

# Controlling protein dynamics through counterdiabatic driving

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# Acknowledgments

Telluride info

engines community...

## Collaborators:

Sebastian Deffner, UMBC

Efe İlker, Institut Curie

Özenç Güngör, CWRU

Benjamin Kuznets-Speck, Berkeley

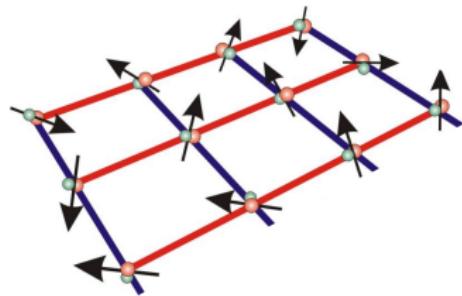
## Funding:

NSF CAREER

MCB-BIO #1651560



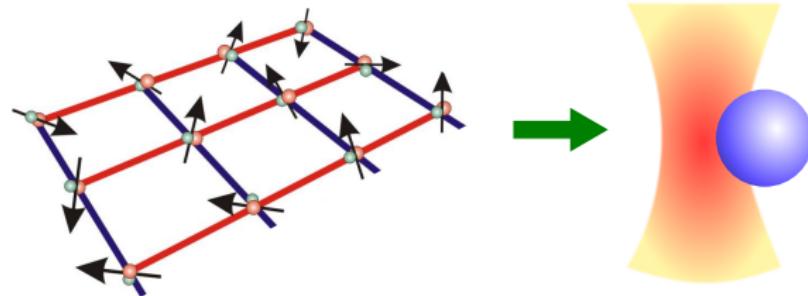
# Shortcuts to adiabaticity



**adiabatic quantum computing:**  
maintaining ground state while  
driving a quantum system

Demirplak, Rice, JPCA (2003)  
Berry, J. Phys. A (2009)

# Shortcuts to adiabaticity



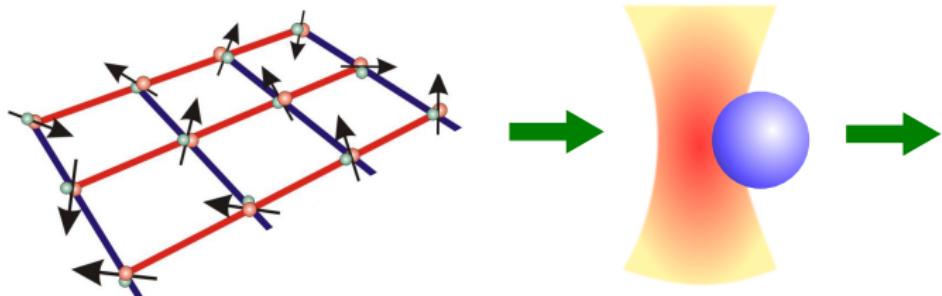
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Martinez *et al* Nature Physics (2016)  
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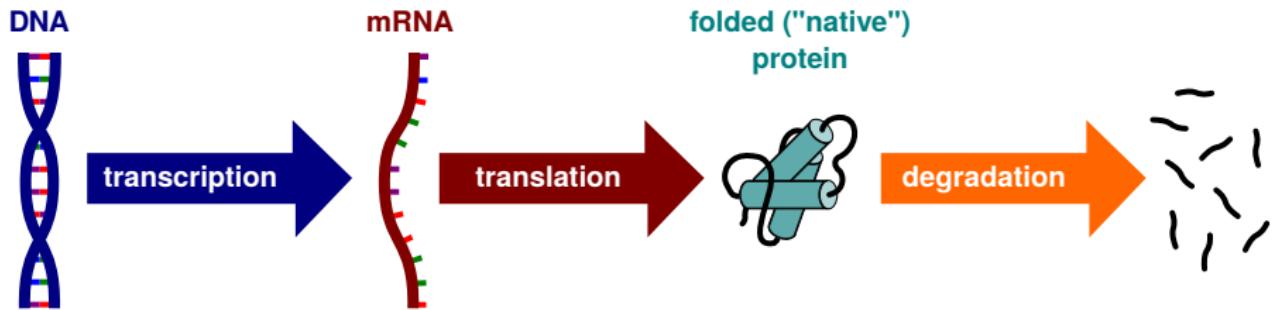
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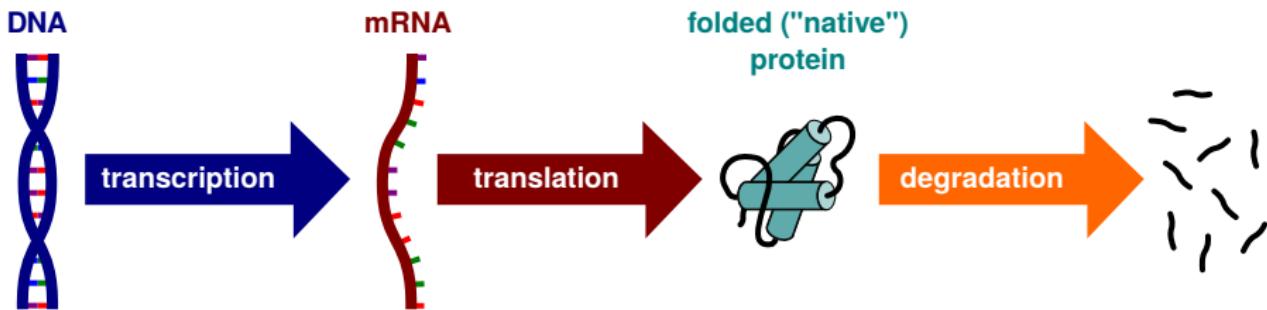


**biological  
applications:**  
population genetics  
molecular chaperones  
force spectroscopy

# Traditional view of protein production



# Traditional view of protein production



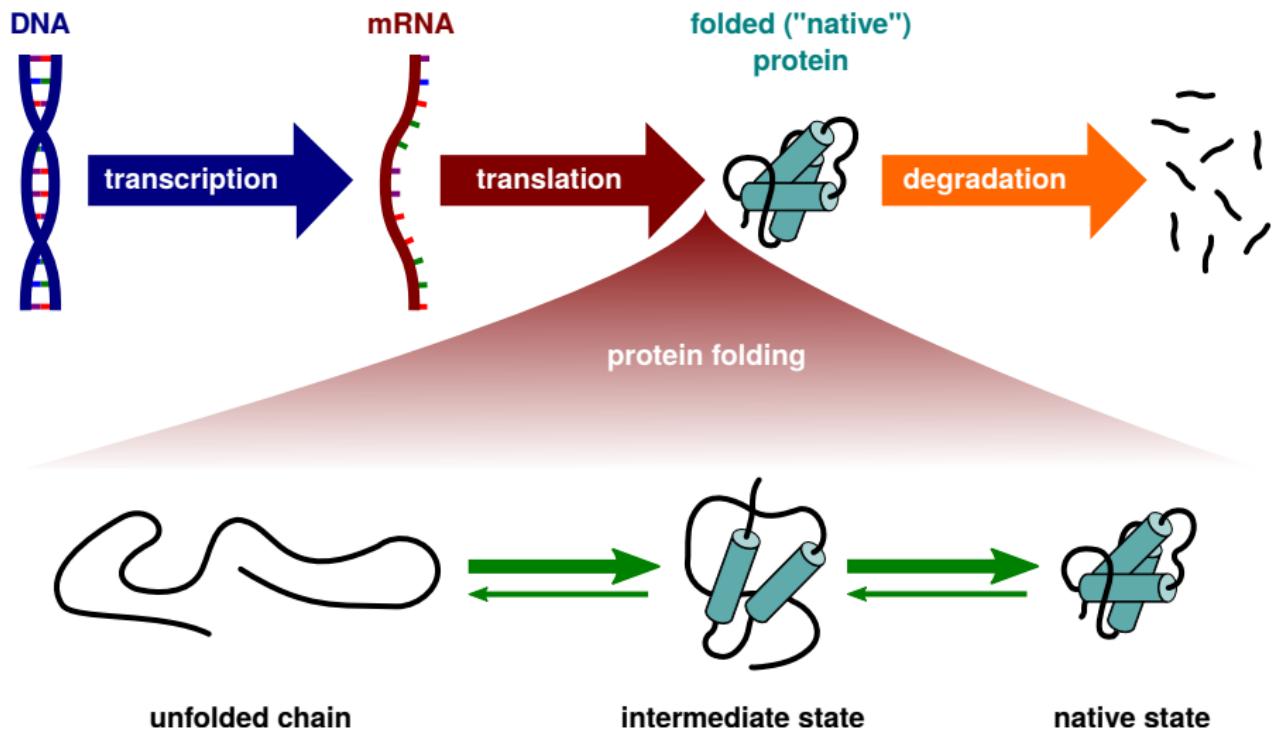
All these processes involve nonequilibrium reaction networks driven by ATP hydrolysis.

