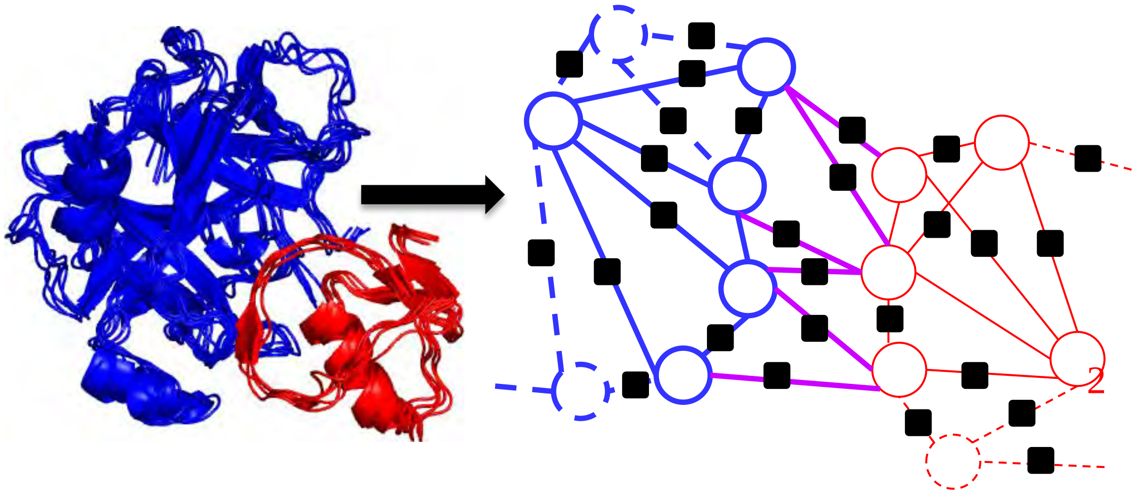
Probabilistic Graphical Model Based Analysis and Modeling of Ensembles of Conformers



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Context within the BTRR

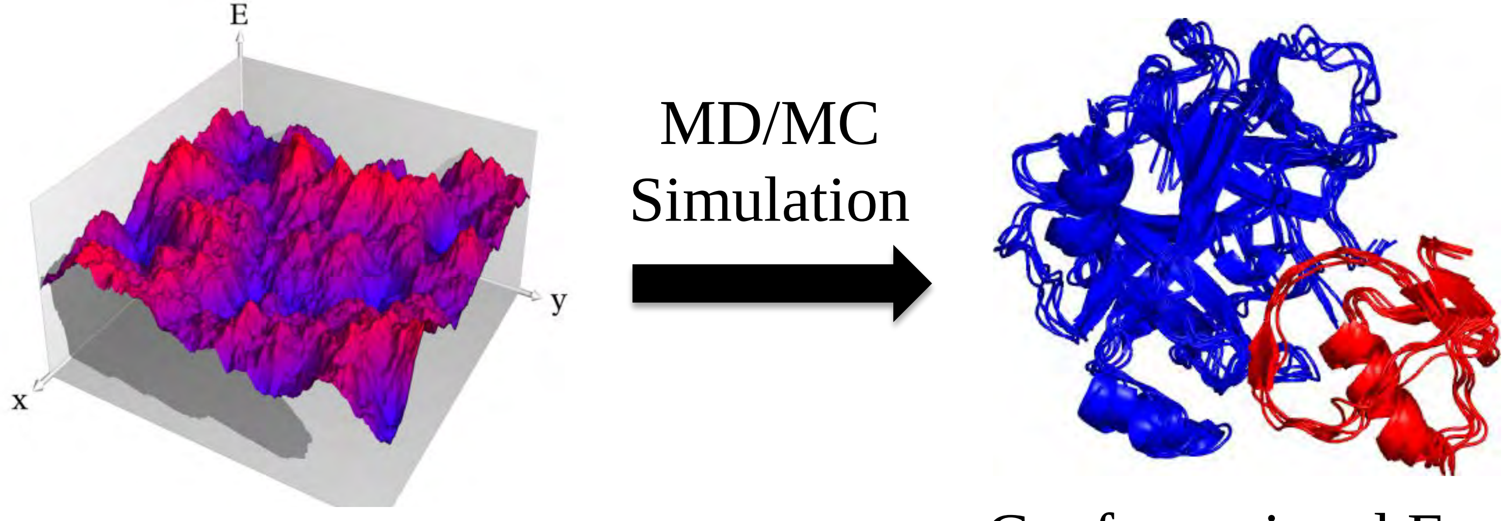
- TR&D1: Molecular Modeling
  - Specific Aims 1 – 3
  - Today's presentation is most relevant to
    - Subaim 1.4: "PGM-based analysis and modeling of ensembles of conformers"
    - Subaim 2.2: "Binding geometry and affinity computations for protein-protein and protein-ligand interactions using novel methods based on PGMs and/or mixed-resolution models with LBMC"

