \langle \hat{E} + Z, Y \rangle + \min_{R \in \mathcal{R}} \langle -V^T Z V, R \rangle \\ &= \min_{Y \in \mathcal{Y}} \langle \hat{E} + Z, Y \rangle - (p+1)\lambda_{\max}(V^T Z V), \end{aligned}$$

Upper Bound

Let $x^{\text{approx}} \in \mathbb{R}^{n_0}$ be the second through to the last elements of

- the first column of Y^{out}, or
- the most dominant eigenvector of Y^{out}.

Find the nearest feasible solution to (**IQP**) from x^{approx} via projection

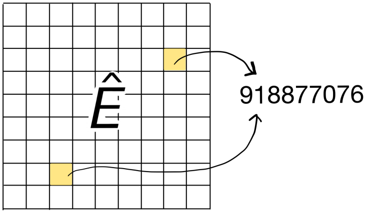
$$\begin{aligned} & \min_x \left\{ \|x - x^{\text{approx}}\|^2 \ : \ Ax = \bar{e}_p, \ x \in \{0,1\}^{n_0} \right\} \\ \equiv \ & \min_x \left\{ \langle x, x^{\text{approx}} \rangle \ : \ Ax = \bar{e}_p, \ x \geq 0 \right\}. \end{aligned}$$

Numerical Result

Data

- The energy values in E are computed by Lennard-Jones potential formula (engages the Euclidean distance between a pair)
- Pre-process: dead-end-elimination (reduction on rotamer sets)

Typical data: very large elements in $\hat{E}$.



$\leftarrow$ Not a problem for us!

Recall the Y-update

$$Y^{k+1} = \mathcal{P}_{0 \le Y \le 1}\left(G_{\mathcal{J}^c}\left(VR^{k+1}V^T - \frac{1}{\beta}(\hat{E} + Z^{k+\frac{1}{2}})\right)\right)$$

$\hat{E}_{i,j}$ a very large element $\longrightarrow \mathcal{P}_{0 \le Y \le 1}$ sets $Y_{i,j}^{k+1} = 0$
(Implicit gangster constraint on the large elements; intuitive)

Problem Data				Numerical Results			Timing		χ angle	
#	name	p	n_0	lbd	ubd	rel-gap	iter	time(sec)	χ_1 angle	χ_{12} angle
1	1AIE	26	34	-46.95892	-46.95892	7.03672e-15	200	0.09	0.654	0.480
2	2ERL	34	103	55.33284	55.33284	5.61228e-14	300	5.52	0.588	0.476
3	1CBN	37	112	-40.42751	-40.42751	2.51561e-13	1652	33.40	0.821	0.727
5	1BX7	41	99	16.96026	16.96026	3.47516e-11	200	3.31	0.610	0.522
6	2FDN	42	51	-59.43092	-59.43092	2.45420e-14	100	0.01	0.738	0.583
7	1MOF	46	94	-79.05580	-79.05580	8.57412e-15	200	2.56	0.717	0.514
8	1CTF	47	74	-97.18893	-97.18893	1.28887e-13	100	0.82	0.766	0.639
9	1NKD	50	199	-51.78466	-51.78466	7.80603e-13	4845	282.37	0.700	0.659
10	2IGD	50	126	-78.50608	-78.50608	8.99352e-15	495	9.91	0.760	0.677
11	2SN3	53	112	-5.56818	-5.56818	4.78619e-12	600	10.95	0.736	0.541
12	1MSI	54	112	-87.46958	-87.46958	1.53466e-14	600	10.97	0.796	0.722
13	1AHO	54	140	24.66925	24.66925	7.76341e-15	1400	39.72	0.722	0.556
15	1CTJ	61	258	-103.32705	-103.32705	1.84748e-12	1919	143.33	0.902	0.679
16	1RZL	65	121	17.26470	17.26470	1.17993e-12	2177	42.27	0.831	0.758
17	1TIF	66	614	-155.17859	-155.17859	5.42223e-14	700	207.67	0.758	0.567
18	1BDO	69	221	-136.29933	-136.29933	3.94748e-15	500	27.28	0.855	0.646
19	1OPD	70	112	-139.64632	-139.64632	4.76581e-14	200	2.86	0.657	0.438
20	1VQB	75	406	-96.94940	-96.94940	2.24575e-14	700	93.15	0.824	0.611
21	1IUZ	75	221	-150.88238	-150.88238	4.31820e-15	3400	194.65	0.880	0.712
22	1ABA	76	376	-137.59962	-137.59963	1.35194e-11	400	46.04	0.895	0.734
23	1FNA	76	131	-172.01313	-172.01313	1.72989e-14	700	13.49	0.800	0.651
24	1CYO	78	220	-75.36668	-75.36668	1.33555e-13	500	27.53	0.833	0.639
26	2MCM	80	123	-135.14024	-135.14024	2.16748e-11	200	3.04	0.850	0.800
28	1A68	81	424	-178.12555	-178.12555	9.54680e-16	1000	142.07	0.840	0.662
30	2ACY	84	580	-146.32254	-146.32254	2.88432e-14	8200	2063.31	0.857	0.667
31	1BM8	85	687	-119.54537	-119.54537	3.55137e-16	1200	405.69	0.835	0.618
32	1BKF	89	339	-170.80514	-170.80514	1.24600e-13	1832	177.58	0.843	0.545
33	3CYR	91	137	-144.06405	-144.06405	1.42138e-11	1900	33.93	0.846	0.593
34	3VUB	92	544	-229.38312	-229.38312	4.94542e-15	900	205.25	0.804	0.574
35	1JER	96	462	-120.78401	-120.78400	6.02020e-13	3050	505.43	0.777	0.541
36	2HBG	97	275	-178.42210	-178.42210	4.28894e-15	300	21.82	0.825	0.520
37	1POA	97	470	278.08280	278.08280	8.16180e-14	4992	860.25	0.773	0.529
38	1C52	99	256	-223.31096	-223.31096	1.18101e-14	2700	172.67	0.828	0.690
39	2A0B	99	642	-161.45228	-161.45228	1.98309e-14	5400	1616.92	0.765	0.650

