FAST Prediction of Protein Thermodynamics

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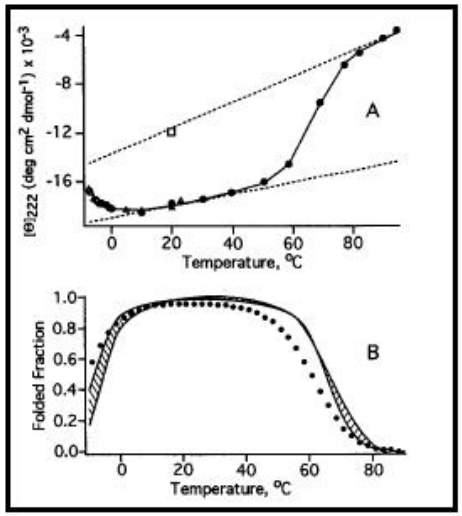
Protein Thermodynamic Stability

Dependence on thermodynamic/solvent conditions and sequence

Temperature induced denaturation

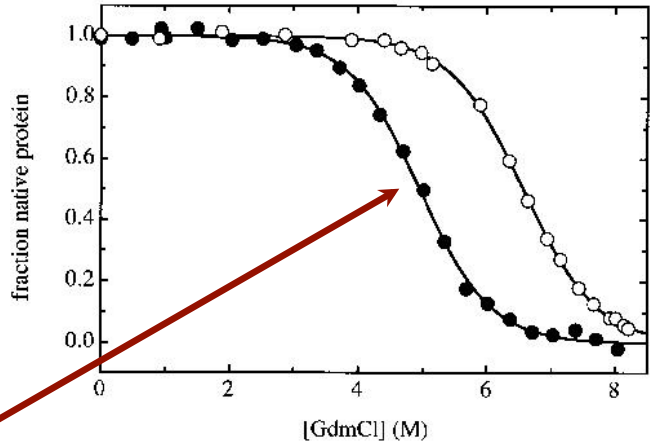
R.M. Ballew, et al., PNAS 93 5759 (1996)



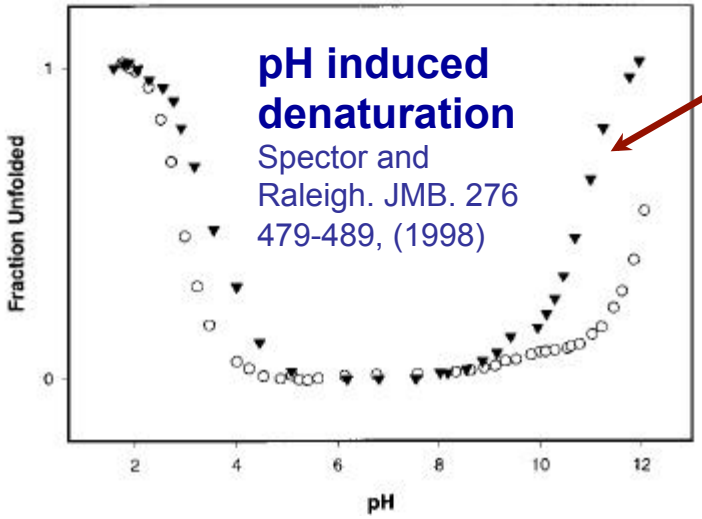
examples of how to denature a protein
(randomly selected)

[co-solute] induced denaturation

G. Pappenberger, Nature: Struct. Biol. 8, 452-458 (2001)

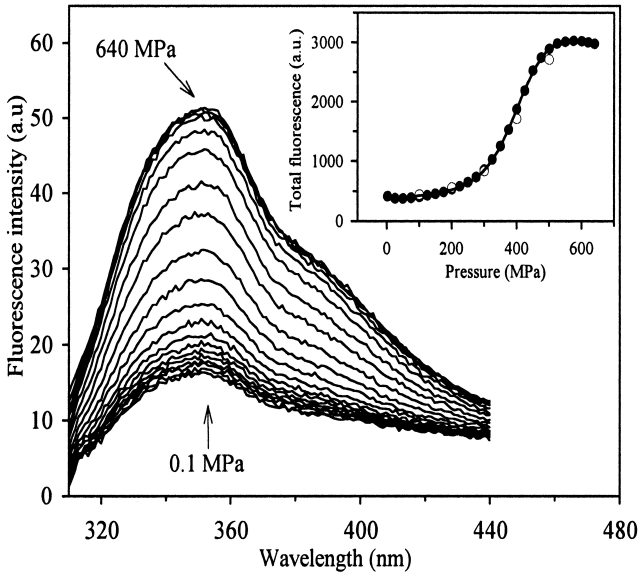


sequence dependence



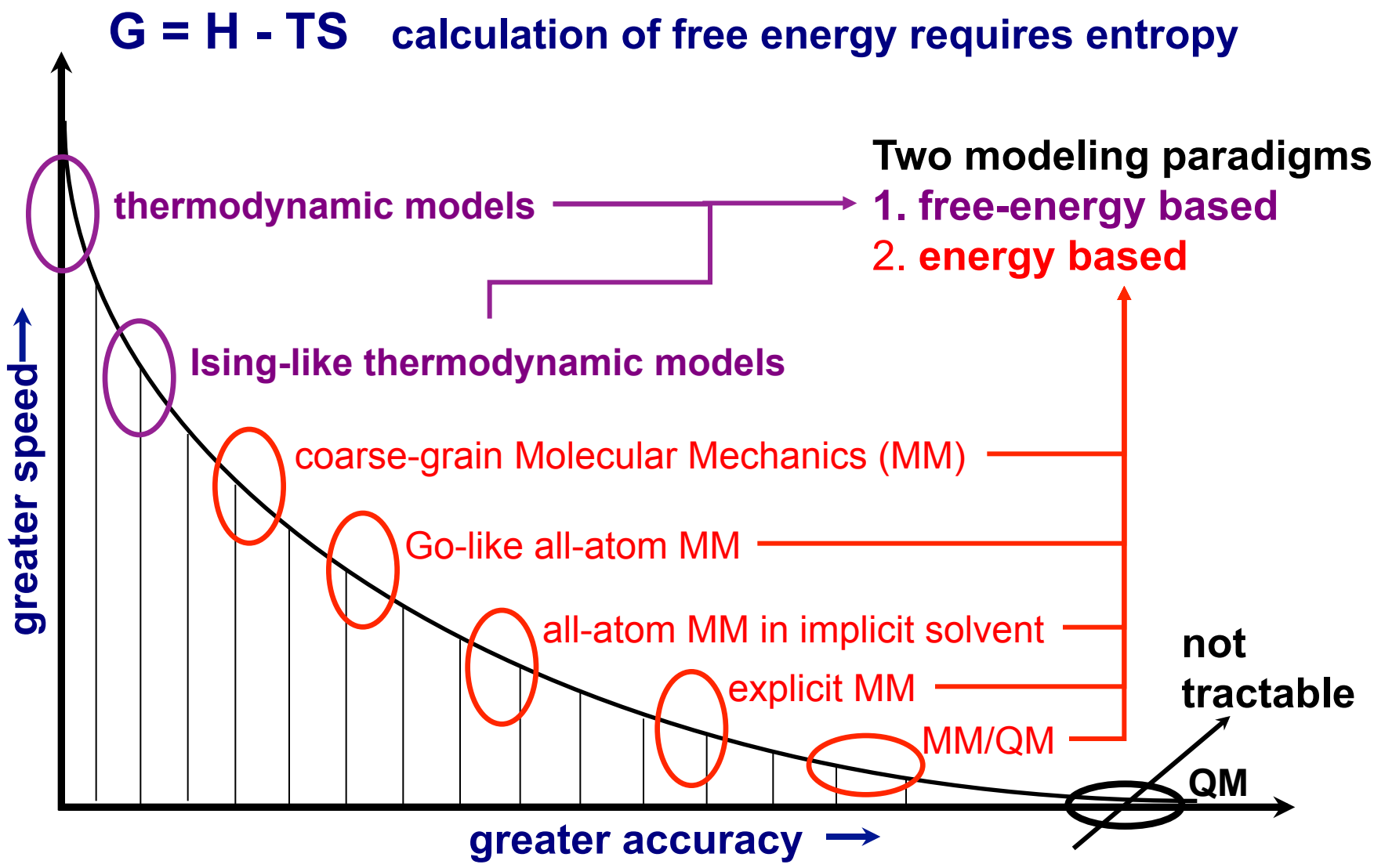
pH induced denaturation
Spector and Raleigh. JMB. 276 479-489, (1998)

pressure induced denaturation
Torrent, *et. al.*, *Biochemistry*, 38, 15952-15961, (1999)



