Landscapes and Beyond--
Glasses, Proteins, and the Cell

Peter G. Wolynes
Rice University

Gateways to Emergent Behavior in Science and Society
An ICAM/SFI Workshop
Santa Fe, NM
September 24 - 26, 2013
Energy Landscapes: Crystals, Glasses and Proteins

Kepler, *De Nive Sexangula*, 1611. The first work on atomic structure of crystals.

Model handbuilt by J.D. Bernal

Haemoglobin, M. Perutz
Is a Virus Living or Dead?

The Big Mystery of the Cell

Humpty-Dumpty sat on a wall
Humpty-Dumpty had a great fall
all the king's horses
all the King's men
Couldn't put Humpty-Dumpty together again

Virus Simulation, K.J. Schulten
The complexity and hierarchy of biological functions

- **Chemical reaction**: form/break bonds
- **Small changes of configurations**
- **Folding**: internal self-assembly
- **Molecular association**
- **Molecular self-assembly**
- **Nonequilibrium assembly**

Size Scale:
- $10^{-10}$ m
- $10^{-9}$ m
- $10^{-8}$ m
- $10^{-7}$ m
- $10^{-6}$ m
- $10^{-5}$ m

Barrier Scale:
- Low $\sim k_B T$
- High $>> k_B T$
At Large Length Scales Inanimate Matter Becomes History Dependent
The Energy Landscapes of Crystals vs. Glasses

Single Crystal Form

Latent heat $O(N)$

Polymorphic Crystal Forms

Gap between globally different structures $O(1)$

No latent heat, but heat capacity jump
REM Thermodynamics and Configurational Entropy Crisis

Thermally occupied states

\[ P_{th} = \frac{P(E)e^{-E/k_BT}}{Z} \]

\[ \Omega(\bar{E}) = k_B \log \Omega_o P(\bar{E}) \]

\[ \bar{E}_{th} = -\Delta E^2/k_BT \]

\[ S = S_o - \Delta E^2/2(k_BT)^2 \]

Entropy Crisis, \( T_g \)

Degrees of Freedom Freezing at \( T_g \)
Kauzmann Paradox and the Levinthal Paradox

Diffusion on a Random Energy Landscape

\[ k_{esc} = \tau_o^{-1} e^{-\frac{(E_o - E_{thermal})}{2k_BT}} \]

\[ = \tau_o^{-1} e^{-\Delta E^2 / 2(k_BT)^2} \]

Bässler Law

At \( T_K \)

\[ k_{esc} = \tau_o^{-1} e^{-\frac{S_c}{k_B}} \]

Funneled vs. Rugged Landscapes

**Liquid ↔ Crystal**

High Temperature

**Funneled**

Below \( T_F \)

\[ T_F = \frac{\Delta E_S}{S_C / k_B} \]

Much below \( T_F \)

**Rugged**

At \( T_G \)

\[ T_G = \frac{\delta E}{\sqrt{S_C / k_B}} \]

Much below \( T_G \)
Thermodynamics and Frustration

Minimally frustrated
“Natural protein”

High Temperature

Below $T_F$

$T_F = \Delta E_S / (S_C / k_B)$

Much below $T_F$

Highly frustrated
Random sequence

High Temperature

At $T_G$

$T_G = \delta E / \sqrt{S_C / k_B}$

Much below $T_G$

For fast reliable folding must have $T_F > T_G$

Principle of Minimal Frustration

JD Bryngelson & PG Wolynes, PNAS, 1987
Ruggedness and Stability Compete in Folding Kinetics and in Crystallization

Glass Transition

Computer Model Protein

Most stable sequence

Least stable sequence

Laboratory Crystallization

Least stable crystal

Most stable crystal

$T_F/T_G$ must be high to self-organize efficiently!
Decoding, Prediction and Design

Sequence

Structure

Minimum
Frustration
Principle

Z-score optimization

Energy Function

$T_F/T_G$ scales like $Z = \Delta E/\delta E$
Structure Prediction Results for 13 Proteins


AWSEM-Md Structure Prediction and Modeling Tools
Predicted Structure (yellow) vs. PDB structure (blue) use AWSEM

Q=0.66, RMSD=3.3 Å
The amino-terminal domain of Phage 434 (PDB-ID: 1R69, 63 res.)

Q=0.65, RMSD=2.6 Å
Calcium-binding protein from bovine intestine (PDB-ID: 3ICB, 75 res.)

Q=0.5, RMSD=4.3 Å
N-terminal domain of E. coli DnaB helicase (PDB-ID: 1JWE, 118 res.)
AWSEM Predicted structures of dimers

Flycasting in Troponin Dimer
Localizing Frustration

\[ E_{G} \approx (-1.25) \Delta E \]

\[ E_{F}(i,j) < E_{G}(i,j) \]

\[ E_{G} < E_{F}(i,j) < \Delta E \]

\[ E_{F}(i,j) > \Delta E \]

Configurational Frustration

native structure (Alpha-spectrin sh3 domain)

native contacts

minimally frustrated

neutral

highly frustrated

Ferreiro, D.U., Hegler, J. & Wolynes, P.G.
Mobile Sites in Allosteric Proteins are often Frustrated

Are There Landscapes Far From Equilibrium?

