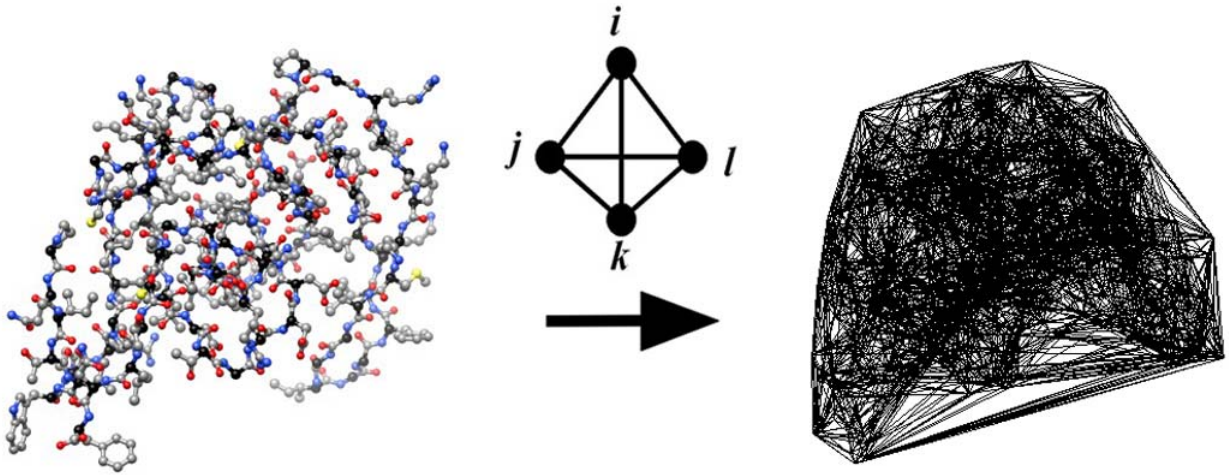
Generation of Atomic Four-Body Statistical Potentials Derived from the Delaunay Tessellation of Protein Structures



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Protein Data Bank (http://www.rcsb.org/pdb)

- PDB – repository of solved (x-ray, nmr, ...) structures
- Each structure file contains atomic 3D coordinate data

	Atom					X	Y	Z			
ATOM	1	N	PRO	E	1	-13.470	40.080	31.429	1.00	20.55	N
ATOM	2	CA	PRO	E	1	-13.130	40.167	30.000	1.00	18.37	C
ATOM	3	C	PRO	E	1	-13.948	39.156	29.184	1.00	19.60	C
ATOM	4	O	PRO	E	1	-14.613	38.254	29.681	1.00	14.33	O
ATOM	5	CB	PRO	E	1	-11.628	39.965	29.977	1.00	18.47	C
ATOM	6	CG	PRO	E	1	-11.271	39.349	31.318	1.00	16.39	C
ATOM	7	CD	PRO	E	1	-12.253	40.025	32.261	1.00	17.03	C
ATOM	8	N	GLN	E	2	-13.954	39.360	27.885	1.00	17.78	N
ATOM	9	CA	GLN	E	2	-14.612	38.615	26.843	1.00	18.54	C
ATOM	10	C	GLN	E	2	-13.519	37.852	26.032	1.00	21.37	C
ATOM	11	O	GLN	E	2	-12.525	38.462	25.599	1.00	18.10	O
ATOM	12	CB	GLN	E	2	-15.431	39.449	25.905	1.00	9.92	C
ATOM	13	CG	GLN	E	2	-16.976	39.087	25.986	1.00	21.78	C
ATOM	14	CD	GLN	E	2	-17.504	39.810	24.755	1.00	28.81	C
ATOM	15	OE1	GLN	E	2	-17.660	39.195	23.731	1.00	28.78	O
ATOM	16	NE2	GLN	E	2	-17.660	41.125	24.919	1.00	42.68	N
						:		:			
						:		:			