Table: The Numerical Result of the Small PDB Instances

Problem Data			Numerical Results			Timing		χ angle	
name	p	n_0	lbd	ubd	rel-gap	iter	time(sec)	χ_1 angle	χ_{12} angle
1AL3	201	1077	119.66598	119.66598	5.10139e-12	12877	9773	0.791	0.549
1ARB	202	1466	-61.52823	-61.52823	1.22112e-13	7200	11157	0.851	0.693
1NLS	203	1060	-297.73578	-297.73578	3.50702e-14	2600	1851	0.818	0.603
1MRJ	208	1178	-295.13711	-295.13711	1.23056e-13	1931	1700	0.813	0.636
1OAA	208	854	-317.83422	-317.83422	2.39277e-14	2300	1012	0.803	0.680
2DRI	210	906	-398.45564	-398.45564	3.10608e-14	6400	3003	0.805	0.616
2CBA	223	1018	-86.52145	-86.52145	1.30549e-11	3200	1979	0.857	0.665
2POR	224	1304	-83.22221	-83.22221	8.82520e-12	12846	14255	0.830	0.642
3SEB	224	1412	77.15853	77.15852	3.38717e-13	267900	346506	0.782	0.592
1MLA	227	1322	-484.10542	-484.10542	1.87677e-14	40100	42801	0.815	0.617
1DCS	232	1170	-342.68600	-342.68600	1.65634e-14	4300	3519	0.817	0.609
1AKO	234	1387	-244.65691	-244.65691	1.39815e-13	5100	6209	0.808	0.605
1PDA	239	891	-423.50226	-423.50226	1.97074e-14	5500	2427	0.860	0.696
1EZM	239	1497	-217.36581	-217.36581	5.10340e-13	2000	3136	0.862	0.575
1C3D	243	1679	-400.69876	-400.69876	1.38850e-14	23900	85403	0.827	0.655
8ABP	245	1743	-273.90716	-273.90716	1.59505e-14	7100	27815	0.802	0.640
1CVL	246	910	-537.04249	-537.04249	4.37792e-14	7900	3525	0.850	0.711
1RYC	248	1831	-202.60568	-202.60568	1.11948e-15	12500	56371	0.802	0.561
1MRP	248	1648	-350.97062	-350.97062	5.27240e-14	11600	44124	0.754	0.596
1IXH	252	1134	-289.75241	-289.75241	1.37089e-14	1000	770	0.821	0.663
1FNC	253	1940	-310.60998	-310.60999	9.51745e-13	27600	151870	0.802	0.627
1SBP	256	1704	-271.08838	-271.08838	4.18600e-15	43300	170625	0.816	0.596
2CTC	264	1536	-213.88596	-213.88596	1.59617e-13	10000	34876	0.826	0.635
1PGS	265	2190	-16.14049	-16.14049	4.69696e-14	22800	156081	0.837	0.541
1MSK	271	1798	-162.50978	-162.50978	1.03393e-13	152200	606216	0.775	0.585
1BG6	271	784	-452.62383	-452.62383	3.17007e-13	13300	4072	0.819	0.640
1ARU	271	939	-314.40589	-314.40589	9.99588e-12	73500	33326	0.775	0.629
1A8E	274	1096	-249.85499	-249.85499	3.17872e-15	103700	68466	0.825	0.613
1AXN	278	2343	-300.34290	-300.34291	2.41852e-14	13400	105053	0.831	0.631
1TAG	279	1330	-253.22167	-253.22167	2.78928e-13	4200	4301	0.817	0.634
1ADS	280	1560	733.91440	733.91440	6.19197e-16	13000	46057	0.771	0.498
3PTE	284	2006	161.17216	161.17216	3.88515e-14	11000	58278	0.856	0.651
1CEM	292	2400	-24.20196	-24.20196	2.92824e-13	7100	55850	0.860	0.662

Table: The Numerical Result of the Large PDB Instances

Conclusion

- Facial reduction technique $\rightarrow$ natural splitting of variables
- Splitting $\rightarrow$ easy to engage constraints individually
- Strong numerical result $\rightarrow$ solved to optimality

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Thank you