Reliable Protein Folding on Non-Funneled Energy Landscapes: The Free Energy Reaction Path

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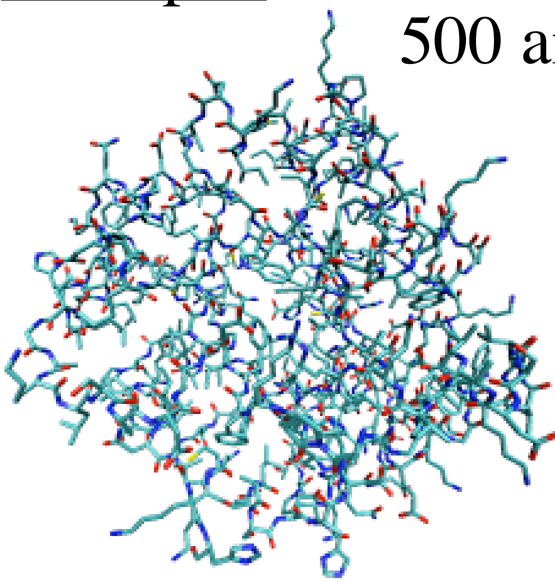
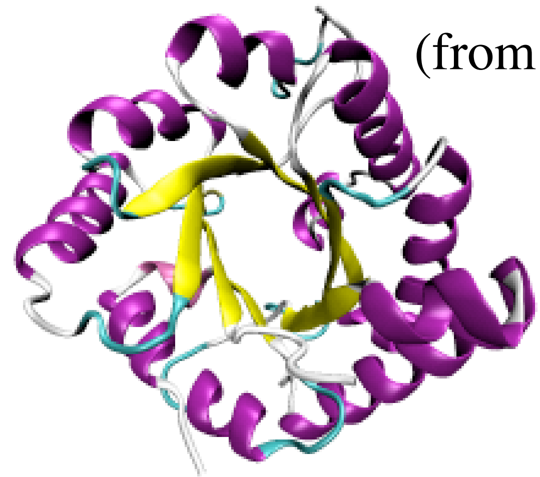
Protein Folding

As temperature decreases, a linear chain of amino acids collapses into a reproducible three dimensional structure.

Example: Triose Phosphate Isomerase
500 amino acids, folds reliably





(from Wikipedia)

Levinthal's Paradox (1968): (as paraphrased by Zwanzig, 1992)
If each amino acid can pair with at least 2 others, and if conformations are randomly sampled no faster than 10^{15} per second.

$$\Rightarrow \quad \text{time to fold} > 2^{500} \times 10^{-15}\,\text{s} \approx 10^{135}\ \text{years}$$

Modern View: Funneled Energy Landscapes

Conformation space is not sampled randomly:

In equilibrium,

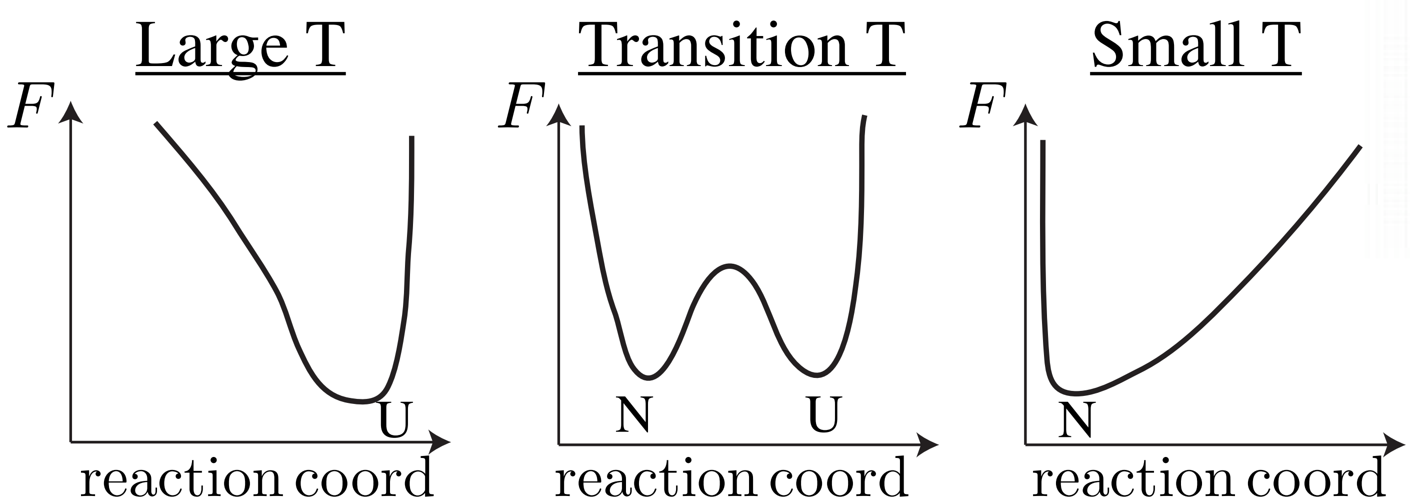
$$\mathrm{Probability} = \exp(-F/T) \quad \text{with} \quad F = E - TS$$

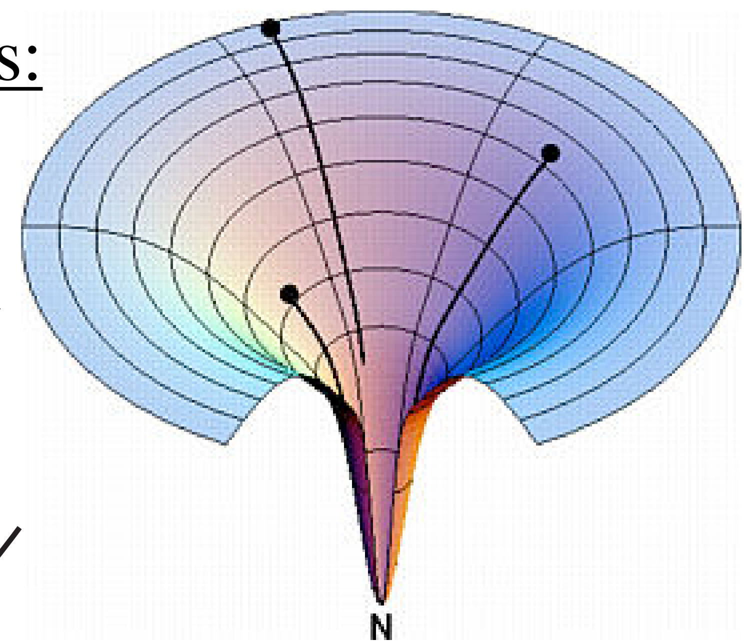
Out of equilibrium, dynamics bias the search.

