Torsion Angle Normal Mode Analysis: A Powerful Tool for Modeling Protein Conformational Change

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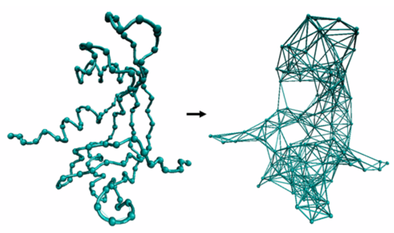
Normal Mode Analysis

- NMA is less computationally intensive and reaches longer time scales than MD
- Models large scale collective motions of proteins
- Assumes potential harmonic about equilibrium conformation

- Treats proteins as beads connected by springs



- A linear combination of the normal modes, which are eigenvectors, describes the dynamics of the system

Normal Modes in Torsion Angle Space

- Focuses on large scale movement by freezing bonds and angles

$$E = \sum_{bonds} K_b (b - b_o)^2$$

$$- \sum_{angles} \tfrac{1}{2} K_\theta (\theta - \theta_o)^2$$

$$E_{torsion} = + \sum_{torsion\_angles} K_\phi \left[1 - \cos(n\phi + \delta)\right]$$

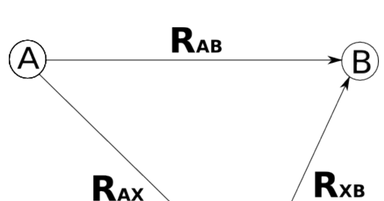
$$+ \sum_{nonbonded\_pairs} \varepsilon \left[\left(\frac{r_o}{r}\right)^{12} - 2\left(\frac{r_o}{r}\right)^{6} \right]$$

$$+ \sum_{partial\_charges} K_q \frac{q_i q_j}{r}$$

- Up to 10 fold decrease in degrees of freedom
- Torsion angle space allows easy way to describe rotation in proteins
- Prevents non-chemical distortion of bonds
- Torsional space is non-orthogonal, which makes calculations more difficult.

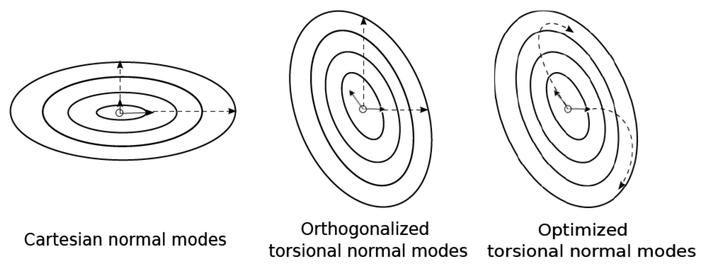
Comparison of Torsional and Cartesian Normal Modes

- Test methods on a test set of 13 pairs of proteins in two conformations
- Determine how close conformation A gets to conformation B with the 10 lowest frequency modes using the fractional RMS (*fRMS*) metric



- When the modes are applied to conformation A, they give conformation X. The distance, in RMS space, between X and B is $|R_{XB}|$, which is then normalized by the original distance between A and B, $|R_{AB}|$, to give $\boldsymbol{fRMS = |R_{XB}|/|R_{AB}|}$. A *fRMS* of 0 represents a perfect conformational change.

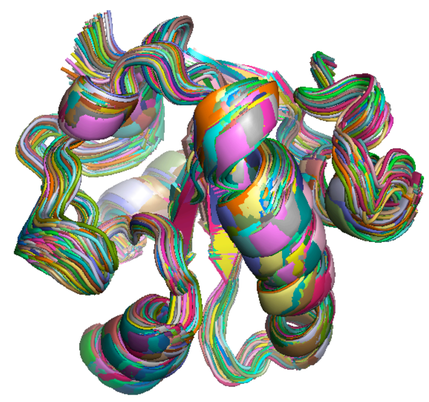
- Need to find optimal combination of the ten modes to get from A to B. For Cartesian, easy to take a linear combination so that $\mathbf{R}_{AX} = \sum_{i}^{N} a_i \mathbf{v}_i$
- For torsional modes, can orthogonalize the displacement vectors and treat the same as Cartesian to get orthogonalized torsional modes. In contrast, allow modes to move along curved paths in Cartesian space. Perform simplex minimization with random starting coefficients to determine best combination of optimized torsional modes.



The energy surface is represented by the elliptical contour lines, the normal mode displacement vectors by the solid arrows and the normal mode movement is represented by dashed lines.

Quickly Sampling Conformational Space

- Use torsional normal modes to quickly sample conformational space, specifying which modes to use, number of structures per 0.1 A bin, and RMSD from the original structure sampled.
- Can apply low and high frequency torsional modes to to capture global and local motion.



- Improves protein function prediction calculations.
- Could be used to improve ligand docking calculations.