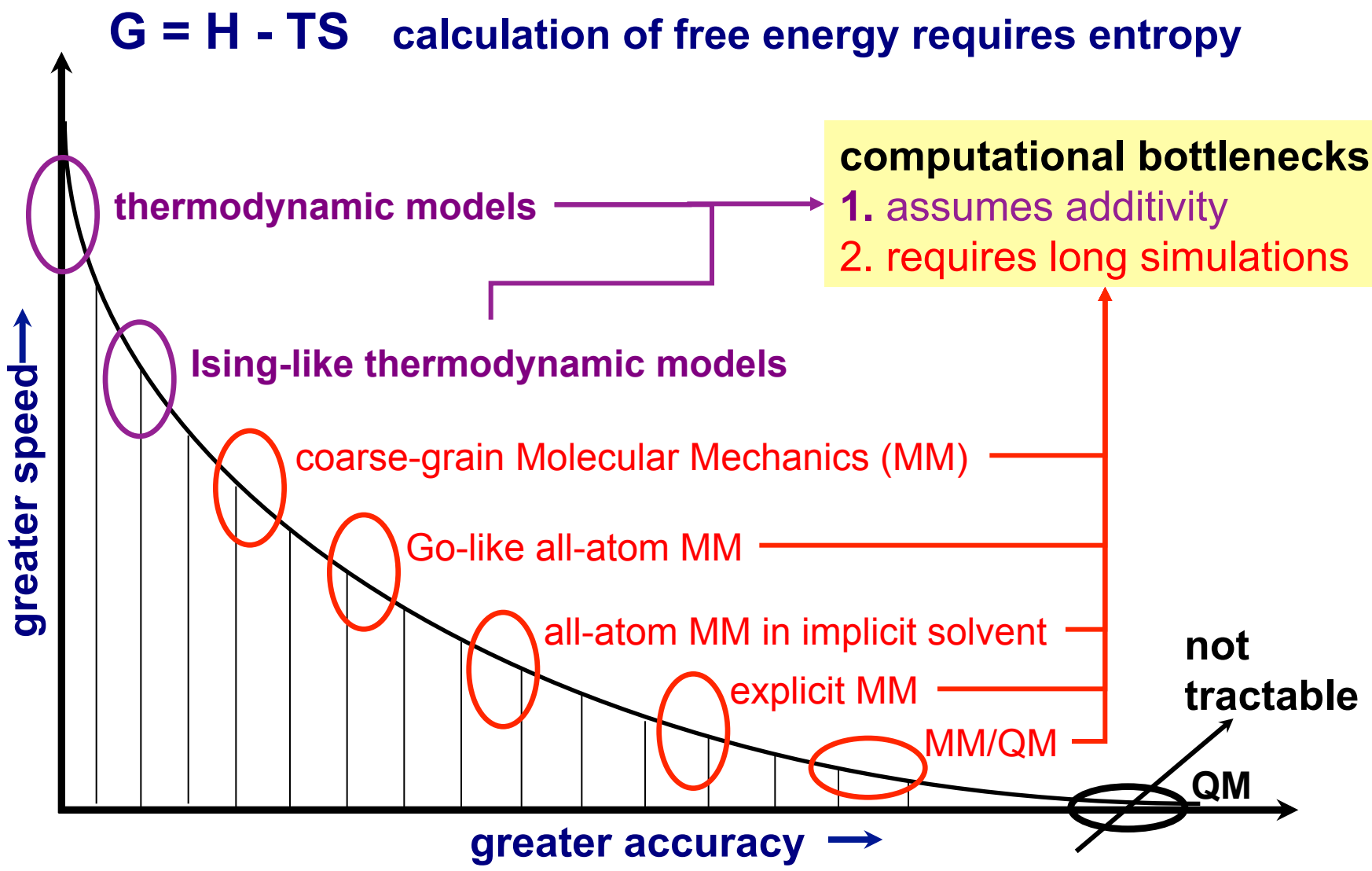
Modeling Protein Thermodynamics

Speed versus accuracy tradeoffs



Modeling Protein Thermodynamics

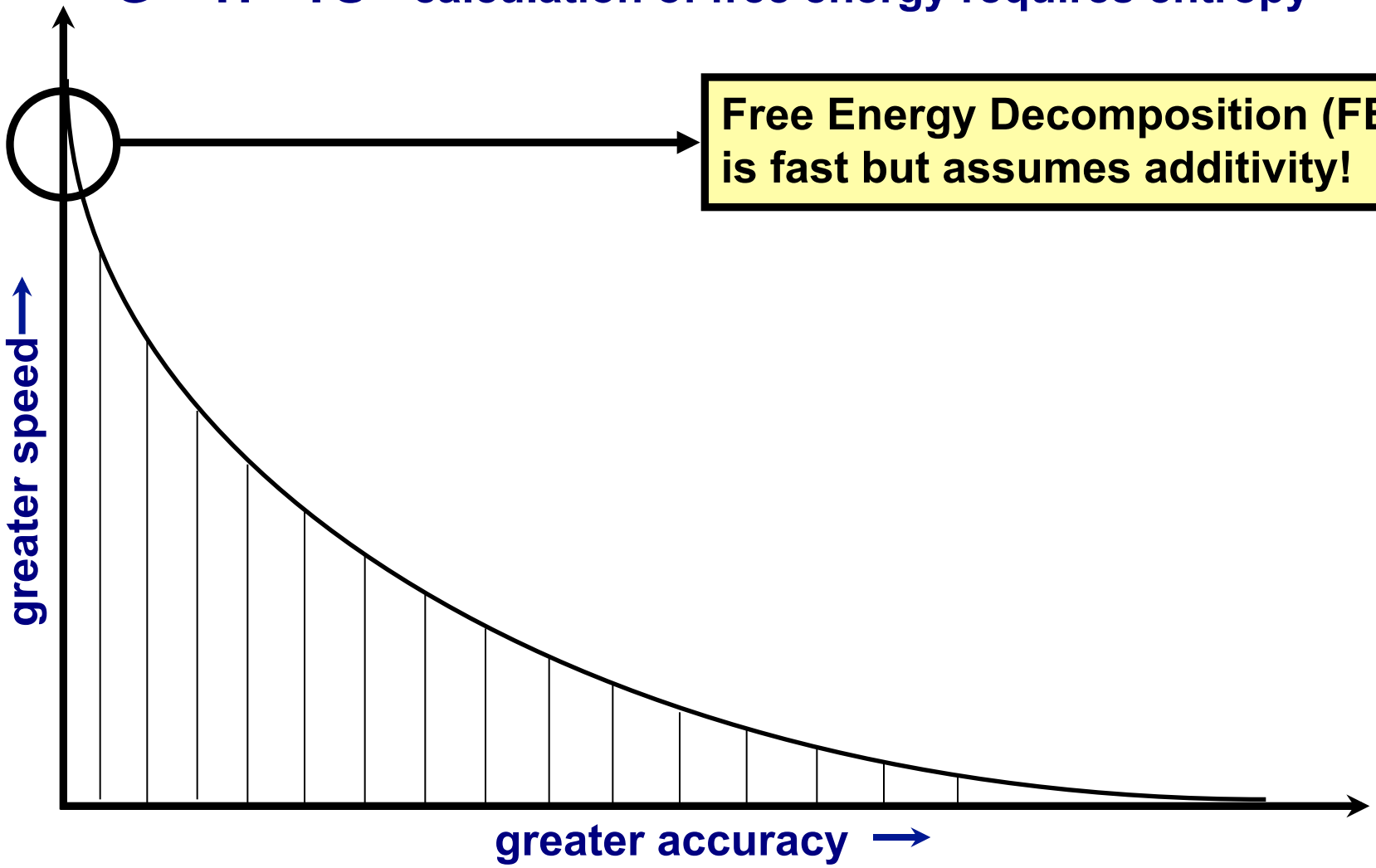
Speed versus accuracy tradeoffs



Modeling Protein Thermodynamics

Speed versus accuracy tradeoffs

G = H - TS calculation of free energy requires entropy



Free Energy Decomposition (FED)

The problem of "hidden" thermodynamics

$$G_{total} \neq \sum_{parts} G_{part}$$

How to add back the parts?
Hidden thermodynamics

No unique way to decompose a system into parts.

Decomposition of the Free Energy of a System in Terms of Specific Interactions
A. E. Mark and W. F van Gunsteren, J. Mol. Biol. 240, 167 (1994)

"*In regard to the detailed separation of free energy components, we must acknowledge that the hidden thermodynamics of a protein will, unfortunately, remain hidden*"

See: Ken A. Dill, "***Additivity Principles in Biochemistry***",
The Journal of Biological Chemistry 272, 701-704 (1997)

The Distance Constraint Model (DCM)

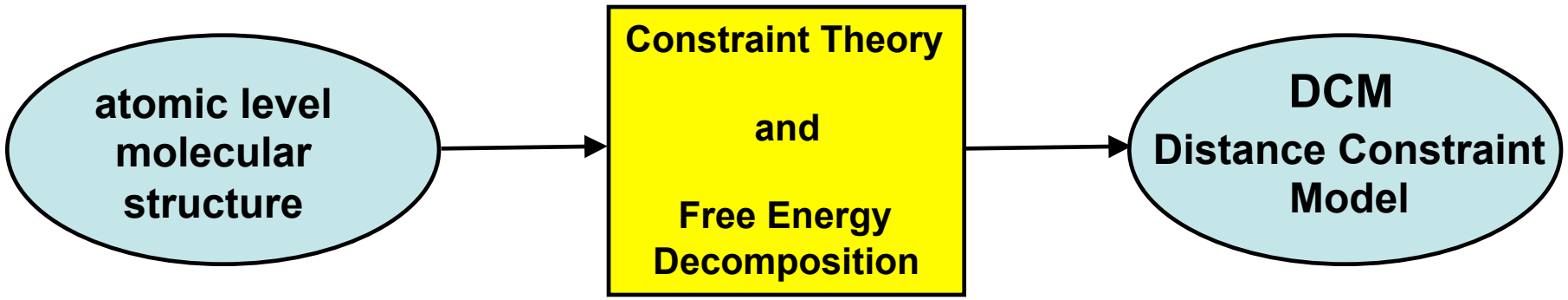
Restoring the utility of a free energy decomposition (FED)

A NEW PERSPECTIVE

D.J. Jacobs,et. al., *Network rigidity at finite temperature: Relationships between thermodynamic stability, the nonadditivity of entropy, and cooperativity in molecular systems*. **Physical Reviews E. 68, 061109 1-21 (2003)**

The DCM resolves the problem of nonadditivity

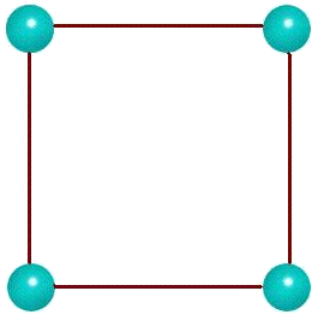
by explicitly regarding network rigidity as a long-range mechanical interaction between components to identify the independent ones.



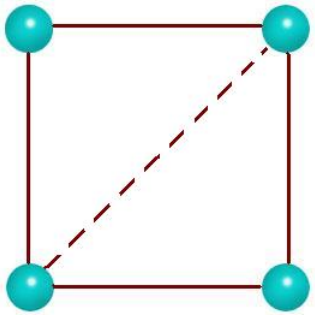
"*I never satisfy myself until I can make a mechanical model of a thing. If I can make a mechanical model I can understand it*"! **--- Lord Kelvin**

Tao of the DCM: Free Energy Reconstitution

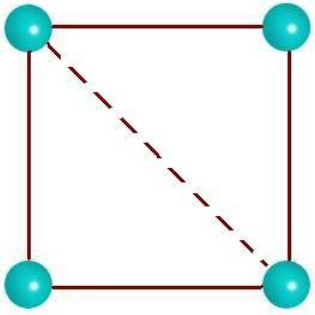
Network rigidity accounts for non-additivity in conformational entropy



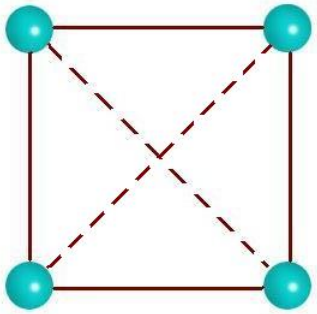
$\Delta H = 0$
$\Delta S = 0$



$\Delta H = -\varepsilon$
$\Delta S = -\delta$



$\Delta H = -\varepsilon$
$\Delta S = -\delta$



$\Delta H = -\varepsilon + -\varepsilon$
$\Delta S = -\delta + 0$

Mind your Ps and Qs

(P,Q) interdependence

$$G(F) = H(F) - TS(F)$$

$$H(F) = \sum_c h_c p_c(F)$$

$$S(F) = \sum_c s_c q_c(F) p_c(F)$$

Regarding NETWORK RIGIDITY as a mechanical interaction accounts for NON-ADDITIVITY IN ENTROPY