The resulting costs of expressing even a single extra protein can be evolutionarily significant for single-celled organisms.

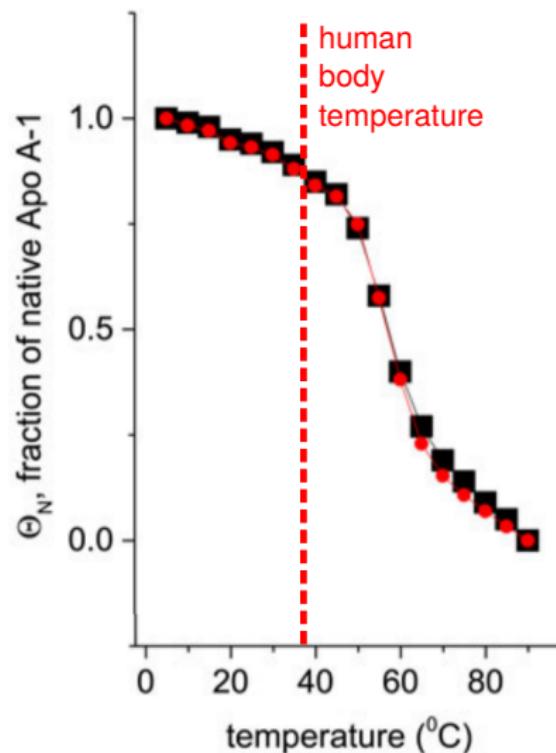
Ilker & Hinczewski, Phys. Rev. Lett. (2019)

Lynch & Marinov, Proc. Natl. Acad. Sci. (2015)

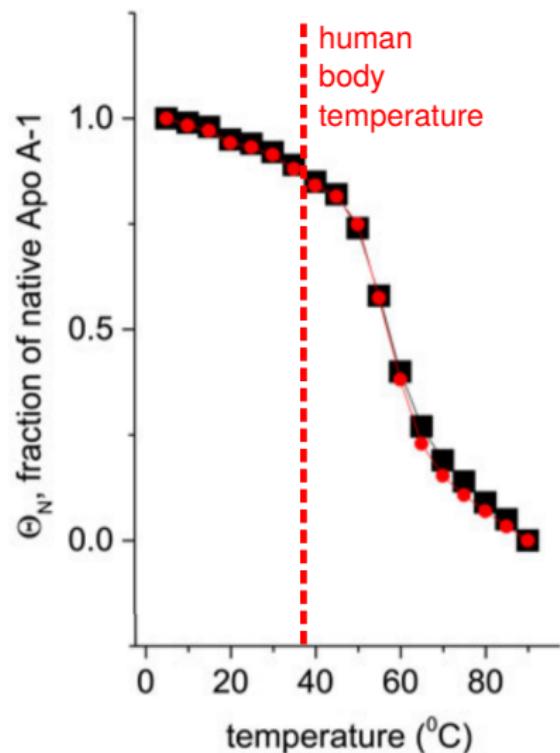
# Traditional view of protein production



# Proteins function at the cliff edge of unfolding

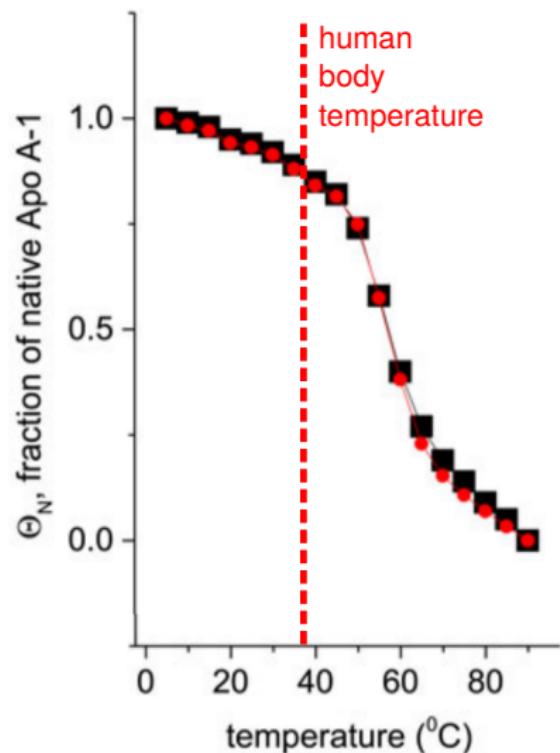


# Proteins function at the cliff edge of unfolding



Being on the verge of melting gives proteins the **dynamical flexibility** essential for their diverse roles as enzymes.

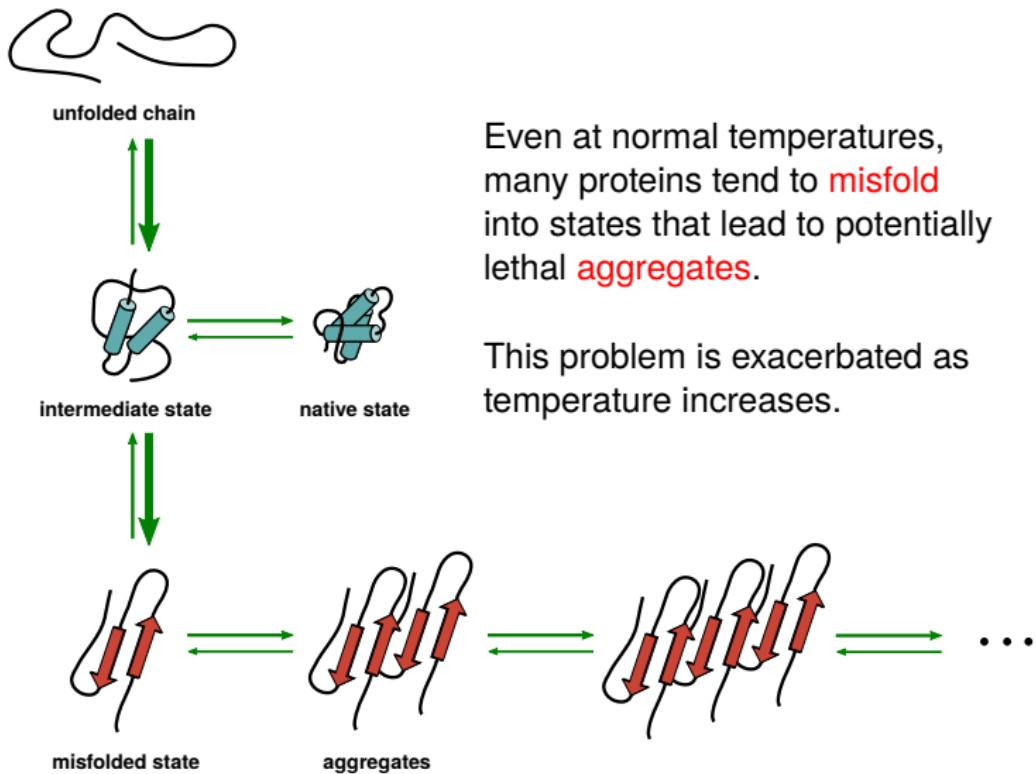
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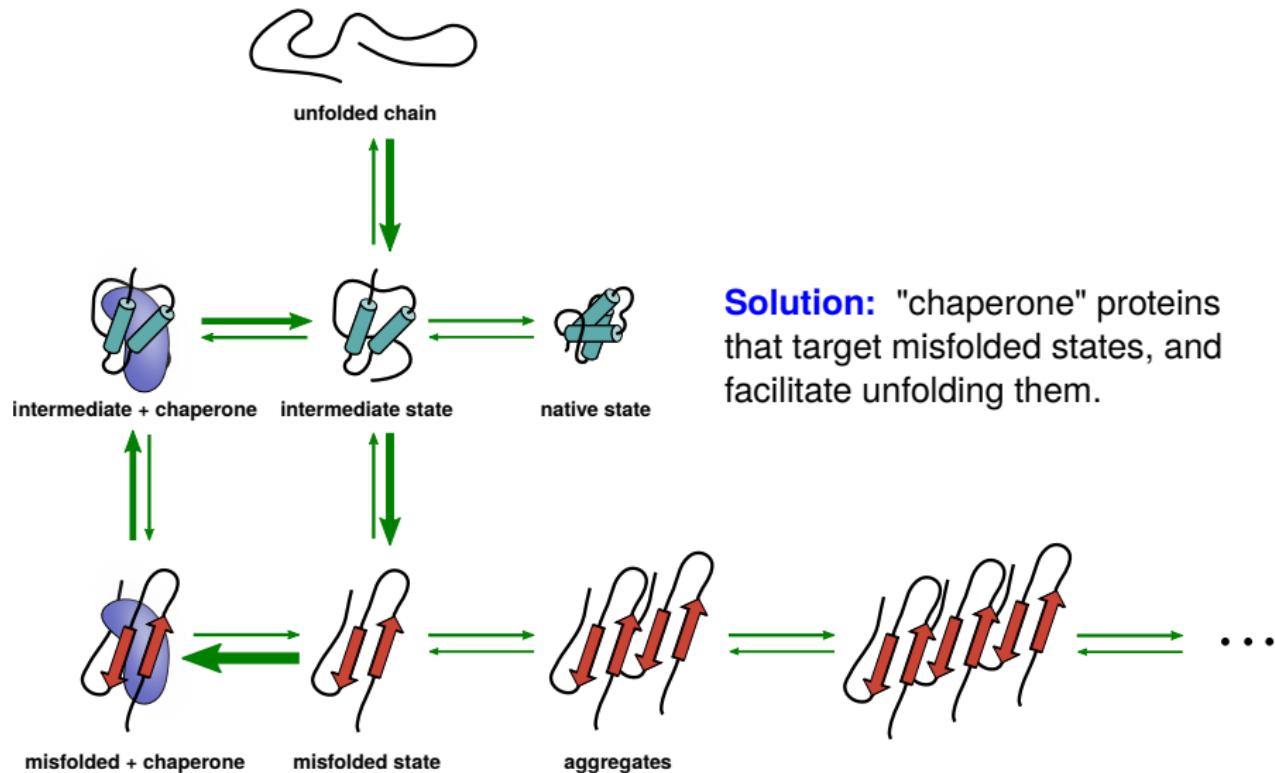
Being on the verge of melting gives proteins the **dynamical flexibility** essential for their diverse roles as enzymes.