Context within the BTRR

- Relevant C&SPs & DBP
  - C&SP3; DBP1
- Our methods are mostly scale and data agnostic, and so they can also be used for TR&Ds 2 and 3
  - Analysis of trajectories
  - Generative Models
  - Parameter Estimation

Conformational Ensembles

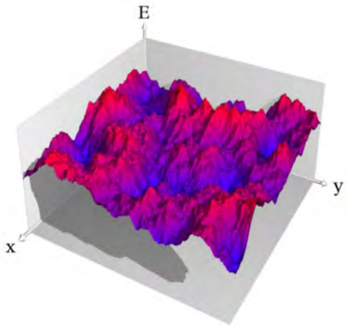
- Molecular Dynamics and Monte Carlo Simulation trajectories consist of molecular conformations sampled from an energy landscape



Energy Landscape

Conformational Ensemble

Motivation



- Conformational Ensembles contain important information relevant to function
- Unfortunately, extracting information from large ensembles (i.e., Big Data) can be challenging
- Our goals are to:
  - Learn generative models from ensembles
  - Use those models to analyze, simulate, and (re)engineer molecular motions

From Conformational Ensembles to Generative Models

- Each conformation corresponds to a point in a high-dimensional space; i.e., $x \in \mathbb{R}^n$
  - One dimension for each degree of freedom
- Examples
  - Internal degrees of freedom
  - Cartesian coordinates
  - Atomic fluctuations from a mean conformation
  - Inter-atomic distance matrices

From Conformational Ensembles to Generative Models

- Let $\mathbf{X} = \{X_1, \ldots, X_n\}$ be a set of random variables corresponding to the degrees of freedom for some system
- A generative model is an encoding of $P(\mathbf{X})$
  - i.e., an encoding of the joint distribution
  - Thus, the ensemble is a sample from $P(\mathbf{X})$

From Conformational Ensembles to Generative Models

- Let $\mathbf{X} = \{X_1, \ldots, X_n\}$ be a set of random variables corresponding to the degrees of freedom for some system
- A generative model is an encoding of $P(\mathbf{X})$
  - i.e., an encoding of the joint distribution
- Question: how can we compactly represent $P(\mathbf{X})$?
- Answer: Probabilistic Graphical Models (PGM)

Probabilistic Graphical Models

- A PGM, (G, Φ), is a factored encoding of a joint probability distribution $P(\mathbf{X})$ over a set of variables $\mathbf{X} = \{X_1, \ldots, X_n\}$, in terms of a graph $G = (V,E)$ and a set of non-negative functions $\Phi = \{\phi_1, \ldots, \phi_m\}$