Knowledge-Based Potentials of Mean Force

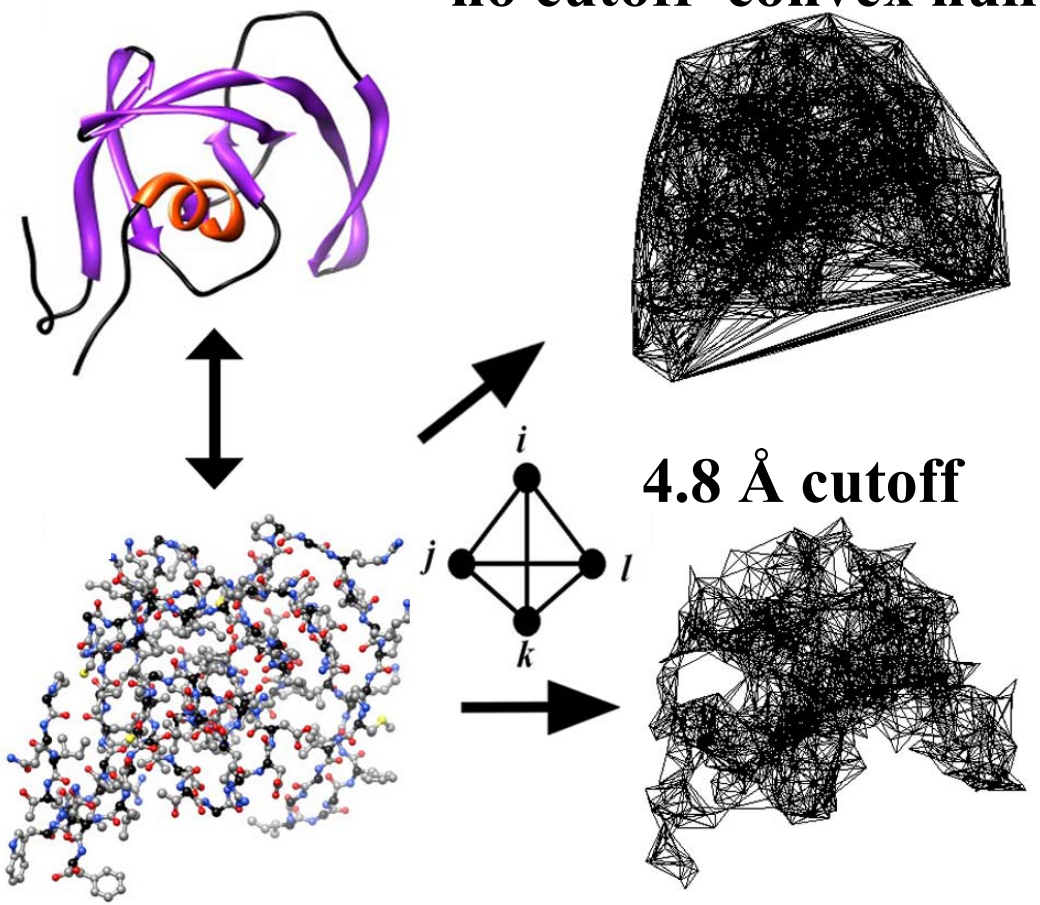
- Generated via statistical analysis of observed features in a diverse subset of protein structures from PDB (training set)
- Alternative to physics or molecular mechanics energy functions
- Assumption: observed features follow a Boltzmann distribution
- Examples:
  - Well-documented in the literature: distance-dependent pairwise interactions at the atomic or amino acid level
  - This study: inclusion of higher-order contributions by developing all-atom four-body statistical potentials
- Motivation (our prior work):
  - Four-body protein potentials at the amino acid level