But it also makes them highly vulnerable to changes in temperature (even of a few degrees): **heat shock**.

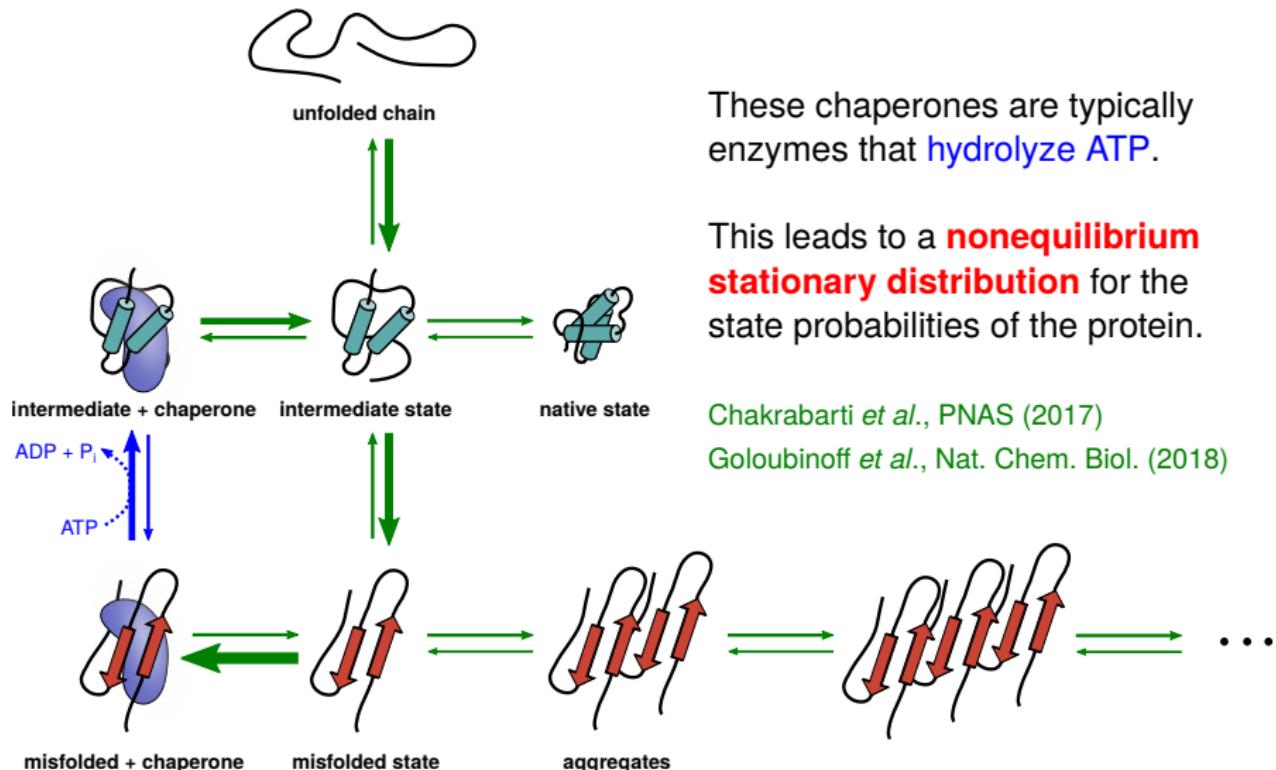
# Constant threats: misfolding and aggregation



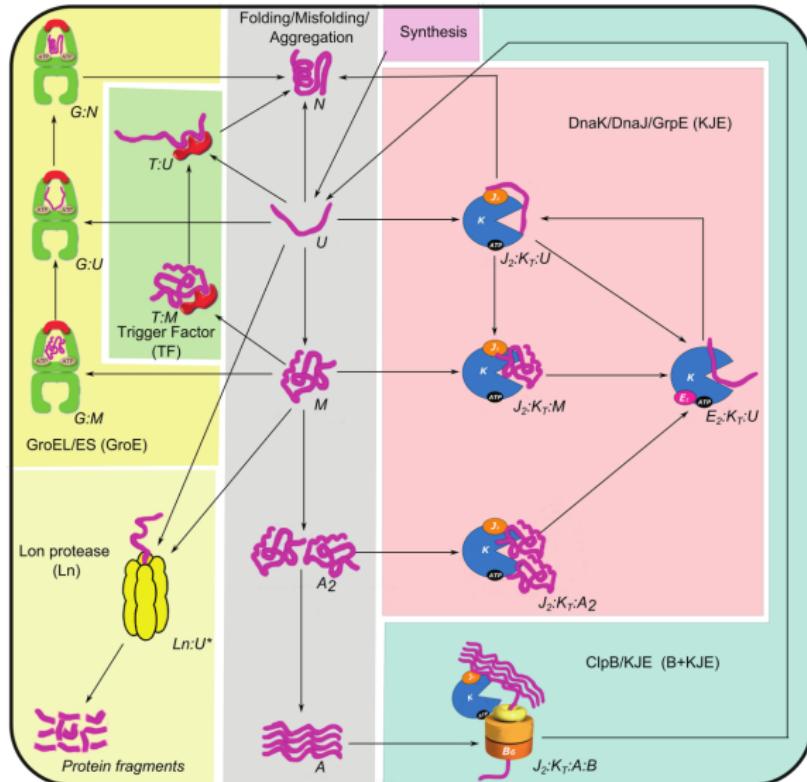
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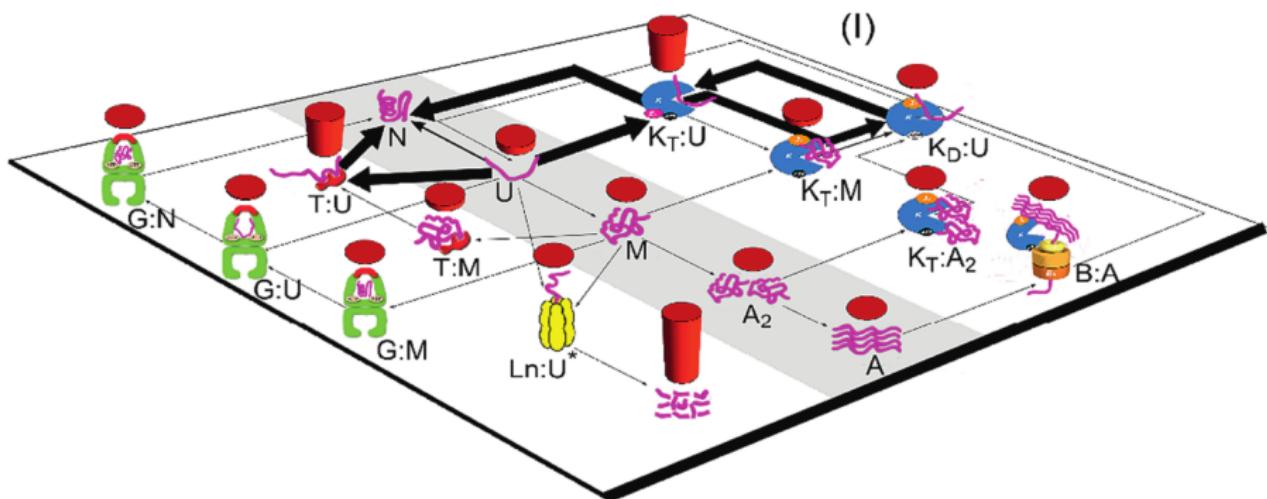
# The protein “hospital”: possible chaperone pathways



