Dimensional Dependence of

Light

Interaction with Nanowires

A Ph.D. defense by

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Outline

Protein Folding

Proteins

- Responsible for wide variety of biological function
- Linear polymer chains of amino acids

Folding

- Central problem: from primary sequence and physiological conditions determine the *unique* native state
- Misfolding and aggregation results in many clinical disorders including neurodegenerative disorders like Huntington's and Alzheimer's disease and diabetes.

Entropy: The Science of Counting

Equilibrium statistical mechanics

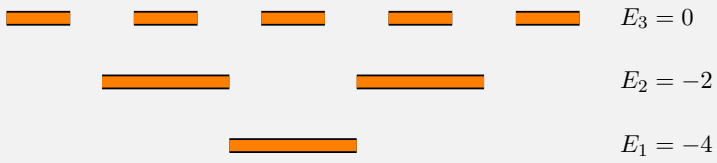
$$Z = \sum g(E_i) e^{-\beta E_i}$$

- The partition function gives a complete description of the system.

$$S = k \ln g(E)$$

- Try to solve for the density of states directly!

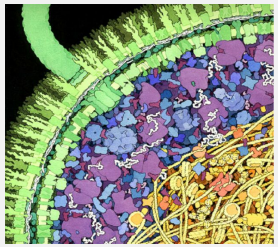
Example:



This gives a DOS of $g(-4) = 1$, $g(-2) = 2$, $g(0) = 5$.

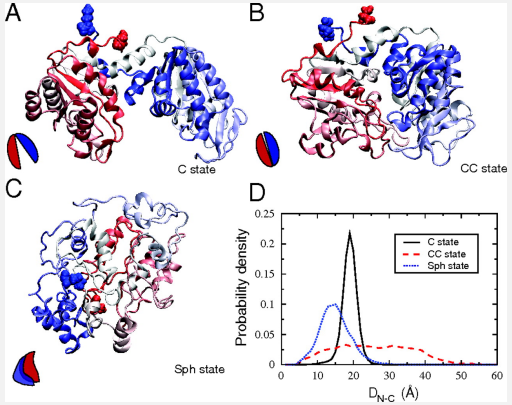
What is Crowding?

$\Rightarrow$



Crowding reduces the conformational state space of the peptide.

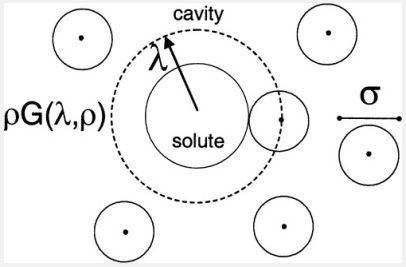
Crowding Induced Function Change



Crowding changes activity rates and function, and may change the native state

Dhar, Gruebele, Cheung, et. al., PNAS 107, 17586 (2010)

Hard-Sphere Experiments, Crowding Insights



Picture from [Heying, 2004], depletion zone traced with dashed lines

Hard-sphere studies of the crowding effect have shown:

- **Changes of the conformations of the cosolute**
- **Motion towards minimal curvature**

Crowding Induced Cosolute Conformation

../entropic_flow_paper/FIG1_EDIT.jpg ../entropic_flow_paper/FIG2_EDI

Hard-sphere experiments with fixed inner elliptical boundary shows standard radial density profiles

Hoppe and Yuan, Phys. Rev. E 80, 011404 (2009)

Crowding Induced Flow

Non-spherical objects generate flows from random initial conditions!

../entropic_flow_paper/FIG3_fourvelocity.jpg

Four vortices of paired spins, net angular momentum is still conserved
Effect: Crowding induced shape change (also considered by Cheung)

Scaled Particle Theory

- Measures the cost of inserting a new particle into a solution
- Rigorous results known for binary hard-sphere solutions
- Extended to aspherical particles by Kihara
- Aspherical SPT for proteins by Minton

Kihara, Rev. Mod. Phys. 25, 831 (1953)
Minton, Method Enzymol. 295, 127 (1998)

Designed β-sheet peptides

Collection of experiments by Feng Gai at U. Penn.

Properties:

- β-sheet motif
- Low aggregation propensity
- Known native-state

- #1 RFSEV^D[PG]KKFITS^D[PG]KTYTEV^D[PG]KKILQ
- #2 RFIEV^D[PG]KKFITS^D[PG]KTYTE

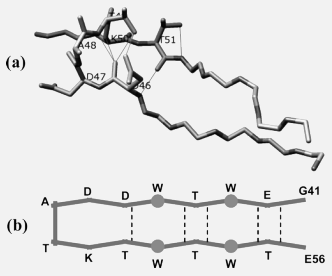
^{D}P = D-Pro

Xu, Gai, et. al., Biochem.47, 2064 (2008)
Hudson and Anderson, Biopolymers.83(4) pg. 424-433 (2006)

Native state representation

Wild-type β-sheet peptide (trpzip-m1)

- #3 GEWTWAD[AT]KTWTWTE

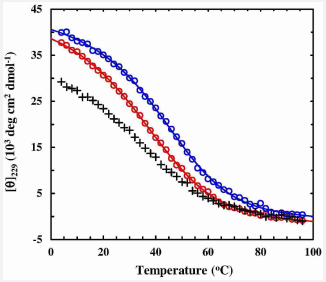


../WL_crowding_paper/PIC_28_residu

Figure: Native state of the wild-type 16-residue and designed 28-residue peptides represented schematically.

