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

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Rice University

*Gateways to Emergent Behavior in Science and Society*
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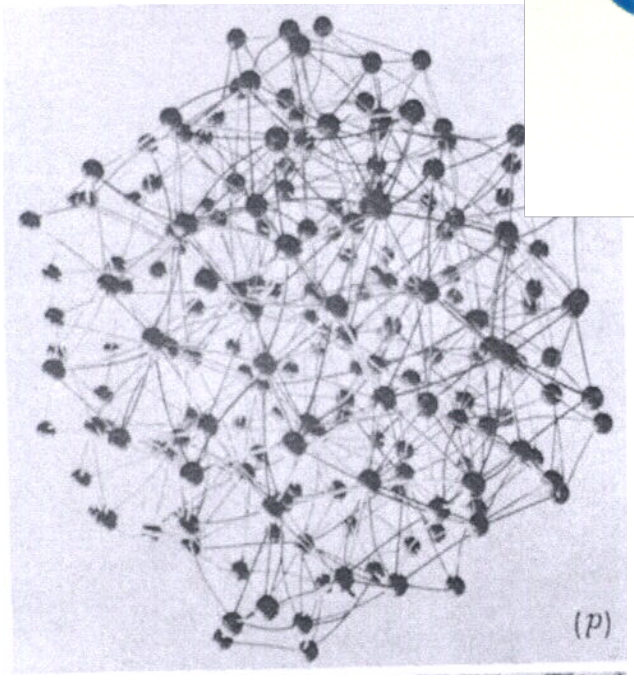
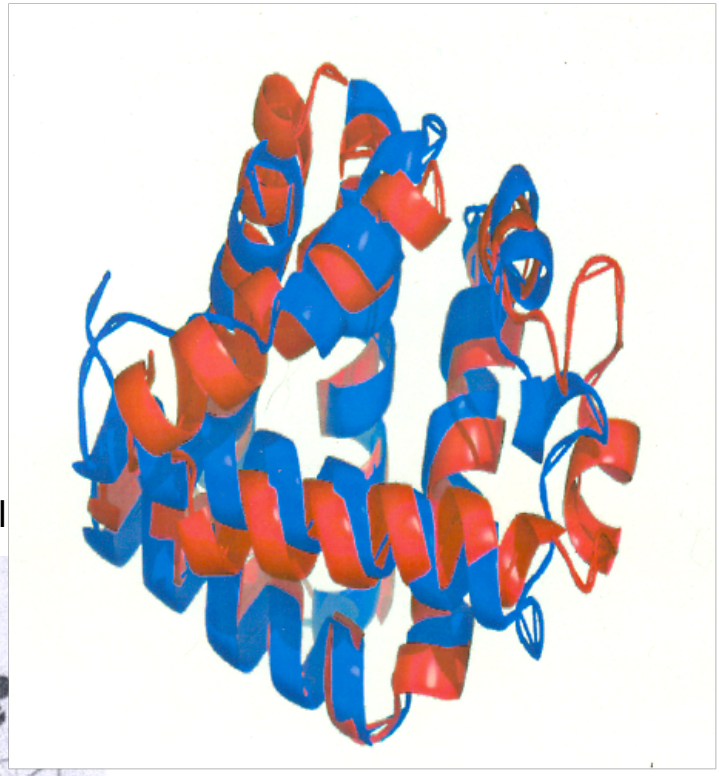
# Energy Landscapes: Crystals, Glasses and Proteins