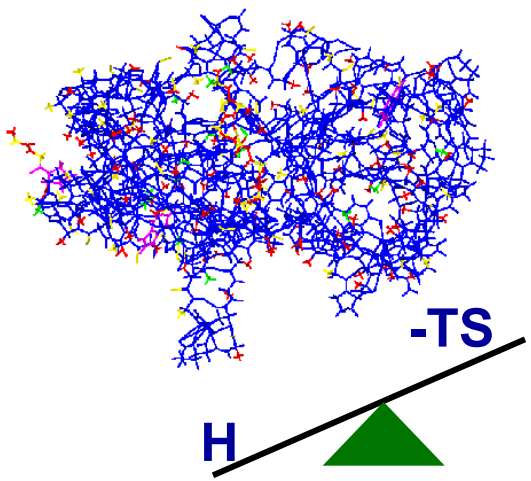
Linking Molecular Structure to Thermodynamics

The Gibbs ensemble consists of all accessible constraint networks

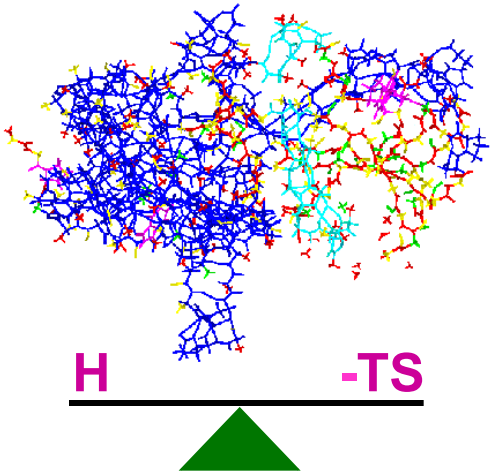
Globally Rigid

MECHANICS

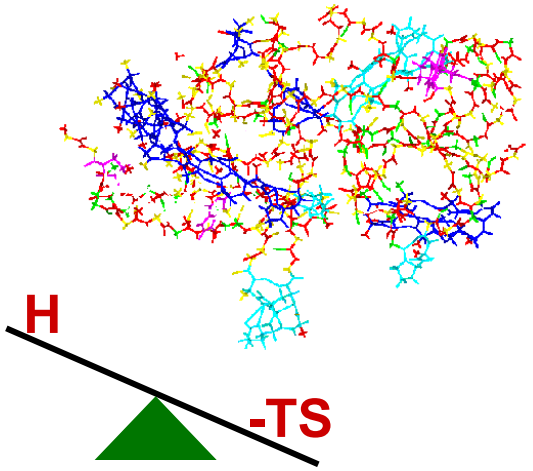
Globally Flexible



STABLE representing the native state



UNSTABLE representing the transition state

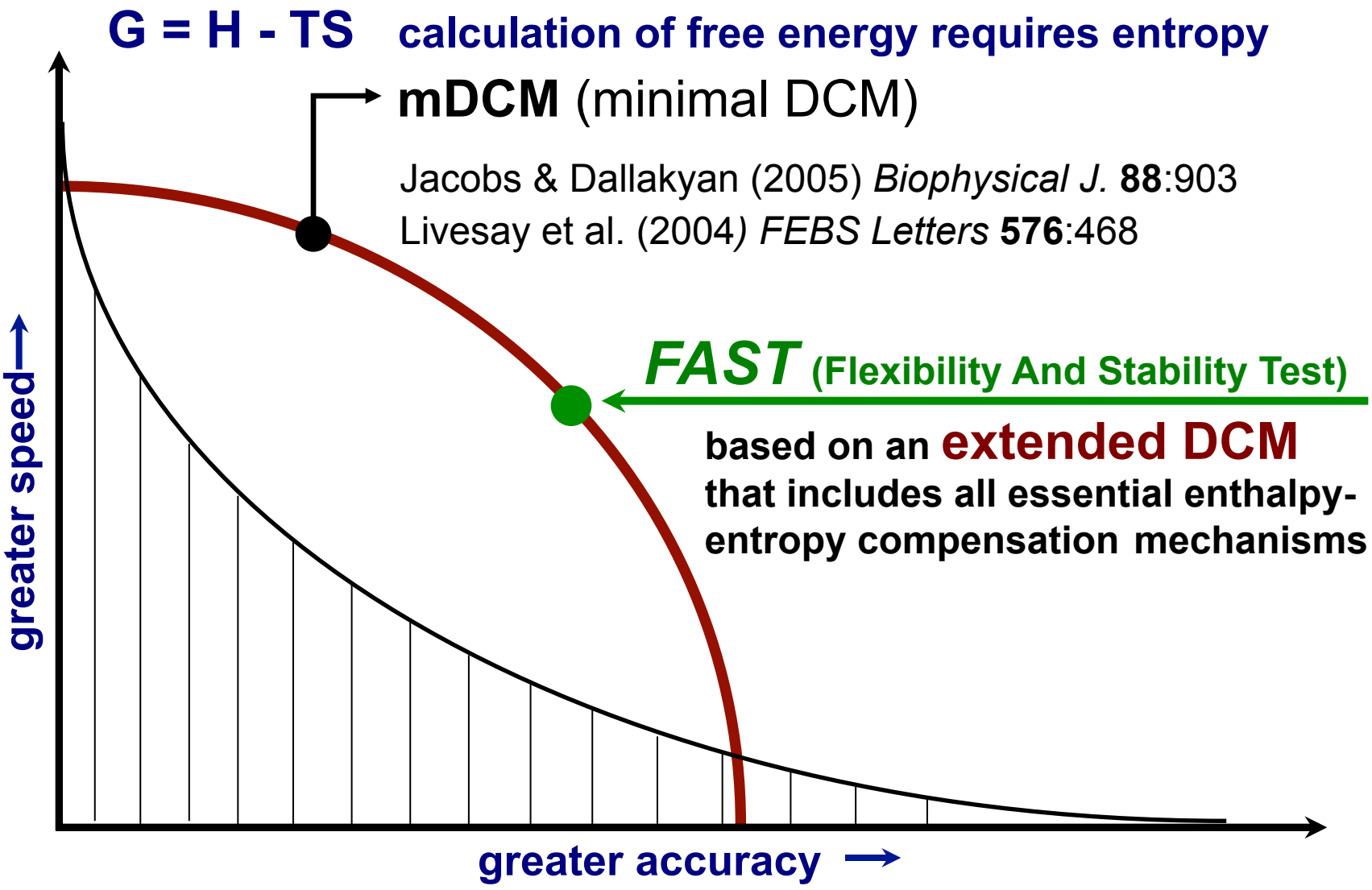


STABLE representing the unfolded state

THERMODYNAMICS

New Modeling Paradigm for Protein Thermodynamics

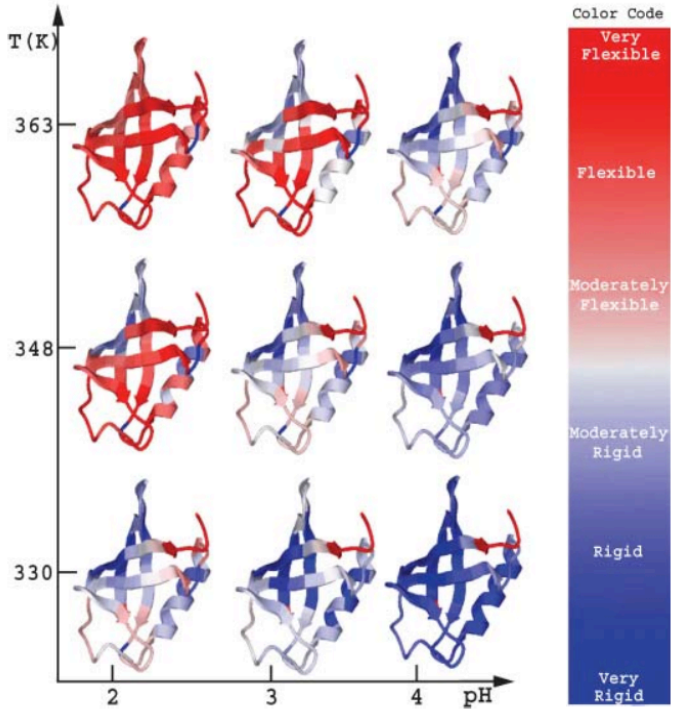
DCM provides high speed and accuracy



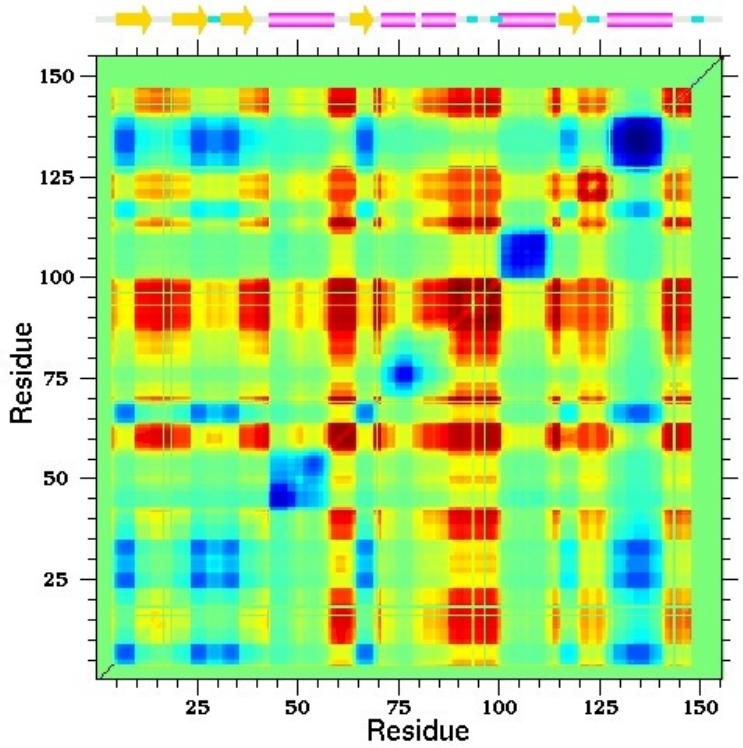
Quantified Stability/Flexibility Relationships (QSFR)

Examples of two mechanical response characterizations

Backbone flexibility is dependent upon temperature and pH



Cooperativity correlation quantifies flexibility/rigidity pairwise couplings



For more information, see the following:

Livesay, et al. *FEBS Letters* (2004) **576**:468.

Jacobs & Dallakyan. *Biophysical J.* (2005) **88**:903.

Livesay & Jacobs. *Proteins* (2006) **62**:130.

Jacobs, et al. *J. Mol. Biol.* (2006) **358**:882.