M.C. Escher
The Geography and Meteorology of the Cell

- Filamentous network
- Structure and shape
  - Remodeling

Bulk

Polar filaments
- track for molecular motors
- directed motion

Cytoplasm
- Cytoplasmic streaming
- Crowded by organelles

W.M. Saxton
Active Matter and “Motorized” Particle Systems

Far from equilibrium chemical energy consumption

\[ \dot{\mathbf{r}}_i = \beta D f^H_i + \eta_i(t) + \nu^m_i(t) \]

- usual mechanical interactions
  \[ f^H_i = -\nabla_i U \]

- thermal noise
  \[ \langle \eta_i^\alpha(t) \eta_j^\beta(t') \rangle = 2D \delta_{\alpha\beta} \delta_{ij} \delta(t-t') \]

- chemical shot noise via allostERIC transitions!
  \[ \nu^m_i(t) = \sum_q \tilde{\eta}_q^{(i)} \delta(t-t_q) \]

from Langevin equation to master equation

\[
\begin{align*}
\hat{L}_{FP} \Psi &= D \sum_i \nabla_i \cdot \left( \nabla_i \Psi - \beta f^H_i \Psi \right) \\
\hat{L}_{NE} \Psi(\{\mathbf{r}\}, t) &= \int \Pi_i d\mathbf{r}_i [K(\{\mathbf{r}'\} \rightarrow \{\mathbf{r}\}) \Psi(\{\mathbf{r}'\}, t) - K(\{\mathbf{r}\} \rightarrow \{\mathbf{r}'\}) \Psi(\{\mathbf{r}\}, t)]
\end{align*}
\]
Systematic expansion: effective equilibrium

* Isotropic kicks & symmetric susceptibility \((s_u = s_d = s)\)

An effective Fokker-Planck equation

\[
\frac{\partial}{\partial t} \Psi(\{\vec{r}\}, t) = D_{\text{eff}} \sum_i \left\{ \nabla_i^2 \Psi - \nabla_i \cdot [(-\nabla_i \beta_{\text{eff}} U) \Psi] \right\}
\]

\[D_{\text{eff}} = D_0 \left( 1 + \frac{1}{2d} \frac{\kappa l^2}{D_0} \right)\]

\[\left( \frac{\beta_{\text{eff}}}{\beta} \right)^{-1} = \frac{T_{\text{eff}}}{T} = \left( 1 + \frac{1}{2d} \frac{\kappa l^2}{D_0} \right) \bigg/ \left( 1 + \frac{s \kappa l^2}{d D_0} \right)\]

\[
s > 1/2 \quad T_{\text{eff}} < T
\]

\[
\Delta \gg 1 \quad T_{\text{eff}}/T \sim 1/(2s) \text{ as } s \to 0
\]

Enhanced diffusion

intense adamant kicks yield very high \(T_{\text{eff}}\)

Systematic expansion: spontaneous motion

Go beyond effective equilibrium \textbf{(quartic order)}

\[
\frac{\partial}{\partial t} \Psi(\{r\}, t) = D_{\text{eff}} \sum_i \left\{ \nabla_i^2 \Psi - \nabla_i \cdot \left( -\nabla_i \beta_{\text{eff}} U \right) \Psi \right\} \\
+ \kappa l^4 \langle \cos^4 \theta \rangle \mathbf{n} \times \sum_i F_i \left( \nabla_i^{(m)} U, \nabla_i^{(n)} \Psi \right).
\]

\[F_i = -\nabla_i \cdot \tilde{J}_i^a\quad \text{Probability conservation for any } i\]

\[-\tilde{J}_i^a = \frac{1}{24} \nabla_i^3 \Psi + \frac{s}{12} \nabla_i \left( \nabla_i^2 \beta U \Psi \right) + \frac{s}{6} \nabla_i \beta U \nabla_i^2 \Psi \]
\[
+ \frac{s^2}{4} \left( \nabla_i \beta U \right)^2 \nabla_i \Psi + \frac{s^3}{6} \left( \nabla_i \beta U \right)^3 \Psi.
\]

a net streaming flow becomes possible!

W.M. Saxton
An optimal connectivity for most efficient flow

- An optimal strength of mechanical feedback/network connectivity for most efficient flow
- Susceptible motors

Wang S & Wolynes PG, PNAS (2011)
Structural development: interplay of network connectivity & motor susceptibility

Aster-like patterns/bundle-connected poles

\( S_u = -1, \quad S_d = 0 \)
\( l = 0.2; \quad P_c = 0.5 \)

Negative susceptibility

\( P \) negative \( T_{\text{eff}} \)
\( P \) thermodynamic instability

Uphill-prone motors:
Maximize the energy by stretching filaments

“novas of asters”

Tense filaments radiate from the central nodes

20 \( \mu \)m
END OF TALK