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

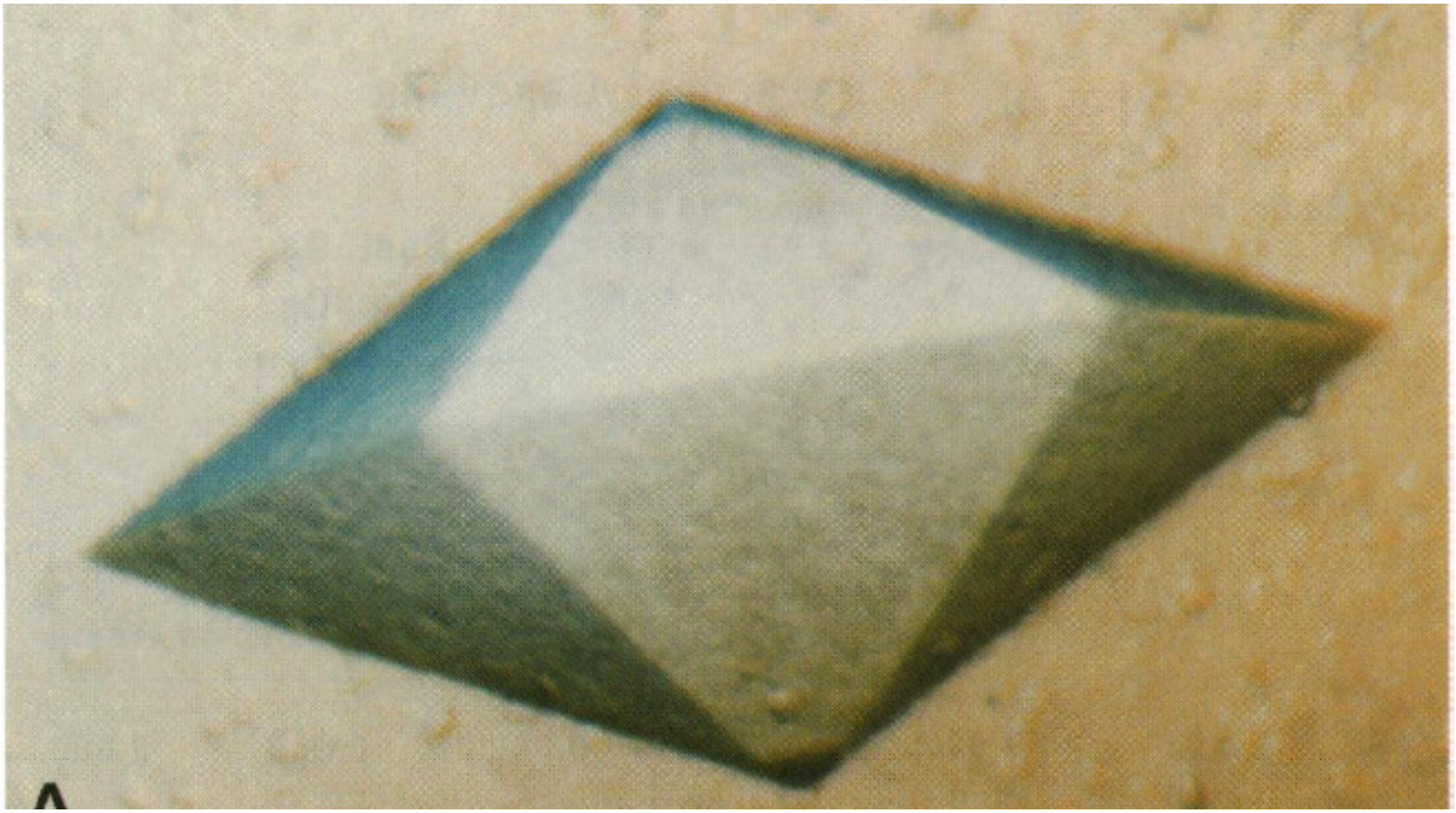
Model handbuilt by J.D. Bernal



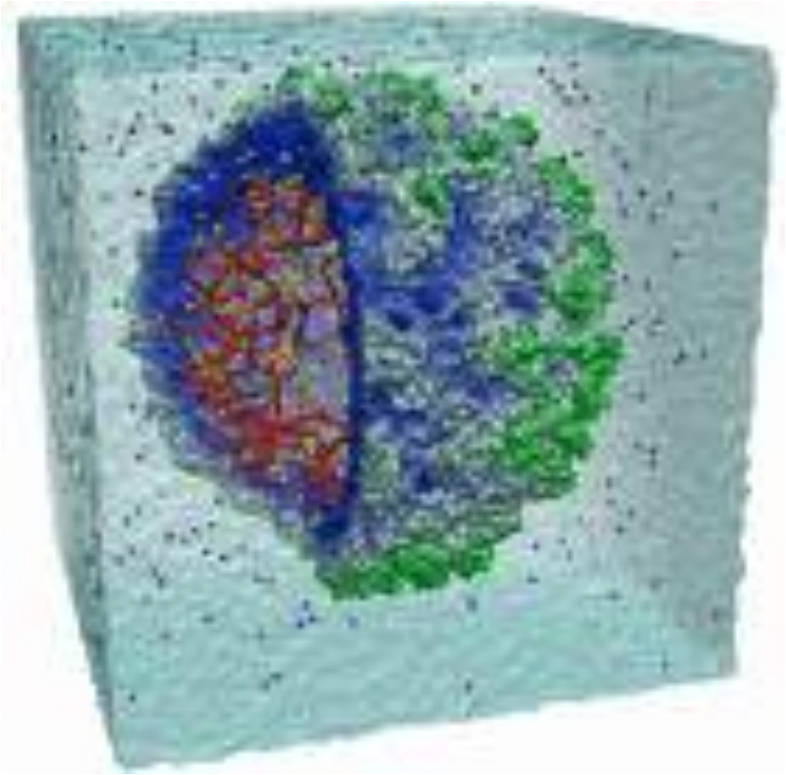
Haemoglobin, M. Perutz

# Is a Virus Living or Dead?



S. Koszelak et al, *Biophys. J*. 69:13-19 (1995*).*

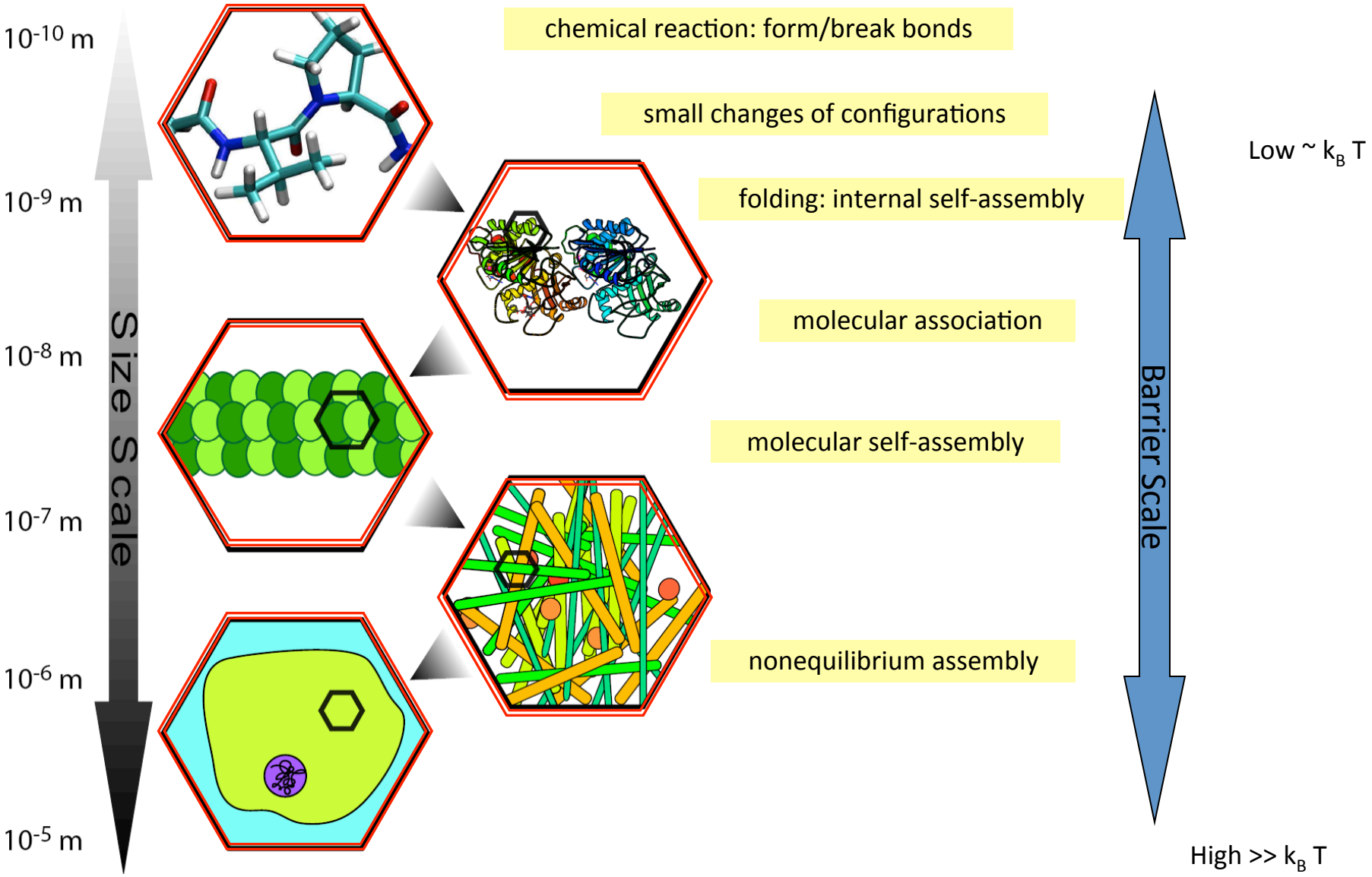
# *The Big Mystery of the Cell*



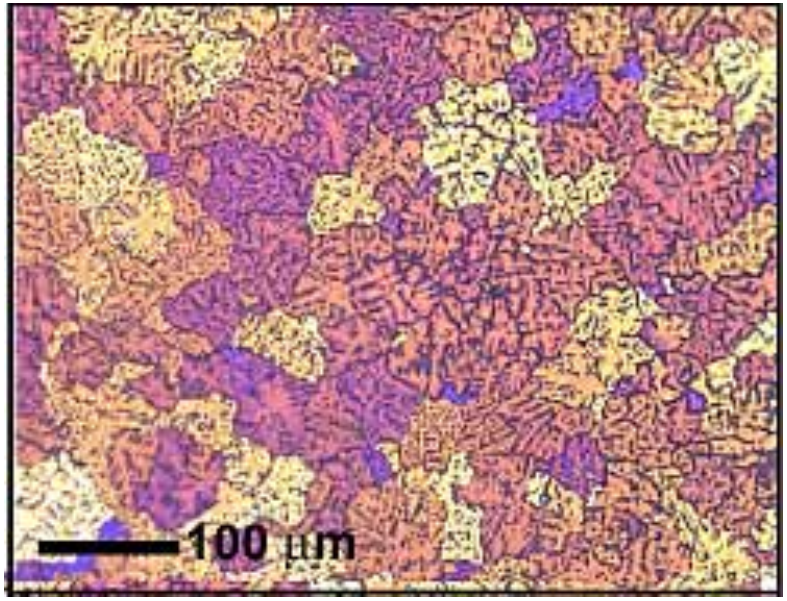
Virus Simulation, K.J. Schulten

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

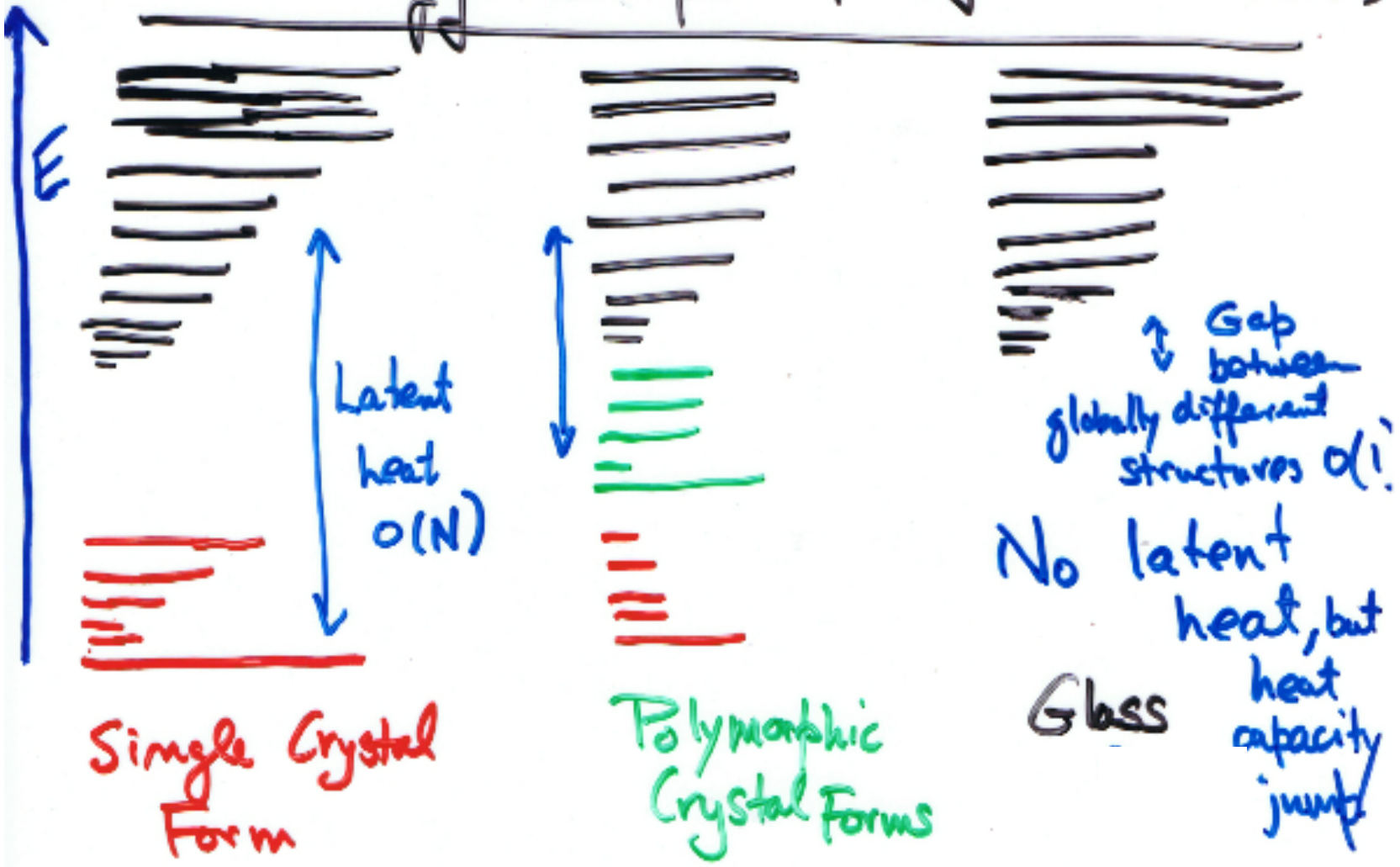
# The complexity and hierarchy of biological functions