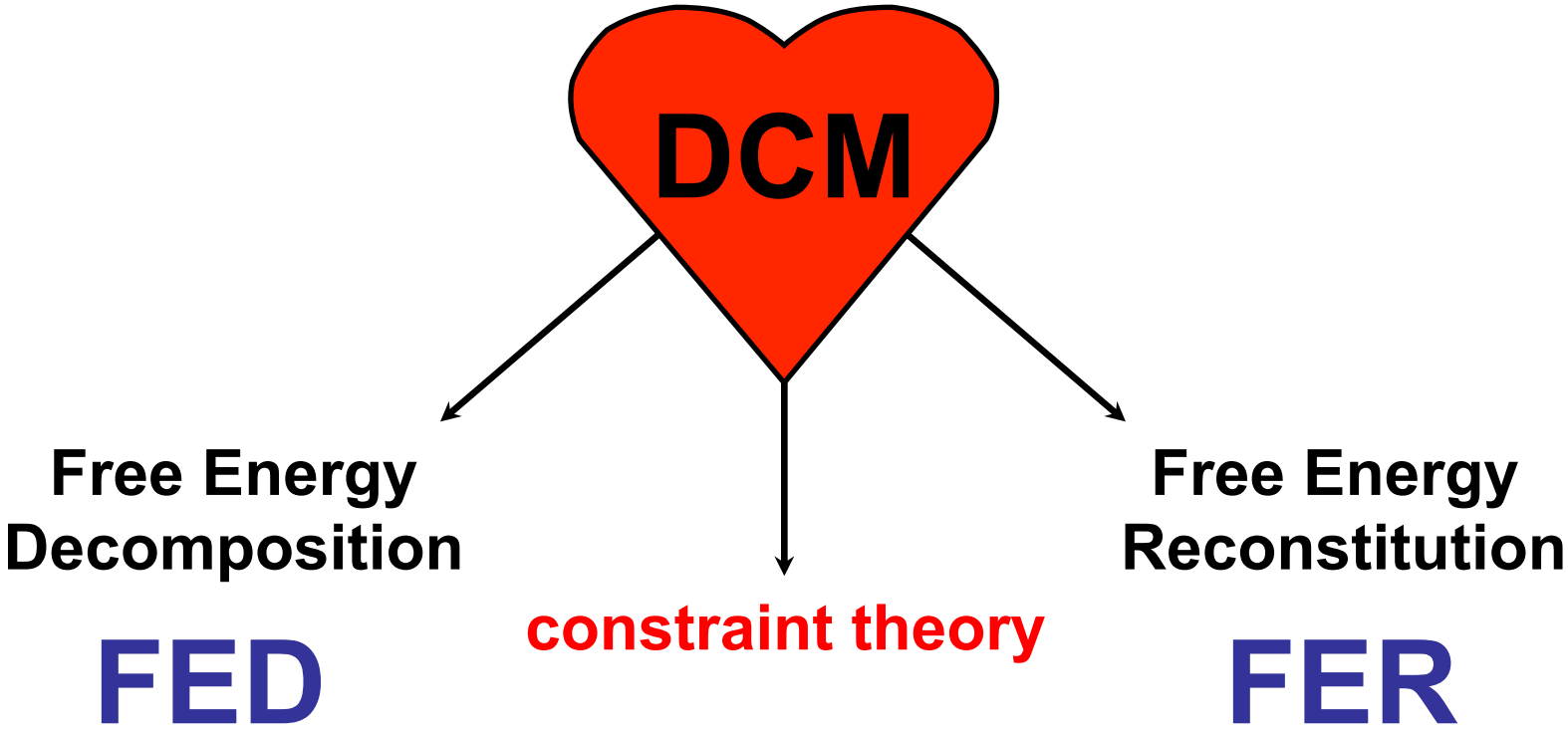
Livesay, et al. *Chem. Cen. J.* (2008) **2**:17.

Mottonen, et al. *Proteins* (2009) **75**:610.

Mottonen, et al., *Biophysical J* (2010) **99**:2245.

Distance Constraint Model

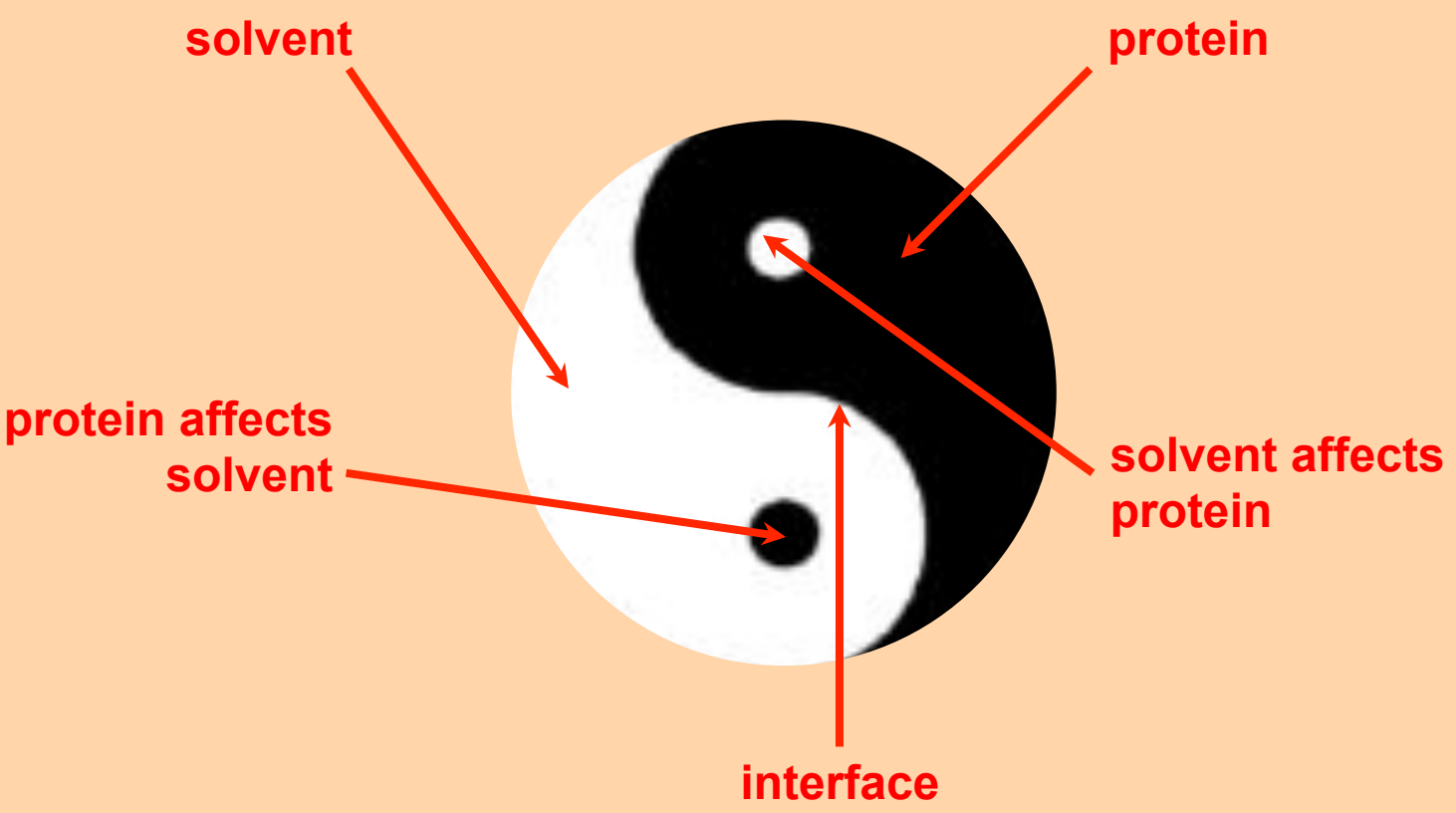
The Heart of the DCM Consists of Three Essential Elements



"I have yet to see any problem, however complicated, which, when you looked at it in the right way, did not become still more complicated". --- Poul Anderson in New Scientist (1969)

Protein Stability is Linked to Solvent

Modeling of solvent and conformational interactions



The Free Energy Functional

FAST models all essential enthalpy-entropy mechanisms

FREE ENERGY DECOMPOSITION

$$G_{FEF} = \overbrace{G^{res}_{slv} + G^{hph}_{slv} + G^{shb}_{slv}}^{G_{slv}} + \overbrace{G^{base}_{ion} + G^{acid}_{ion} - TS^{prot}_{ion}}^{G_{ion}} - TS^{hb}_{mix} + \overbrace{G^{res}_{cnf} + G^{lnk}_{cnf} + G^{ihb}_{cnf} + G^{pck}_{cnf}}^{G_{cnf}} + G_{str} + G_{vib}$$

solvation

electrostatics

disorder

conformation

strain

vibration

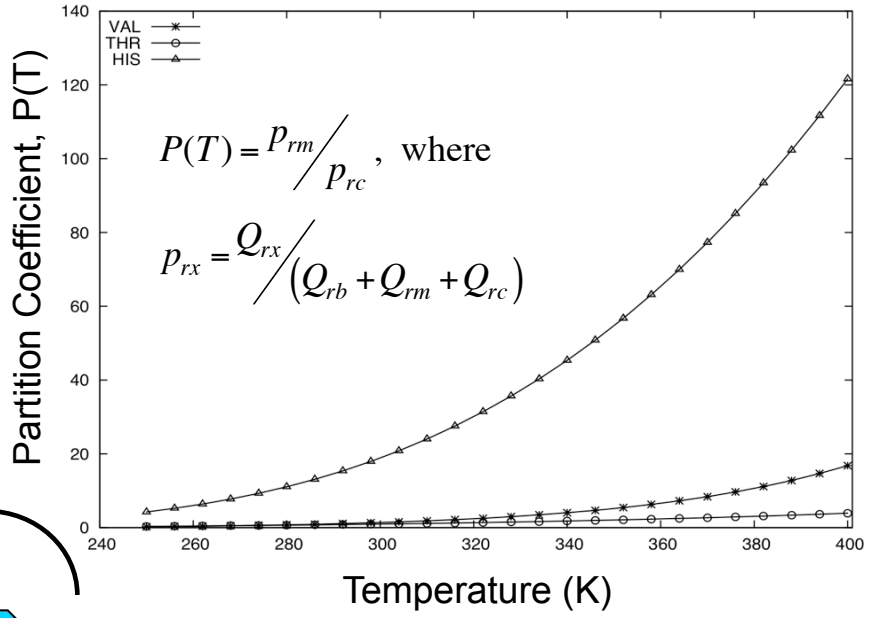
Free Energy Decomposition (FED)

Model highlights: Solvent penetration using transfer free energies

$$G_{\mathrm{FEF}} = \overbrace{G^{\mathrm{res}}_{\mathrm{slv}} + G^{\mathrm{hph}}_{\mathrm{slv}} + G^{\mathrm{shb}}_{\mathrm{slv}}}^{G_{\mathrm{slv}}} + \overbrace{G^{\mathrm{base}}_{\mathrm{ion}} + G^{\mathrm{acid}}_{\mathrm{ion}} - TS^{\mathrm{prot}}_{\mathrm{ion}}}^{G_{\mathrm{ion}}} - TS^{\mathrm{hb}}_{\mathrm{mix}} + \overbrace{G^{\mathrm{res}}_{\mathrm{cnf}} + G^{\mathrm{lnk}}_{\mathrm{cnf}} + G^{\mathrm{ihb}}_{\mathrm{cnf}} + G^{\mathrm{pck}}_{\mathrm{cnf}}}^{G_{\mathrm{cnf}}} + G_{\mathrm{str}} + G_{\mathrm{vib}}$$

Local environments for residues, are classified using 3 solvent states.