*E. coli* chaperone network: Santra *et al.*, PNAS (2017)

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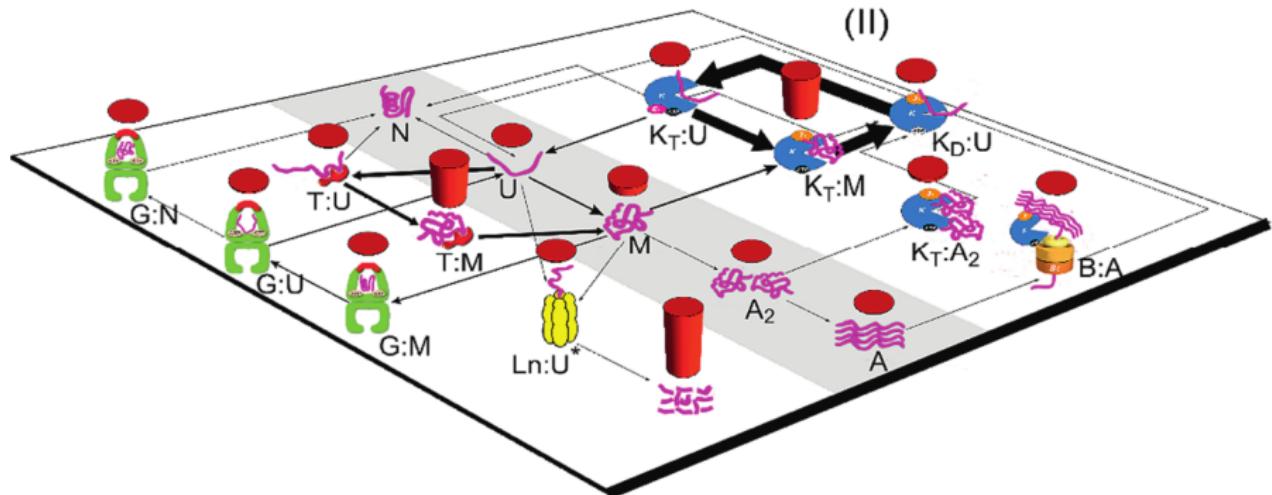
Different classes of proteins interact primarily with different chaperone sub-systems:



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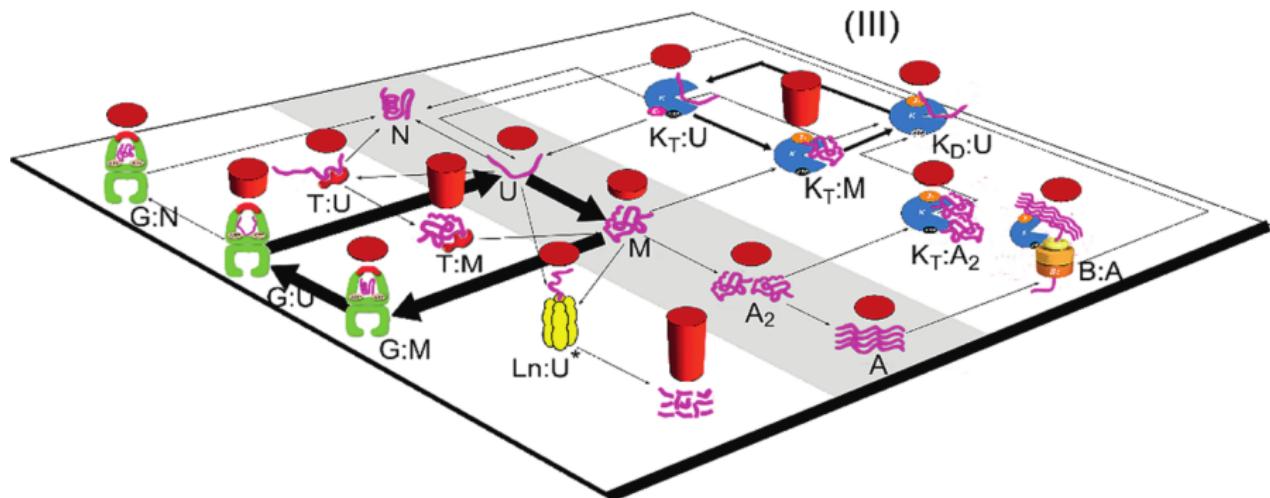
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# The protein “hospital”: possible chaperone pathways

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Under optimal growth conditions, chaperones are nearly fully occupied by “patient” proteins: spare capacity is too energetically costly.

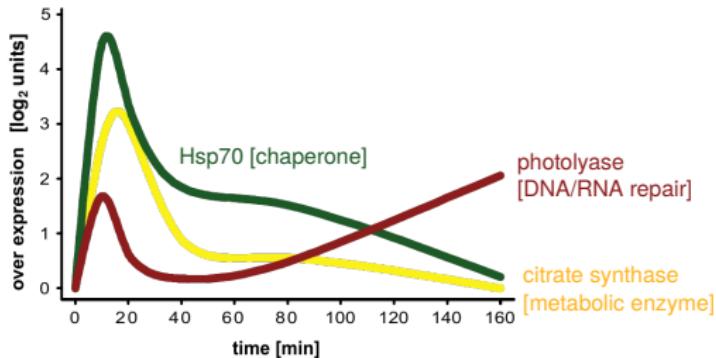
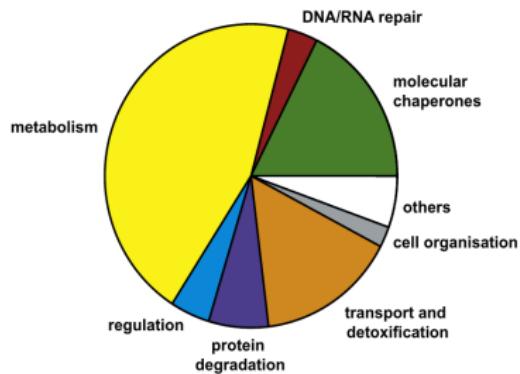
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Functional classes of upregulated genes in yeast after a heat shock from 25°C to 35°C over 10 min (out of total of 91 genes upregulated by more than 2.8x):

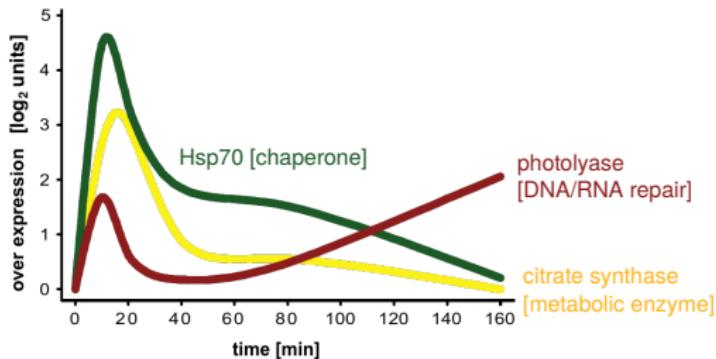
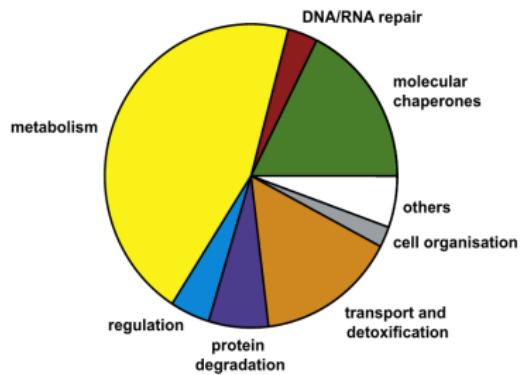


[Richter *et al.*, Molec. Cell (2010)]

