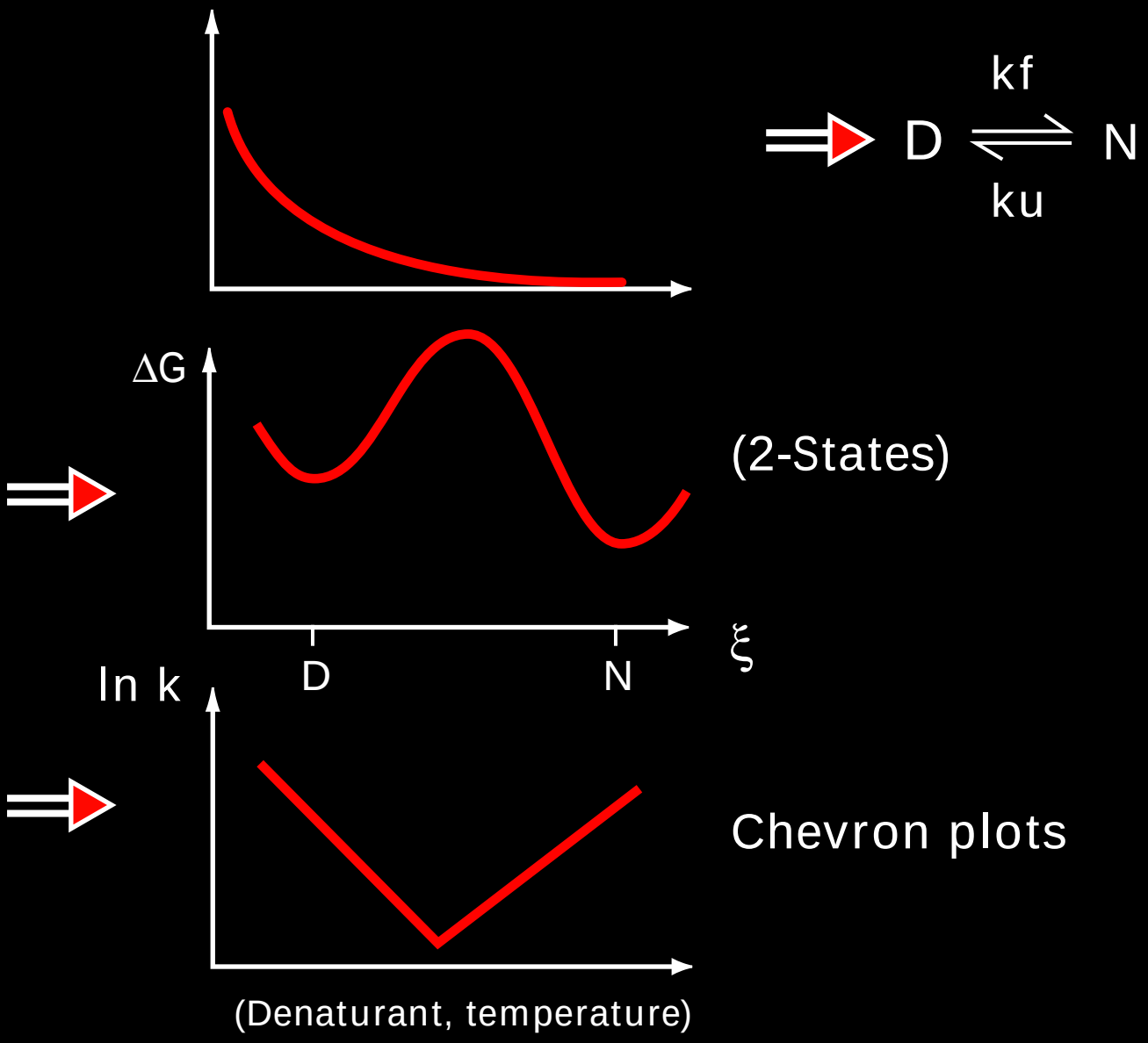
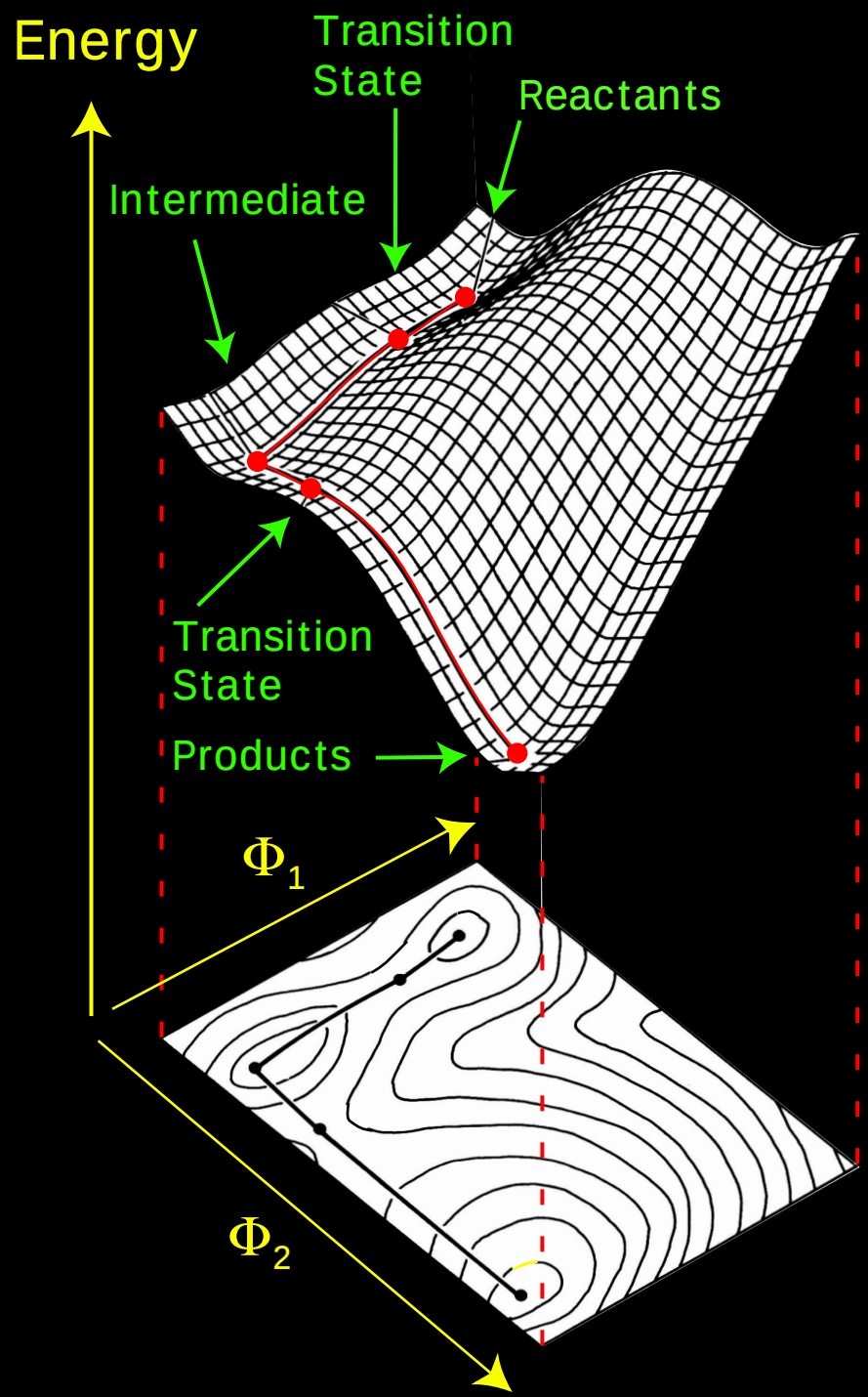
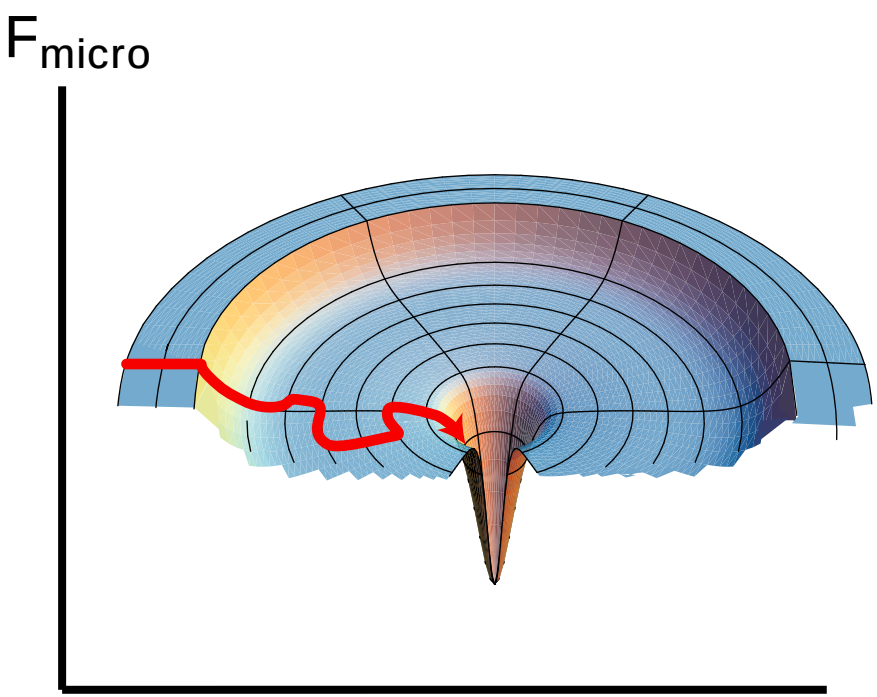