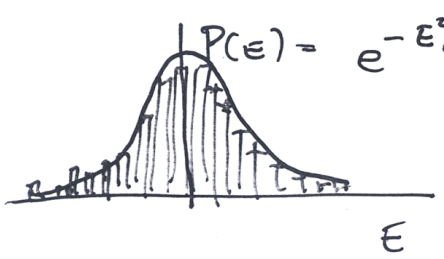
At Large Length Scales
Inanimate Matter
Becomes History
Dependent



# The Energy Landscapes of Crystals vs. Glasses



# REM Thermodynamics and Configurational Entropy Crisis



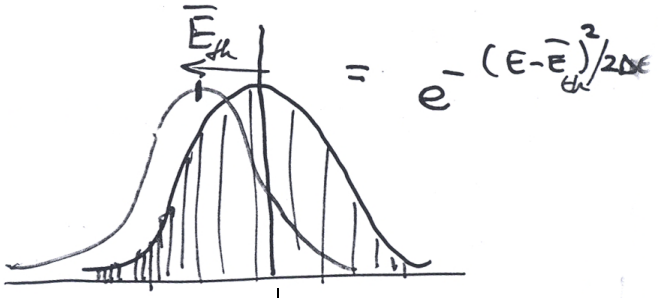

Thermally occupied states

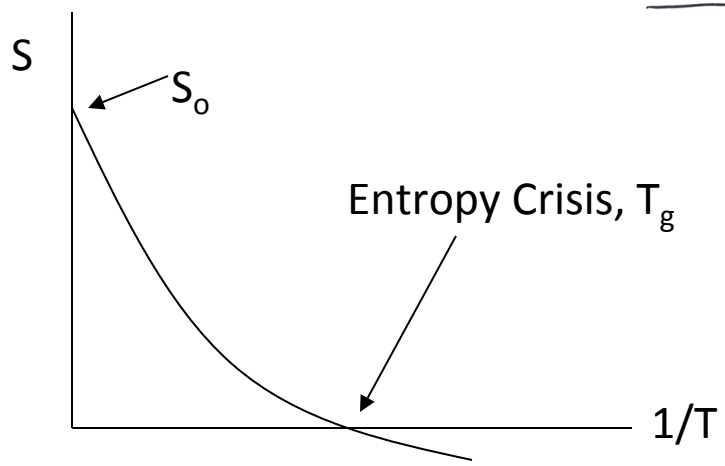
$$P_{th} = \frac{P(E)e^{-E/k_BT}}{Z}$$

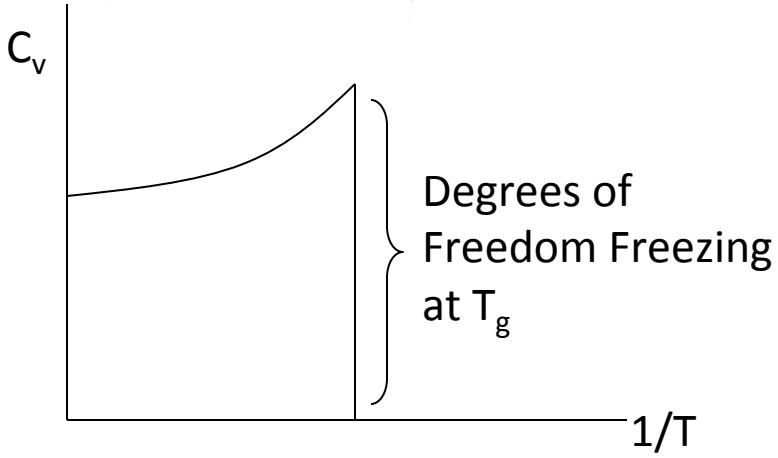
$$\Omega(\bar{E}) = k_B \log \Omega_o P(\bar{E})$$

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

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

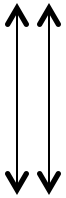


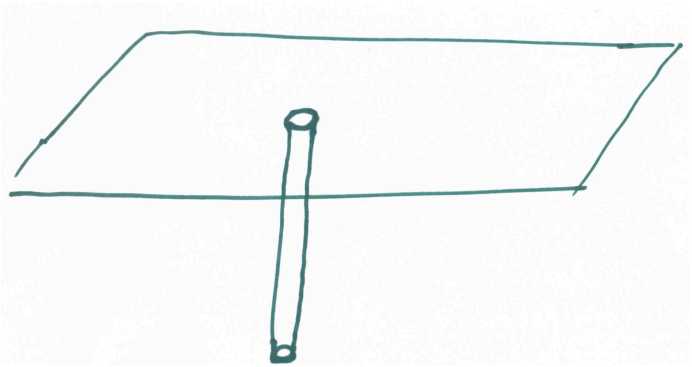



# Kauzmann Paradox and the Levinthal Paradox


Rugged Mountain Landscape





Golf Course

Diffusion an a Random Energy Landscape

$$k_{esc} = \tau_o^{-1} e^{-(\bar{E}_o - \bar{E}_{thermal})/2k_BT}$$

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

Bässler Law

At $T_K$

$$k_{esc} = \tau_o^{-1} e^{-S_c/k_B}$$

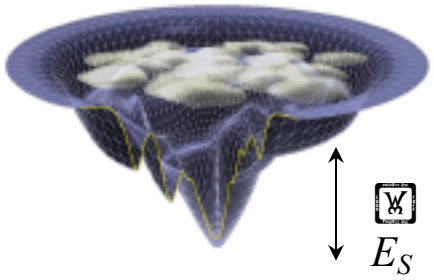

Bryngelson/PGW *J. Phys. Chem.* 93, 6902 (1989)
J. Wang, S. Plotkin, PGW,*J. de Phys.* Z, 395 (1997)