Energy Landscapes are shaped like funnels:

Out of equilibrium, dynamics go to N

In equilibrium, there is a phase transition

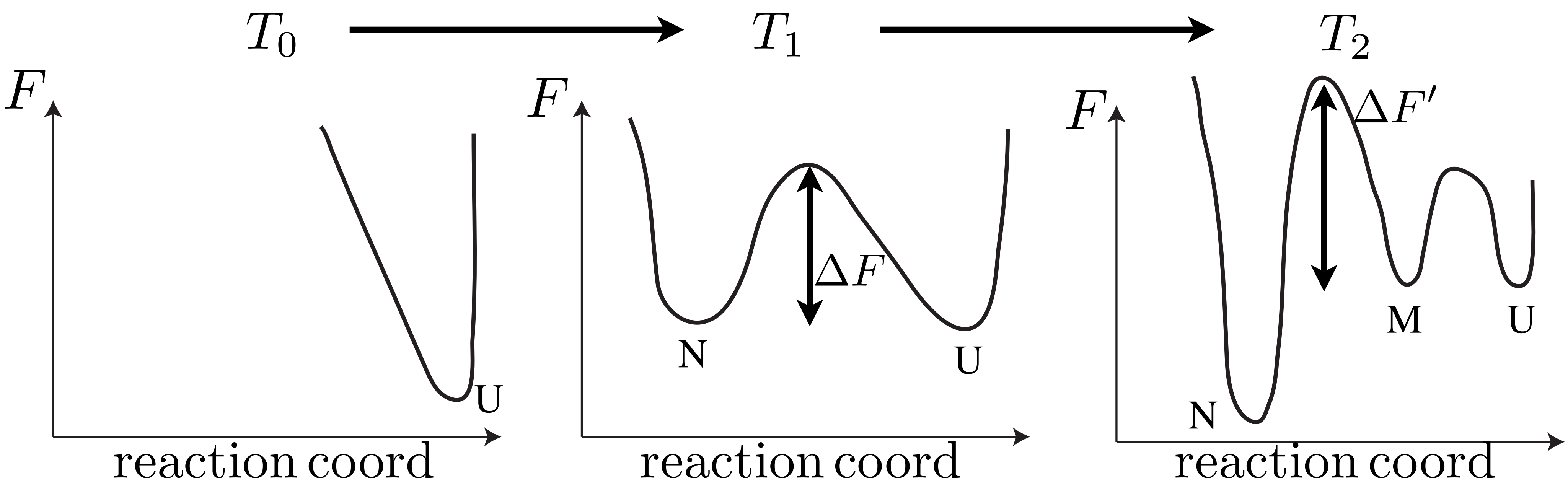




(From Dill & Chan, 1997)

Folding on Non-Funneled Landscapes

If there are many minima of E then there are many minima of F



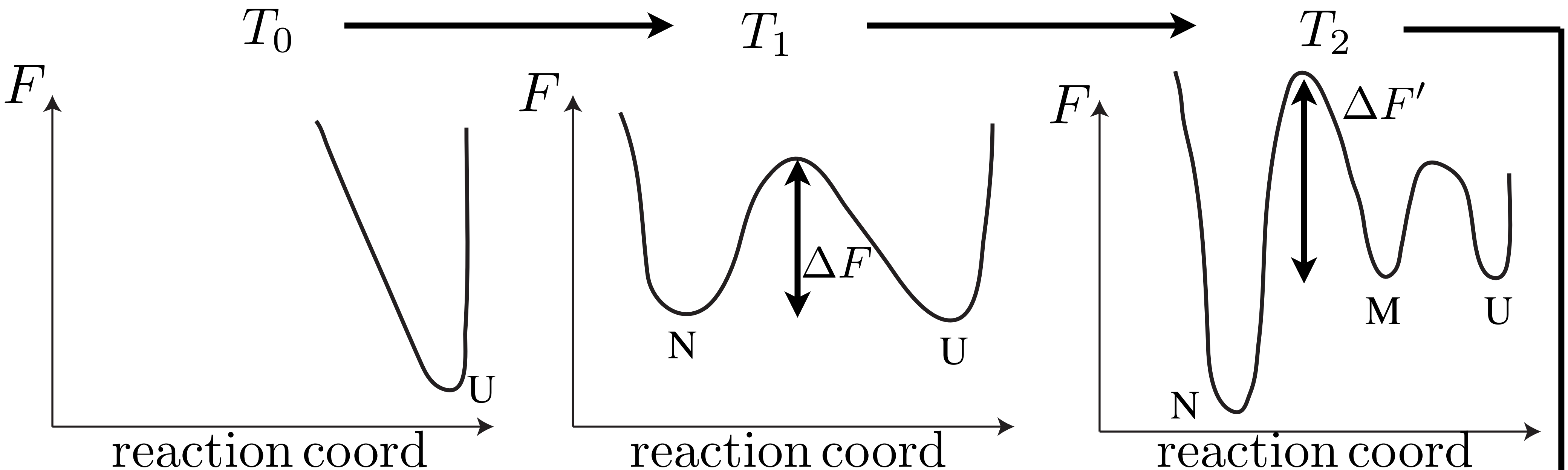
at T_1 the time to fold is $\propto \exp(\Delta F/T_1)$

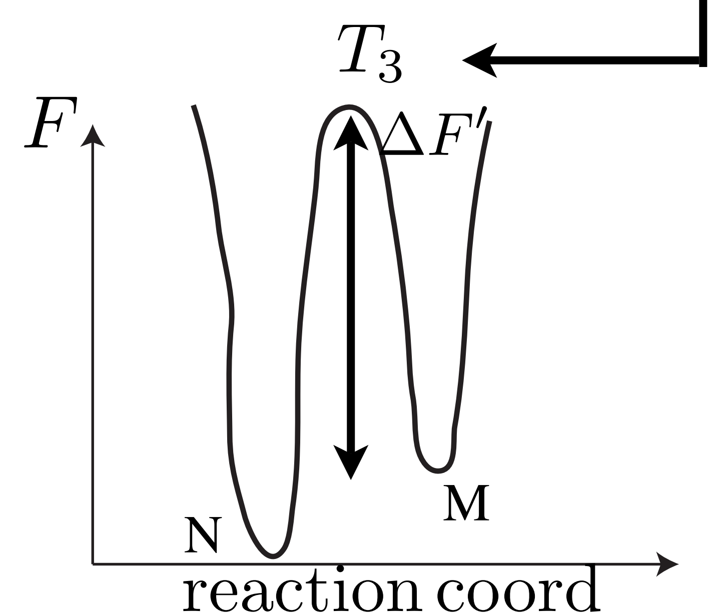
Given that $T(t) = T_0(1 - rt)$ this sets a bound on r.