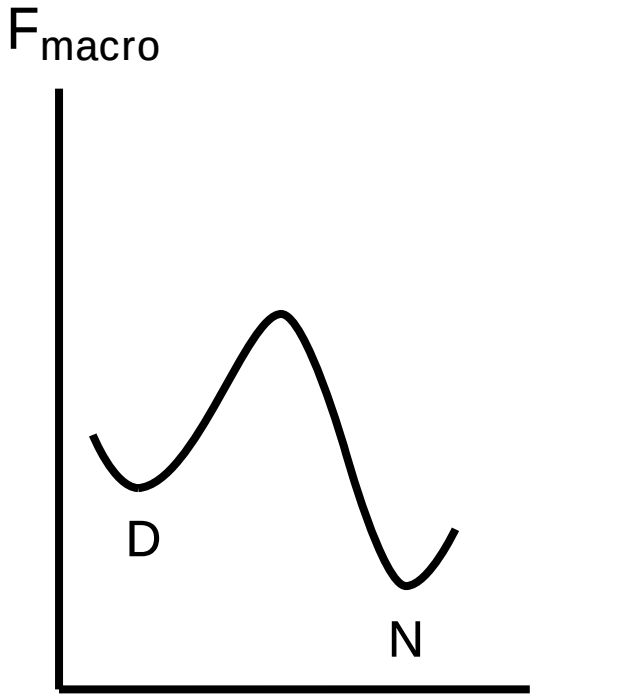
Protein Folding Kinetics
As seen from Transition-State Theory