# Funneled vs. Rugged Landscapes

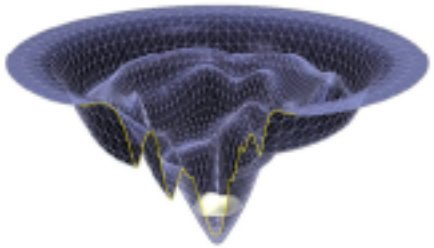
*Liquid* ⟷ *Crystal*

**High Temperature**

**Funneled**

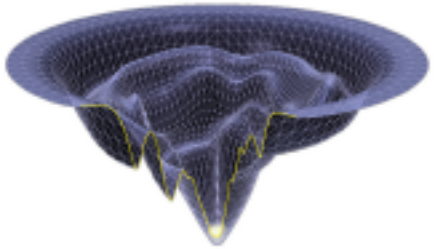



**Below $T_F$**



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

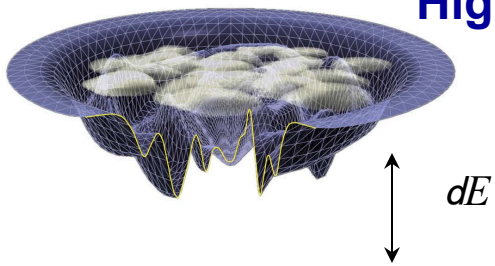
**Much below $T_F$**



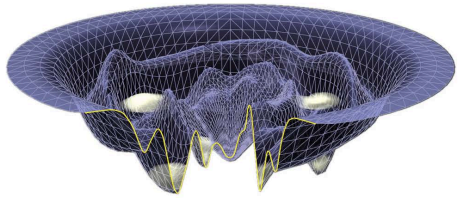
*Liquid* ⟷ *Glass*

**High Temperature**

**Rugged**

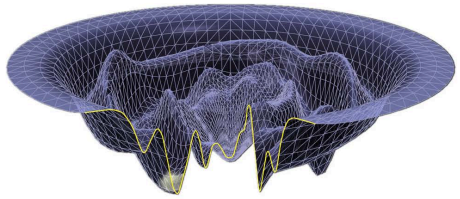



**At $T_G$**



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

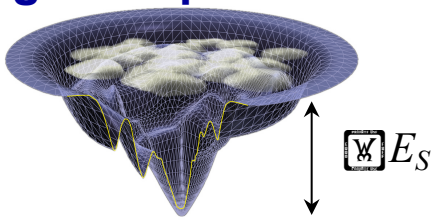
**Much below $T_G$**



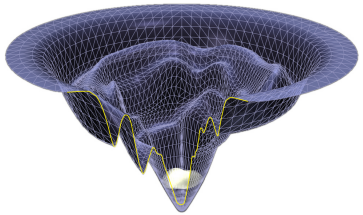
# Thermodynamics and Frustration

*Minimally frustrated*
*"Natural protein"*

**High Temperature**

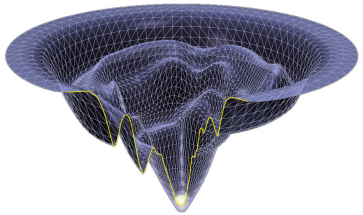



**Below $T_F$**



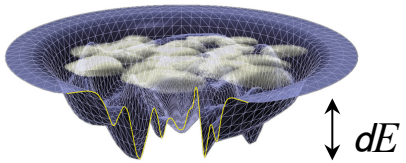
$$T_F = \Delta E_S / (S_C / k_B)$$

**Much below $T_F$**

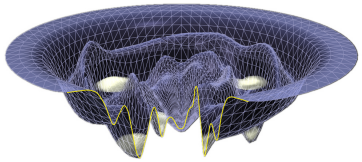


*Highly frustrated*
*Random sequence*

**High Temperature**

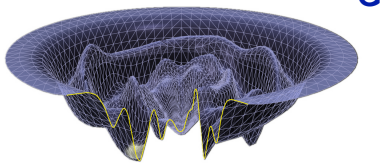



**At $T_G$**



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

**Much below $T_G$**



For fast reliable folding must have $T_F > T_G$

**Principle of Minimal Frustration**

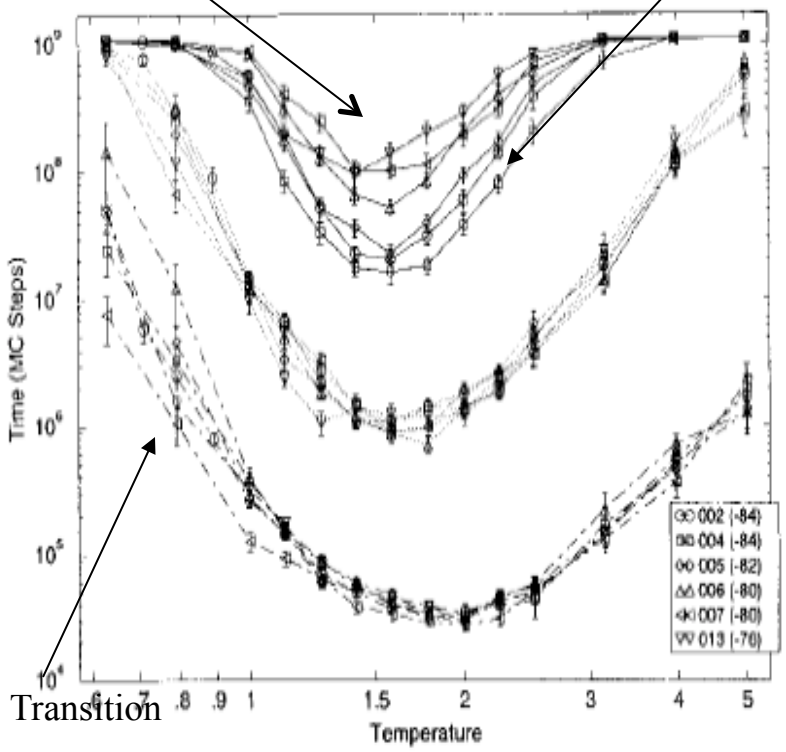
JD Bryngelson & PG Wolynes, *PNAS*, 1987

# Ruggedness and Stability Compete in Folding Kinetics and in Crystallization

Computer Model Protein

Least stable sequence

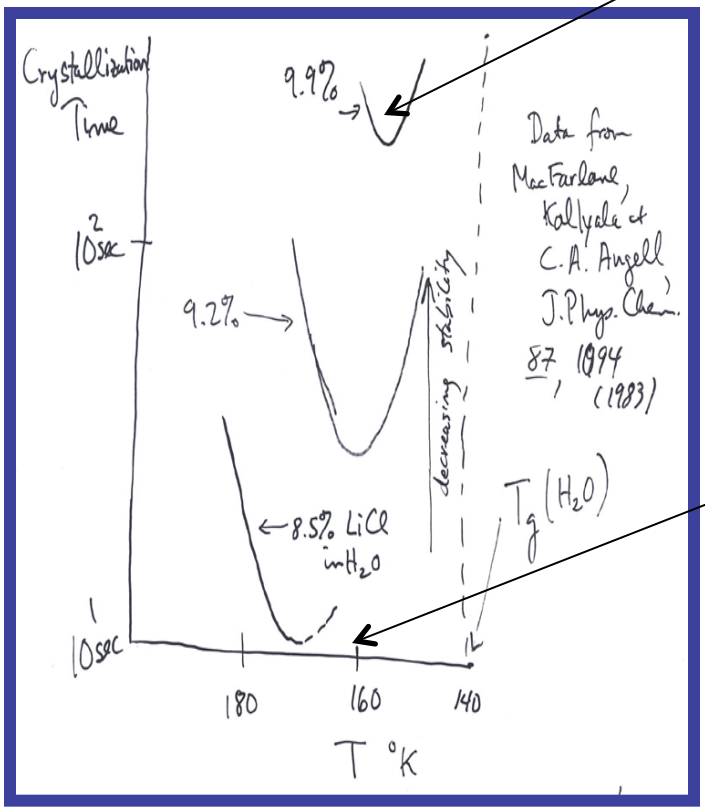
Most stable sequence




Glass Transition

Laboratory Crystallization

Least stable crystal

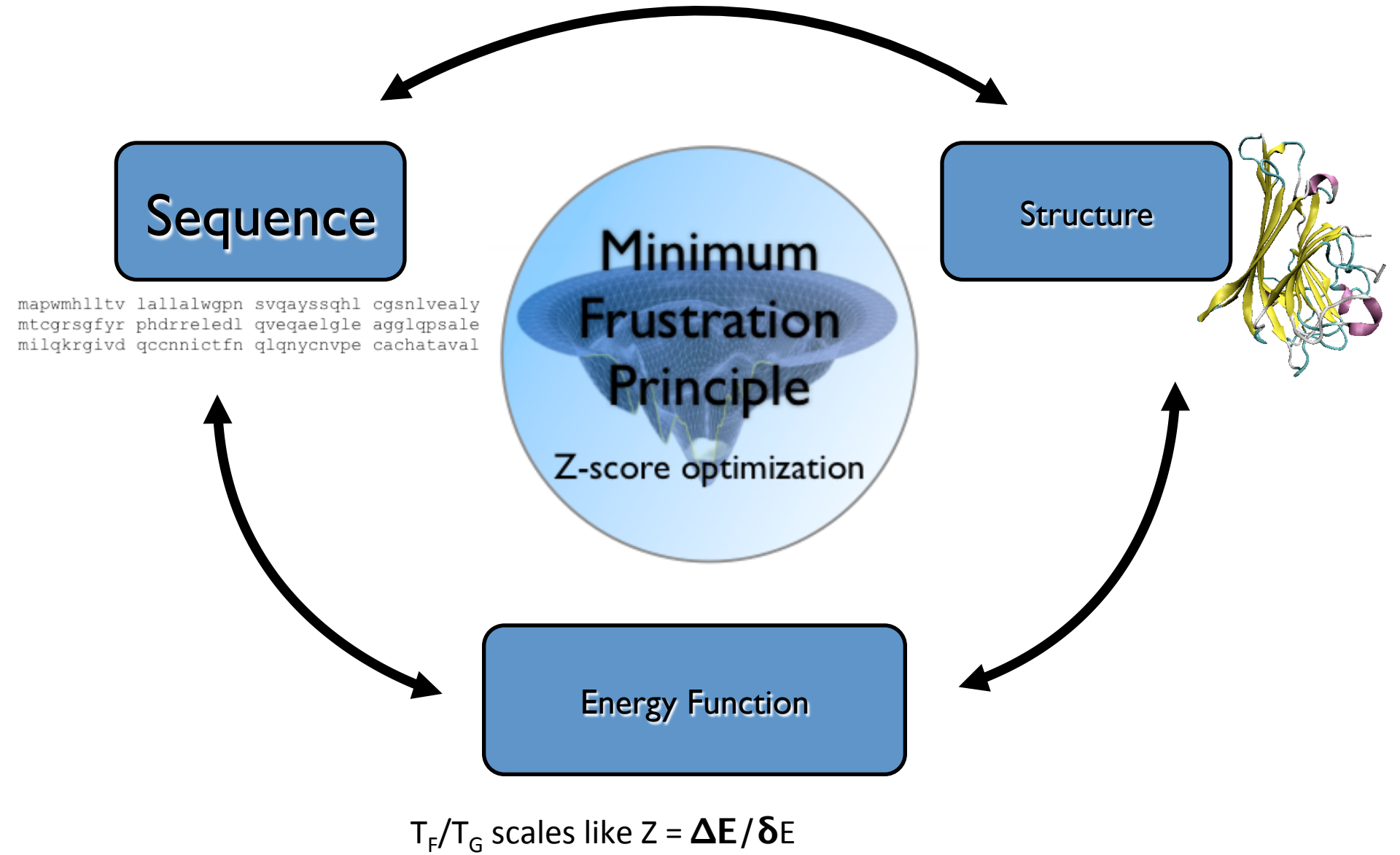



Most stable crystal

Bryngelson, Onuchic, Socci, PGW, *Proteins*,1995

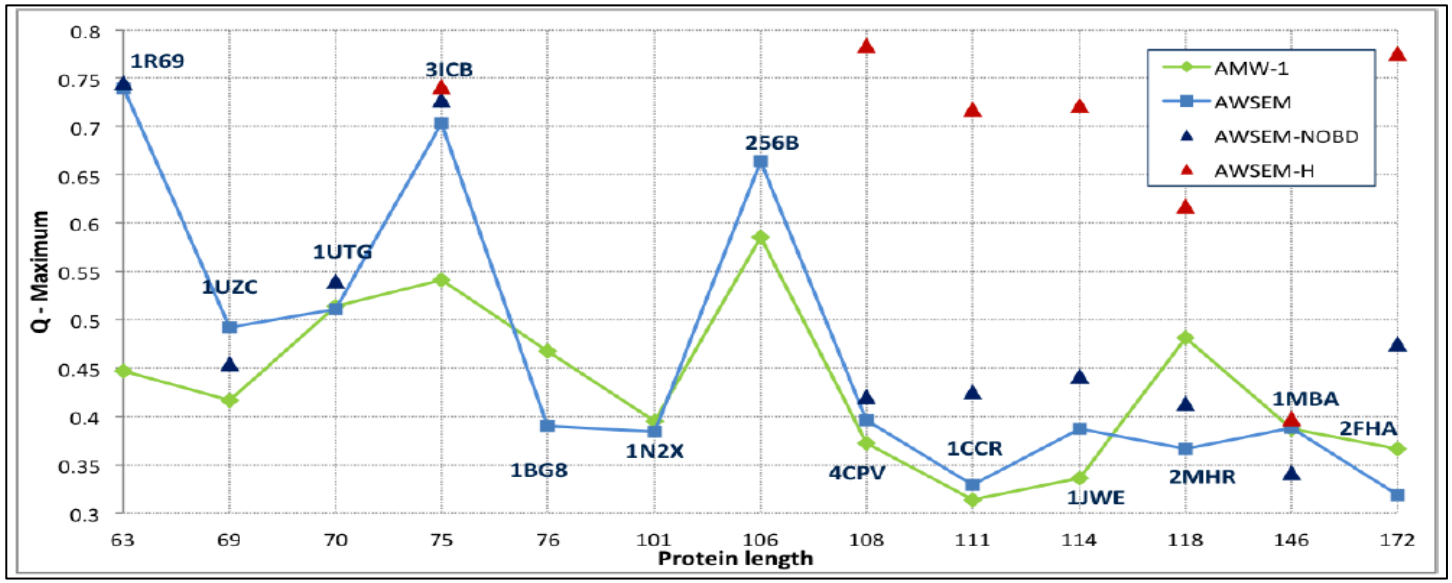
$T_F/T_G$ must be high to self-organize efficiently!