If $r > r^f$ the protein can fall into a metastable state

Folding on Non-Funneled Landscapes

If there are many minima of E then there are many minima of F



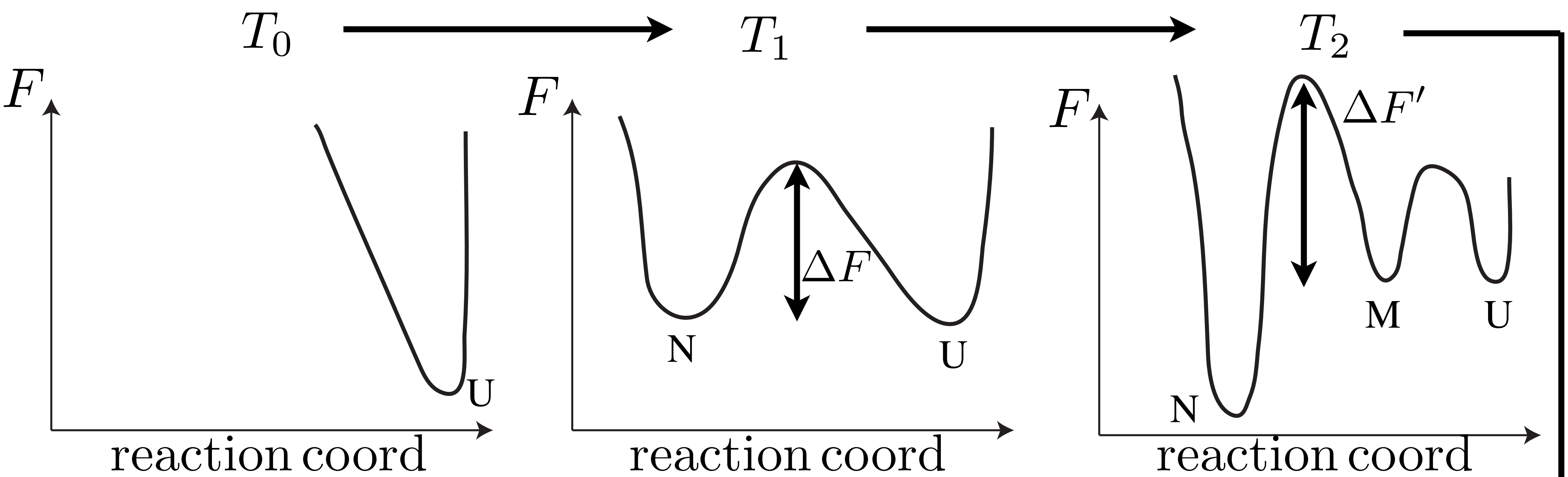


Since $T(t) = T_0(1 - rt)$, the barrier $\Delta F'$ increases faster for large r.

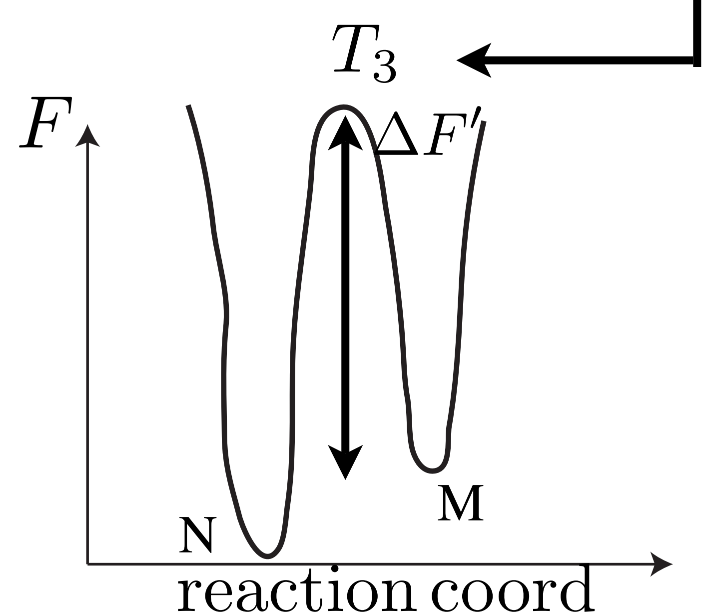
If $r > r^s$ the protein will remain in M indefinitely

Folding on Non-Funneled Landscapes

If there are many minima of E then there are many minima of F



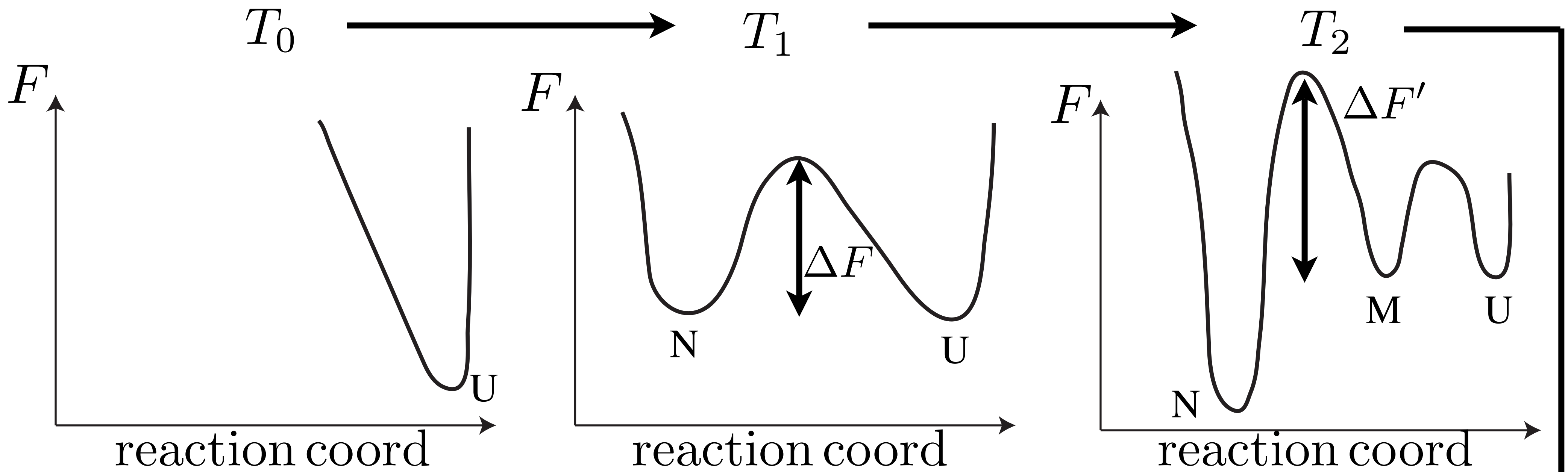
Protein folding on non-funneled landscapes is rate dependent