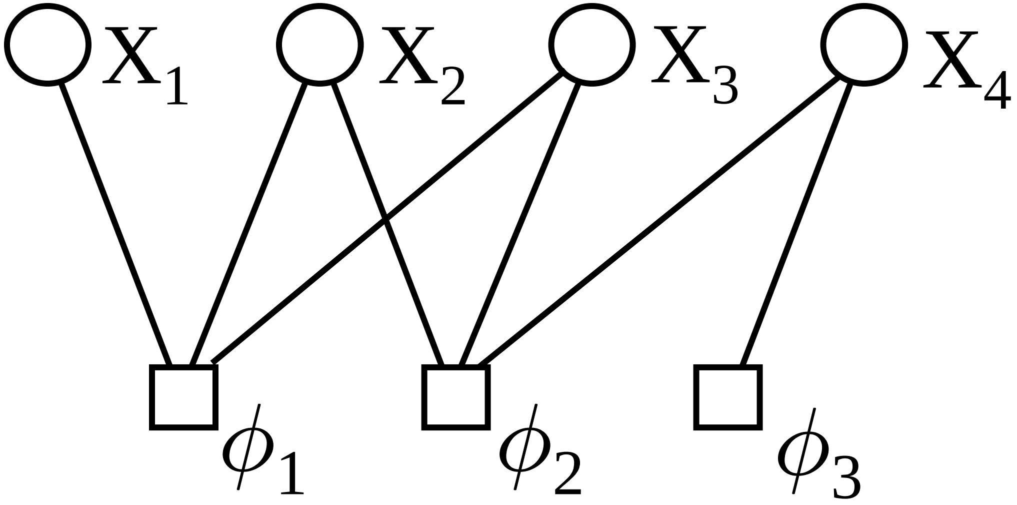
The Graphical Model Zoo

- Bayes Nets
- Hidden Markov Models
- Kalman Filters
- Dynamic Bayesian Networks

- Ising Model
- Potts Model
- Markov Random Fields
- Factor Graphs

Etc

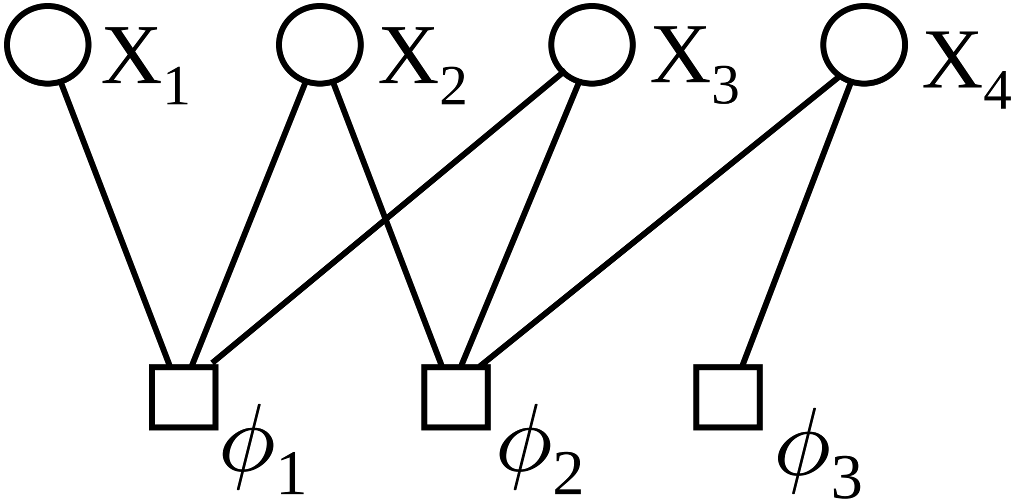
Factor Graphs



Circles correspond to random variables

Squares correspond to factors (functions) over the variables

Factor Graphs



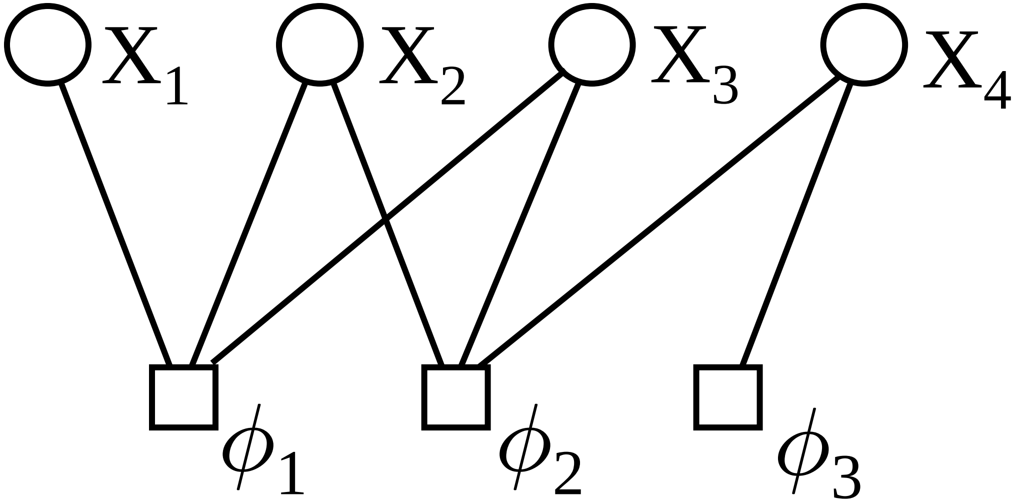
If each ϕ_i is a positive function …

Theorem (Hammersely and Clifford)

$$\boxed{P(x) = \frac{1}{Z}\prod_{a\in\Phi}\phi_a(x_a)}$$

$$\boxed{Z = \sum_x \prod_{a\in\Phi}\phi_a(x_a)}$$

Example

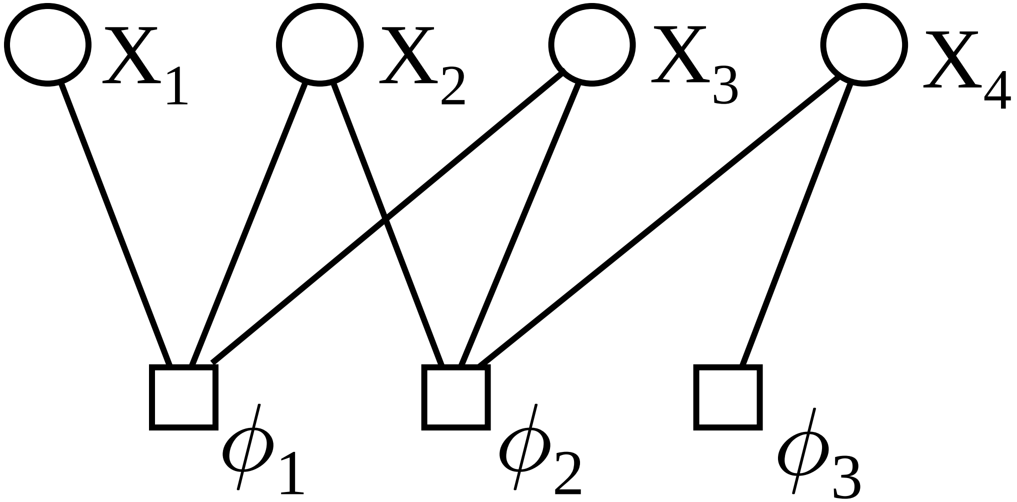


$$p(x_1, x_2, x_3, x_4) = \frac{1}{Z}\phi_1(x_1, x_2, x_3)\phi_2(x_2, x_3, x_4)\phi_3(x_4)$$