# Decoding, Prediction and Design




$T_F/T_G$ scales like $Z = \Delta E / \delta E$

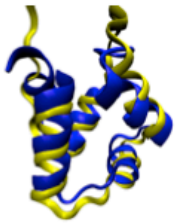
# Structure Prediction Results for 13 Proteins




Davytan A., Schafer, N., Zheng, W., Clementi, C., Wolynes, P.G., Papoian. G.A., "AWSEM-MD: Protein Structure Prediction Using Coarse-grainecd Physical Potentials and Bioinformatically Based Local Structure Biasing," *J. Phys. Chem* 2012

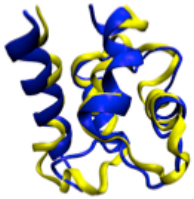
## AWSEM-Md Structure Prediction and Modeling Tools

Predicted Structure (yellow) vs. PDB structure (blue) use AWSEM



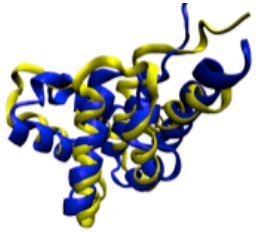
Q=0.66, RMSD=3.3 A

The amino-terminal domain of Phage 434 (PDB-ID: 1R69, 63 res.)



Q=0.65, RMSD=2.6 A

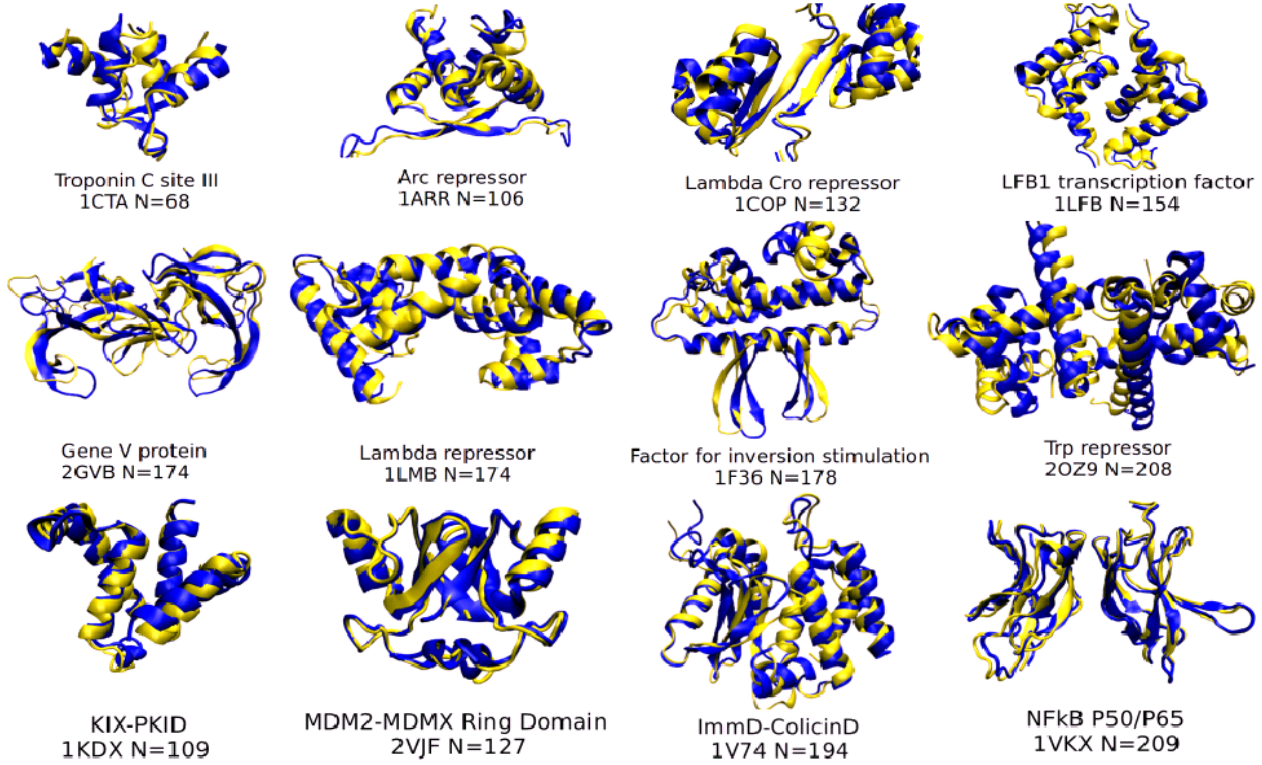
Calcium-binding protein from bovine intestine (PDB-ID: 3ICB, 75 res.)

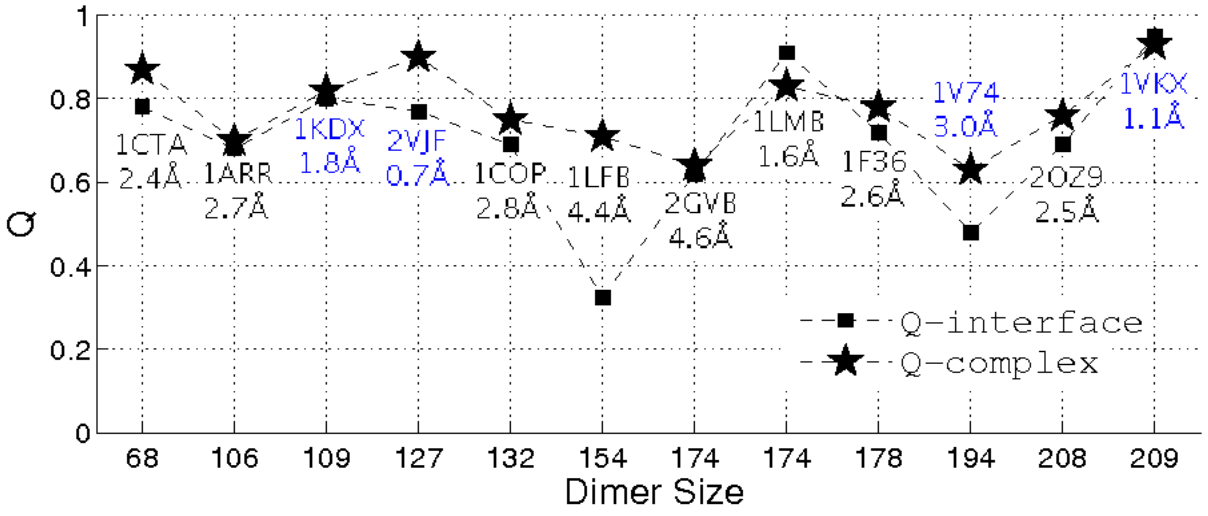


Q=0.5, RMSD=4.3 A

N-terminal domain of E. coli DnaB helicase (PDB-ID: 1JWE, 118 res)