Empirical Parameterization ⟷



non-polar env. **aqueous env.**

buried p_{rb}

clathrate p_{rc}

mobile p_{rm}

Free Energy Decomposition (FED)

Model highlights: Electrostatics determined by optimizing pKa values

$$G_{\mathrm{FEF}} = \overbrace{G_{\mathrm{slv}}^{\mathrm{res}} + G_{\mathrm{slv}}^{\mathrm{hph}} + G_{\mathrm{slv}}^{\mathrm{shb}}}^{G_{\mathrm{slv}}} + \overbrace{G_{\mathrm{ion}}^{\mathrm{base}} + G_{\mathrm{ion}}^{\mathrm{acid}} - TS_{\mathrm{ion}}^{\mathrm{prot}}}^{G_{\mathrm{ion}}} - TS_{\mathrm{mix}}^{\mathrm{hb}} + \overbrace{G_{\mathrm{cnf}}^{\mathrm{res}} + G_{\mathrm{cnf}}^{\mathrm{lnk}} + G_{\mathrm{cnf}}^{\mathrm{ihb}} + G_{\mathrm{cnf}}^{\mathrm{pck}}}^{G_{\mathrm{cnf}}} + G_{\mathrm{str}} + G_{\mathrm{vib}}$$

$$G_{\mathrm{ion}}^{\mathrm{base}} = TR\ln(10) \sum_{r\in\mathrm{base}} \sum_{s} p_{rs}\left[\mathrm{pKa}(s,r) - \mathrm{pH}\right] p_{rs}^{\mathrm{dp}}$$

$$G_{\mathrm{ion}}^{\mathrm{acid}} = TR\ln(10) \sum_{r\in\mathrm{acid}} \sum_{s} p_{rs}\left[\mathrm{pH} - \mathrm{pKa}(s,r)\right] p_{rs}^{\mathrm{pr}}$$

$$S_{\mathrm{ion}}^{\mathrm{prot}} = -R \sum_{r\in\mathrm{titrable}} p_{rs}\left[p_{rs}^{\mathrm{pr}} \ln(p_{rs}^{\mathrm{pr}}) + p_{rs}^{\mathrm{dp}} \ln(p_{rs}^{\mathrm{dp}}) \right]$$

protonation states

deprotonated

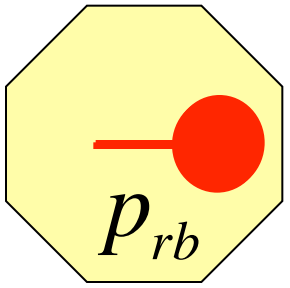
$$p_{rs}^{\mathrm{dp}} = 1 - p_{rs}^{\mathrm{pr}}$$

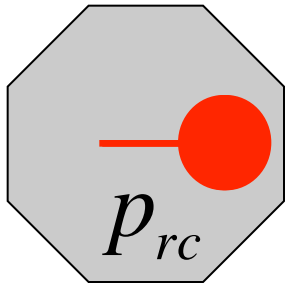
protonated

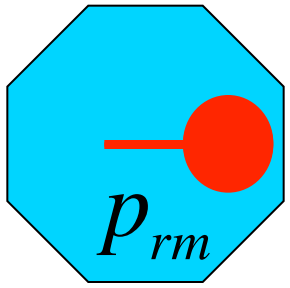
$$p_{rs}^{\mathrm{pr}} = \frac{10^{-[\mathrm{pH}-\mathrm{pKa}(s,r)]}}{1+10^{-[\mathrm{pH}-\mathrm{pKa}(s,r)]}}$$

$p_{rs}^{\mathrm{pr}} \rightarrow$

$p_{rs} \rightarrow$







Free Energy Decomposition (FED)

Model highlights: Electrostatics determined by optimizing pKa values

$$G_{\mathrm{FEF}} = \overbrace{G_{\mathrm{slv}}^{\mathrm{res}} + G_{\mathrm{slv}}^{\mathrm{hph}} + G_{\mathrm{slv}}^{\mathrm{shb}}}^{G_{\mathrm{slv}}} + \overbrace{G_{\mathrm{ion}}^{\mathrm{base}} + G_{\mathrm{ion}}^{\mathrm{acid}} - TS_{\mathrm{ion}}^{\mathrm{prot}}}^{G_{\mathrm{ion}}} - TS_{\mathrm{mix}}^{\mathrm{hb}} + \overbrace{G_{\mathrm{cnf}}^{\mathrm{res}} + G_{\mathrm{cnf}}^{\mathrm{lnk}} + G_{\mathrm{cnf}}^{\mathrm{ihb}} + G_{\mathrm{cnf}}^{\mathrm{pck}}}^{G_{\mathrm{cnf}}} + G_{\mathrm{str}} + G_{\mathrm{vib}}$$

$$G_{\mathrm{ion}}^{\mathrm{base}} = TR\ln(10) \sum_{r\in\mathrm{base}} \sum_{s} p_{rs}\left[\mathrm{pKa}(s,r) - \mathrm{pH}\right] p_{rs}^{\mathrm{dp}}$$

$$G_{\mathrm{ion}}^{\mathrm{acid}} = TR\ln(10) \sum_{r\in\mathrm{acid}} \sum_{s} p_{rs}\left[\mathrm{pH} - \mathrm{pKa}(s,r)\right] p_{rs}^{\mathrm{pr}}$$

$$S_{\mathrm{ion}}^{\mathrm{prot}} = -R \sum_{r\in\mathrm{titrable}} p_{rs}\left[p_{rs}^{\mathrm{pr}} \ln(p_{rs}^{\mathrm{pr}}) + p_{rs}^{\mathrm{dp}} \ln(p_{rs}^{\mathrm{dp}}) \right]$$

protonation states

deprotonated

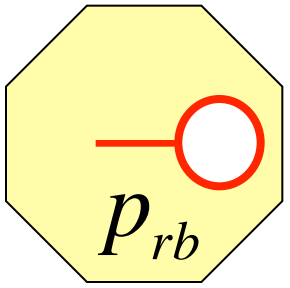
$$p_{rs}^{\mathrm{dp}} = 1 - p_{rs}^{\mathrm{pr}}$$

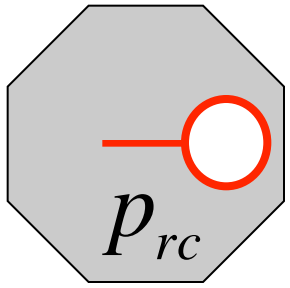
protonated

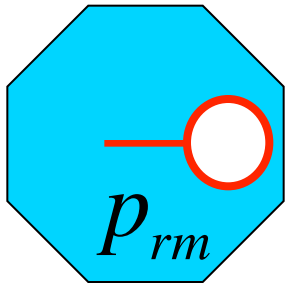
$$p_{rs}^{\mathrm{pr}} = \frac{10^{-[\mathrm{pH}-\mathrm{pKa}(s,r)]}}{1+10^{-[\mathrm{pH}-\mathrm{pKa}(s,r)]}}$$

$p_{rs}^{\mathrm{dp}} \rightarrow$

$p_{rs} \rightarrow$



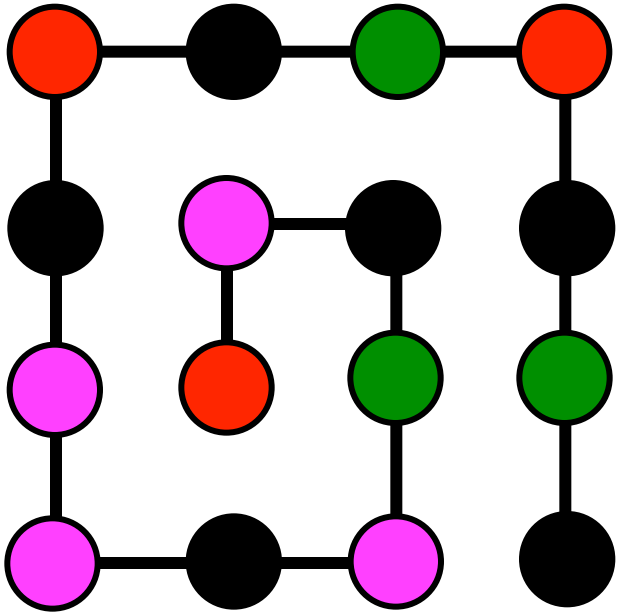




Free Energy Decomposition (FED)

Covalent bond network defines structural template

$$G_{\mathrm{FEF}} = \overbrace{G^{\mathrm{res}}_{\mathrm{slv}} + G^{\mathrm{hph}}_{\mathrm{slv}} + G^{\mathrm{shb}}_{\mathrm{slv}}}^{G_{\mathrm{slv}}} + \overbrace{G^{\mathrm{base}}_{\mathrm{ion}} + G^{\mathrm{acid}}_{\mathrm{ion}} - TS^{\mathrm{prot}}_{\mathrm{ion}}}^{G_{\mathrm{ion}}} - TS^{\mathrm{hb}}_{\mathrm{mix}} + \overbrace{G^{\mathrm{res}}_{\mathrm{cnf}} + G^{\mathrm{lnk}}_{\mathrm{cnf}} + G^{\mathrm{ihb}}_{\mathrm{cnf}} + G^{\mathrm{pck}}_{\mathrm{cnf}}}^{G_{\mathrm{cnf}}} + G_{\mathrm{str}} + G_{\mathrm{vib}}$$



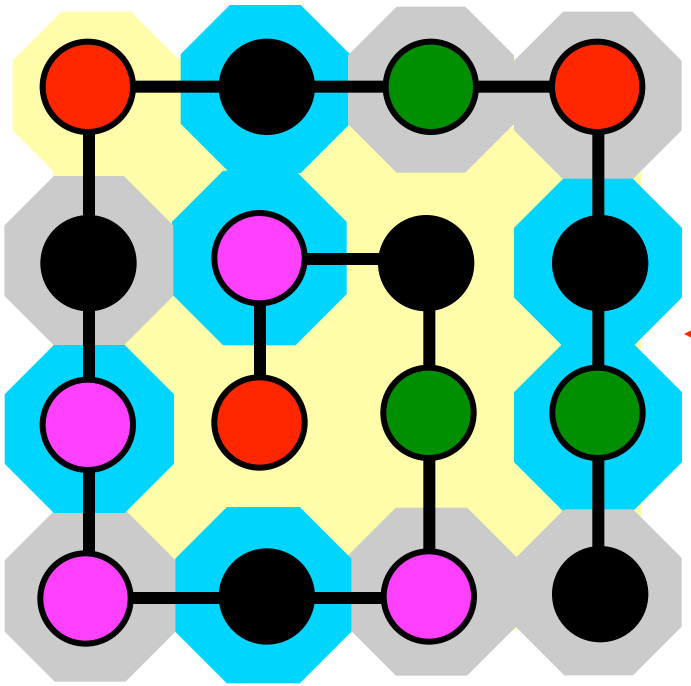
covalent bonding between different types of residues

2D schematic of the process

Free Energy Decomposition (FED)