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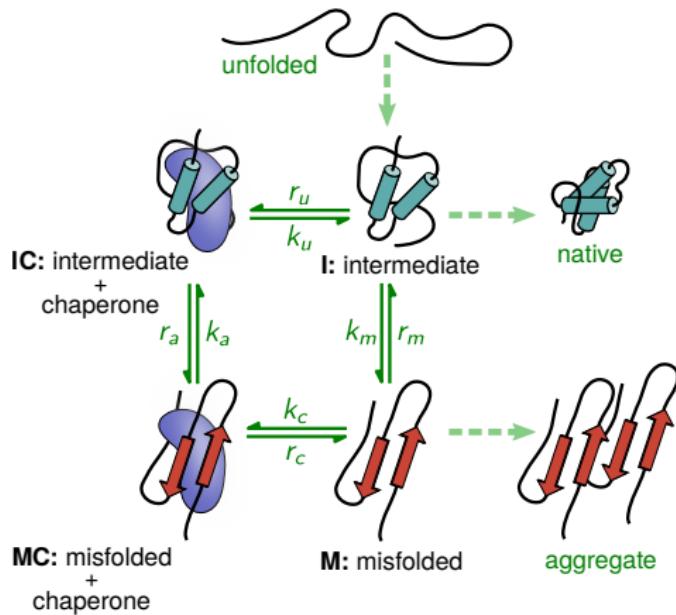
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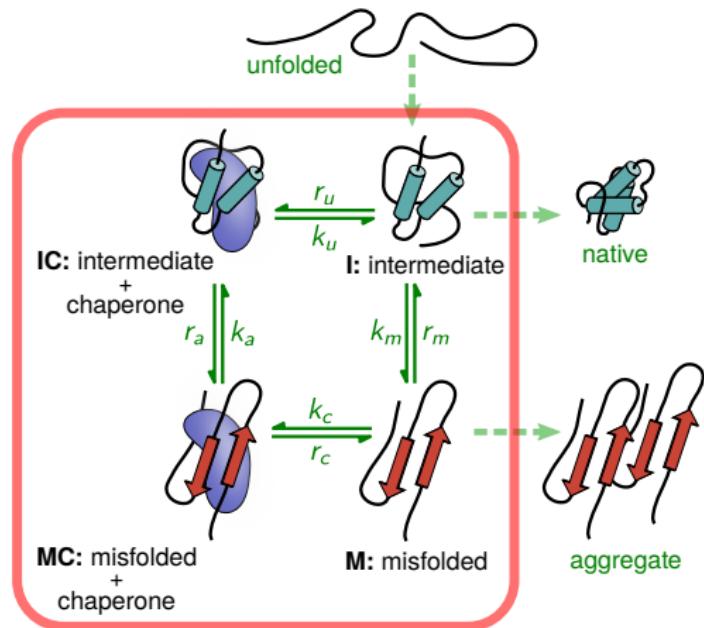
Can we understand this upregulation of chaperones using ideas from thermodynamic control?

# Markov model for chaperone-protein interaction



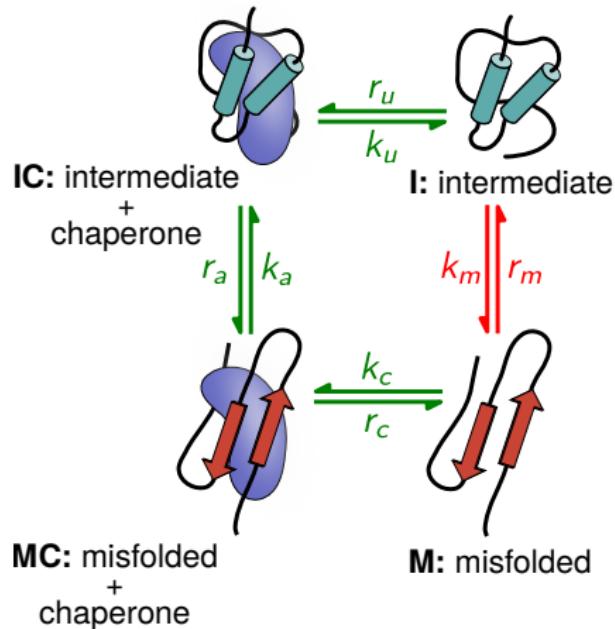
Using separation of timescales we can construct a simplified **Markov model** for a protein that tends to misfold under heat shock, focusing on four key states.

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# Markov model for chaperone-protein interaction



We assume the system is undergoing heat shock, where conditions favor the misfolded over the intermediate state:

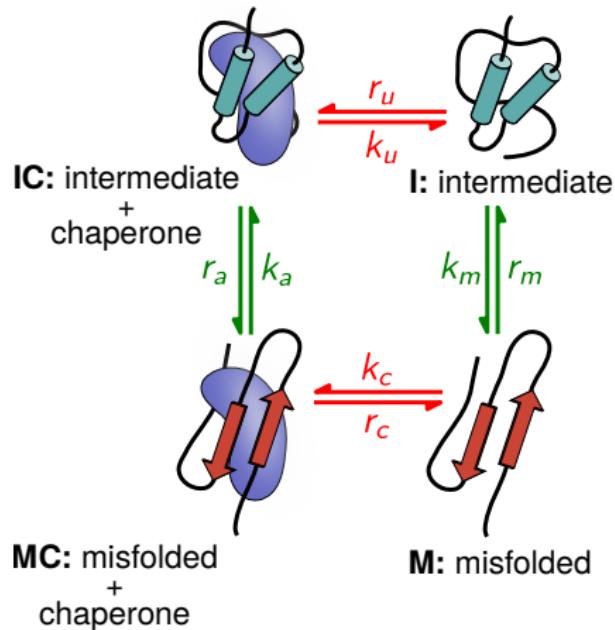
$$\frac{k_m}{r_m} = e^{\beta\epsilon} \gg 1$$

where  $\epsilon > 0$  is the free energy difference between the I and M states.

Typical parameter values:

$$k_m = 10 \text{ s}^{-1}, \epsilon = 10 k_B T$$

# Markov model for chaperone-protein interaction



Binding rates depend on free chaperone concentration  $C$ :

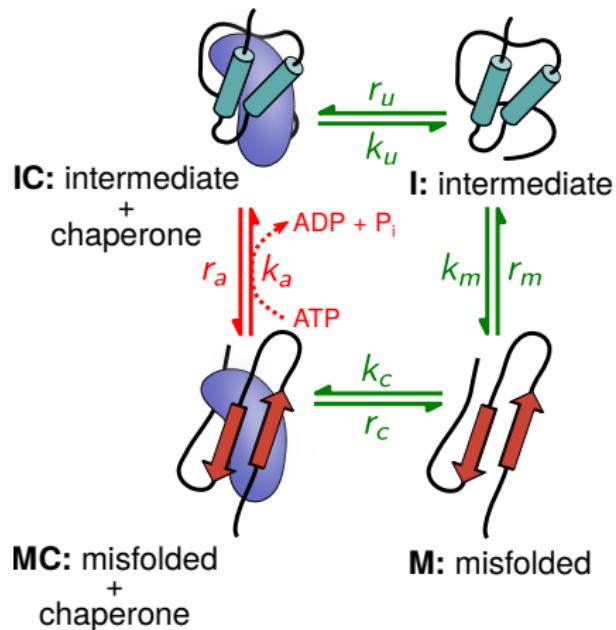
$$k_c = \gamma_c C, \quad r_u = \gamma_u C$$

where usually  $\gamma_c \gg \gamma_u$  (chaperone favors binding to misfolded states).

Typical parameter values:

$$\gamma_c = 10^6 \text{ M}^{-1}\text{s}^{-1}, \gamma_u = 10^4 \text{ M}^{-1}\text{s}^{-1},$$
$$r_c = 5 \times 10^{-3} \text{ s}^{-1}, k_u = 0.2 \text{ s}^{-1}$$

# Markov model for chaperone-protein interaction



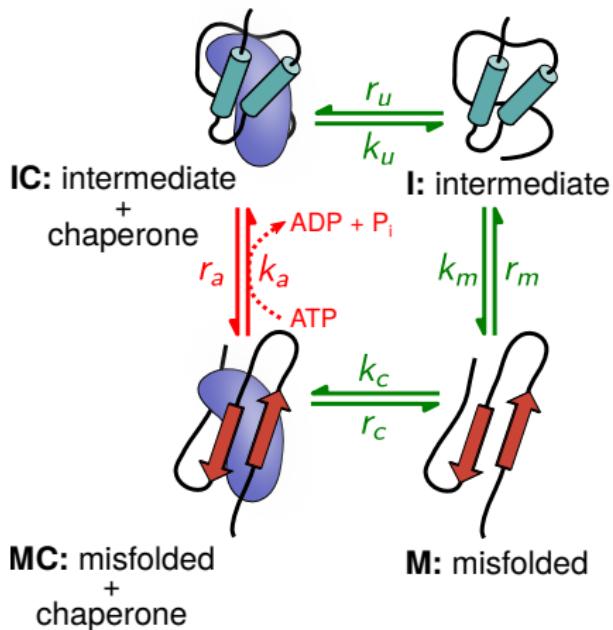
Chaperone-catalyzed reactions follow Michaelis-Menten kinetics that depend on **ATP concentration  $A$**  and **ADP concentration  $B$** :

$$k_a = \frac{k_{f,cat}A}{K_{f,M} + A}, \quad r_a = \frac{k_{r,cat}B}{K_{r,M} + B}$$

Typical parameter values:

$$k_{f,cat} = 10^{-2} \text{ s}^{-1}, K_{f,M} = 400 \mu\text{M},$$
$$A = 1 \text{ mM}, B = 0.1 \text{ mM}, \Delta\mu = 22 k_B T$$