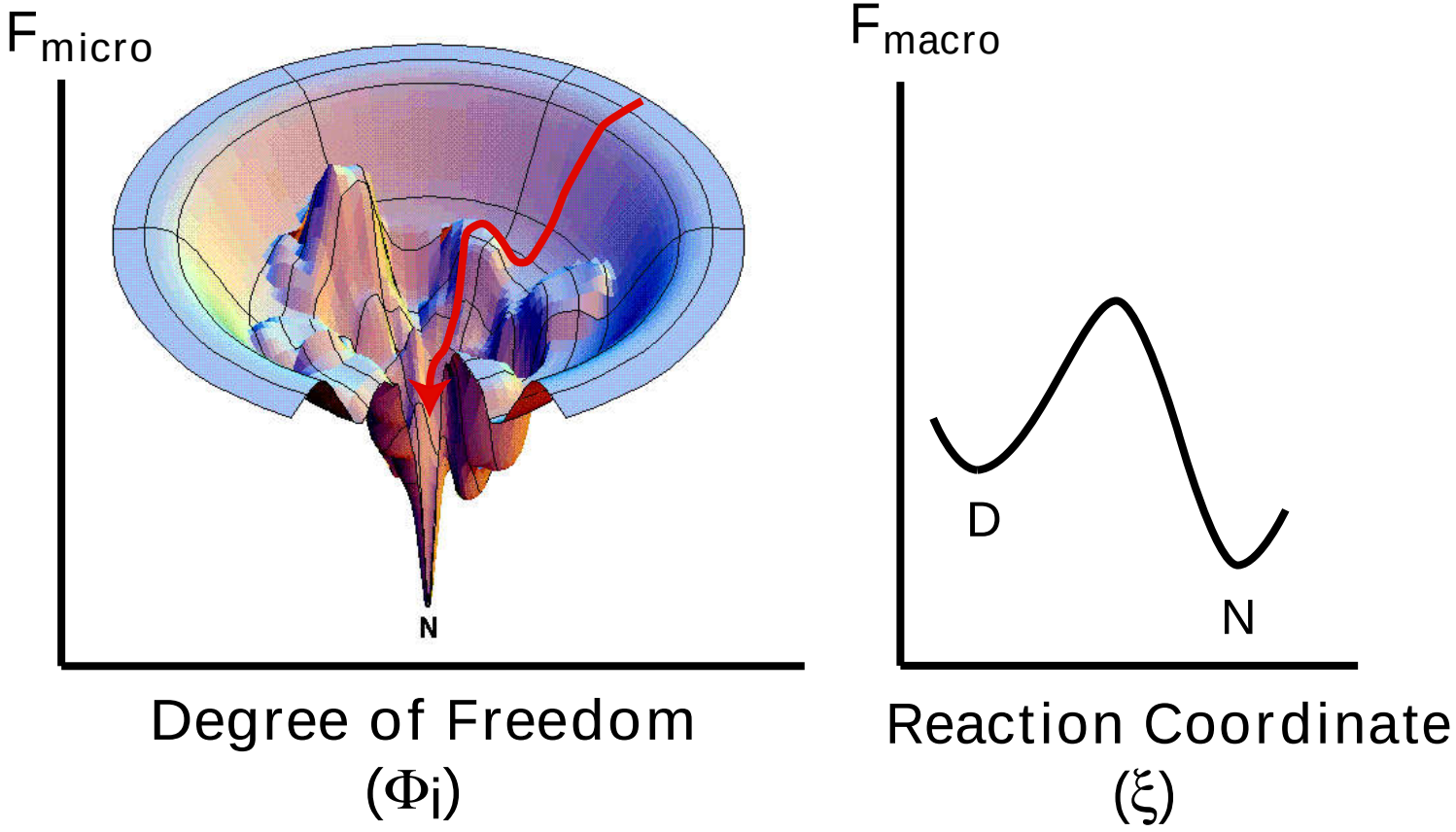



Energy
Transition State
Reactants
Intermediate
Transition State
Products
Φ_1
Φ_2





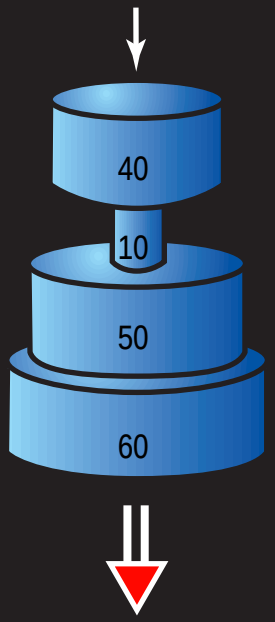
Conformational Entropy Barrier



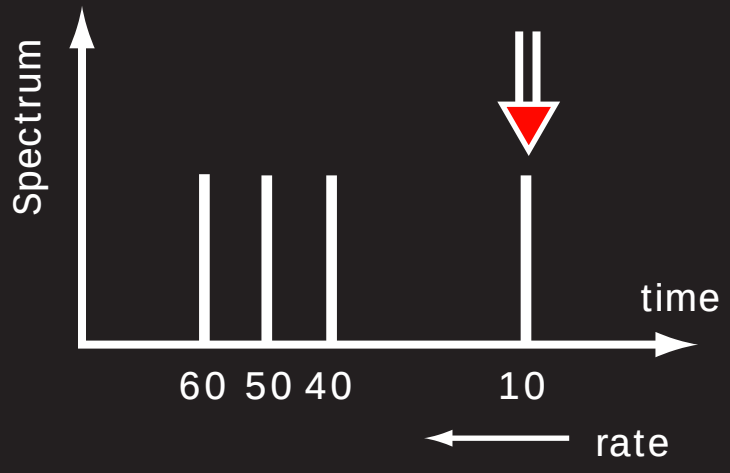