Conditional Independencies

- The topology of the graph defines a set of conditional independencies (CI)
  - Variables A and B are conditionally independent, given C (denoted $A \perp B \mid C$) iff $P(A,B|C) = P(A|C)P(B|C)$ or, equivalently, $P(A|B,C) = P(A|C)$
- Informally, CIs let us use ‘simpler’ functions to encode the joint distribution

Example



$$p(x_1, x_2, x_3, x_4) = \frac{1}{Z} \phi_1(x_1, x_2, x_3) \phi_2(x_2, x_3, x_4) \phi_3(x_4)$$

In this graph:

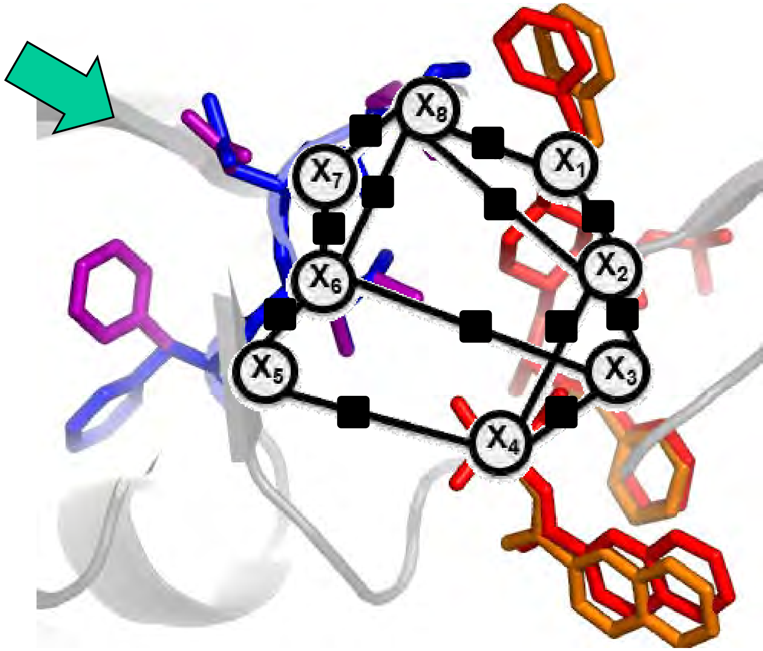
$X_1 \perp X_4 | X_2 , X_3$

Key Point

- *Any* joint probability distribution over N variables can be represented via a suitably defined factor graph
- User must specify (or learn from data):
  1. Topology of the graph
  2. Functional form and parameters of the factors

PGMs of Molecular Structures

- The user gets to decide which degrees of freedom they wish to model
  - Internal degrees of freedom
  - Cartesian coordinates
  - Atomic fluctuations
  - Inter-atomic distances



Learning PGMs from Ensembles

GAMELAN (GrAphical Models of Energy LANdscapes)

- Input
  - Ensemble encoded as an $n \times t$ matrix, D
    - n is the number of covariates $\mathbf{X} = \{X_1, \ldots, X_n\}$
    - t is the number of conformations in the ensemble
- Output : PGM (G, Φ) over $\mathbf{X}$ that "fits" D
  - Algorithmic subtasks:
    1. Learn topology of the graphical mode, $G = (V,E)$
    2. Learn model parameters (i.e., Φ), given G

Learning PGMs from Ensembles

GAMELAN (GrAphical Models of Energy LANdscapes)

- Optimization problem

$$(G,\mathit{\Phi})^* = \mathrm{argmax}_{G,\mathit{\Phi}}\ f(G, \mathit{\Phi}; D) = \sum_t \log P_{G,\mathit{\Phi}}(d_t) - \lambda R(G, \mathit{\Phi})$$

Learning PGMs from Ensembles

GAMELAN (GrAphical Models of Energy LANdscapes)

- Optimization problem

$$(G,\Phi)^* = \mathrm{argmax}_{G,\Phi}\ f(G, \Phi; D) = \underbrace{\textstyle\sum_t \log P_{G,\Phi}(d_t)}_{\text{1st term reflects the PGM's fit to the data}} - \lambda R(G, \Phi)$$

Learning PGMs from Ensembles

GAMELAN (GrAphical Models of Energy LANdscapes)

- Optimization problem

$$(G,\Phi)^* = \mathrm{argmax}_{G,\Phi}\ f(G,\Phi; D) = \sum_t \log P_{G,\Phi}(d_t) - \underbrace{\lambda R(G,\Phi)}$$

2nd term penalizes complex PGMs by counting the number of edges (and thus parameters)