# Markov model for chaperone-protein interaction



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Local detailed balance leads to two constraints: the “Haldane relation”,

$$\frac{k_{f,cat}K_{r,M}\gamma_c k_u}{k_{r,cat}K_{f,M}\gamma_u r_c} = e^{-\beta\epsilon}$$

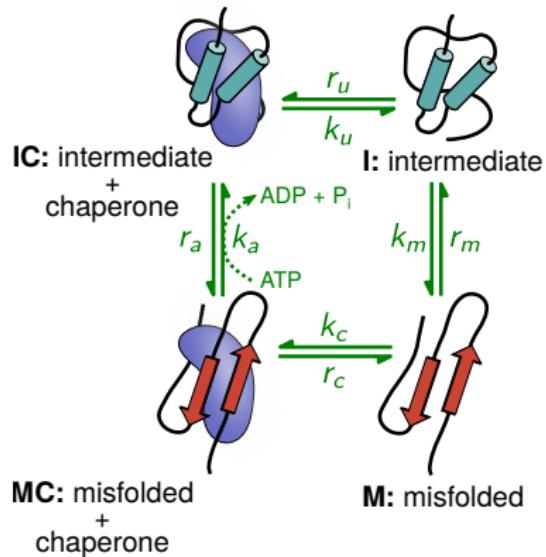
and

$$\frac{k_m\gamma_c k_a k_u}{r_m r_c r_a \gamma_u} = e^{\beta\Delta\mu}$$

where  $\Delta\mu = \Delta\mu_0 + k_B T \ln(A/B)$  is the ATP hydrolysis chemical potential.

# Markov model: dynamics

The state probabilities



$$\mathbf{p}(t) = (p_M(t), p_{MC}(t), p_{IC}(t), p_I(t))$$

obey the master equation

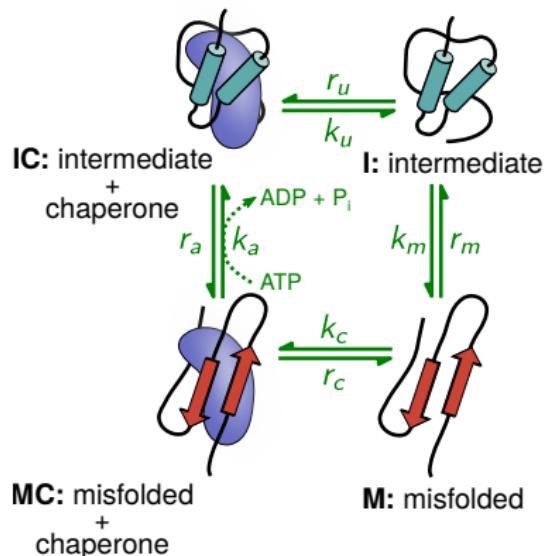
$$\dot{\mathbf{p}}(t) = \Omega \mathbf{p}(t)$$

with transition matrix

$$\Omega =$$

$$\begin{pmatrix} -k_c(C)-r_m & r_c & 0 & k_m \\ k_c(C) & -r_c-k_a(A) & r_a(B) & 0 \\ 0 & k_a(A) & -r_a(B)-k_u & r_u(C) \\ r_m & 0 & k_u & -k_m-r_u(C) \end{pmatrix}$$

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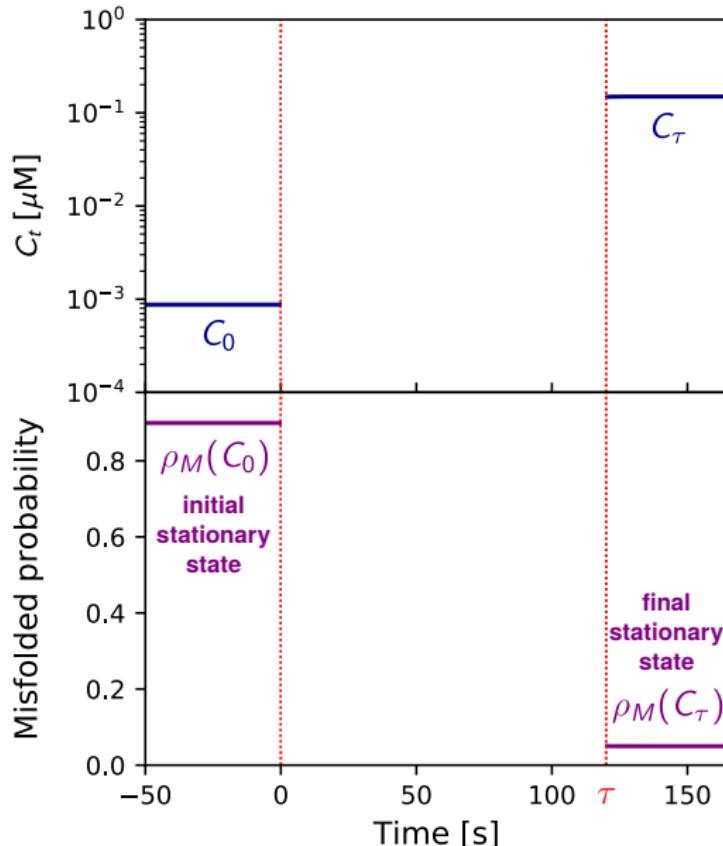
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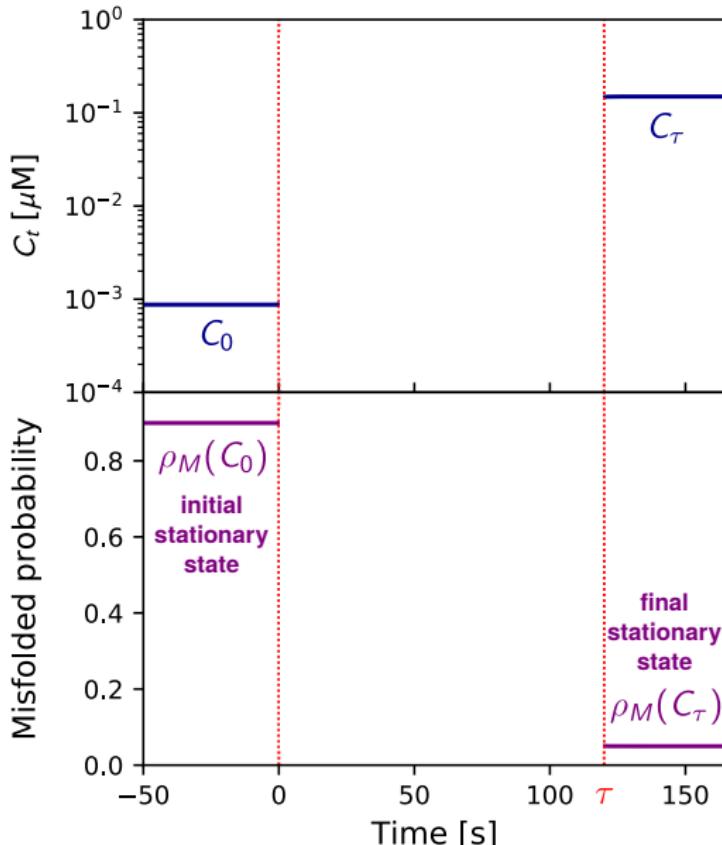
For given  $A, B, C$ , the **stationary distribution**  $\rho$  satisfies:  $\Omega\rho = 0$ .

# Chaperone upregulation as a control problem



Right after heat shock,  
system relaxes quickly to  
stationary state for free  
chaperone concentration  $C_0$ .

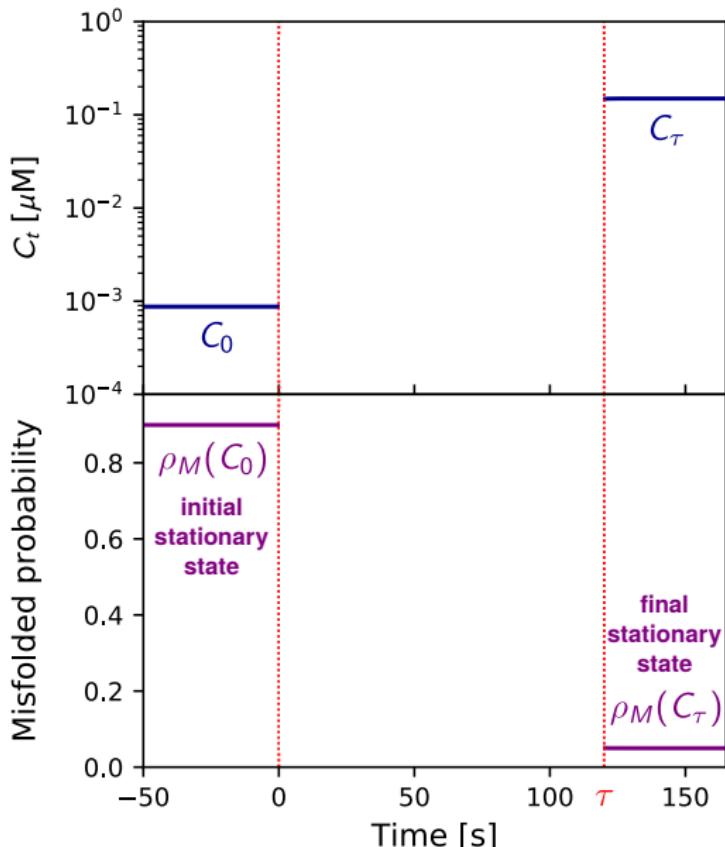
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There are insufficient chaperones available, so probability of being misfolded is high.