Why study these peptides?

- Thermal transition data
- Crowding data under equilibrium properties



- Isolated β-sheet experiments are relatively new
- Comparison between theoretical/experimental studies
- Detailed thermodynamic MD studies are feasible, but time consuming
- **What effect do crowders have on the folding process?**

Monte Carlo: How to sample

Most methods rely on Monte-Carlo, i.e. a selection method that is probabilistically determined. Any method must overcome two obstacles:

- Enthalpic barriers
- Entropic barriers (Levinthal's paradox)

The enthalpic barriers are usually directly observable from the Hamiltonian while the entropic ones are often more subtle.

Traditional Sampling Methods

The typical method uses a Metropolis-Hastings selection scheme:

$$P(A \to B) = \exp\left(\frac{\Delta E_{A,B}}{kT}\right)$$

This works well at finding local minimum - however it needs help getting out. Various models have been designed to get around this such as: Replica Exchange, Simulated Annealing, Reversible Jump Dynamics, etc...

These simulations only collect data at fixed temperatures; thermodynamic parameters like the free energy or the specific heat at arbitrary temperatures are time consuming

$$C_V = T\left(\frac{\partial S}{\partial T}\right)_{N,V}$$

Wang-Landau

- Originally designed to solve the Ising model
- Extremely effective when the cardinality of Ω (density of states) is small
- Can usually be made parallel trivially
- Works best when energy levels are discrete

F. Wang and D. P. Landau, Phys. Rev. Lett. 86(10), 2001

Wang-Landau: The equations

$$P(A \to B) = \frac{\Omega(E_A)}{\Omega(E_B)}$$

On accepting state:

$$\Omega(E_{ex}) \to c\Omega(E_{ex})$$

where c is a constant that is iteratively reduced (originally as):

$$c \to \sqrt{c}$$

Once $\Omega(E)$ has converged, we have the partition function *for all temperatures*

$$Z(T) = \sum \Omega(E_i) \exp(E_i/kT)$$

Wang-Landau

- Starts as a random walk across the state space
- As high entropic states are sampled they become less likely
- Random walk → biased random-walk
- As it converges - detailed balance is obeyed
- **Flat histogram in energy space**

Difficult Questions

How to model?

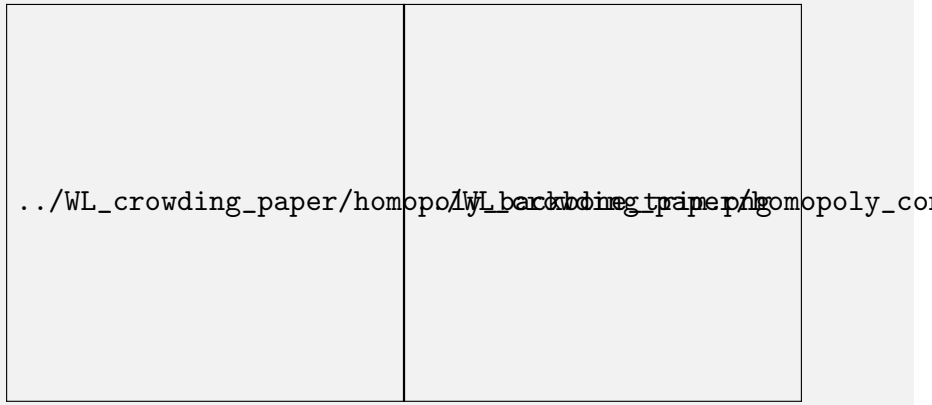
- All-atom?
- Explicit water?
- Effective forces?
- Level of coarse-graining?

We use a face-centered cubic lattice Gō-model, with a Potts/Ising approximation for the dihedral angles and aspherical scaled-particle theory to model a crowded solution.

lets break that down...