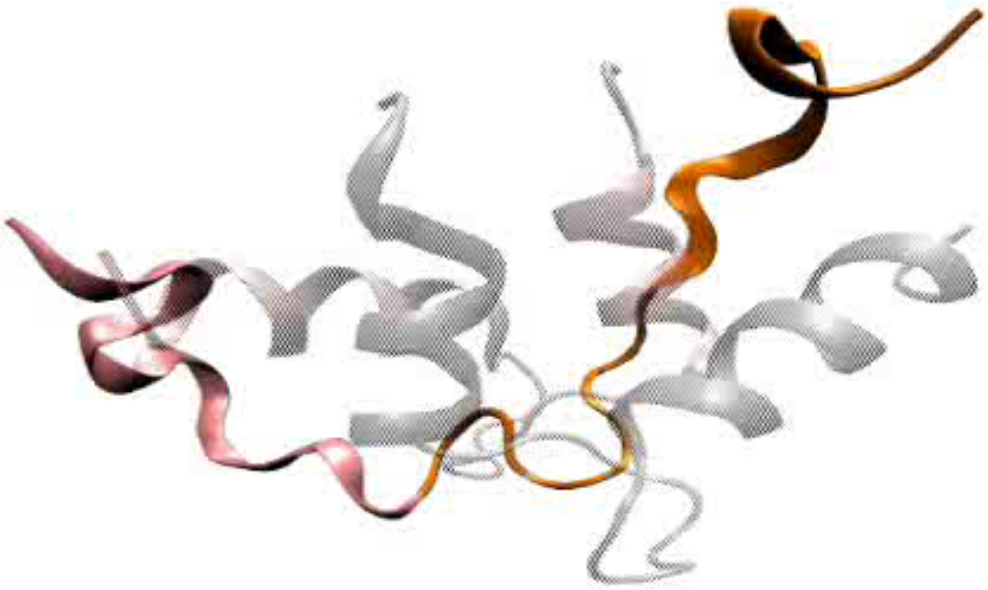
# AWSEM Predicted structures of dimers



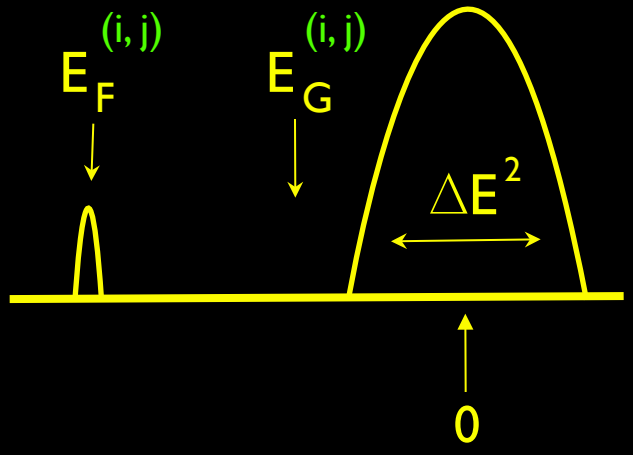




Zheng W, Schafer N, Davtyan A, Papoian G, Wolynes PG, "Predictive Energy Landscapes for Protein-Protein Association" *PNAS* [In Press] 2012.

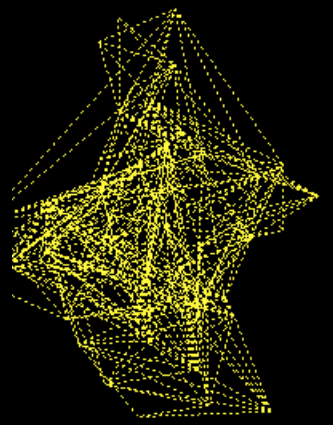
# *Flycasting in Troponin Dimer*



# Localizing Frustration




native structure
(Alpha-spectrin sh3 domain)



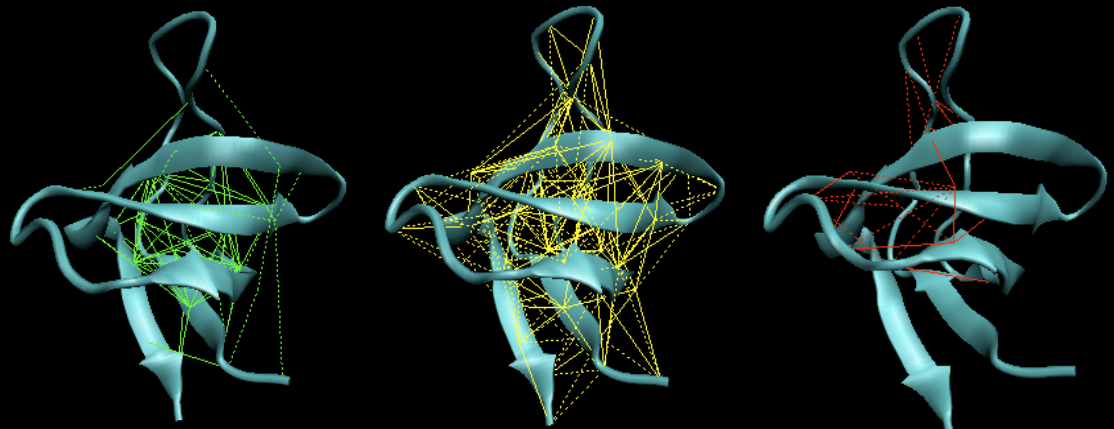
native contacts

$$E_G \cong (-1.25)\ \Delta E$$

$$E_F^{(i,j)} < E_G^{(i,j)}$$

$$E_G^{(i,j)} < E_F^{(i,j)} < \Delta E$$

$$E_F^{(i,j)} > \Delta E$$



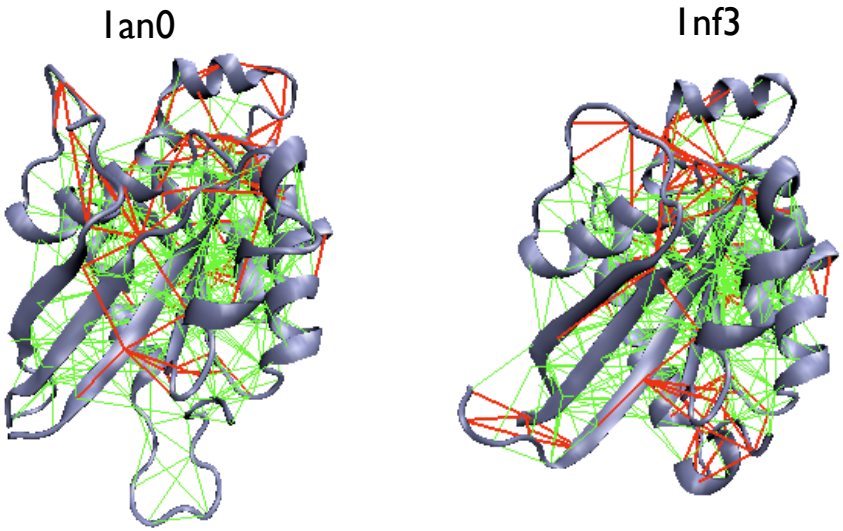
minimally frustrated

neutral

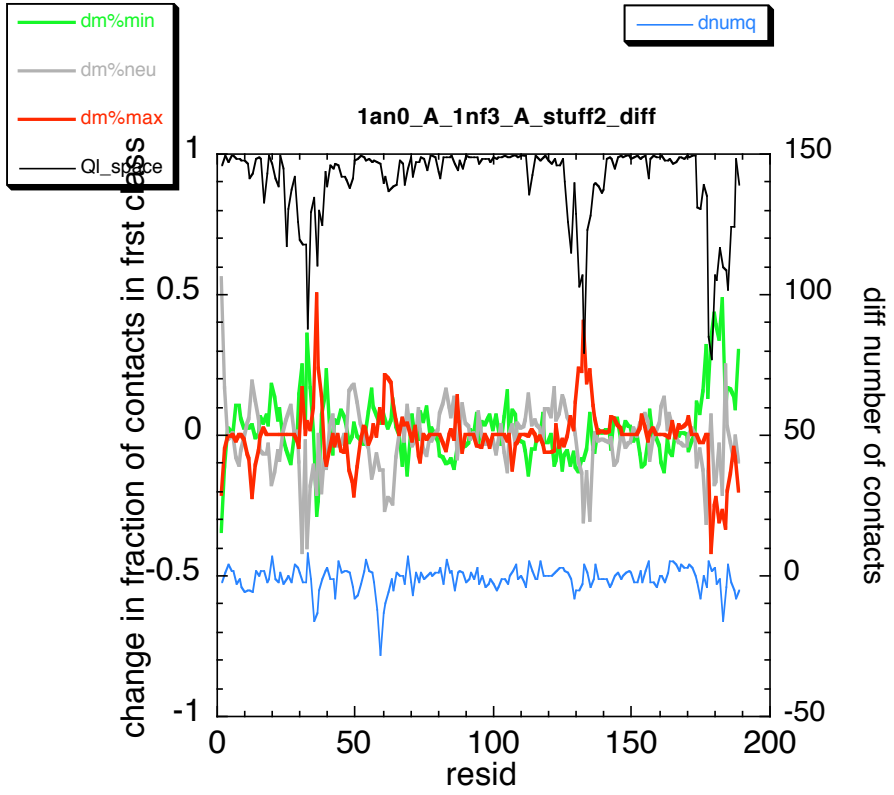
highly frustrated

Ferreiro, D.U., Hegler, J. & Wolynes, P.G.