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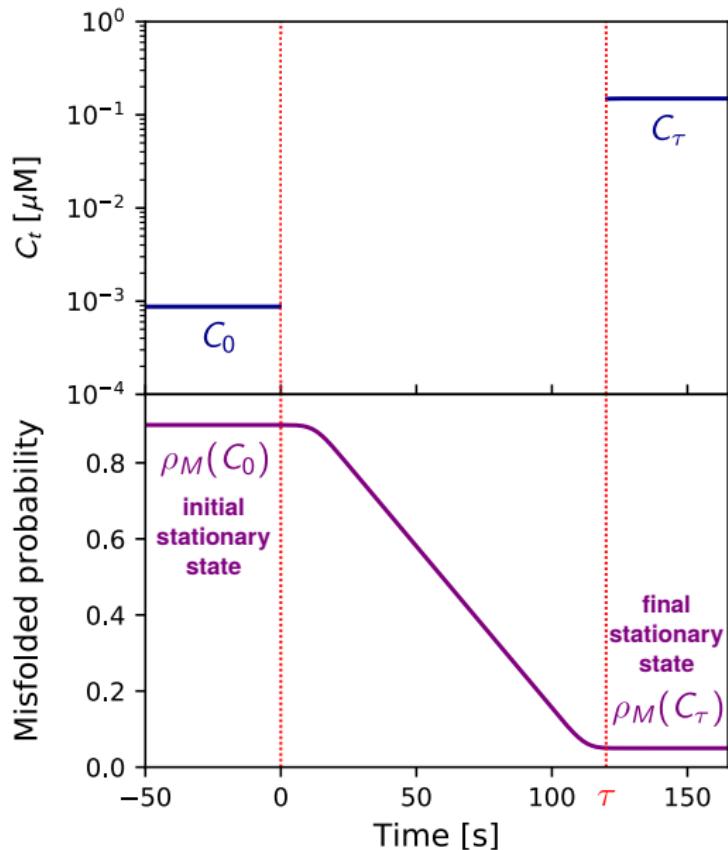


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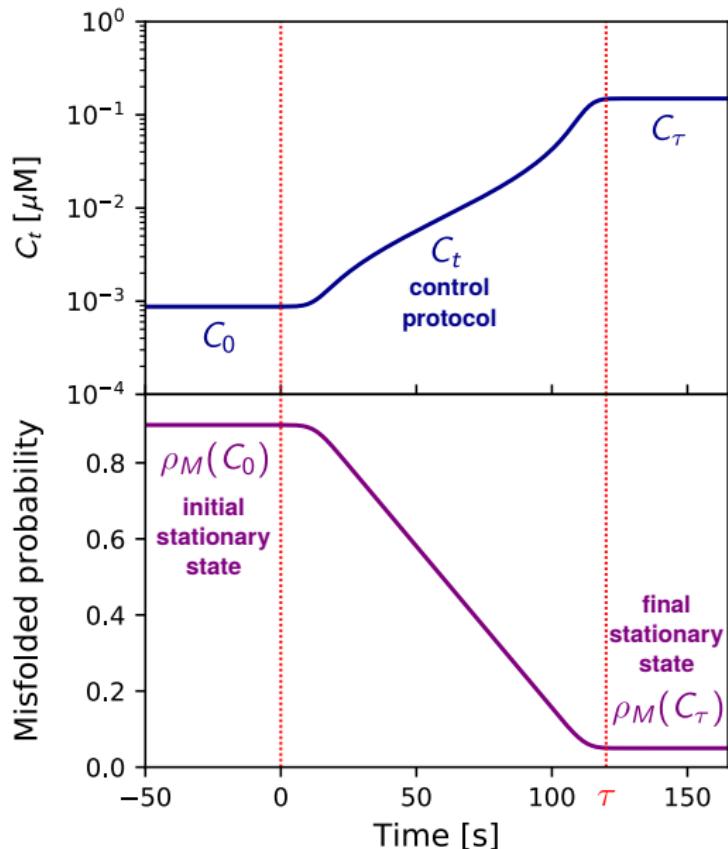
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We would like to drive the system to a new stationary state with less misfolding by increasing chaperone concentration to some  $C_\tau$ .

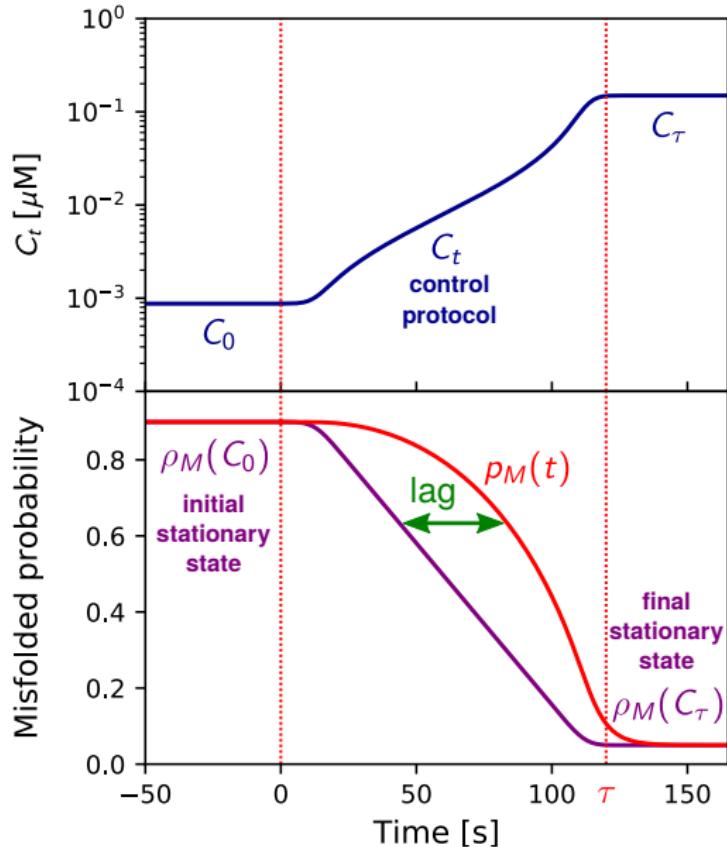
# Chaperone upregulation as a control problem



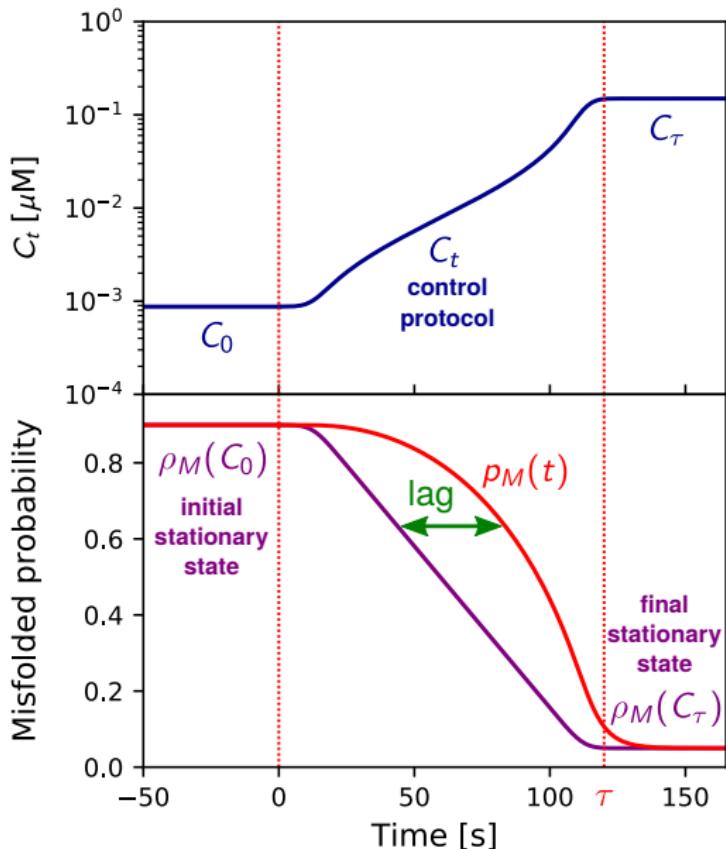
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For a given  $\rho_M(C_t)$ , can we effectively eliminate the lag, so that  $p_M(t) = \rho_M(C_t)$  at all  $t$ ?