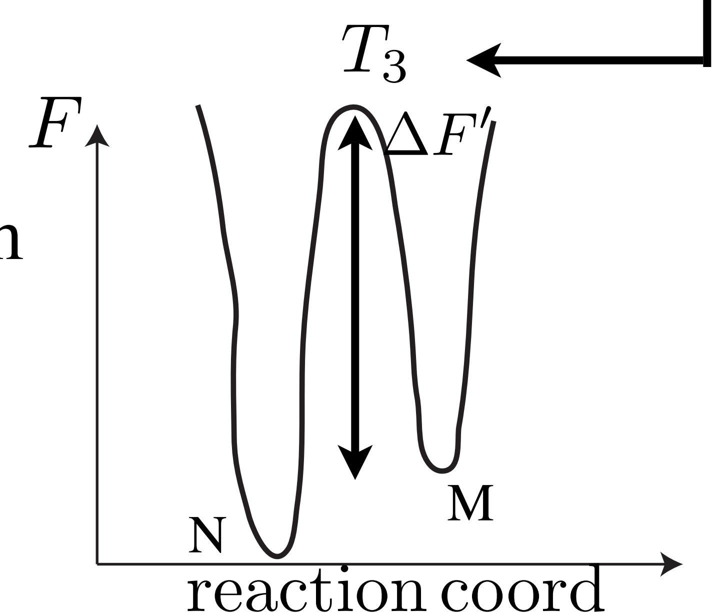


Reliable folding from $U \rightarrow N$ occurs
if $r < r^f$ or $r < r^s$

Folding on Non-Funneled Landscapes

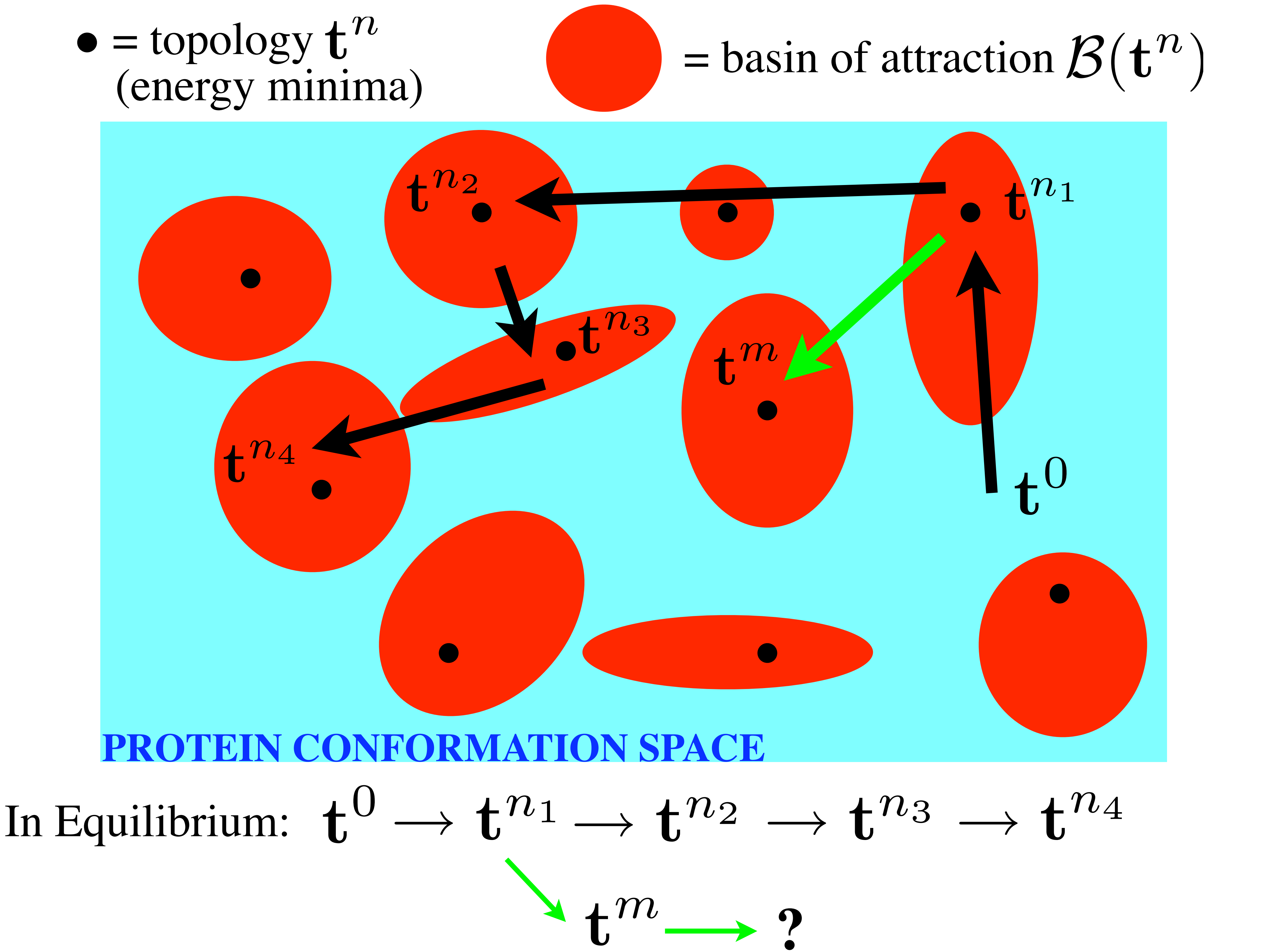
If there are many minima of E then there are many minima of F





If $r < r^s$ folding is in equilibrium

If $r^s < r < r^f$ folding is out of equilibrium



● = topology $\mathbf{t}^n$ (energy minima)
= basin of attraction $\mathcal{B}(\mathbf{t}^n)$
$\mathbf{t}^{n_2}$
$\mathbf{t}^{n_1}$
$\mathbf{t}^{n_3}$
$\mathbf{t}^{m}$
$\mathbf{t}^{n_4}$
$\mathbf{t}^{0}$
PROTEIN CONFORMATION SPACE
In Equilibrium: $\mathbf{t}^0 \longrightarrow \mathbf{t}^{n_1} \longrightarrow \mathbf{t}^{n_2} \longrightarrow \mathbf{t}^{n_3} \longrightarrow \mathbf{t}^{n_4}$
$\mathbf{t}^{m} \longrightarrow$?

The Free Energy Reaction Path

$$\text{Unfolded} \quad \mathbf{t}^0 \underset{\substack{r_1^f \\ r_1^s}}{\longrightarrow} \mathbf{t}^{n_1} \underset{\substack{r_2^f \\ r_2^s}}{\longrightarrow} \mathbf{t}^{n_2} \underset{\substack{\cdots \\ \cdots}}{\longrightarrow} \mathbf{t}^{n_3} \longrightarrow \mathbf{t}^{n_4} \cdots \quad \text{Folded}$$

Given $T = T_0(1 - rt)$

① If $r < r_i^s$ for all transitions i

⇨ Reliable Equilibrium Folding to global minimum

② If $r_i^s < r < r_i^f$ for a single transition i

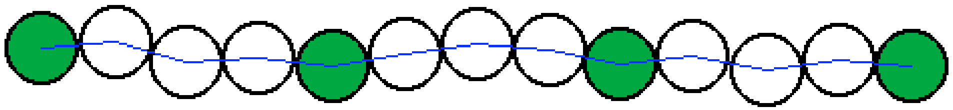
⇨ Reliable Out-of-Equilibrium Folding to $\mathbf{t}^{n_i}$