Lattice Models

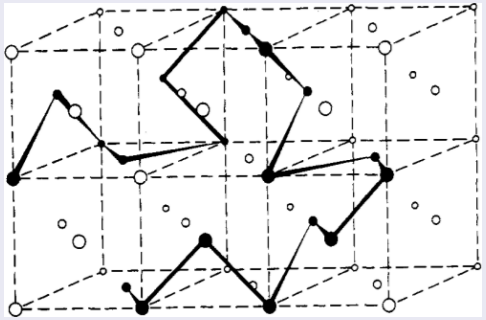
- Discretize the positions of the amino acids onto a fixed lattice
- Short-range interactions dominate (hydrophobicity, charge, etc)
- Lattice geometry can play a role on the pairing of amino acids



Chan and Dill, J. Chem. Phys. 118, 8106 (1994)

Lattice Choice

- High coordination number (FCC vs SC)
- Common motifs are better represented (alpha, beta)
- Still a crude approximation to an off-lattice model



Picture from [Downey, 1986]

Ising Model

- Analytical solution for 1D (Ising 1925), 2D (Onsager 1944) grids
- Each vertex on a graph has spin $\sigma \in \{-1, 1\}$, Hamiltonian is the sum over all adjacent spins

$$\mathcal{H} = -J \sum_{i,j \in \text{edges}} \sigma_i \sigma_j + h \sum_{k \in \text{vertices}} \sigma_k \delta_{1,\sigma_k}$$

- Gives true phase transitions for 2D infinite grids
- Finite graphs can be solved *exactly*

Gō-model & extensions

Gō-model

- Only native-state contacts contribute (all-or-nothing)

Extensions

- Extra degree of freedom, each bead now has a 'spin'.
- Accounts for the missing oriental entropy of $\phi - \psi$ angles
- Only native-state contacts *and* aligned spins contribute, reducing the conformation to a simple graph

../WL_crowding_paper/homopoly../WL_crowding_paper/3d_example_

General solution to Potts/Ising model (with external fields!)

With Self-Similarity

- Can often be solved/approximated with RG
- e.g. n-dimensional lattices, Cayley/Bethe trees

General Solution

- Solved with a subgraph decomposition

$$Z = \sum_{A \subseteq G} \prod_{c \in C_A}^{k(A)} \sum_{j}^{q} \left(w_j^{n(c)} v_j^{e(c)} \right)$$

Model Hamiltonian

Hamiltonian counts aligned native contacts in close proximity

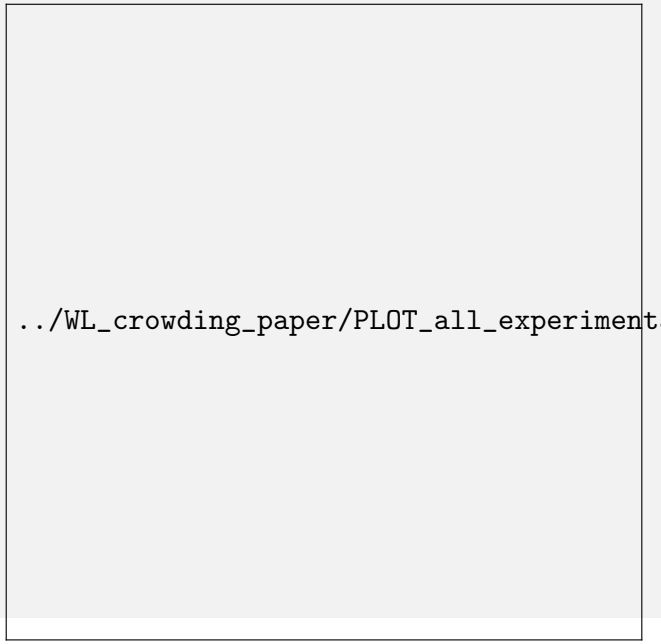
$$\mathcal{H}(\mathbf{c},\mathbf{s}) = -J_+ k_+ + J_- k_-$$
$$k_+ = \sum_{i=1}^{L}\sum_{j=i+2}^{L} \omega_{ij}\mathbf{s}_i\mathbf{s}_j\mathbf{G}_{ij}$$
$$k_- = \sum_{i=1}^{L}\sum_{j=i+2}^{L} \omega_{ij}(1-\mathbf{G}_{ij})$$

Free energy terms for crowding $\Delta\mu$ and entropic cost of alignment $\Delta\psi$

$$\mathcal{F}(\mathbf{c},\mathbf{s}) = \mathcal{H}(\mathbf{c},\mathbf{s}) - \beta\Delta\psi(\sigma) - \beta\Delta\mu(\mathbf{c}) \quad (1)$$