Solvent penetration defines a heterogeneous local environments

$$G_{FEF} = \overbrace{\overbrace{G_{slv}^{res} + G_{slv}^{hph} + G_{slv}^{shb}}^{G_{slv}} + \overbrace{G_{ion}^{base} + G_{ion}^{acid} - TS_{ion}^{prot}}^{G_{ion}}}^{} - TS_{mix}^{hb} + \overbrace{G_{cnf}^{res} + G_{cnf}^{lnk} + G_{cnf}^{ihb} + G_{cnf}^{pck}}^{G_{cnf}} + G_{str} + G_{vib}$$



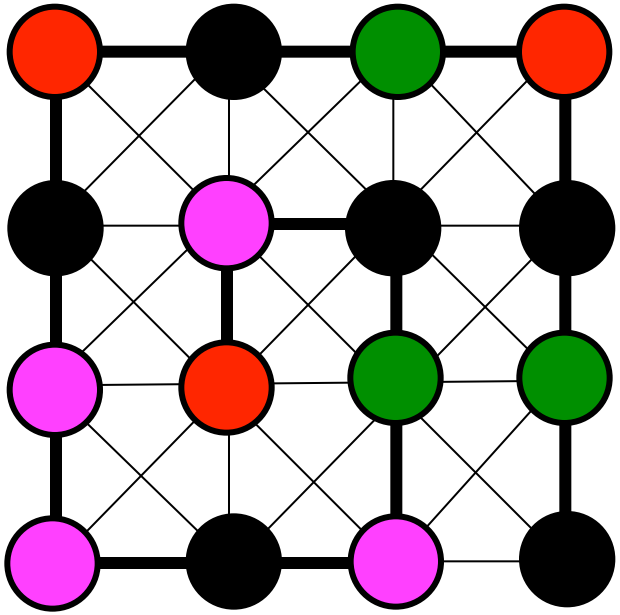
The solvation state of a protein is defined at the residue level.

2D schematic of the process

Free Energy Decomposition (FED)

Crosslinking distance constraints couple to solvent penetration

$$G_{\mathrm{FEF}} = \overbrace{G_{\mathrm{slv}}^{\mathrm{res}} + G_{\mathrm{slv}}^{\mathrm{hph}} + G_{\mathrm{slv}}^{\mathrm{shb}}}^{G_{\mathrm{slv}}} + \overbrace{G_{\mathrm{ion}}^{\mathrm{base}} + G_{\mathrm{ion}}^{\mathrm{acid}} - TS_{\mathrm{ion}}^{\mathrm{prot}}}^{G_{\mathrm{ion}}} - \overbrace{TS_{\mathrm{mix}}^{\mathrm{hb}} + G_{\mathrm{cnf}}^{\mathrm{res}} + G_{\mathrm{cnf}}^{\mathrm{lnk}} + G_{\mathrm{cnf}}^{\mathrm{ihb}} + G_{\mathrm{cnf}}^{\mathrm{pck}}}^{G_{\mathrm{cnf}}} + G_{\mathrm{str}} + G_{\mathrm{vib}}$$



DCM

Based on the solvation state, all crosslinking interactions are added to the covalent bond network to form a constraint network.

2D schematic of the process

Constructing the Free Energy Functional

Modeling Essential Mechanisms

FED **MOLECULAR PARTITION FUNCTION (MPF)**

$$Z(T) = e^{S_o/R - \beta_0 U_0} \int P(E \mid T_o) e^{-(\beta - \beta_0)E} dE$$

sampled mean energy

sampled energy distribution function at reference temperature T_o.
$\beta_o = 1/(R\ T_o)$

$$S_o = R \sum_k \sigma_k$$

The **Schlitter** quasi-harmonic approximation is used to estimate S_o from the eigenvalues $\{\lambda_k\}$ of the mass weighted covariance matrix of atomic displacements in XYZ-coordinates.

$$\sigma_k = \tfrac{1}{2} \ln\left[\left(k_B T e^2 / \hbar\right) \lambda_k + 1\right]$$

The $\{\sigma_k\}$ define a "**pure entropy spectrum**" for which there will be $3N - 6$ finite values.

Constructing the Free Energy Functional

Modeling Essential Mechanisms

FED **MOLECULAR PARTITION FUNCTION (MPF)**

$$Z(T_o) = e^{S_o/R - \beta_0 U_0}$$

sampled mean energy

$$S_o = R\sum_k \sigma_k$$

$$\int P(E \mid T_o)dE = 1$$

The **Schlitter** quasi-harmonic approximation is used to estimate S_o from the eigenvalues $\{\lambda_k\}$ of the mass weighted covariance matrix of atomic displacements in XYZ-coordinates.

$$\sigma_k = \tfrac{1}{2}\ln\left[\left(k_B T e^2/\hbar\right)\lambda_k + 1\right]$$

The $\{\sigma_k\}$ define a "pure entropy spectrum" for which there will be $3N - 6$ finite values.

Constructing the Free Energy Functional

Modeling Essential Mechanisms

FED **MOLECULAR PARTITION FUNCTION (MPF)**

$$g^{\text{int}} \equiv -RT \ln\left[e^{-\beta_0 U_0} \int P^{\text{int}}(E) e^{-(\beta-\beta_0)E} dE\right] \quad \text{int} \Rightarrow \text{interaction}$$

$$-RT \ln\left(Z^{\text{int}}(T)\right) \equiv G^{\text{int}}(T) = g^{\text{int}} - T\left(R \sum_{k=1}^{3N-6} \sigma_k^{\text{int}}\right)$$

molecular free energy for a specified interaction

Constructing the Free Energy Functional

Modeling Essential Mechanisms

FED **MOLECULAR PARTITION FUNCTION (MPF)**

$$Z^{\text{int}}(T) = \sum_{j=1}^{N_{\text{states}}} Z_{\text{j}}^{\text{int}}(T) = e^{-\beta G^{\text{int}}}$$

$$p_j = \frac{Z_j^{\text{int}}}{Z^{\text{int}}}$$

$$G^{\text{int}}(T) = \sum_{j=1}^{N_{\text{states}}} \left[g_j^{\text{int}} - T\left(R \sum_{k=1}^{3N-6} \sigma_{kj}^{\text{int}} \right) + TR\ln(p_j) \right] p_j$$

molecular free energy for a specified interaction

subdividing configuration space

j=1	j=4
j=2	j=3

Constructing the Free Energy Functional

Modeling Essential Mechanisms

FED $G_{\text{cnf}} = G_{\text{cnf}}^{\text{res}} + G_{\text{cnf}}^{\text{lnk}} + G_{\text{cnf}}^{\text{ihb}} + G_{\text{cnf}}^{\text{pck}}$

Conformational components define a distance constraint network

generic form:

$$G_{\Psi}^{\text{int}} = \sum_{j=1}^{N_{\text{states}}} \left[g_{\Psi j}^{\text{int}} - T\left(R \sum_{k=1}^{3N^{\text{int}}-6} \sigma_{\Psi jk}^{\text{int}} \sum_{i=1}^{N_k^{\text{int}}} W_{\Psi ki}^{\text{int}} q_{\Psi jki}^{\text{int}} \right) + TR\ln(p_{\Psi j}^{\text{int}}) \right] p_{\Psi j}^{\text{int}}$$

Accounts for the many-body mechanical interactions

Accounts for nonadditivity in conformational entropy

Constructing the Free Energy Functional

Modeling Essential Mechanisms

FED $G_{\text{cnf}} = \underbrace{G_{\text{cnf}}^{\text{res}} + G_{\text{cnf}}^{\text{lnk}} + G_{\text{cnf}}^{\text{ihb}} + G_{\text{cnf}}^{\text{pck}}}$

Conformational components define a distance constraint network

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A set of distance constraints are used to model each entropy mode.

The probability for a distance constraint to be independent as determined by graph-rigidity calculations.

normalization condition: $\sum_{i=1}^{N_k^{\text{int}}} W_{\Psi ki}^{\text{int}} = 1$

Constructing the Free Energy Functional

Modeling Essential Mechanisms

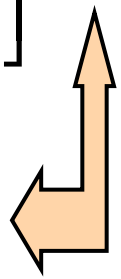
FED $G_{\mathrm{cnf}} = \underbrace{G_{\mathrm{cnf}}^{\mathrm{res}} + G_{\mathrm{cnf}}^{\mathrm{lnk}} + G_{\mathrm{cnf}}^{\mathrm{ihb}} + G_{\mathrm{cnf}}^{\mathrm{pck}}}$

Conformational components define a distance constraint network

generic form:

$$G_{\Psi}^{\mathrm{int}} = \sum_{j=1}^{N_{\mathrm{states}}} \left[g_{\Psi j}^{\mathrm{int}} - T\left(R \sum_{k=1}^{3N^{\mathrm{int}}-6} \sigma_{\Psi jk}^{\mathrm{int}} \sum_{i=1}^{N_k^{\mathrm{int}}} W_{\Psi ki}^{\mathrm{int}} q_{\Psi jki}^{\mathrm{int}} \right) + TR \ln(p_{\Psi j}^{\mathrm{int}}) \right] p_{\Psi j}^{\mathrm{int}}$$

$$p_{\Psi j}^{\mathrm{int}} = \frac{\exp\left(-\beta g_{\Psi j}^{\mathrm{int}} + \sum_k \sigma_{\Psi jk}^{\mathrm{int}} \sum_i w_{\Psi ki}^{\mathrm{int}} q_{\Psi jki}^{\mathrm{int}} \right)}{Z_{\Psi}^{\mathrm{int}}}$$

