Donald Jacobs, Associate Professor
Active areas of research (2011-current)

Investigation of physiochemical interactions in …

- Bulk and interfacial water
- Aqueous salt solutions (new endeavor)
- Polypeptides exhibiting a helix-coil transition
- Aqueous globular proteins
- Protein-solvent interactions
- Protein-protein complexes (new endeavor)
- Membrane bound proteins (new endeavor)
- Protein mutants related to structure/function studies
- Ligand binding related to allosteric effects
- Native and transition states: Partial unfolding events
- Protein folding (newest endeavor)
- Protein formulation and aggregation (newest endeavor)

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Molecular systems being studied

Aqueous solutions

inorganic and organic salt mixtures	Conc. from 0 to 1 M

Proteins

	# of residues
thioredoxin	~110
bacterial chemotaxis protein (CheY)	~130
lysozyme	~130
chemokines (CXC dimmer complexes)	~130
major histocompatibility complex (MCH II)	~200
adenylate kinase	~210
scFv linked antibody fragments	~250
undecaprenyl pyrophosphate synthase	~250
beta-lactamase (class A)	~280
Fab antibody fragment	~440
gelsolin (complex)	~500
myosin V (monomer complex)	~1,000
human liver pyruvate kinase (tetramer)	~2,000

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Computational models for . . .

Rapid free energy calculations:

Distance Constraint Model (DCM)

HCT-DCM (exact transfer matrix method) (1st DCM ever! 2003)
minimal DCM (mDCM) with pebble game (2nd DCM most used, 2004)
Maxwell-counting (transfer matrix method) (simplified DCM, 2011)
mDCM with pebble game & Maxwell-counting (newest, 2012)

Interfacial Thermodynamics Model (ITM)

DCM with Self Consistent Constraint Theory (**SCCT**) (newest 2012)

Rapid long-range electrostatic reaction field calculations:

Image Charge Solvation Model (ICSM)

Quasi periodic boundary conditions (1st ICSM, 2009)
Finite boundary conditions (newest, 2013)

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Creation of Novel Efficient Algorithms

Non-parametric Determination of Probability Distributions

Applies maximum entropy method without specified functional form
Finite moments is an unnecessary requirement
Handles low number of samples without over fitting the data

Rapid optimization method for generic multivariate systems

Auto-scaling & auto-adaptive simulated annealing without temperature
Accuracy tolerances and user-specified constraints respected

Inhomogeneous hierarchical adaptive sparse grid method

Rapid interpolation and integration of smooth multivariable functions

Virtual Pebble Game

Mean field approximation for ensemble averaged network rigidity

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Creation of Novel Efficient Algorithms (continued)

Geometrical Simulation (Improved version of FRODA, FRODAN)

Optimizes atomic motions using rigid cluster decomposition

Numerically stable against changes in constraint topology

Amplitude of atomic motions consistent with thermodynamic fluctuations

Monte Carlo method to investigate conformational pathways

mDCM-GS hybrid: Combines mDCM with Geometrical Simulation

Calculates free energy landscape (FEL) of a protein using mDCM

Using the FEL, protein conformations are explored efficiently

Enables investigation of large scale, long-time protein dynamics

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Active areas of research (2011-current)

Quantitative Stability/Flexibility Relationships (QSFR)

Comparative analysis over a collection of proteins

- Backbone flexibility is well conserved over protein families
- Molecular cooperativity is specific and sensitive to structural details
- Point mutations frequently cause long range responses
- Fluctuations in constraint topology invariably affect protein function
- Compensating mutations usually exhibit non-additive effects

Protein re-design and structure/function relationships

- Application of several computational methods (new endeavor)

Connecting stability/flexibility relationships to dynamics

- Combining MD simulation with mDCM (new protocols)
- Running hybrid mDCM-GS Monte Carlo simulations (new)
- Computational modeling of protein dynamics

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Software Development (contact me to inquire about availability)

EDAT: Essential Dynamics Analysis Tool (beta version coming soon!)

- Written in Java
- Employs PCA and Kernel PCA methods with subspace filtering
- Quantifies subspace dimension overlaps
- Enables easy comparative analysis between proteins
- Enables visualization of motions associated with PCA modes

ICSM-module for TINKER: (available at www.fastmultipole.org)

- Written in FORTRAN 95
- O(N) method to calculate linearized Poisson-Boltzmann equation
- Implemented with quasi periodic boundary conditions
- Faster than PME method for N > 75,000 charges in the system
- Based on the Fast Multipole Method (FMM)

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Software Development (continued)

FAST: Flexibility And Stability Test (alpha version only)

- Written in C++
- Given a 3D all-atom structure of a protein, generic multi-dimensional free energy landscapes such as $G(O_1,O_2,O_3,T,p,pH,c_1,c_2)$ are rapidly calculated where O_1,O_2,O_3 are order parameters and $\{T,p,pH,c_1,c_2\}$ defines the thermodynamic and solvent conditions.
- Completely describes heat and cold denaturation
- Predicts all thermodynamic properties, such as heat capacity
- Relates solvation penetration to partial unfolding events
- Calculates **Quantitative Stability/Flexibility Relationships (QSFR)**
- Rate limiting calculations are parallelized with superb scalability
- Applications include high-throughput screening for drug discovery

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Active areas of research (2011-current)

Software Development (continued)

PDP: Probability Density Predictor (beta version coming soon!**)**

Written in Java

Given list of N ≥ 8 random numbers, predicts probability density

Auto control prevents over fitting the data points

Provides multiple solutions consistent with available statistics

Free Academic Software Routinely Used in the Lab

GROMACS: A powerful Molecular Dynamics simulation package

FRODA II: Geometrical Simulation for native state constraint topology

Commercial Software Routinely Used in the Lab

MOE: An awesome tool from Chemical Computing Group, Inc