Energy Barrier

Macroscopic rate is a collective property, not a property of a single bottleneck

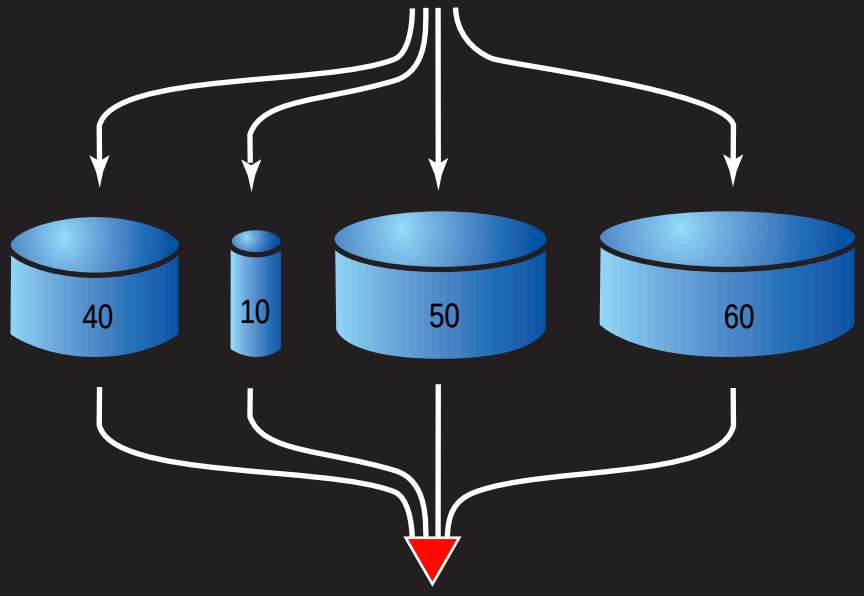
Series Process



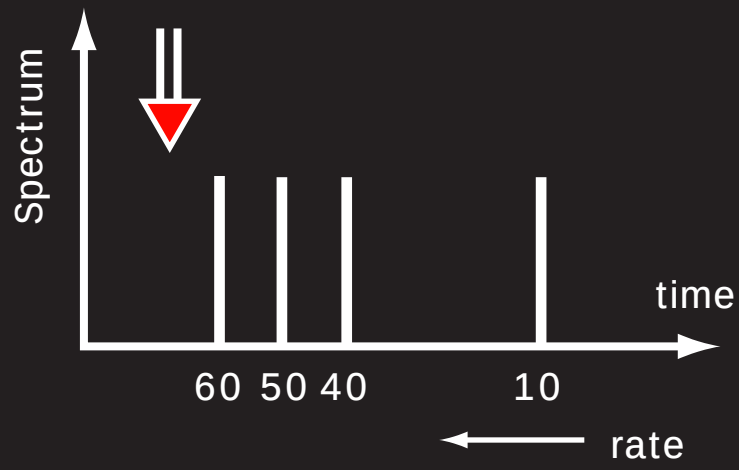
macroscopic rate ≡ bottleneck rate