All-Atom Four-Body Statistical Potential

- Diverse PDB dataset consisting of 1417 single protein chains
- Represent each structure as a collection of atomic points in 3D
- 1st adjustable parameter – atomic alphabet size for labeling points:
  - 4-letter (N, C, O, S), the focus of this talk
  - 8-letter (Backbone: N, Cα, C, O; Side-chain: N', C', O', S)
  - 20-letter (defined as in Summa *et al.*, *JMB*, 2005)

All-Atom Four-Body Statistical Potential

- Apply Delaunay tessellation to the atomic point coordinates of each PDB file – objectively identifies all nearest neighbor quadruplets of atoms in the structure
- 2nd adjustable parameter – tetrahedral simplex edge length cutoff, if any, to ensure all 4 atoms are interacting with one other



All-Atom Four-Body Statistical Potential

- $K = 4$ atomic alphabet size ➔ $N = 35$ possible atomic quadruplets that may appear on the four vertices of a tetrahedron
- Assumption: letters can be repeated in a quad, but the permutation of letters in any given quad does not constitute a new one
- Other cases: $K = 8$ ➔ $N = 330$; $K = 20$ ➔ $N = 8855$
- For each atomic quadruplet (i, j, k, l), calculate proportion f_{ijkl} of all the tetrahedra generated by the 1417 protein tessellations that have the quad appearing on the four vertices (i.e., the observed relative frequency of quad occurrence)

All-Atom Four-Body Statistical Potential

- Compute a rate p_{ijkl} expected by chance from a multinomial reference distribution:

$$p_{ijkl} = \frac{4!}{\prod_{n=1}^{K}(t_n!)} \prod_{n=1}^{K} a_n^{t_n}, \text{where } \sum_{n=1}^{K} a_n = 1 \text{ and } \sum_{n=1}^{K} t_n = 4.$$

- a_n = proportion of atoms from the proteins that are of type n
- t_n = number of occurrences of atom type n in the quad
- Apply inverted Bolzmann principle: score $s_{ijkl} = \log(f_{ijkl} / p_{ijkl})$ quantifies interaction propensity and is proportional to the energy of interaction (by a factor of '$-RT$')
- How to use it to calculate total potential energy of any protein? 1) Tessellate its atomic coordinates; 2) score each tetrahedron based on the atomic quad at its vertices; 3) add up the scores

Summary Data for the 1417 Protein Chains and their Delaunay Tessellations

Four-Letter Atom Types	Count	Proportion
(carbon) C	1,572,222	0.634149
(nitrogen) N	425,874	0.171774
(oxygen) O	469,869	0.189520
(sulfur) S	11,299	0.004557
Total atom count:	2,479,264	
Total tetrahedron counts		
No edge-length cutoff:	16,152,638	
12 Å edge-length cutoff:	15,497,203	
4.8 Å edge-length cutoff:	9,569,503	

3rd Adjustable Parameter – Reference Choice

- Potential drawback of previous reference distribution: implicitly assumes atoms from different protein chains are capable of forming the four vertices of a Delaunay simplex
- Alternative approach: weighted averaging by protein chain

$$p_{ijkl} = \sum_{m=1}^{1417} \frac{R_m}{R} p^m_{ijkl}$$

- R_m = number of atoms in protein chain m
- R = total number of atoms in all 1417 protein chains
- p^m_{ijkl} = multinomial dist applied only to atoms of protein chain m

All-Atom Four-Body Statistical Potential:

4-letter, no simplex edge cutoff, unweighted reference

Quad	Count	f_{ijkl}	p_{ijkl}	s_{ijkl}
CCCC	1711740	0.105973	0.161720	-0.183570
CCCN	1823746	0.112907	0.175223	-0.190871
CCCO	2807489	0.173810	0.193325	-0.046213
CCCS	119435	0.007394	0.004649	0.201538
CCNN	832442	0.051536	0.071195	-0.140340
CCNO	3838549	0.237642	0.157100	0.179748
CCNS	53655	0.003322	0.003778	-0.055872
CCOO	1643096	0.101723	0.086665	0.069578
CCOS	86638	0.005364	0.004168	0.109530
CCSS	6408	0.000397	5.01E-05	0.898511
CNNN	64504	0.003993	0.012857	-0.507783
CNNO	961282	0.059512	0.042554	0.145664
CNNS	7628	0.000472	0.001023	-0.335839
CNOO	1380693	0.085478	0.046950	0.260215
CNOS	44097	0.002730	0.002258	0.082434
CNSS	2153	0.000133	2.71E-05	0.691035
COOO	336824	0.020853	0.017267	0.081946
COOS	17883	0.001107	0.001246	-0.051201
COSS	2068	0.000128	3.00E-05	0.630846
CSSS	214	1.32E-05	2.40E-07	1.741768
NNNN	4632	0.000287	0.000871	-0.482308
NNNO	36223	0.002243	0.003842	-0.233848
NNNS	407	2.52E-05	9.24E-05	-0.564301
NNOO	190771	0.011811	0.006359	0.268893
NNOS	3088	0.000191	0.000306	-0.204035
NNSS	236	1.46E-05	3.68E-06	0.599166
NOOO	129494	0.008017	0.004677	0.234026
NOOS	5426	0.000336	0.000337	-0.001929
NOSS	436	2.70E-05	8.11E-06	0.522015
NSSS	138	8.54E-06	6.50E-08	2.118466
OOOO	39551	0.002449	0.001290	0.278298
OOOS	1462	9.05E-05	0.000124	-0.137035
OOSS	158	9.78E-06	4.48E-06	0.339520
OSSS	22	1.36E-06	7.18E-08	1.278314
SSSS	50	3.10E-06	4.31E-10	3.855858

Effect of Reference State on the Potential:

4-letter, 4.8 Å simplex edge cutoff

Quad	Count	S_{ijkl} (unweighted)	S_{ijkl} (weighted)
CCCC	922742	-0.224573	-0.225145
CCCN	1229054	-0.134910	-0.134801
CCCO	1533444	-0.081509	-0.081269
CCCS	53175	0.077468	0.080517
CCNN	612799	-0.046021	-0.046302
CCNO	2695736	0.253612	0.254318
CCNS	28817	-0.098480	-0.096682
CCOO	796121	-0.017752	-0.017954
CCOS	36077	-0.043594	-0.040613
CCSS	3685	0.885580	0.763552
CNNN	18568	-0.821250	-0.822983
CNNO	647785	0.201598	0.201779
CNNS	3499	-0.446952	-0.447508
CNOO	757532	0.226873	0.227017
CNOS	22706	0.021519	0.022970
CNSS	1312	0.703279	0.575108
COOO	65646	-0.400894	-0.402722
COOS	4711	-0.403174	-0.401559
COSS	1001	0.543084	0.416103
CSSS	125	1.735618	1.308914
NNNN	133	-1.796871	-1.800957
NNNO	5948	-0.791107	-0.792435
NNNS	58	-1.183114	-1.187162
NNOO	97822	0.206171	0.205677
NNOS	1061	-0.440643	-0.441841
NNSS	79	0.351235	0.215194
NOOO	26079	-0.234579	-0.236150
NOOS	1832	-0.246129	-0.246333
NOSS	220	0.452305	0.318451
NSSS	48	1.887182	1.441123
OOOO	1542	-0.903421	-0.908012
OOOS	78	-1.182534	-1.183627
OOSS	32	-0.126633	-0.260776
OSSS	5	0.862215	0.415567
SSSS	31	3.875603	2.870350

References and Acknowledgments

- PDB (structure DB): http://www.rcsb.org/pdb
- Qhull (Delaunay tessellation): http://www.qhull.org/
- UCSF Chimera (ribbon/ball-stick structure visualization): http://www.cgl.ucsf.edu/chimera/
- Matlab (tessellation visualization): http://www.mathworks.com/products/matlab/
- Perl programming language used exclusively for performing all data extraction, formatting, and analyses.