# Mobile Sites in Allosteric Proteins are often Frustrated

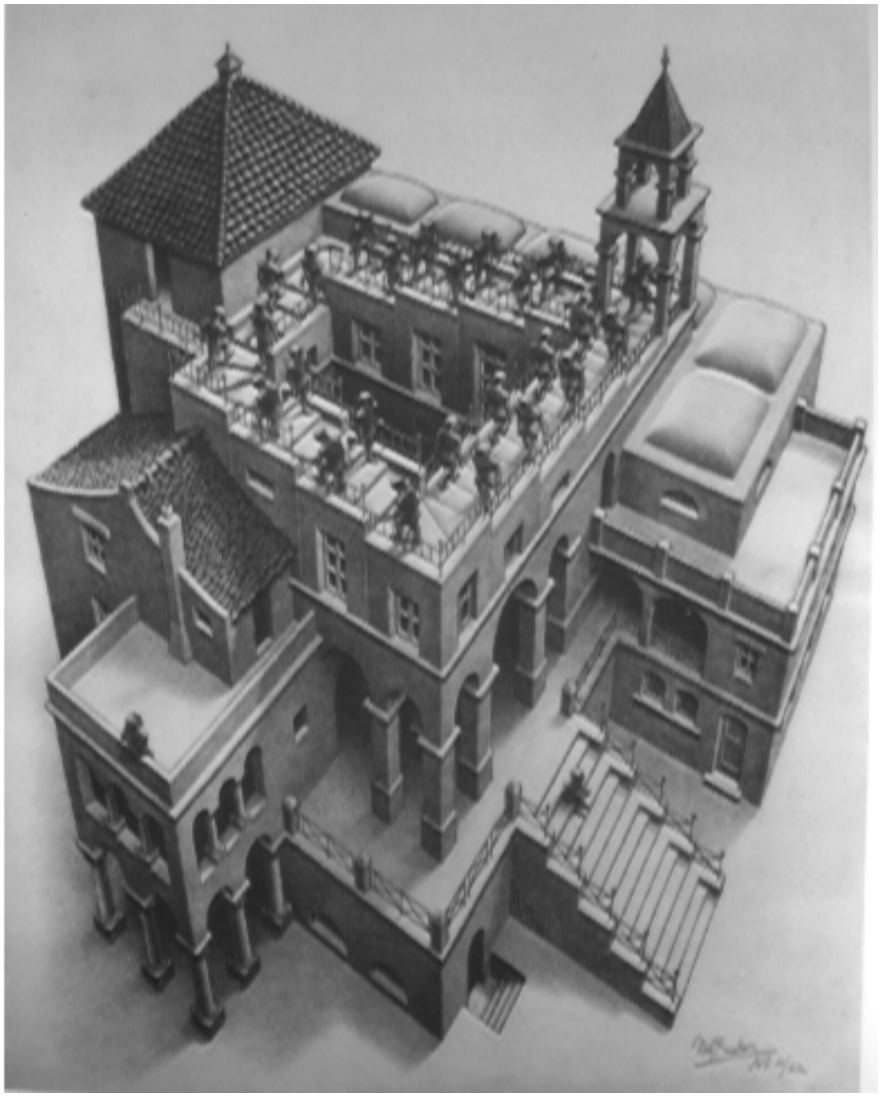



CDC42 signalling protein



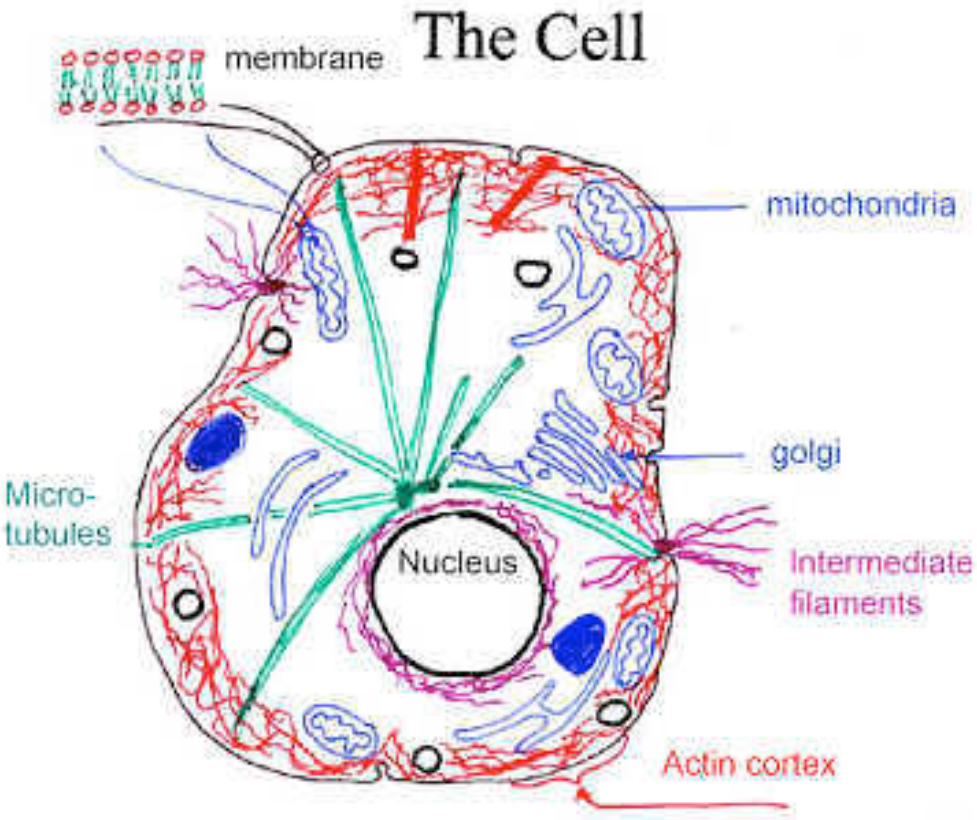

D. Ferreiro, J.A. Hegler, E.A. Komives, P.G.W., *PNAS* 108, 3499 (2011)

# Are There Landscapes Far From Equilibrium?



M.C. Escher

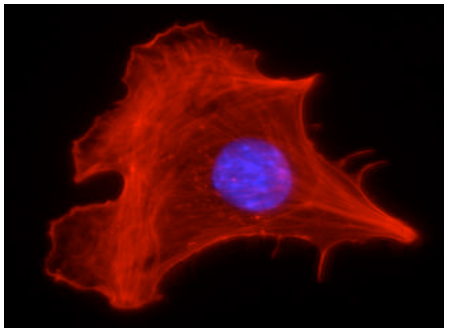
# The Geography and Meteorology of the Cell



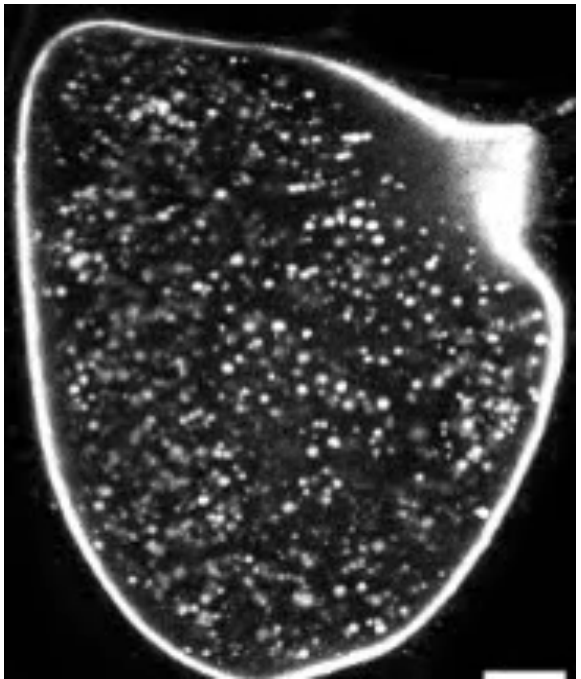

**Polar filaments**

- track for molecular motors
- directed motion

**Bulk**



- Filamentous network
- Structure and shape
- Remodeling



**Cytoplasm**

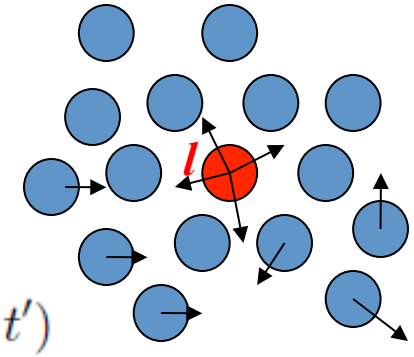
- Cytoplasmic streaming
- Crowded by organelles

W.M. Saxton

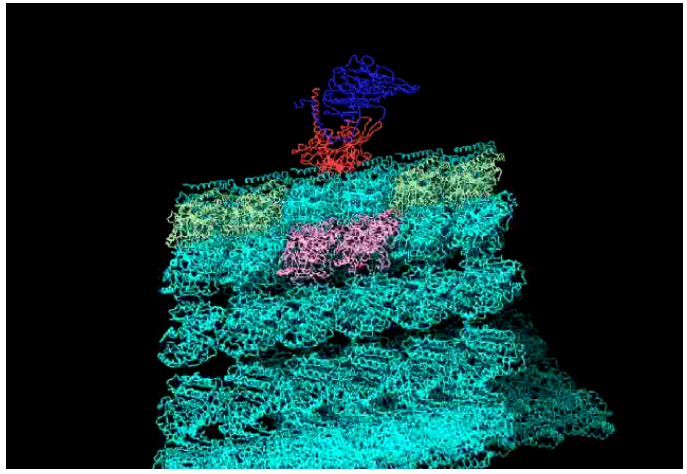
# Active Matter and "Motorized" Particle Systems

## Far from equilibrium chemical energy consumption

$$\dot{\vec{r}}_i = \beta D \vec{f}_i^H + \vec{\eta}_i(t) + \vec{v}_i^m(t)$$




- usual mechanical interactions $\vec{f}_i^H = -\nabla_i U$
- thermal noise $< \eta_i^\alpha(t)\eta_j^\beta(t') >= 2D\delta_{\alpha\beta}\delta_{ij}\delta(t-t')$
- chemical shot noise via allosteric transitions! $\vec{v}_i^m(t) = \sum_q \vec{l}_q^{(i)}\delta(t-t_q)$



from Langevin equation to master equation

$$\begin{cases} \hat{L}_{FP}\Psi = D\sum_i \nabla_i \cdot \left(\nabla_i\Psi - \beta\vec{f}_i^H\Psi\right) \\ \hat{L}_{NE}\Psi(\{\vec{r}\},t) = \int \Pi_i d\vec{r}_i'[K(\{\vec{r}'\}\to\{\vec{r}\})\Psi(\{\vec{r}'\},t) - K(\{\vec{r}\}\to\{\vec{r}'\})\Psi(\{\vec{r}\},t)] \end{cases}$$