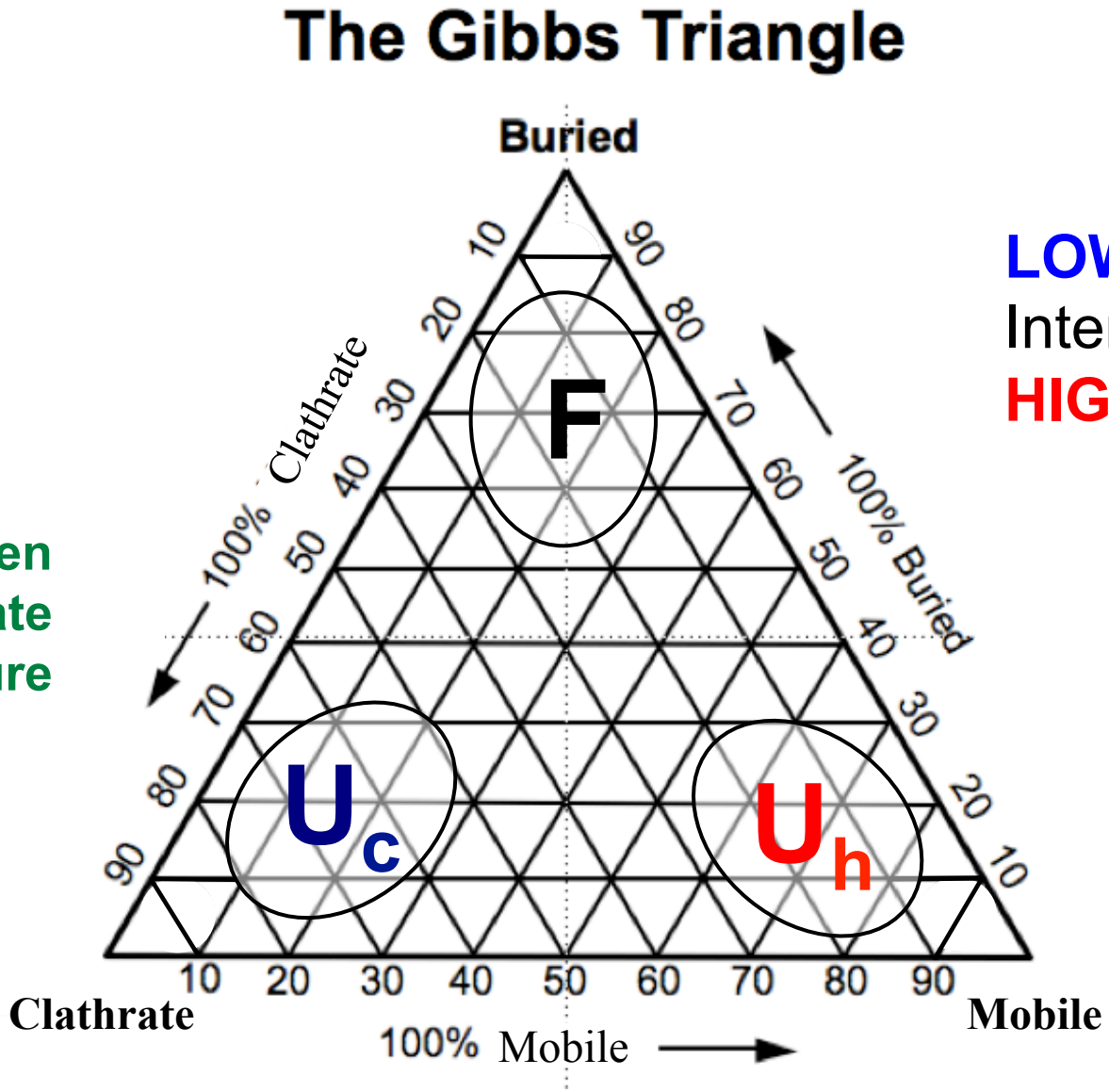


The probability for an interaction to form depends on all other interactions

Free Energy Landscape

Constraint Networks are Defined by Solvent Macrostates

FER



LOW T

Intermediate T

HIGH T

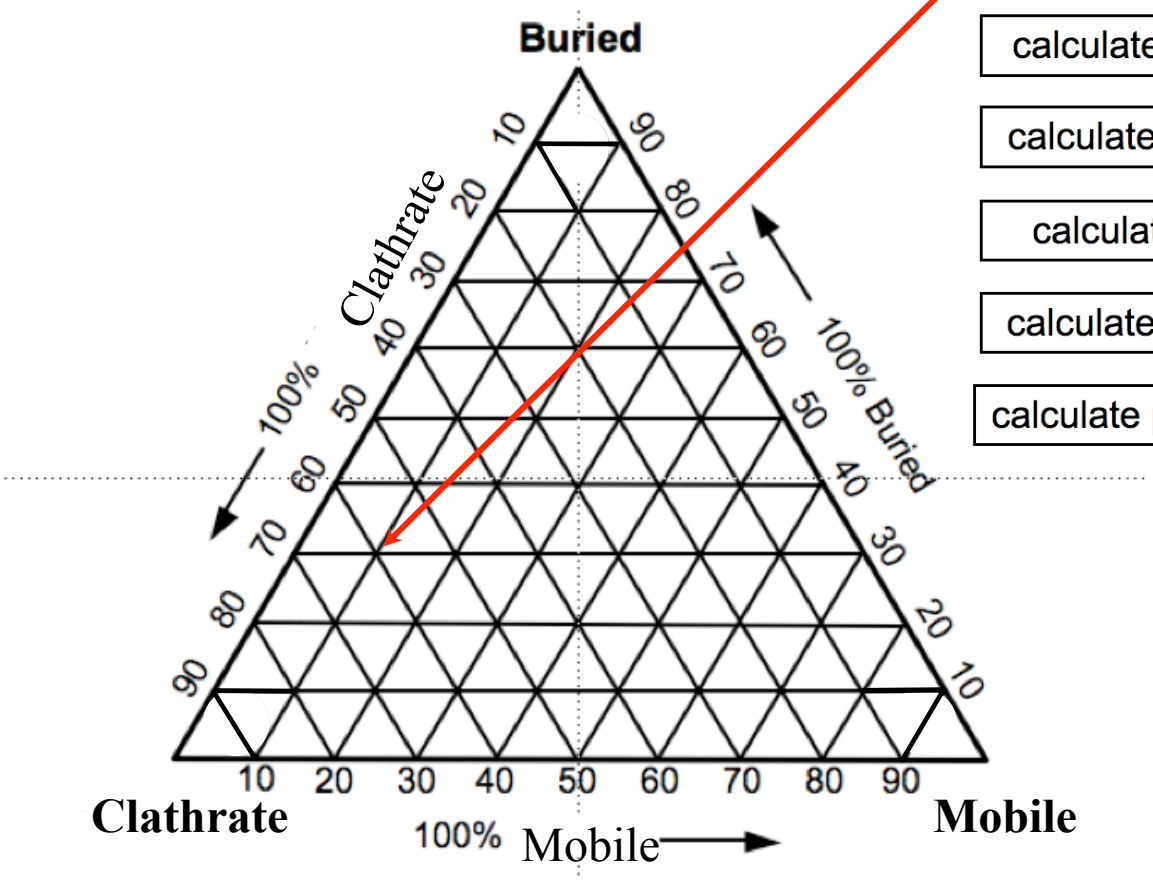
For a given template structure

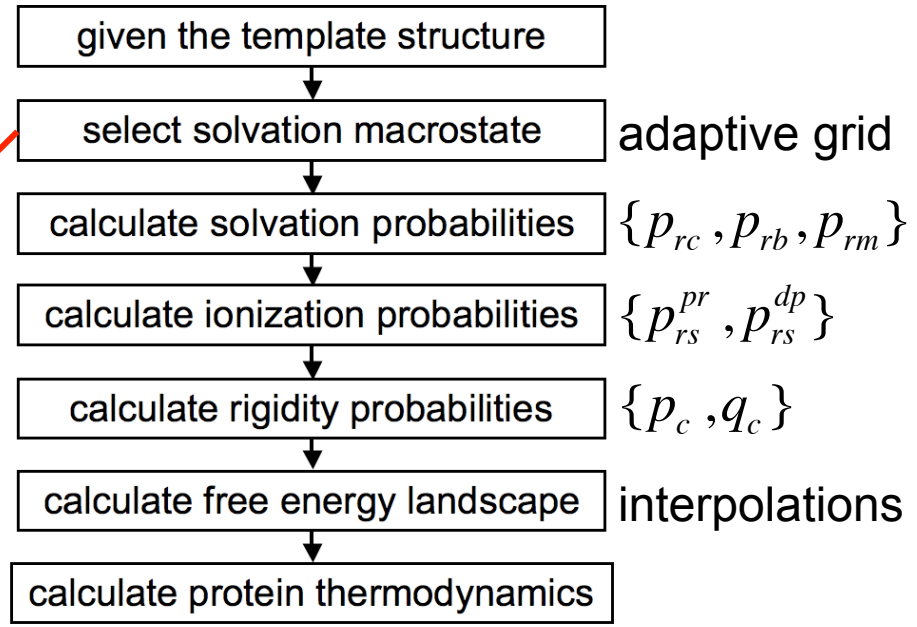
Free Energy Reconstruction (FER)

Self-consistent process is used to solve the free energy functional

FER

The Gibbs Triangle





Network Rigidity Calculations

Accounts for non-additivity in conformational entropy

conformational entropies renormalize

nonadditive

$$G_{cnf} \neq \sum_c G_c \Leftrightarrow \prod_c Z_c$$

road to additivity

with q_c=1 ∀ c ⇒ bare parameters

$$Z = e^{S_0/k_B - \beta_0 U_0} \int P_0(E) e^{-(\beta-\beta_0)E} dE$$

from Z_c and $\{q_c\}$ → calculate $\{p_c\}$

"I have yet to see any problem, however complicated, which, when you looked at it in the right way, did not become still more complicated". --- Poul Anderson in New Scientist (1969)

Jacobs, US Patent # 8244504

Self-consistent Network Rigidity Calculation

Local environments and nonadditivity in conformational entropy

conformational entropies renormalize

nonadditive

$$G_{cnf} \neq \sum_c G_c \Leftrightarrow \prod_c Z_c$$

road to additivity

with q_c=1 ∀ c ⇒ bare parameters

$$Z = e^{S_0/k_B - \beta_0 U_0} \int P_0(E) e^{-(\beta-\beta_0)E} dE$$

from Z_c and $\{q_c\}$ → calculate $\{p_c\}$

based on network rigidity and
from $\{p_c\}$ → calculate $\{q_c\}$

$$S_o^{new} \rightarrow q^{new} S_o$$

Self-consistent Network Rigidity Calculation

Local environments and nonadditivity in conformational entropy

conformational entropies renormalize

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Self-consistent Network Rigidity Calculation