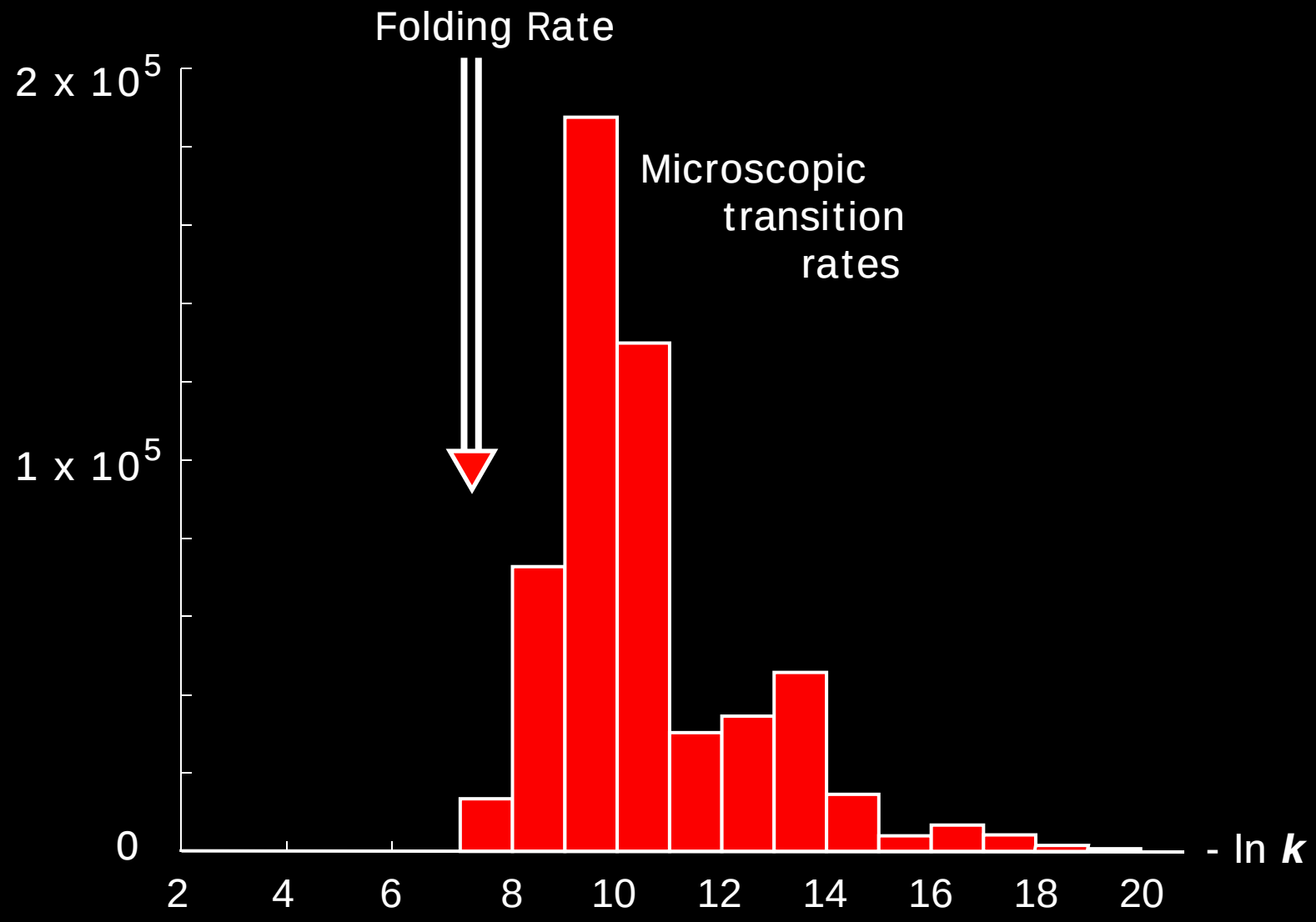
Parallel Process



macroscopic rate > μrates

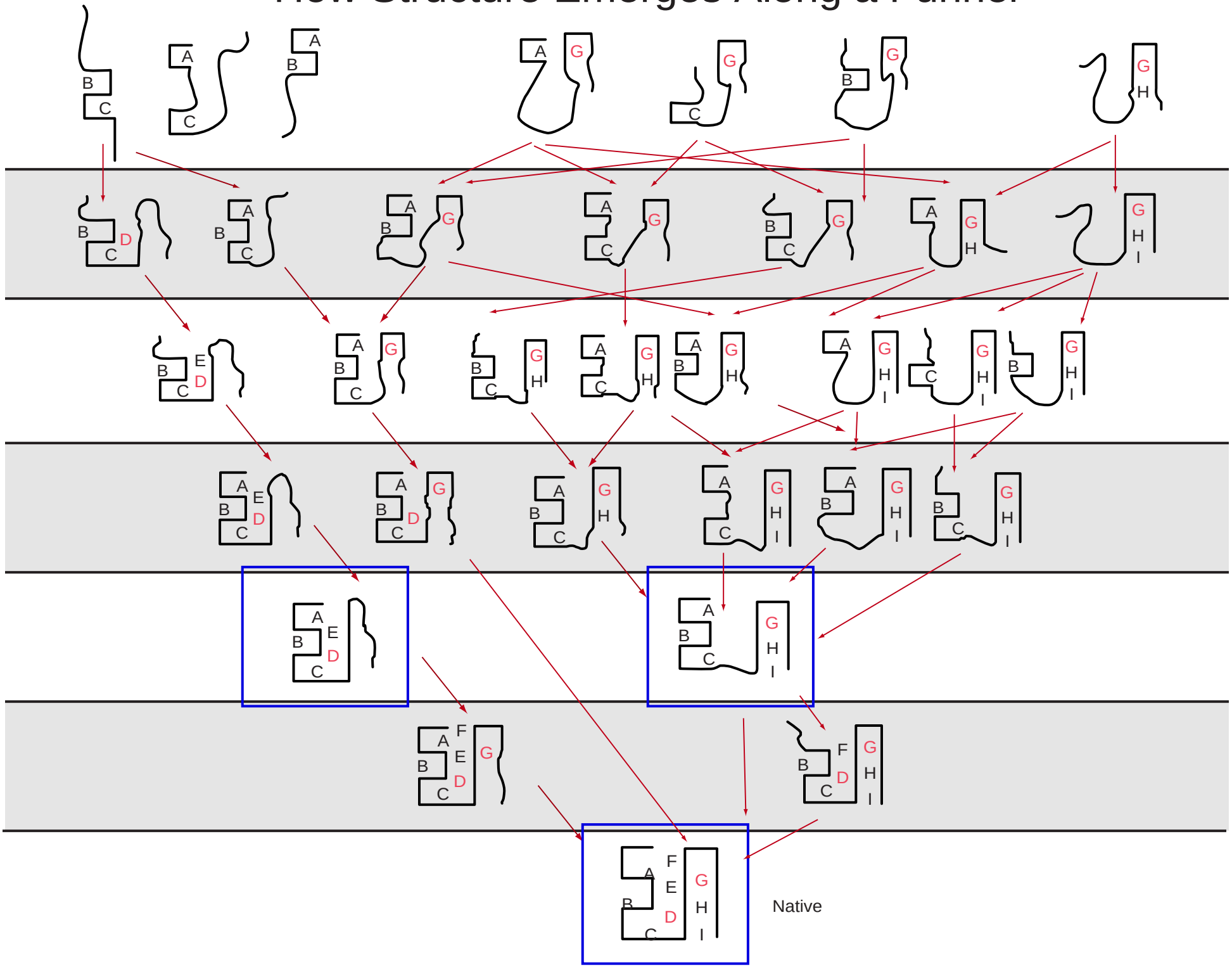


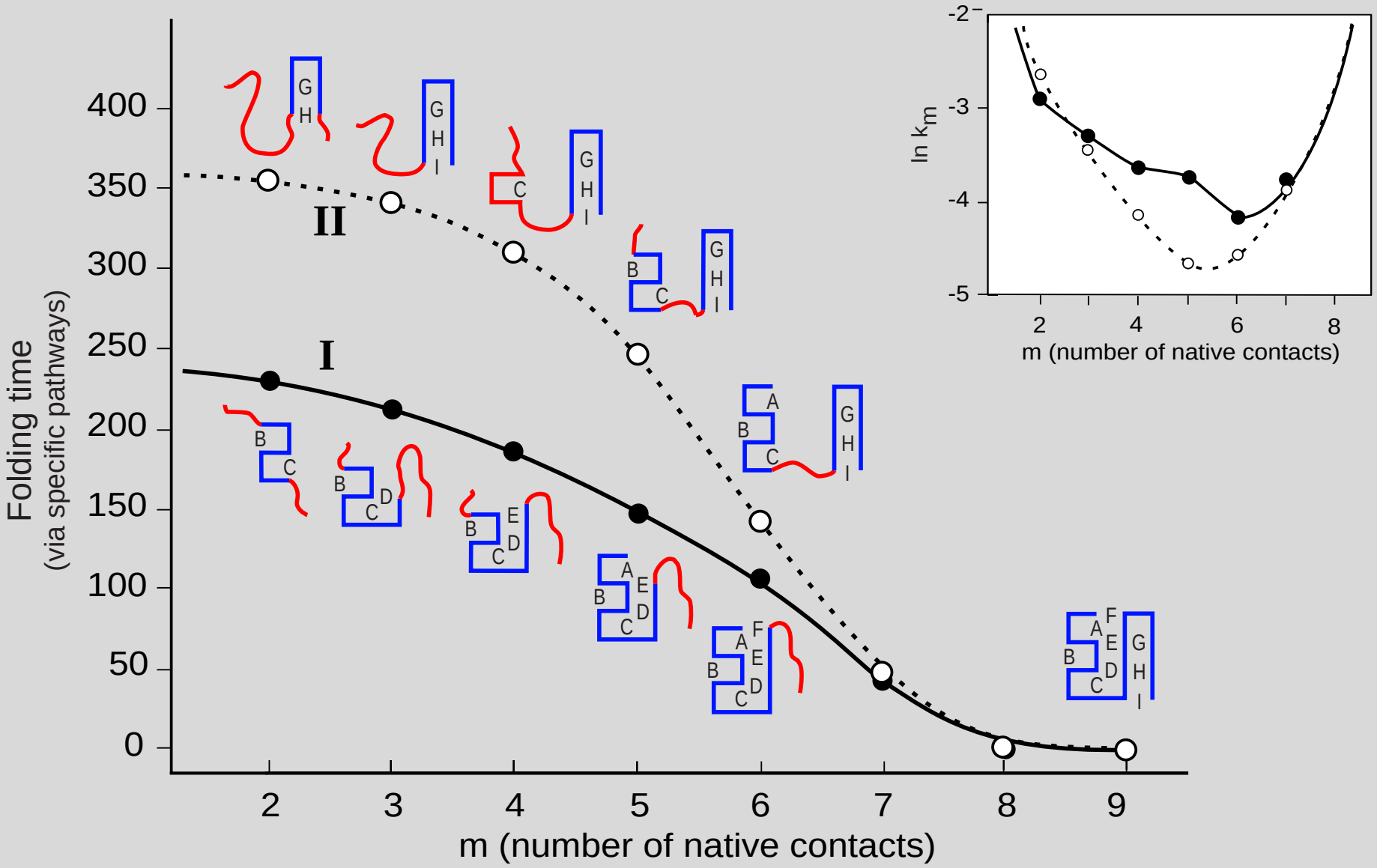
Folding is Faster than Microscopic Transition Rates