③ If $r > r_i^f$ and $r > r_i^s$ for a single transition i

⇨ Un-reliable folding

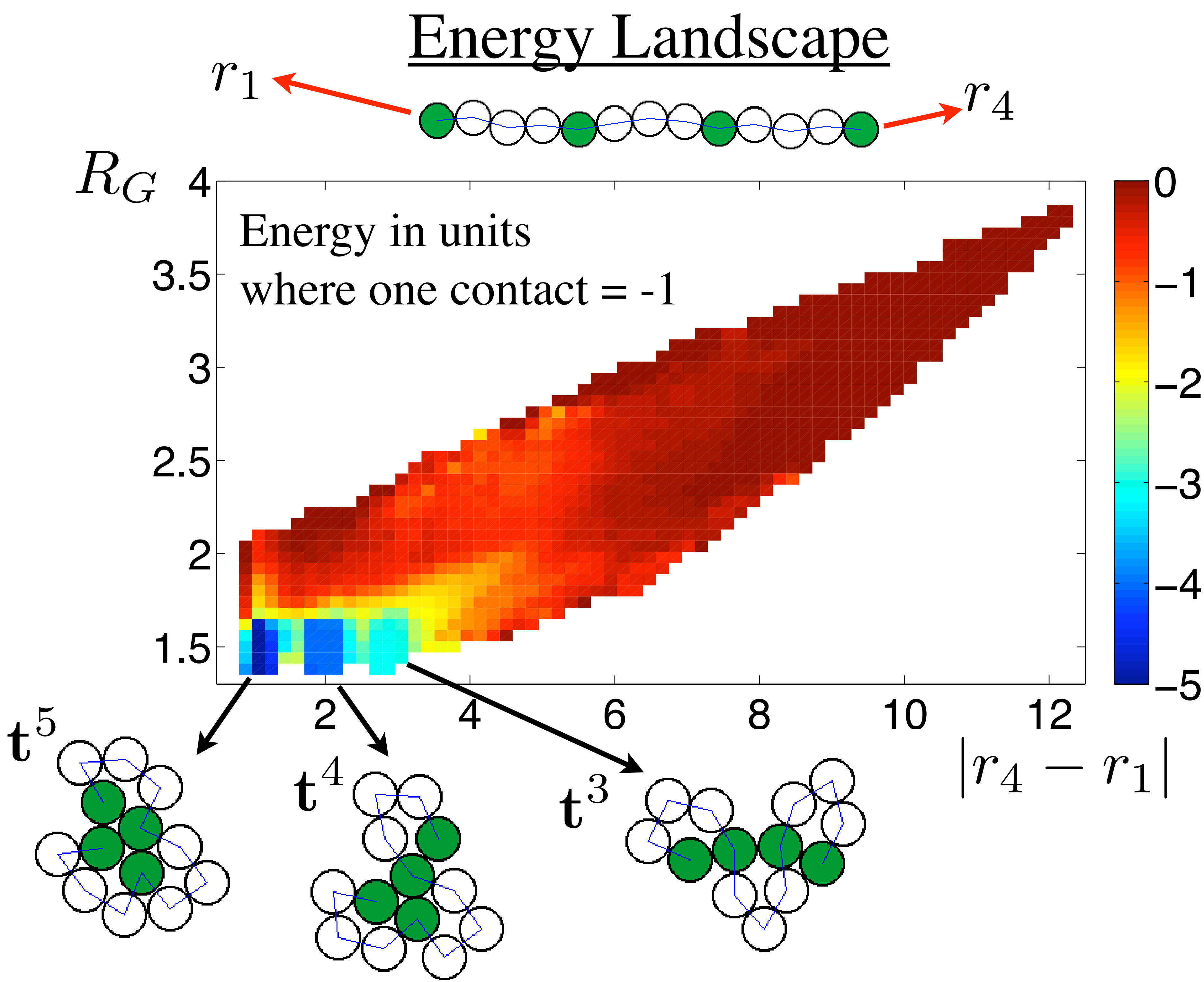
Simulations

A particular two dimensional C^{α} model



Folding is induced by lowering temperature or increasing attractive strength

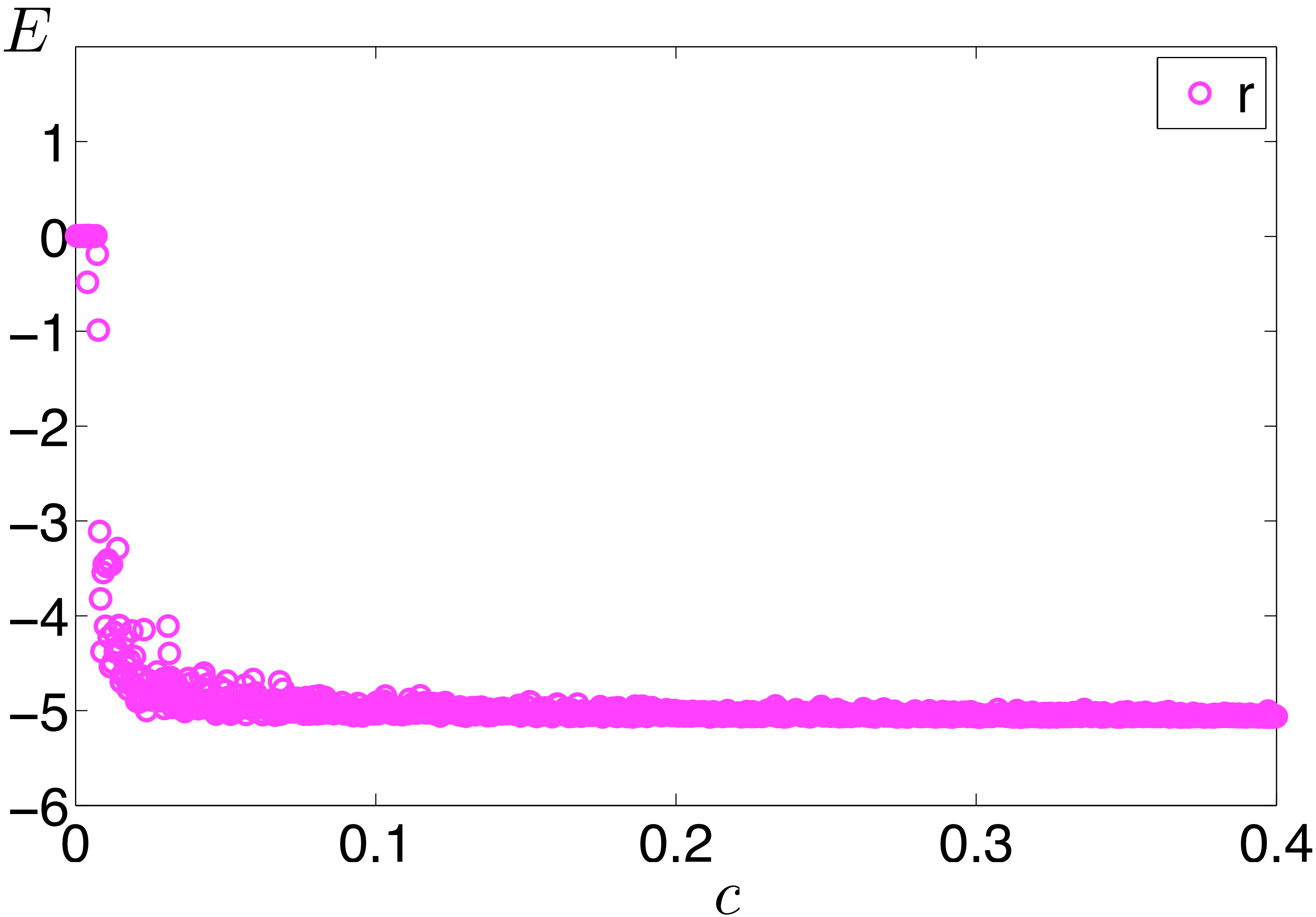
$$c \equiv \frac{|E_{\mathrm{att}}|}{T} = rt$$