Local environments and nonadditivity in conformational entropy

conformational entropies renormalize

nonadditive

$$G_{cnf} \neq \sum_c G_c \Leftrightarrow \prod_c Z_c$$

with $q_c=1\ \forall\ c \Rightarrow$ bare parameters

$$Z = e^{S_0/k_B - \beta_0 U_0} \int P_0(E) e^{-(\beta-\beta_0)E} dE$$

self consistent constraint theory

road to additivity

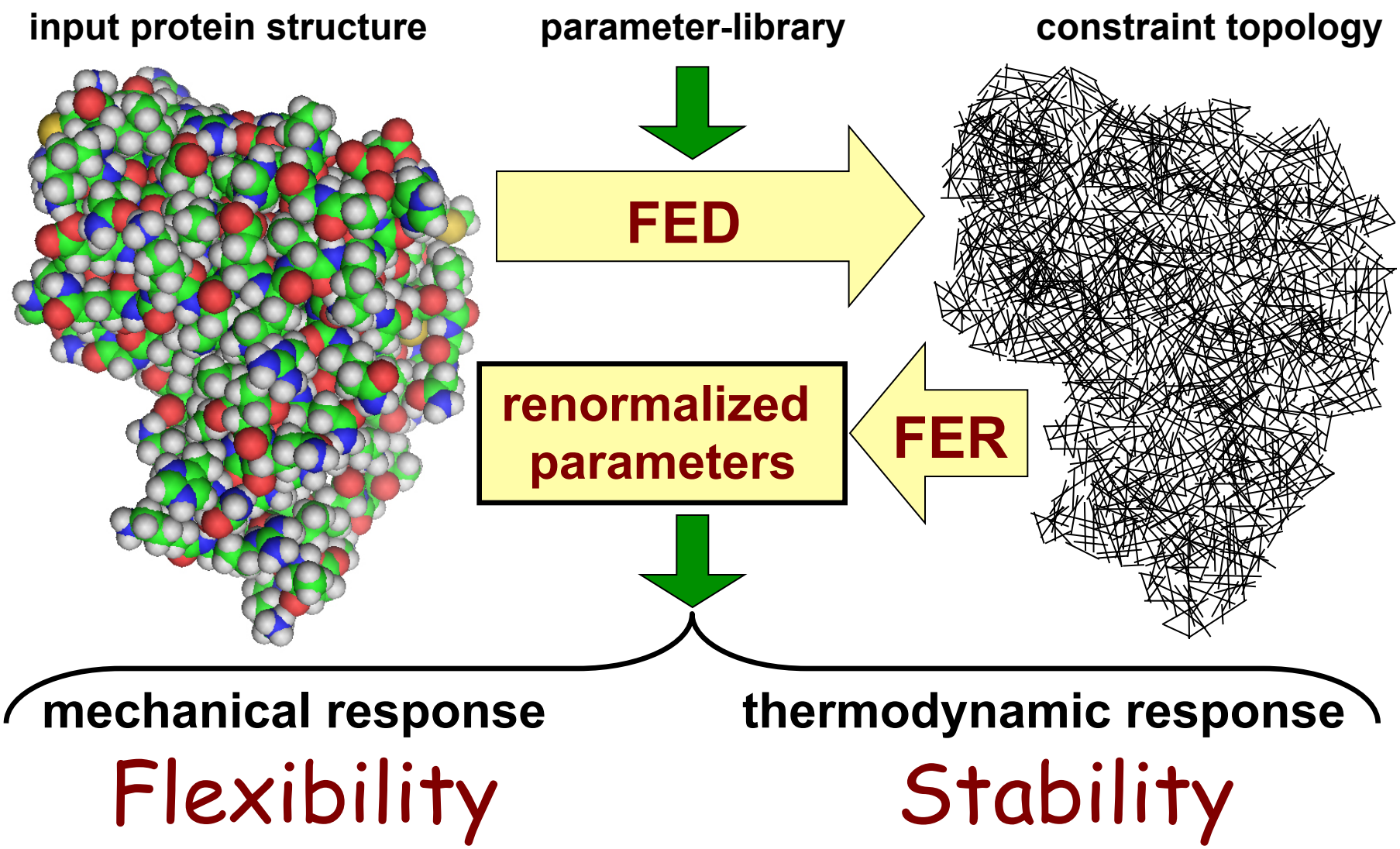
additive

$$G_{cnf} = \sum_c \tilde{G}_c \Leftrightarrow \prod_c \tilde{Z}_c$$

$$\tilde{Z} = e^{\tilde{S}_o/K_B - \beta_o U_o} \int P_o(E) e^{-(\beta-\beta_o)E} dE$$

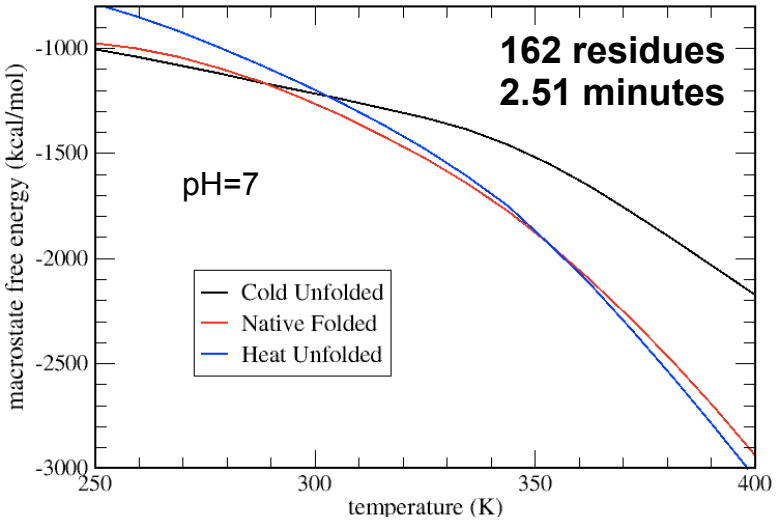
Flexibility And Stability Test (*FAST*)

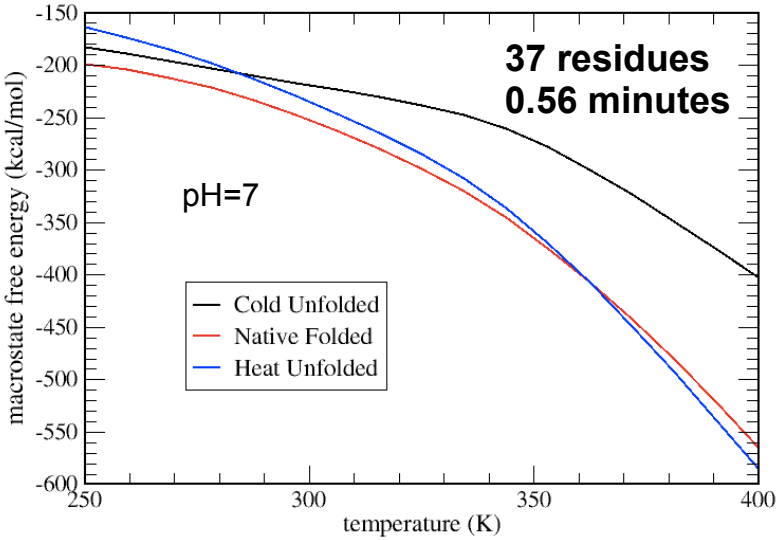
DCM = FED + FER

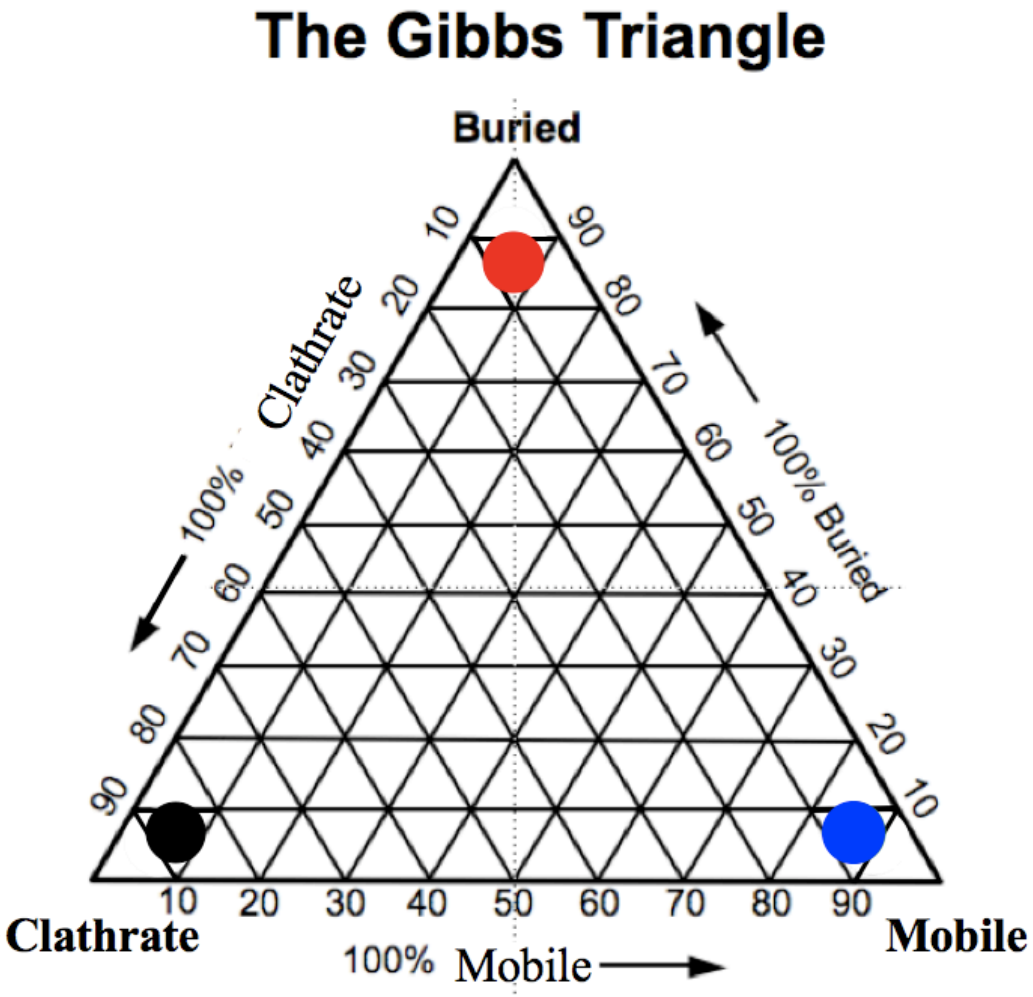


Stability Curves

Results for three typical macrostates







Scalability of *FAST*

Efficient parallelized sparse-hierarchical-adaptive grid methods

FAST **calculation of multi-dimensional free energy landscape**

FAST

performance characteristics

Example:

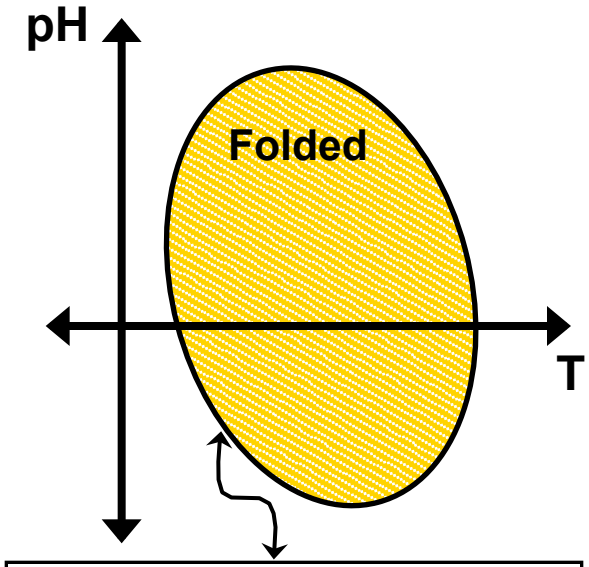
Protein size: 150 residues

domain: (150 K ≤ T ≤ 400 K) @ ΔT=1K

(2 ≤ pH ≤ 12) @ ΔpH=0.1

wall time: < 6hrs using 50×(2.3 GHz CPUs)

Scales nearly linear with # of atoms



phase boundary line
depending on:
- sequence
- bound ligand
- solute concentrations
- pressure
- temperature
- etc

Newtonian Mechanics

Conclusions and Acknowledgements

Boltzmann Statistics

Network rigidity is a fundamental mechanical property that directly links protein stability, flexibility and dynamics

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Work supported by:

NIH R01 GM 073082, S10 SRR026514
MedImunne, Inc.
Charlotte Research Institute (CRI)
Center for Biomedical Engineering and Science (CBES)