jack schonbrun

How Structure Emerges Along a Funnel



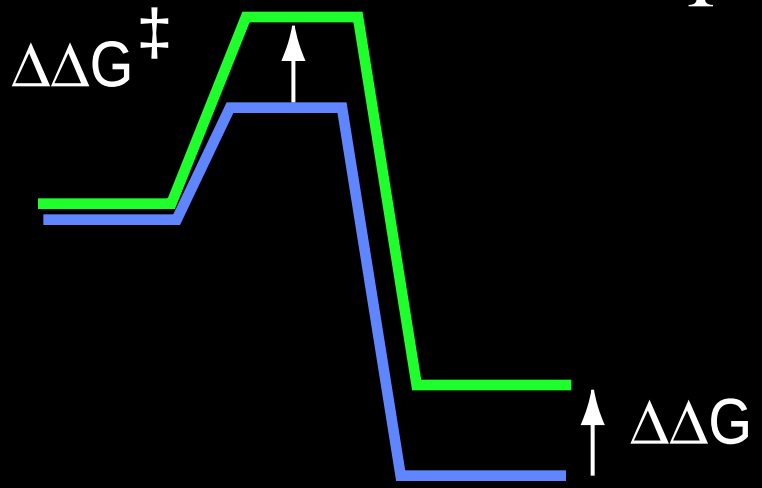

Folding time
(via specific pathways)
400
350
300
250
200
150
100
50
0
2
3
4
5
6
7
8
9
m (number of native contacts)
II
I
G
H
I
C
B
A
D
E
F
ln k_m
-2
-3
-4
-5
2
4
6
8
m (number of native contacts)

Φ Value Analysis *

$\Delta G = -RT \ln K$

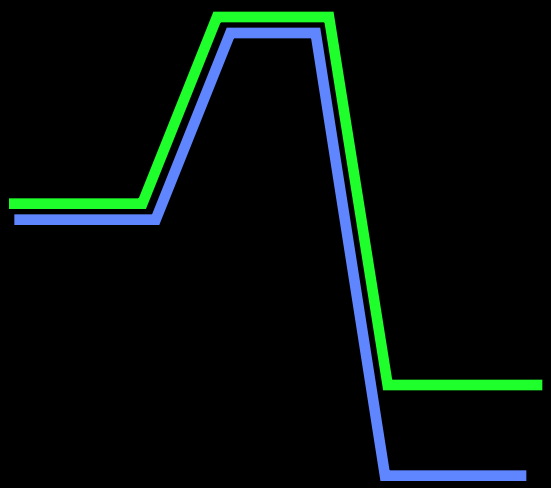
$\Delta G^{\ddagger} = -RT \ln k_f$

$$\Phi = \frac{\Delta\Delta G^{\ddagger}}{\Delta\Delta G}$$



$\Phi = 1$

At mutation site:
TS has Native-like structure

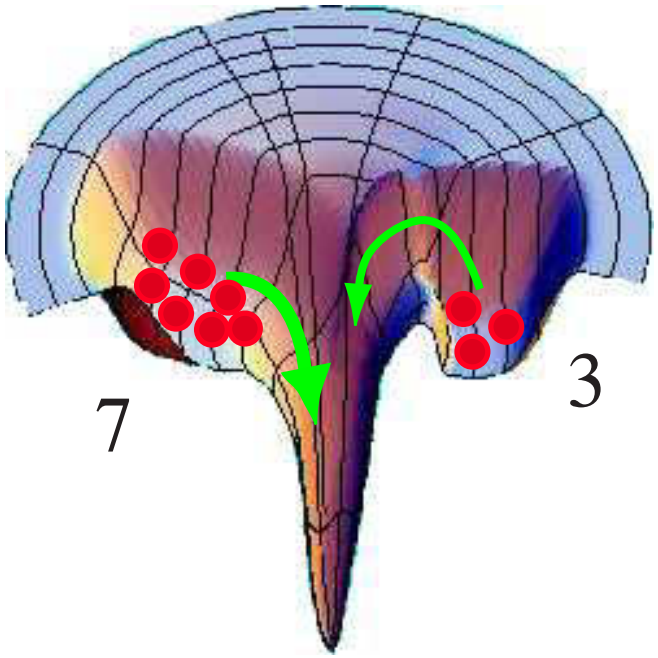


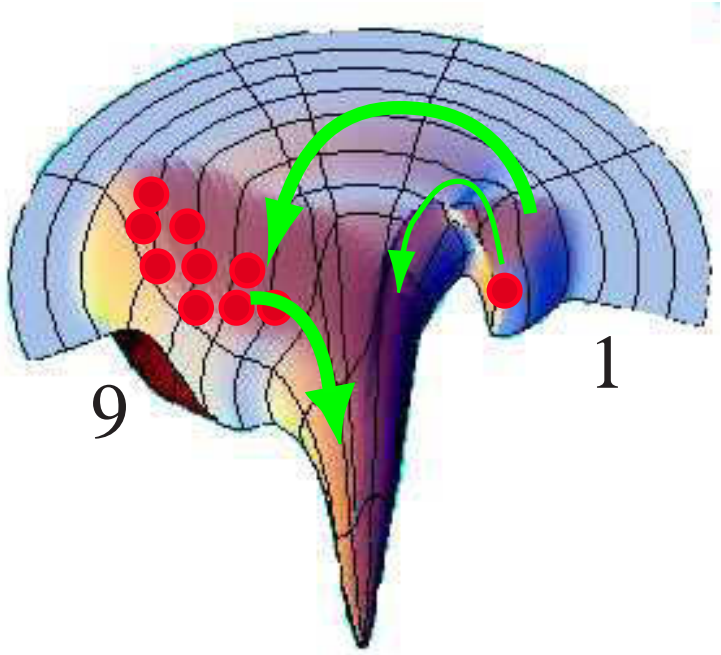
$\Phi = 0$

TS has Denatured-like structure

* A Fersht, Structure and Mechanism in Protein Science. Freeman (1999)

Negative Φ values come from Redirected Flow in Parallel Processes





$$\text{Rate} = \left(\frac{7}{10}\right)1 + \left(\frac{3}{10}\right)(0.1) = 0.73$$

$$\text{Rate} = \left(\frac{9}{10}\right)1 + \left(\frac{1}{10}\right)(0.1) = 0.91$$