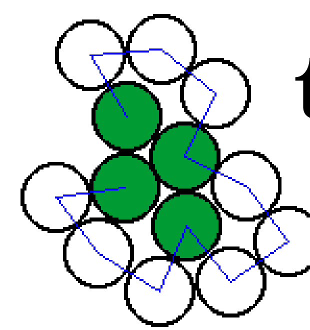


Energy Landscape
r_1
r_4
R_G
Energy in units
where one contact = -1
$|r_4 - r_1|$
$\mathbf{t}^5$
$\mathbf{t}^4$
$\mathbf{t}^3$

Rate Dependence

$$c = rt$$





$\mathbf{t}^5$

Rate Dependence

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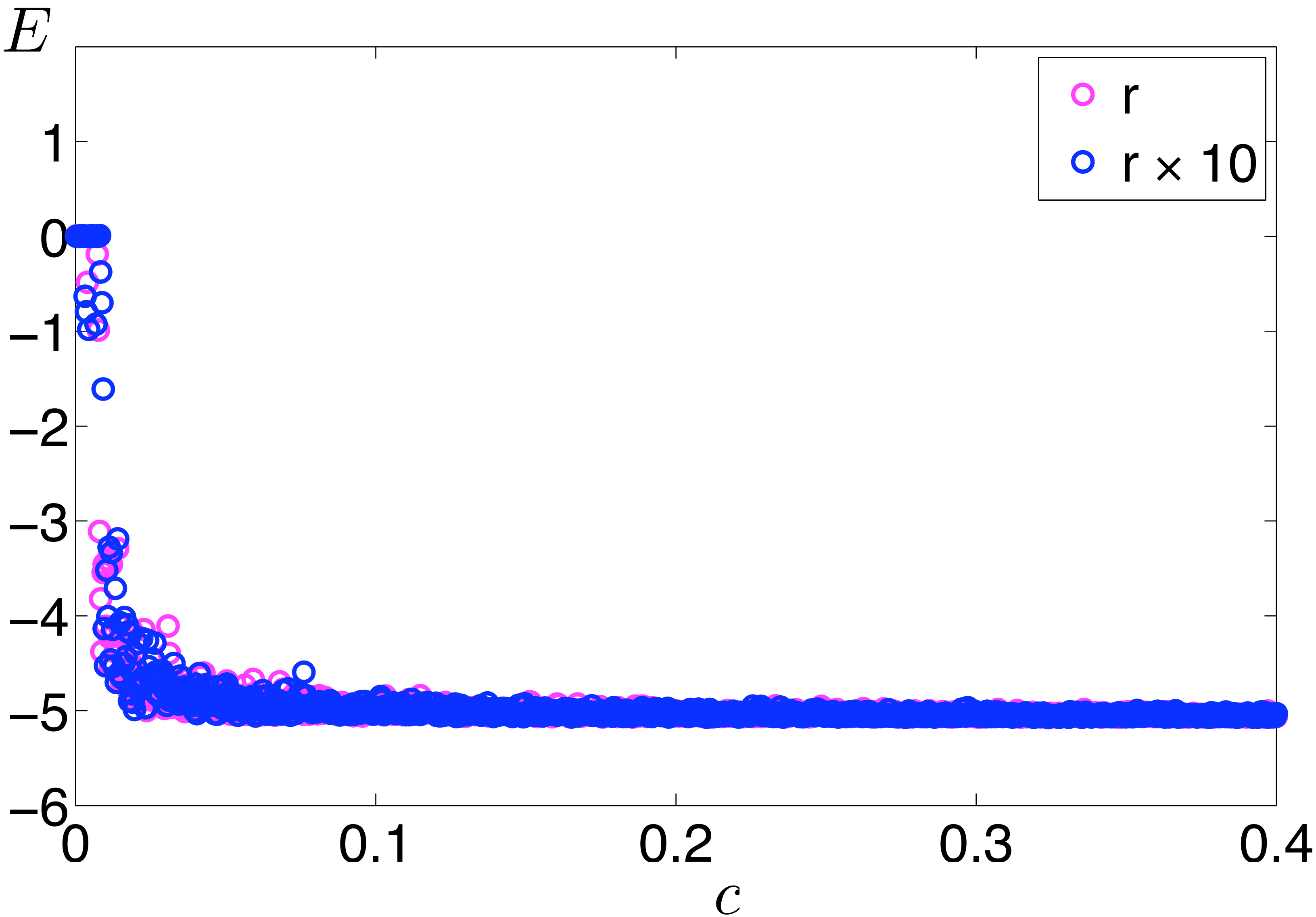