Learning PGMs from Ensembles

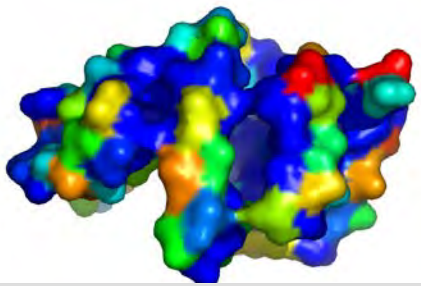
GAMELAN (GrAphical Models of Energy LANdscapes)

- Algorithms for solving optimization problem
  - Discrete Random Variables: BKLCL11
  - Continuous Random Variables
    - Angular Data (von Mises distribution): RKL11
    - Unimodal distributions: RKL12
    - Multi-modal Distributions: RL12; L14
  - Time-varying models: RMKL10; L14

*P41 acknowledged

Using PGMs of Molecular Structures

- Given a PGM, there are algorithms for:
  - Computing (approximate) free energies
    - KXL07; KL08; KBL09; KXL11; KGLB14
  - Visualizing entropic contributions to the free energy
    - KXL11
  - Sampling new configurations
    - RKL11



Heatmap of Configurational Entropy for Lysozyme

*P41 acknowledged

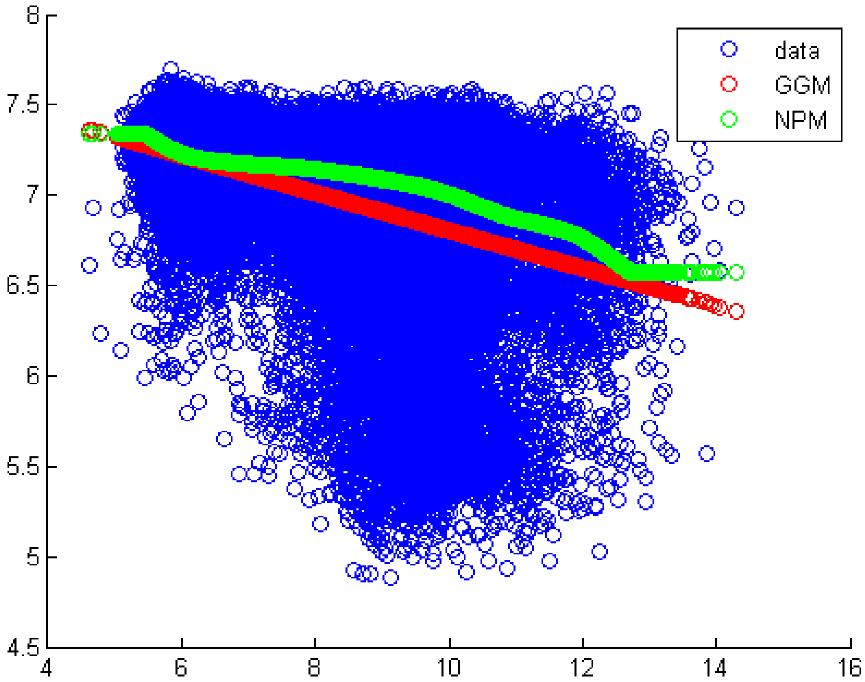
Using PGMs of Molecular Structures

- Given a PGM, there are algorithms for:
  - (re)Designing Proteins
    - KGBL09; KGLB14
  - Predicting how the distribution changes under perturbations [i.e., P(**X** | Y)]
    - Examples: allosteric regulation; effects of mutations
    - KXL11; RKL12; L14

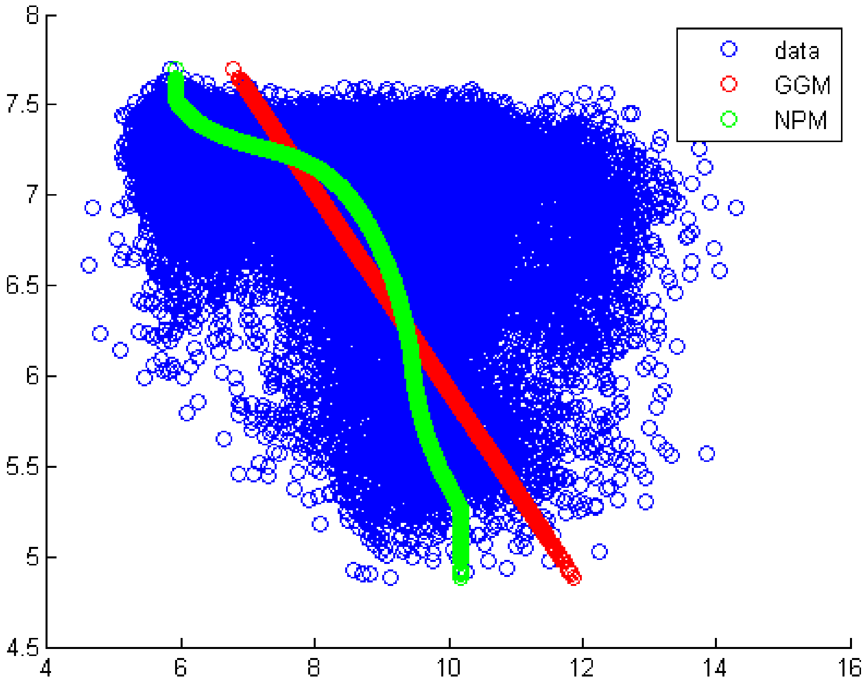
*P41 acknowledged

Example: Inference in GGM vs NPN [L14]