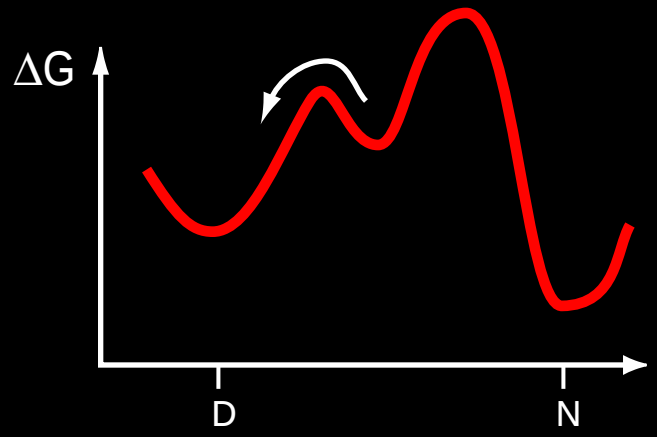
Destabilization leads to higher folding rates

- Banu Ozkan

Mechanism of Chaperone Action

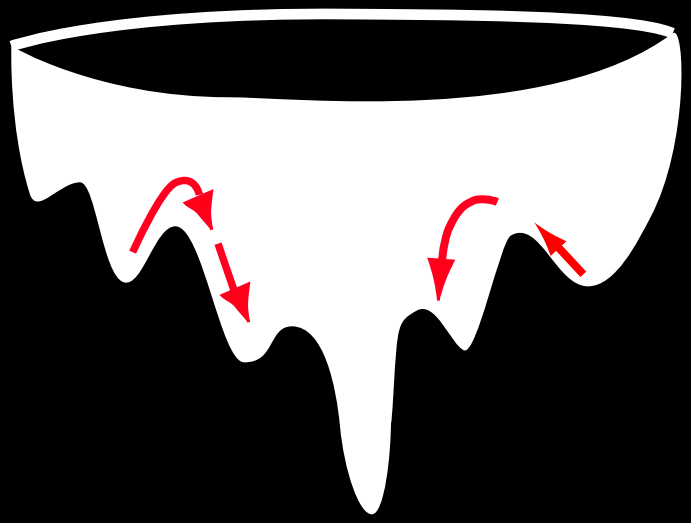
Series model dilemma:

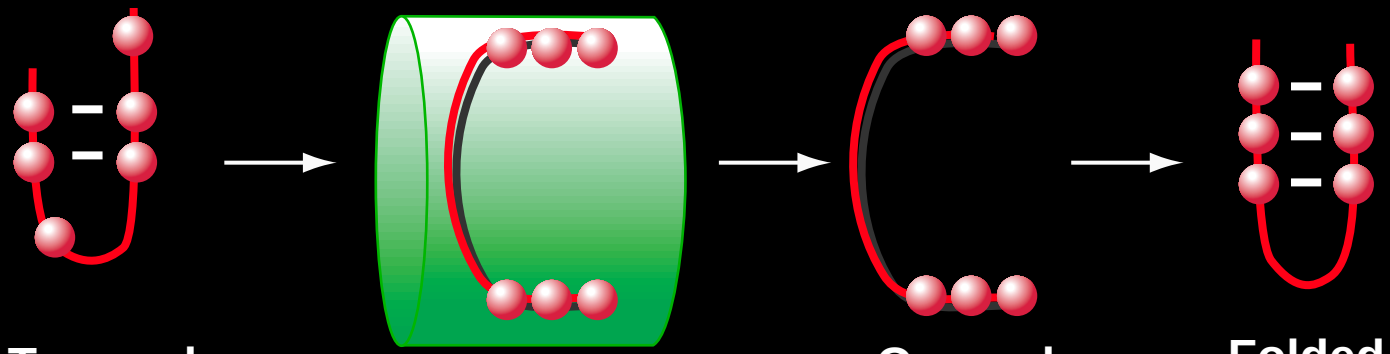
- How to recognize specific TS?
- Unfolding can't help a protein fold



Parallel model solution

- Unfolding a protein can help it fold





- Lorimer, Thirumalai, 1996. - Chan, Dill, 1996

Summary--
2-state Kinetics can come from:

Pathways
single rxn coord,
bottleneck step,
macro-rate < slowest micro-rate,
macrostates correspond to microstates

OR

Funnels
multiple routes,
early acceleration,
macro-rate > fast micro-rates
macrostates are ensembles

- Kinetics is a collective property of landscapes.
  Not a property of a single trajectory.

- In 2-state folding, what is the barrier?
  The whole folding process, not just collapse.

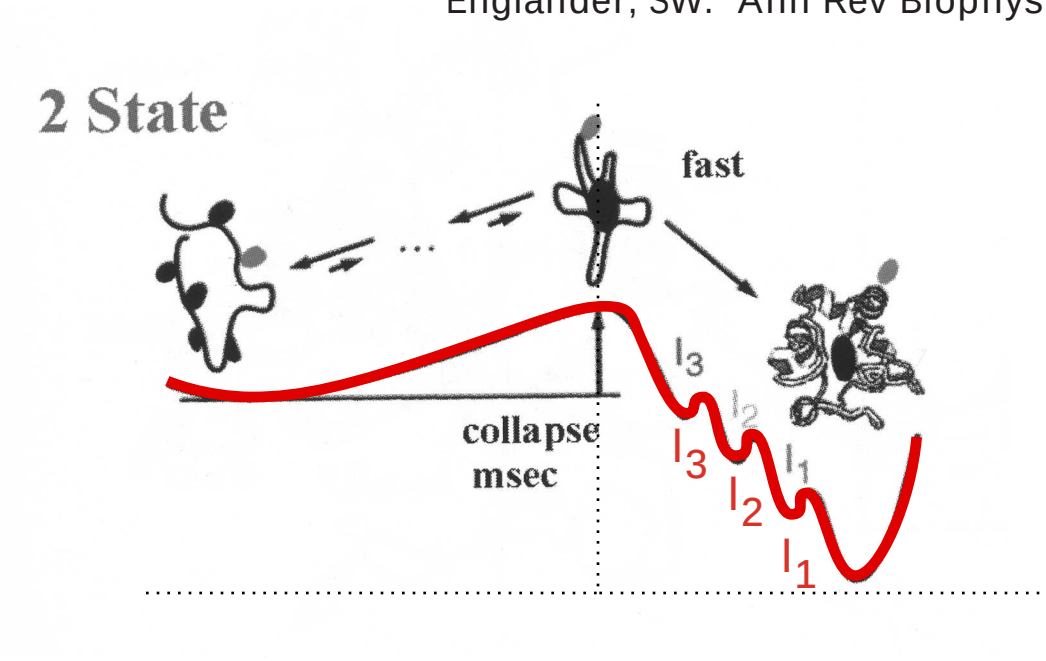
- Transition States are broad.
  They overlap with Denatured States.