Fraction Folded

Measure of fraction folded well-described by model



Crowded Conditions → Folding Stability

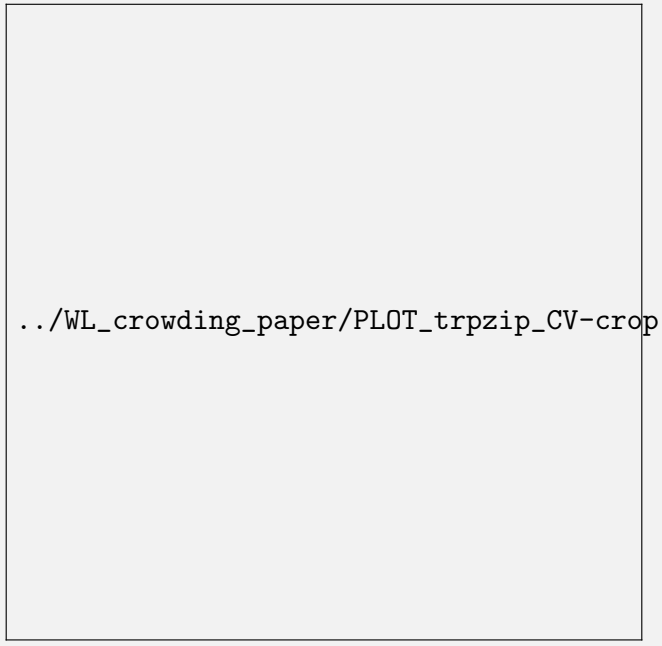


Figure: Specific heat per residue count for the wild-type peptide trpzip4-m1 in the

Crowded Conditions → Folding Instability

While the smaller peptide trpzip4-m1 displays crowding enhanced stability, the larger designed β-sheet peptides show (small) instability!

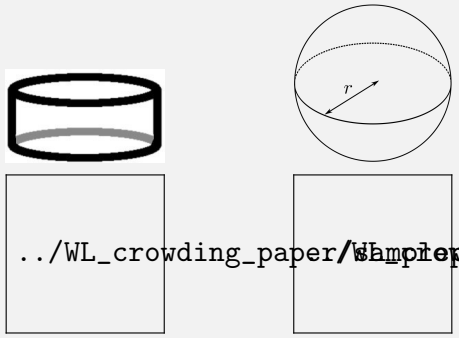
Simulations predict that the entropic effect due to the crowding of aspherical proteins may be destabilizing.

Why might this be so?

- Ensemble of states has to be considered
- Only possible with a full density of states calculation

Crowded Conditions → Folding Instability

Consider the underlying geometry of our β-sheets



Change of native state conformation under crowding of 3-strand peptide

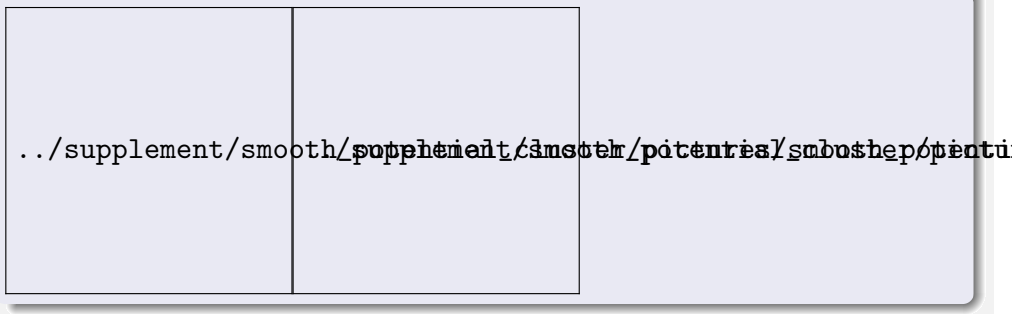
Trade-off between the **energetically favored native-state**, and an **entropically unfavorable conformation**.

Macrostate Clustering

Group microstates into macrostates

- Coarse-grain from kinetics, compute transition probabilities
- Transpose of eigenvectors suggest clustering

Example: Random walk in a three-well potential



Future Work

Where is the field going?
What are the important questions?

Nuanced Interactions

- Electrostatic Effects
- Hydrophobicity
- Hydrogen Bonds

Beyond thermodynamics

- Protein function and activity
- Aggregation models and kinetics
- Diffusion rates in crowded environments

Thank You.

Extra: Scaled Particle Theory Equations

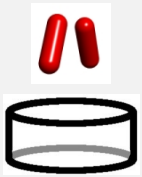
Activity coefficient

$$\ln \gamma_i = -\ln(1-(V)) + \frac{H_i(S)+S_i(H)+V_i(1)}{1-(V)} + \frac{H_i^2(S)^2+2V_i(H)(S)}{2(1-(V))^2} + \frac{V_i\left(H^2\right)(S)^2}{3(1-(V))^3}$$

H is the Kihara support function, geometrical measure of 'roundness'
For example:

$$H_{\text{sphereocylin}} = r\pi/4 + L/2$$

$$H_{\text{cylinder}} = r + L/4$$



We model the crowders, Ficoll 70, as sphereocylinders and the β-sheet peptides as cylinders to best match their native state geometry.

Fodeke and Minton, J. Phys. Chem. B 114, 10876 (2010)