- Data: 50 μs simulation of the engrailed homeodomain
- Conditioned model on one variable, computed MLE of remaining variable



argmax $_y$ P(y|x)



argmax $_x$ P(x|y)

Ongoing Work

- Distribution GAMELAN Software
  - Custom-version for Anton Trajectories
- PGM-based Markov-State Models
- Writing manuscripts for semi- and non parametric models
- Rory and Dan are integrating Dan’s high-resolution rotamer libraries into our framework

Potential Applications to other areas of the BTRR

- Analyzing MCELL/BNG trajectories
- Alternative algorithms for learning PGMs from image data
- Parameter estimation
  - Specifically, learning PGMs over model parameters

Thank you!

- Students & Post Docs
  - – Dr. Hetunandan Kamisetty
  - – Dr. Narges Sharif Razavian
  - – Subhodeep Moitra
- Collaborators
  - – Dr. Chris Bailey-Kellogg
  - – Dr. Jaime Carbonell

References

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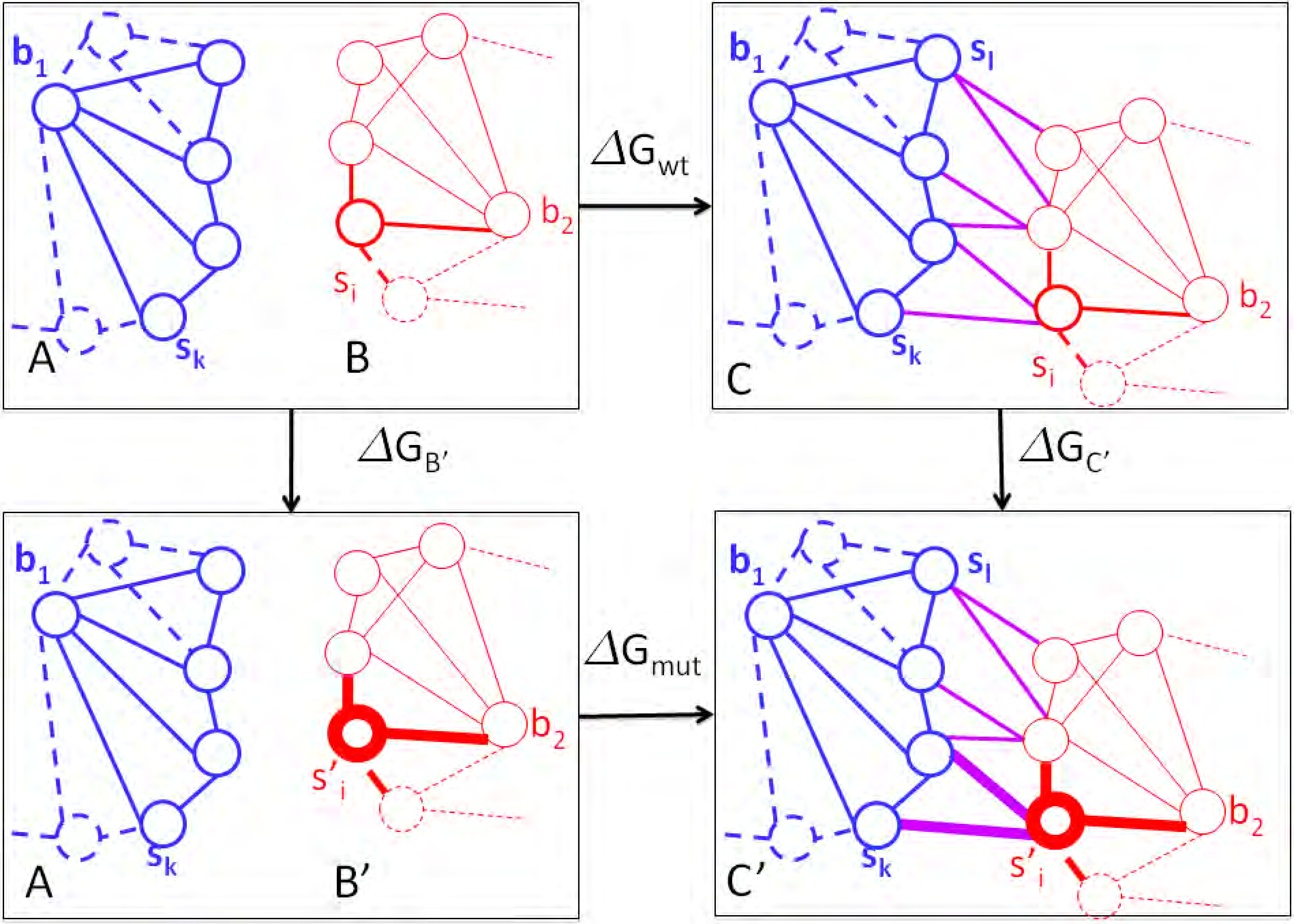
- [KGLB14] H. Kamisetty, B. Ghosh, C.J. Langmead, C. Bailey-Kellogg “*Learning Sequence Determinants of Protein:Protein Interaction Specificity with Sparse Graphical Models*”. RECOMB pp129-143, 2014