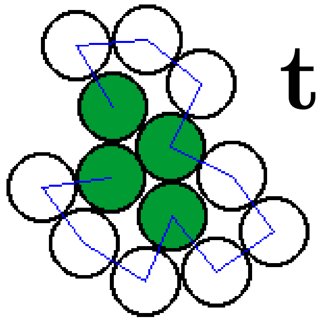

$\mathbf{t}^5$

Rate Dependence

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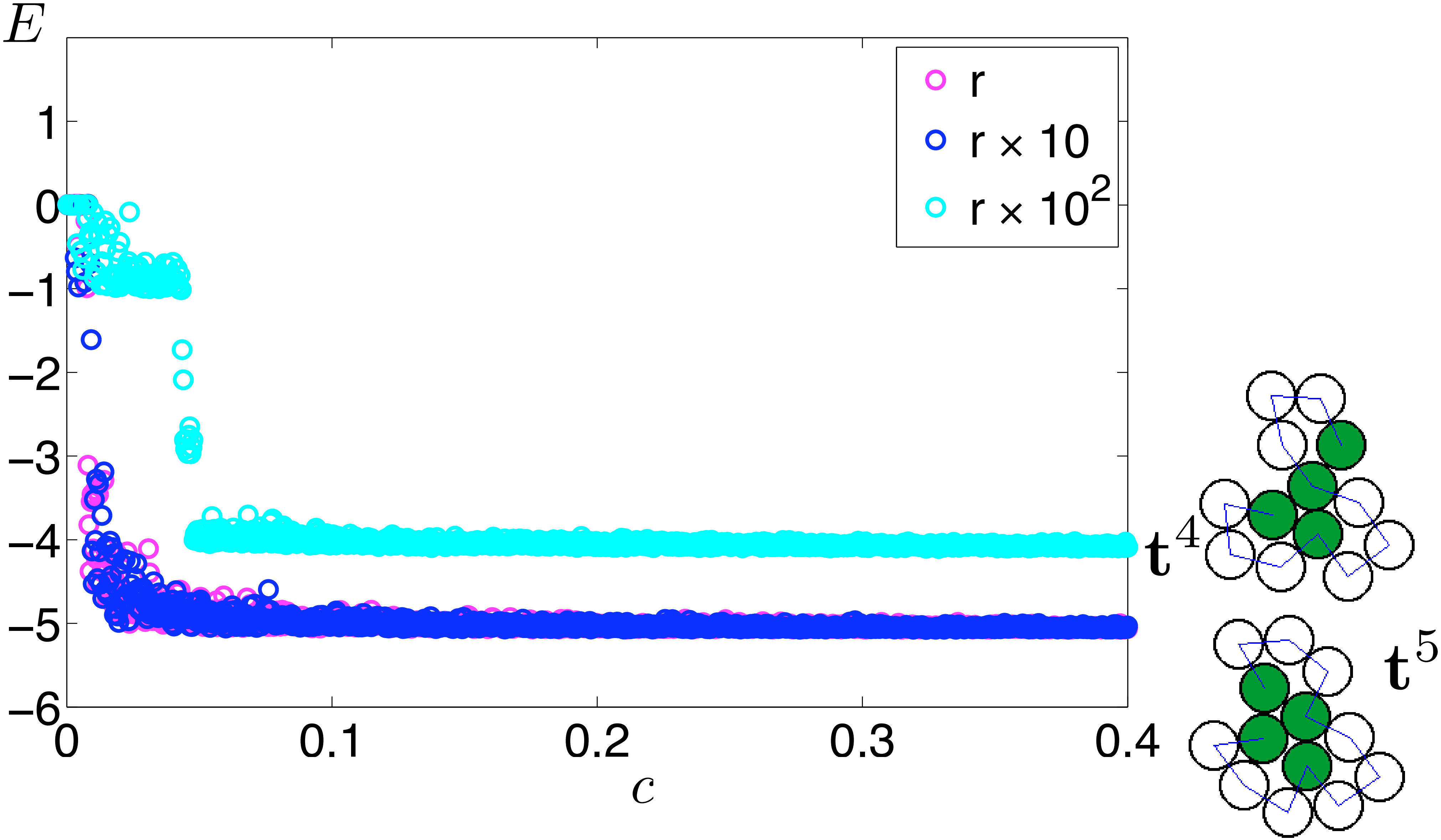