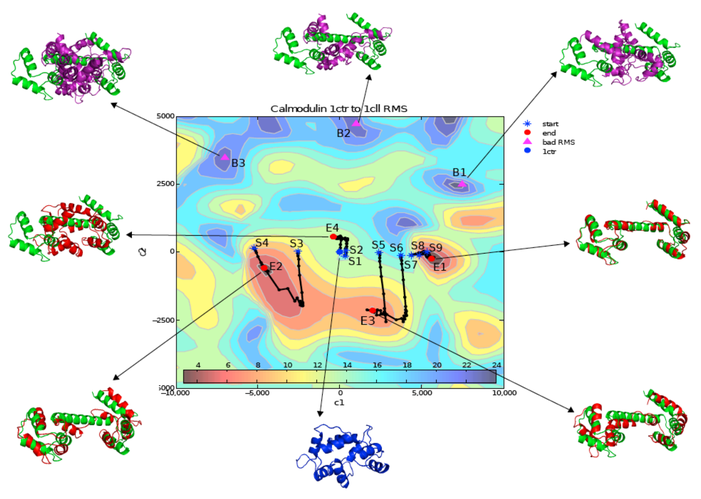
Performance of Cartesian, orthogonalized torsional and optimized torsional modes

Protein	PDB ID A	PDB ID B	# AA	# Chains	RMS A-B (Å)	*fRMS* A ⇨ B: Cart	Orth Tors	Opt Tors	*fRMS* B ⇨ A: Cart	Orth Tors	Opt Tors	Min. Num. Modes A ⇨ B	Min. Num. Modes B ⇨ A
Ribose-binding protein	1BA2_A	2DRI	271	1	6.2	0.244	0.221	0.136	0.440	0.466	0.480	2	10
Calmodulin	1CLL	1CTR	144	1	14.8	0.561	0.580	0.194	0.655	0.709	0.133	2	1
LAO binding protein	2LAO	1LST	238	1	4.7	0.227	0.244	0.225	0.809	0.867	0.833	10	10
Ribonuclease III	1YZ9_AB	1YYO_AB	436	2	7.3	0.287	0.462	0.273	0.876	0.792	0.376	10	3
Diptheria toxin	1DDT	1MDT_A	535	1	15.6	0.653	0.637	0.383	0.781	0.826	0.729	3	8
Lactoferrin	1LFH	1LFG	691	1	6.4	0.358	0.415	0.441	0.510	0.642	0.538	10	10
Aspartate transcarbamoylase	8ATC	5AT1	912	4	4.9	0.447	0.451	0.461	0.703	0.444	0.425	10	4
Aspartate aminotransferase	9AAT_A	1AMA	401	1	1.7	0.502	0.495	0.470	0.519	0.496	0.519	8	10
Skeletal muscle Ca2+ ATPase	1SU4_A	1IWO_A	994	1	14	0.546	0.544	0.472	0.778	0.861	0.732	8	5
5'-Nucleotidase	1HPU_D	1OID_A	525	1	9.3	0.663	0.661	0.529	0.676	0.758	0.615	9	9
Scallop myosin II	1QVI_AYZ	1KK8_ABC	1079	3	27.6	0.709	0.719	0.567	0.774	0.810	0.612	4	4
T7 RNA polymerase	1MSW_D	1QLN_A	883	1	18.3	0.808	0.783	0.779	0.982	0.980	0.970	5	9
NtrC	1DC8_A	1DC7_A	123	1	3.2	0.963	0.956	0.892	0.944	0.938	0.939	2	10
Average fractional RMS						**0.536**	**0.551**	**0.448**	**0.727**	**0.738**	**0.608**		

The fractional RMS (*fRMS*) values of Cartesian normal modes (*Cart*), orthogonalized torsional normal modes (*Orth Tors*) and optimized torsional normal modes (*Opt Tors*). The *fRMS* values are calculated using the 10 lowest frequency modes. The lowest *fRMS* for each conformational change is shaded in gray. The minimum number of modes (*Min. Num. Modes*) is the number of optimized torsional modes that are needed to achieve the *fRMS* for 10 Cartesian modes.

- Optimized torsional modes describe conformational changes significantly better than Cartesian modes or orthogonalized torsional modes.
- In many cases, most notably calmodulin, just 1 or 2 optimized torsional modes are needed to describe the motion of 10 Cartesian modes.

Mapping Out Conformational Landscapes in 2 Dimensions



Conclusions

- Cartesian and orthogonalized torsional modes perform similarly, and significantly worse than the optimized torsional modes.
- Protein motion is more naturally described by curved paths than by straight displacement vectors in Cartesian space.
- Optimized torsional normal mode analysis is a powerful new method for representing protein conformational changes.

Acknowledgements

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