- Nonclassical Φ values are evidence for parallel steps.

- Terminology that applies to series processes,
  but not necessarily to parallel processes:
  (before, after)
  (backward, forward),
  (productive, unproductive (intermediates))

Pathway Model: Collapse comes first, then detailed structure.

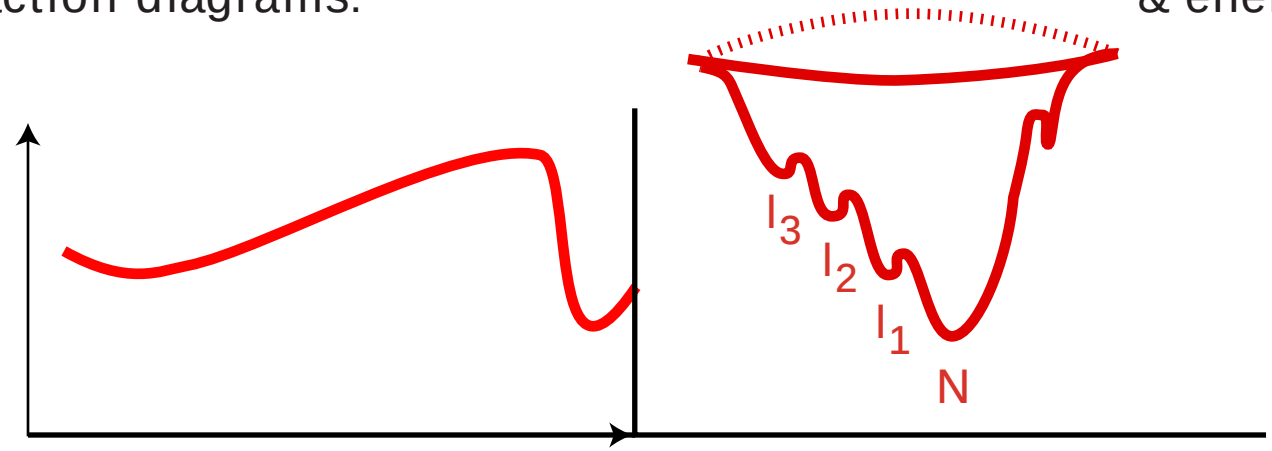
Englander, SW. Ann Rev Biophys Biomol Struc 29:213 (2000)



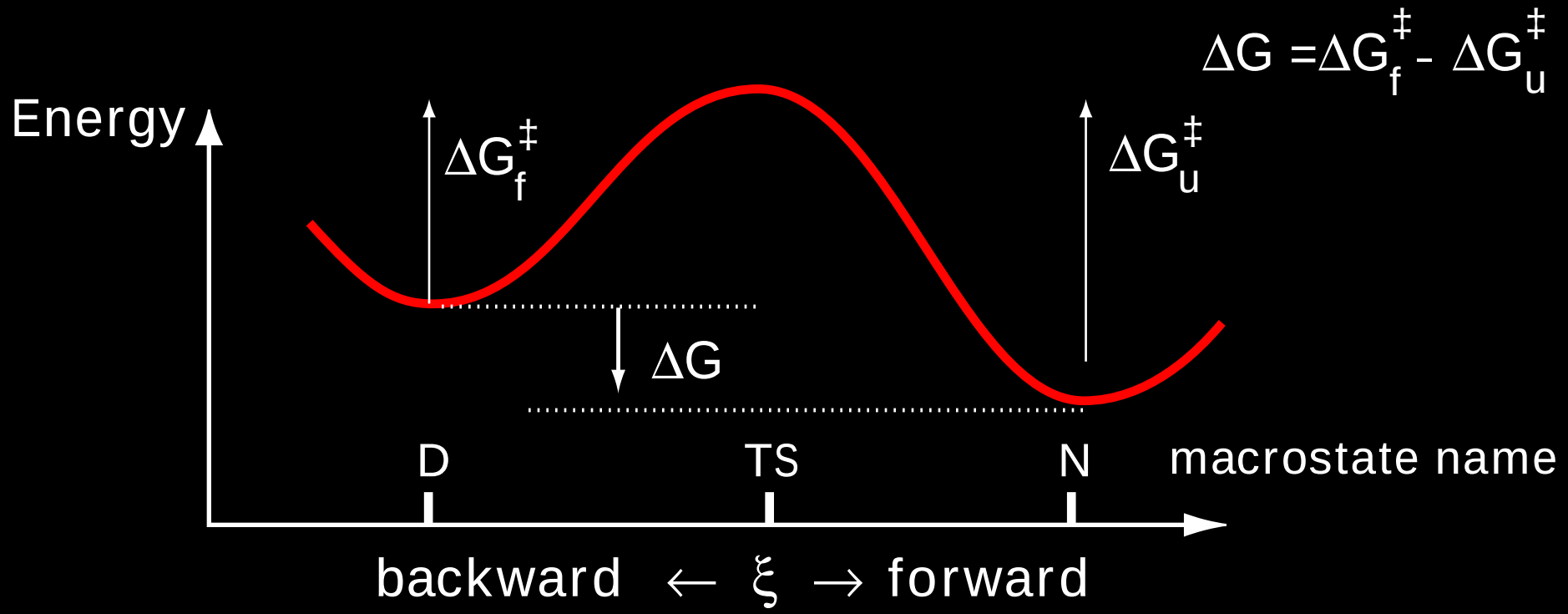
Funnel Model: Collapse and structure formation are simultaneous

This side is about
kinetics,
reaction diagrams:

This side is about
thermodynamics
& energy landscapes:



The Classical Transition State



localized ensembles	$(C_1\ C_2\ C_3)$.....	$(C_i\ C_{i+1})$	(C_N)	microstates

- Macrostates are localized ensembles of microstates.
- States are in series and don't overlap.
- Single reaction coordinate. Forward & backward directions.