Timeline

	Timeline	Year1		Year2		Year3		Year4		Y5
Aim 1	1. Inclusion of lipid bilayer into network models	🟥	🟥	🟥	🟦	🟦	🟩	🟩	🟧	🟧
	2. Dev of a hybrid methodology that integrates ENMs, MD & MC	🟥	🟥	🟦	🟩	🟩	🟧	🟧	🟧	🟧
	3. Analysis suite for WE sim & application to neurosignaling proteins	🟥	🟦	🟦	🟩	🟧	🟧	🟧	🟧	🟧
	4. Critical assessment and sampling quality	🟦	🟦	🟩	🟧	🟧	🟧	🟧	🟧	🟧
	5. PGM-based analysis modeling of ensembles of conformers	🟥	🟥	🟦	🟩	🟧	🟧	🟧	🟧	🟧
	6. Combined use of ENM-, WE- and PGM-based methods				🟥	🟥	🟦	🟩	🟧	🟧
Aim 2	1. Improving QC methods in hybrid QC/MM	🟦	🟦	🟩	🟧	🟧	🟧	🟧	🟧	🟧
	2. Affinity calculations using mixed resolution models with LBMC			🟥	🟥	🟦	🟩	🟩	🟧	🟧
	3. PGM-based binding affinity calculations					🟥	🟦	🟩	🟧	🟧
	4. Combining PGMs with statistical mechanical libraries					🟥	🟥	🟦	🟩	🟧
	5. Elucidating allosteric signaling mechanisms & multimerization effects	🟥	🟦	🟩	🟧	🟧	🟧	🟧	🟧	🟧
Aim 3	1. Information transfer across scales - scale integration		🟥	🟥	🟦	🟦	🟦	🟩	🟩	🟧
	2. Application of WE methods to accelerate MCell simulations			🟥	🟥	🟦	🟦	🟩	🟩	🟧
	3. Analysis of MCell trajectories using PGMs and PCA-based methods		🟥	🟥	🟦	🟦	🟩	🟩	🟧	🟧
	4. Software optimization and parallelization		🟦	🟦	🟩	🟩	🟧	🟧	🟧	🟧
	5. PGM-based software and API				🟥	🟥	🟦	🟩	🟩	🟧
	6. Development of interfaces for easy access and interoperation					🟥	🟥	🟦	🟩	🟧
	7. Alternative strategies:ENMs & resolution exchange applied to MCell						🟥	🟥	🟦	🟩

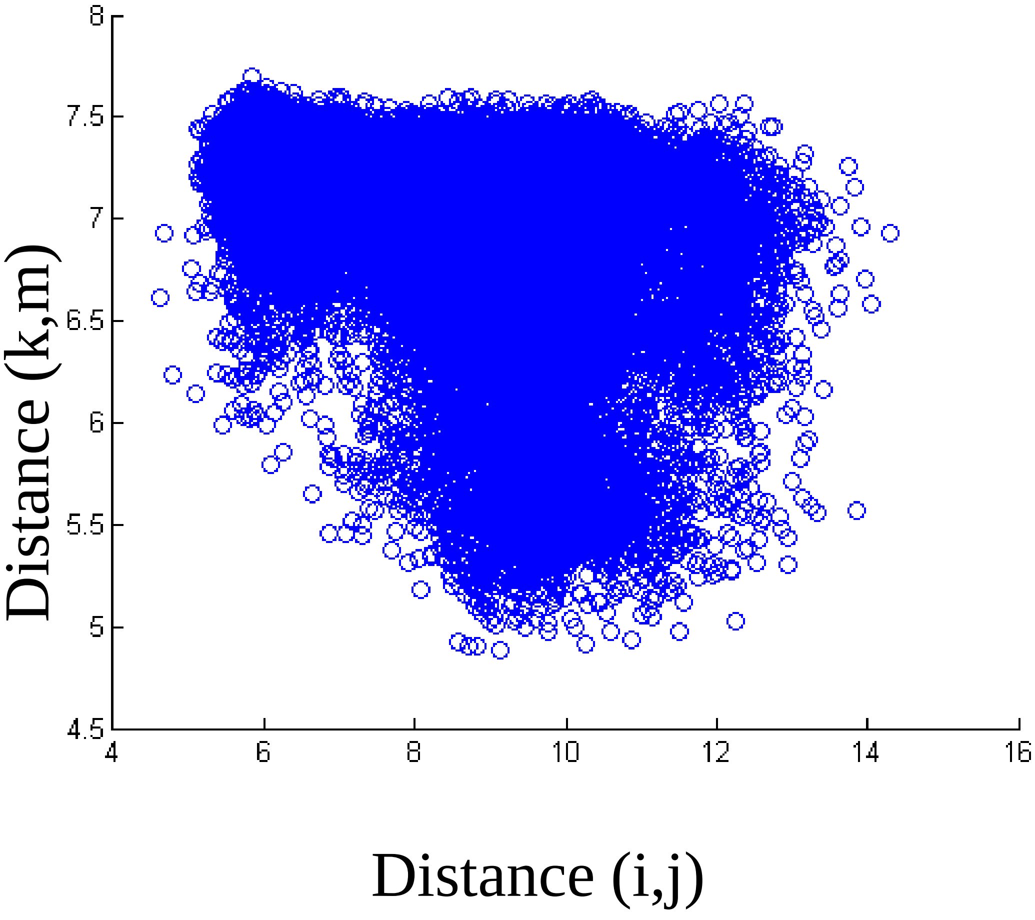
🟥 Design	🟦 Implementation and improvements	🟩 Alpha testing	🟧 User evaluation and refinements (beta testing)