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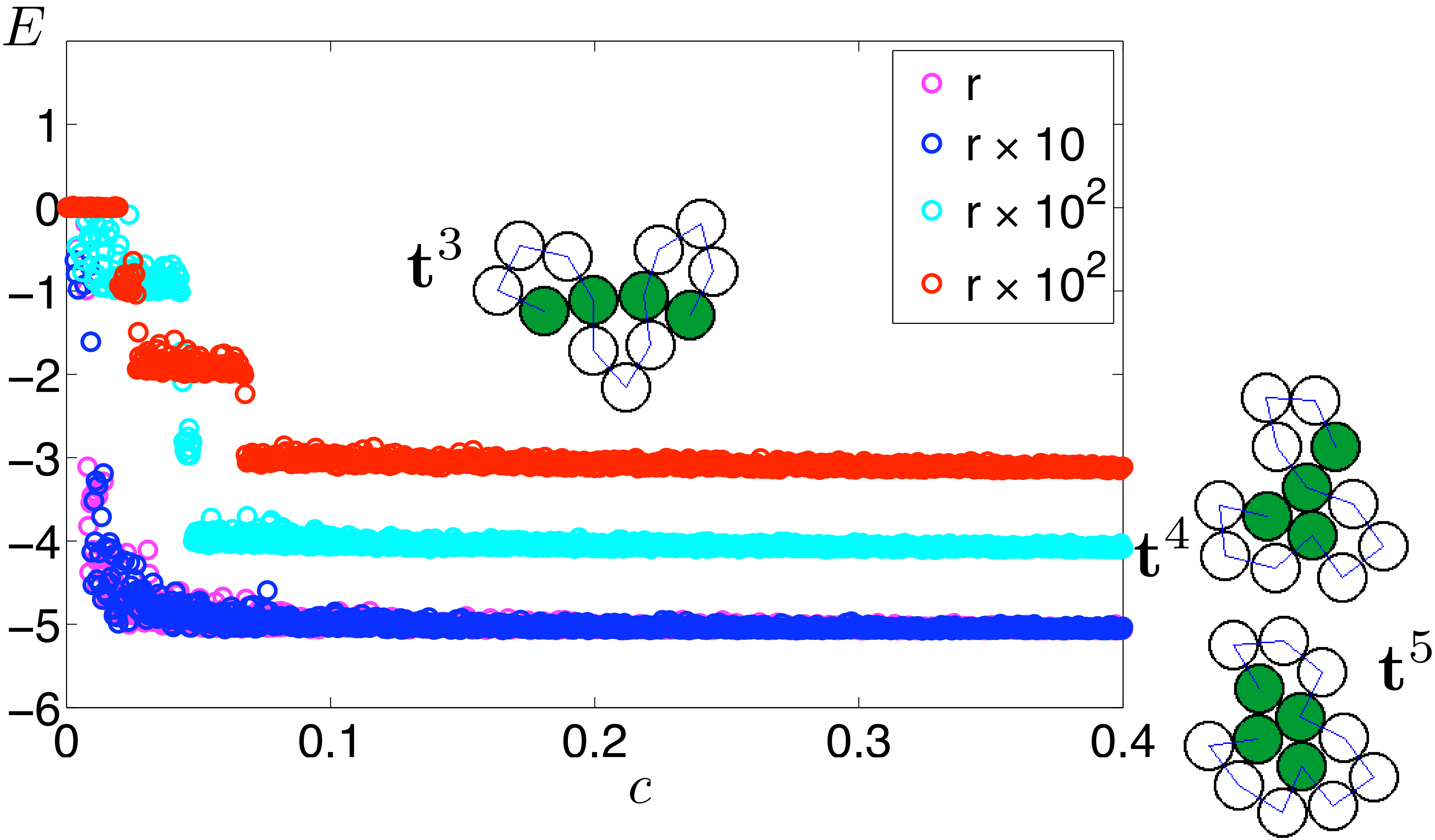
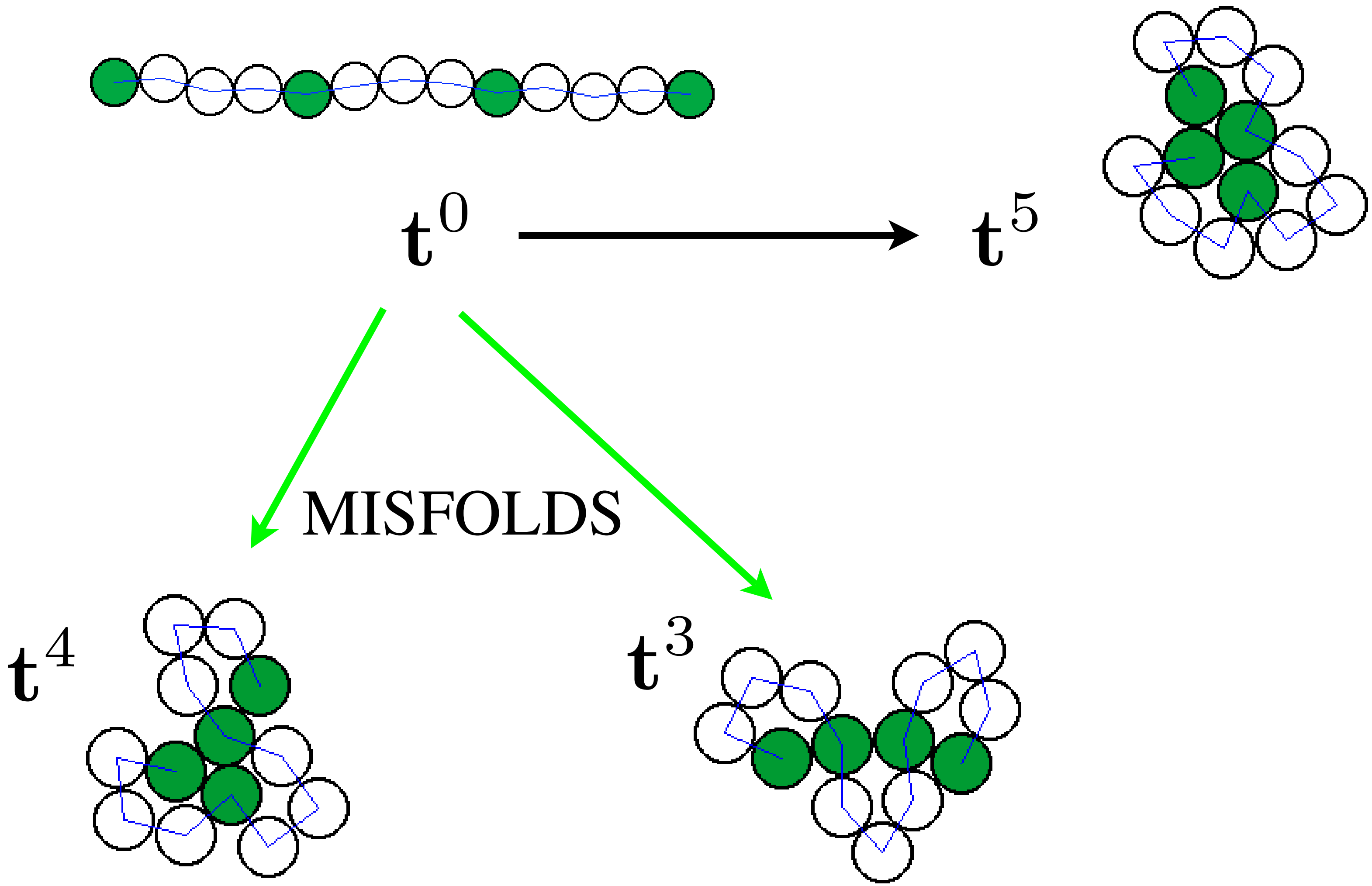
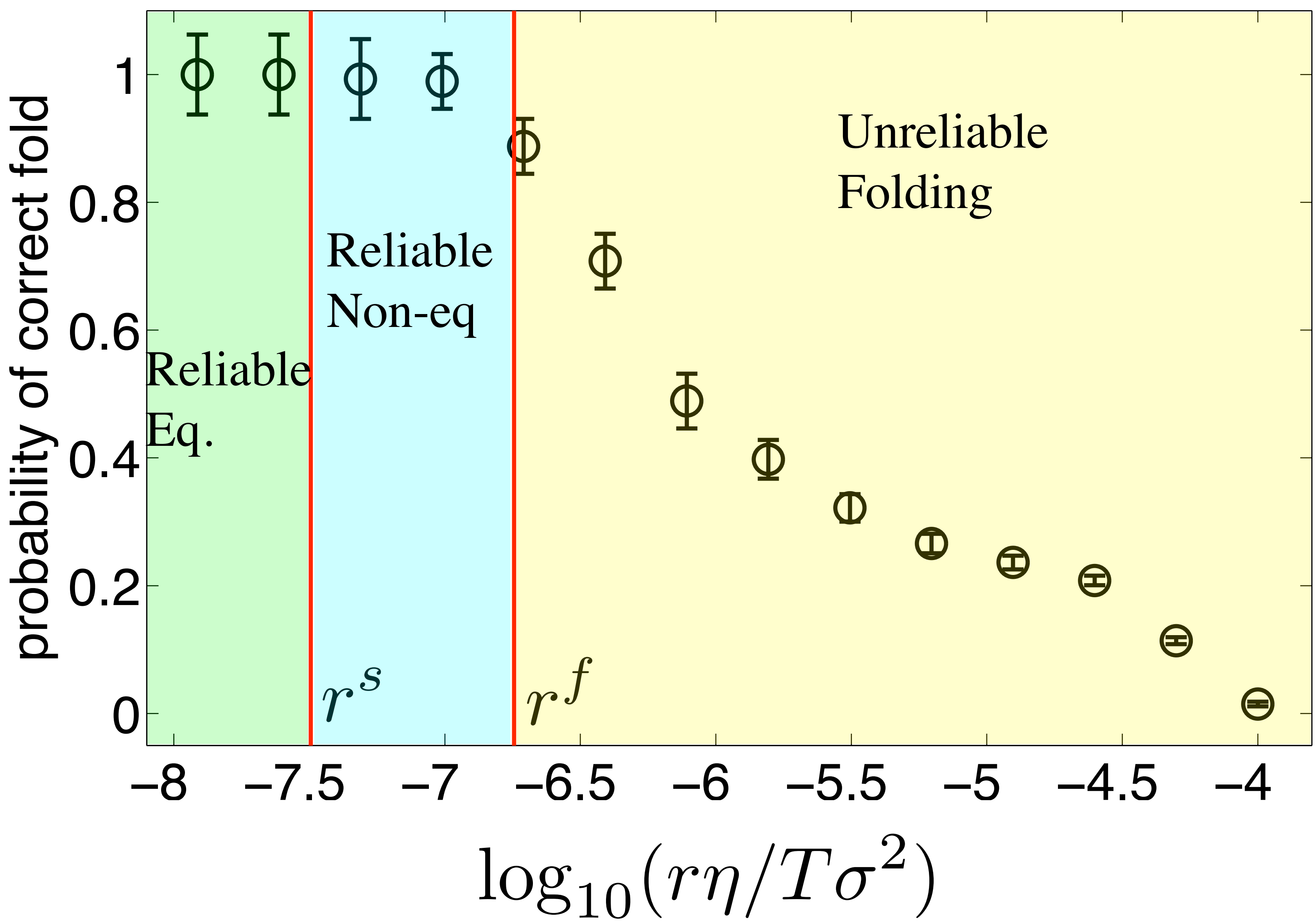


Free Energy Reaction Path



We calculate r^f and r^s for this transition

Reliable Folding



Summary

- Reliable Folding can occur on Non-Funneled Energy Landscapes, depending on the folding-induction rate r.
- The Free Energy Reaction Path is a useful framework to understand the dynamics.
- Folding can occur either as an equilibrium process or out of equilibrium.
- The native state can be a global or local minimum of free energy.
- These predictions can be tested in simulations and experiments by investigating rate dependence.