# Systematic expansion: effective equilibrium

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

An effective Fokker-Planck equation

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

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

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

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

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

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

*Wang S & Wolynes PG, JCP **135**, 051101 (2011)*

# Systematic expansion: spontaneous motion

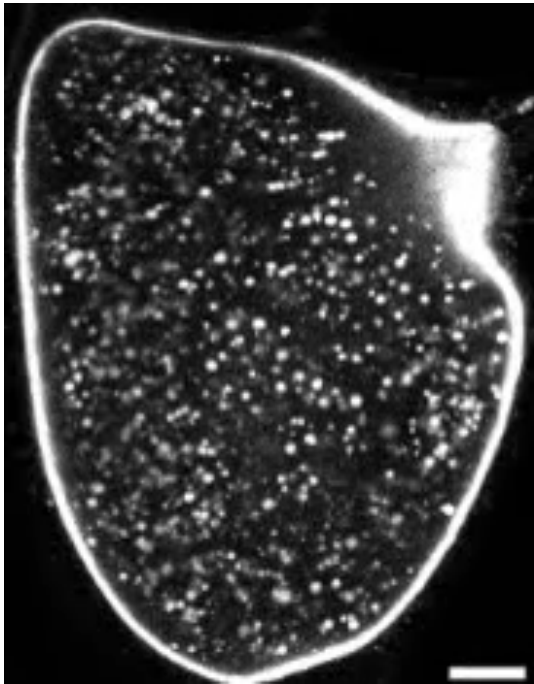
Go beyond effective equilibrium (quartic order)

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

$F_i = -\nabla_i\cdot\vec{J}_i^a$ Probability conservation for any l

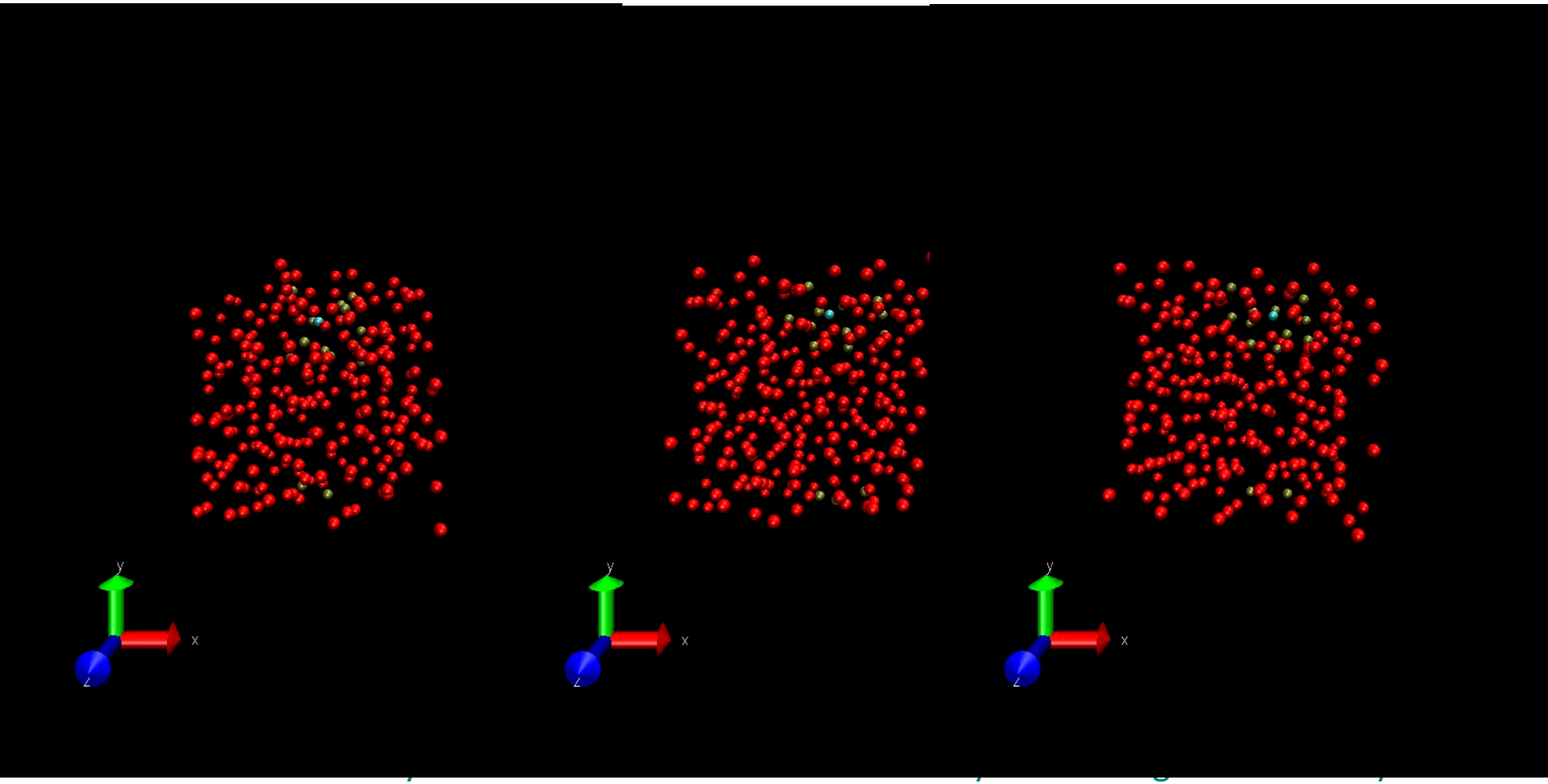
$$-\vec{J}_i^a = \frac{1}{24}\nabla_i^3\Psi + \frac{s}{12}\nabla_i\left(\nabla_i^2\beta U\Psi\right) + \frac{s}{6}\nabla_i\beta U\nabla_i^2\Psi$$
$$+ \frac{s^2}{4}(\nabla_i\beta U)^2\nabla_i\Psi + \frac{s^3}{6}(\nabla_i\beta U)^3\Psi.$$

a net streaming flow becomes possible!



W.M. Saxton

# An optimal connectivity for most efficient flow



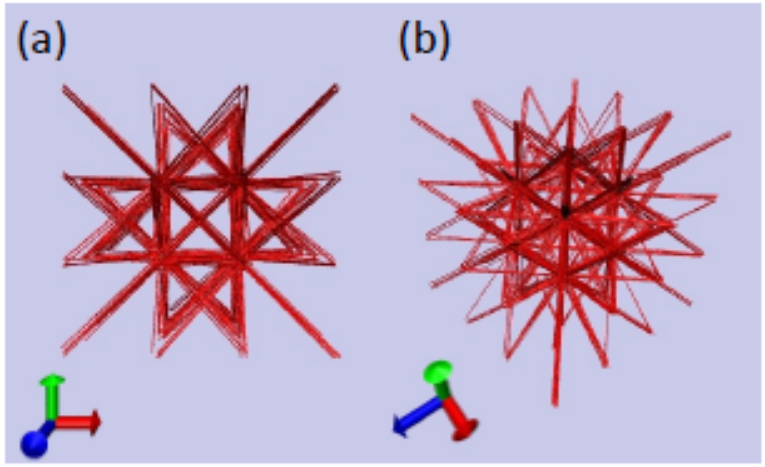
- An optimal strength of mechanical feedback/network connectivity for most efficient flow
- susceptible motors

*Wang S & Wolynes PG, PNAS (2011)*

# Structural development: interplay of network connectivity & motor susceptibility

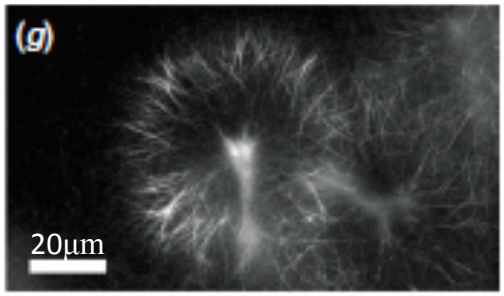
Aster-like patterns/
bundle-connected poles

$s_u$=-1, $s_d$=0
$l$=0.2; $P_c$=0.5

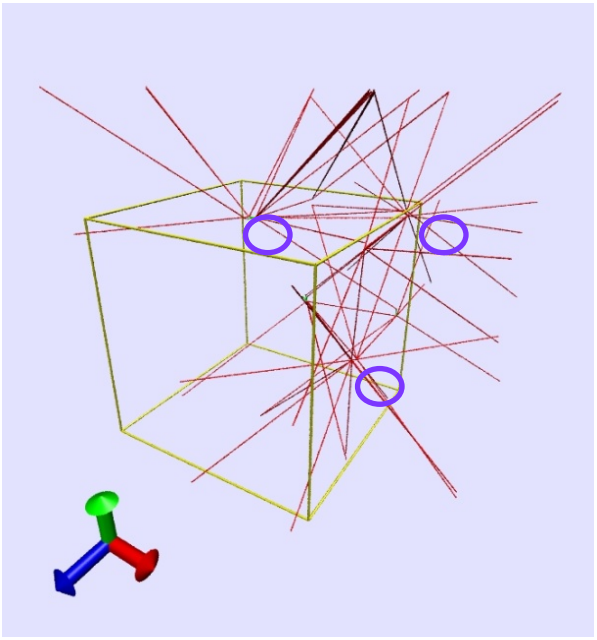



Uphill-prone motors:
Maximize the energy by stretching filaments

"novas of asters"




negative susceptibility
Þ negative $T_{eff}$
Þ thermodynamic instability



tense filaments radiate
from the central nodes

# END OF TALK