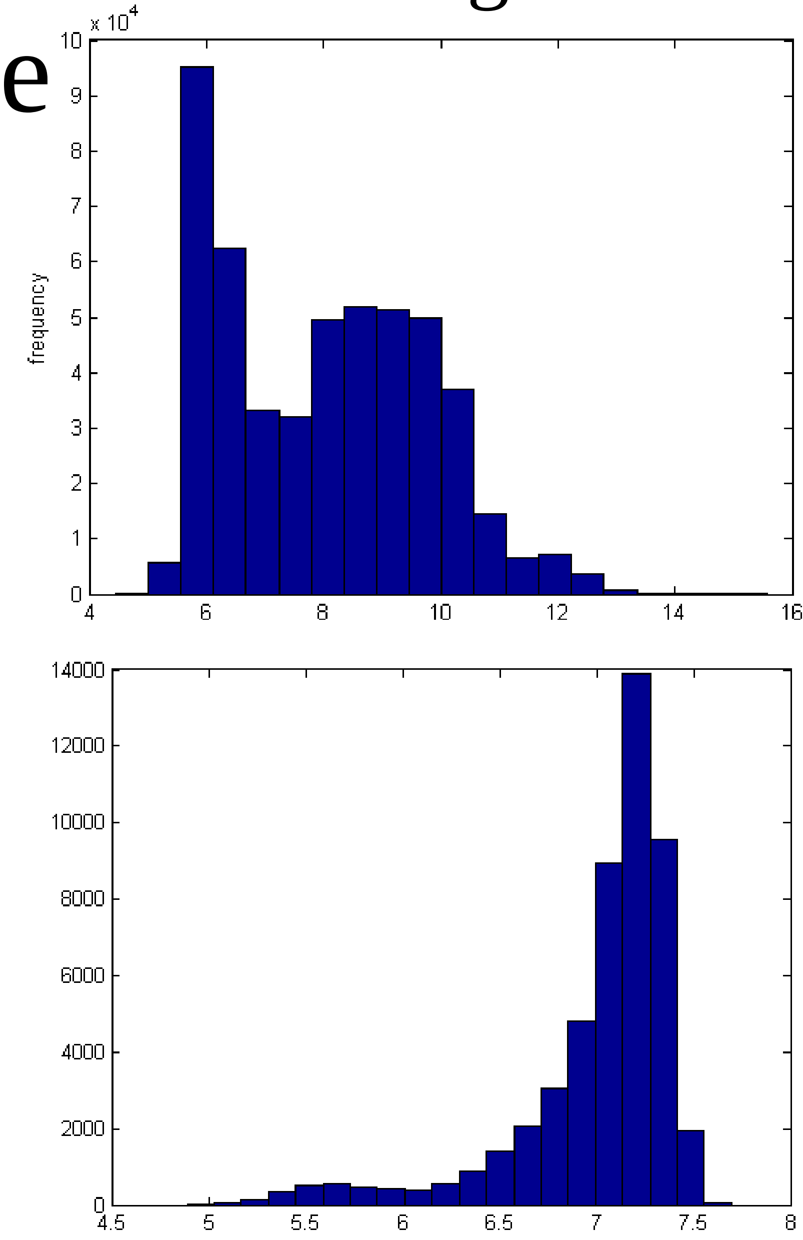
b1
A
sk
B
si
b2
ΔGwt
C
sl
ΔGB′
ΔGC′
ΔGmut
B′
s′i
C′

Example

Joint Distribution



Marginals


x 10^4
frequency