Answer: Yes, via a counterdiabatic protocol.

# Counterdiabatic protocols for Markov models

## Ingredients:

- ▶  $N$  state Markov model with transition matrix  $\Omega(\lambda_t)$  that depends on time-dependent control parameter(s)  $\lambda_t$  for  $0 \leq t \leq \tau$

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$$\Omega(\lambda_t)\rho(\lambda_t) = 0$$

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$$\dot{\rho}(t) = \Omega(\lambda_t)\rho(t)$$

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**Problem:** Find counterdiabatic transition matrix  $\tilde{\Omega}(\lambda_t, \dot{\lambda}_t)$  such that  $\rho(\lambda_t)$  is a solution to the new master equation:

$$\dot{\rho}(\lambda_t) = \tilde{\Omega}(\lambda_t, \dot{\lambda}_t)\rho(\lambda_t)$$

## Solving the CD problem

**Solution:** Infinitely many CD solutions for  $\tilde{\Omega}(\lambda_t, \dot{\lambda}_t)$ . But most of them may be physically unrealizable in a given system.

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In our case, the external control parameter is  $\lambda_t = C_t$ , and we work in the limit of large  $k_m$ , small  $r_a$ , so  $\Omega(C_t)$  is approximately:

$$\Omega(C_t) \approx \begin{pmatrix} -k_c(C_t) - r_m & r_c & 0 & k_m \\ k_c(C_t) & -r_c - k_a(A) & 0 & 0 \\ 0 & k_a(A) & -k_u & r_u(C_t) \\ r_m & 0 & k_u & -k_m - r_u(C_t) \end{pmatrix}$$

Really only two knobs for control:

- ▶ free chaperone concentration  $C_t$
- ▶ ATP concentration  $A$  (fixed in original protocol)

# Solving the CD problem

Approximate CD solution  $\tilde{\Omega}(C_t, \dot{C}_t)$  takes the form:

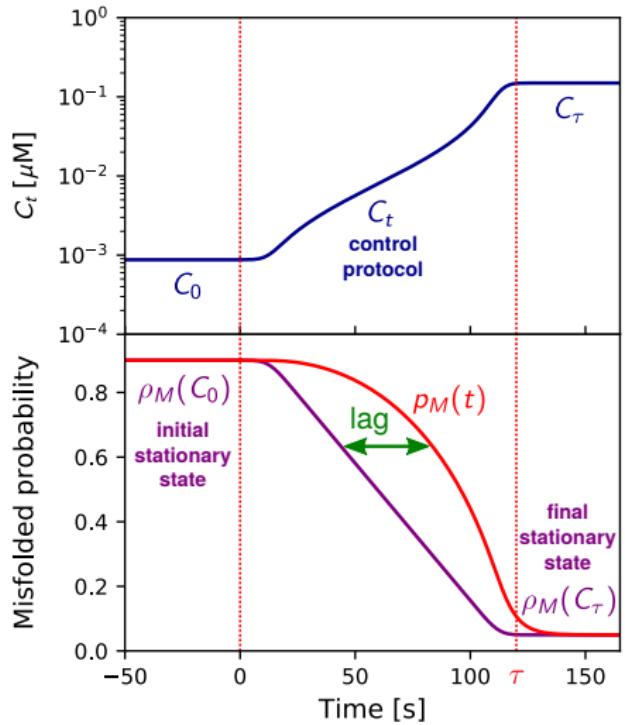
$$\tilde{\Omega}(C_t, \dot{C}_t) \approx \begin{pmatrix} -k_c(\tilde{C}_t) - r_m & r_c & 0 & k_m \\ k_c(\tilde{C}_t) & -r_c - k_a(\tilde{A}_t) & 0 & 0 \\ 0 & k_a(\tilde{A}_t) & -k_u & r_u(\tilde{C}_t) \\ r_m & 0 & k_u & -k_m - r_u(\tilde{C}_t) \end{pmatrix}$$

where

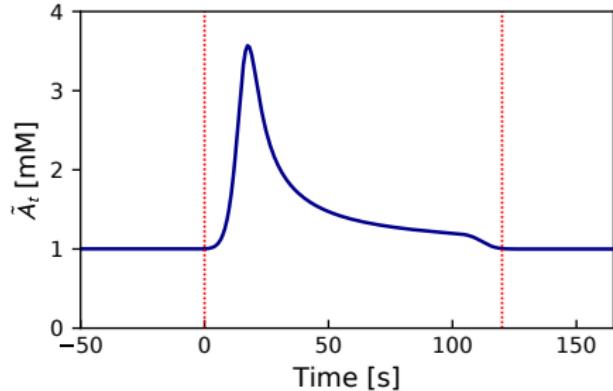
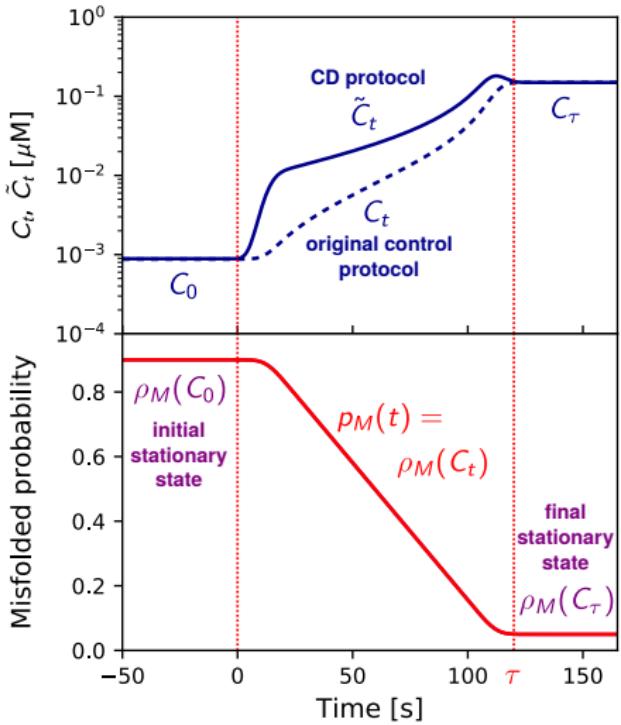
$$\tilde{C}_t \approx C_t - \underbrace{\frac{\dot{C}_t}{\gamma_c} \frac{d}{dC_t} \ln \rho_M(C_t)}_{\text{CD correction term}}$$

$$k_a(\tilde{A}_t) = \frac{k_{f,\text{cat}} \tilde{A}_t}{K_{f,M} + \tilde{A}_t} \approx k_a(A) - \underbrace{\frac{k_a(A) \rho_M(t) \dot{C}_t}{k_u(1 - \rho_M(t))} \frac{d}{dC_t} \ln \rho_M(C_t)}_{\text{CD correction term}}$$

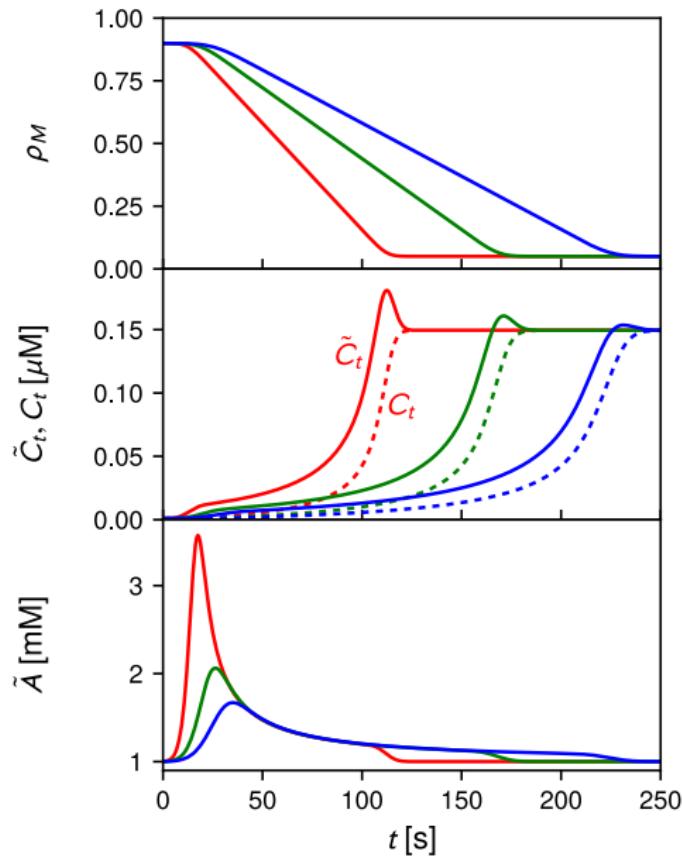
# CD protocol



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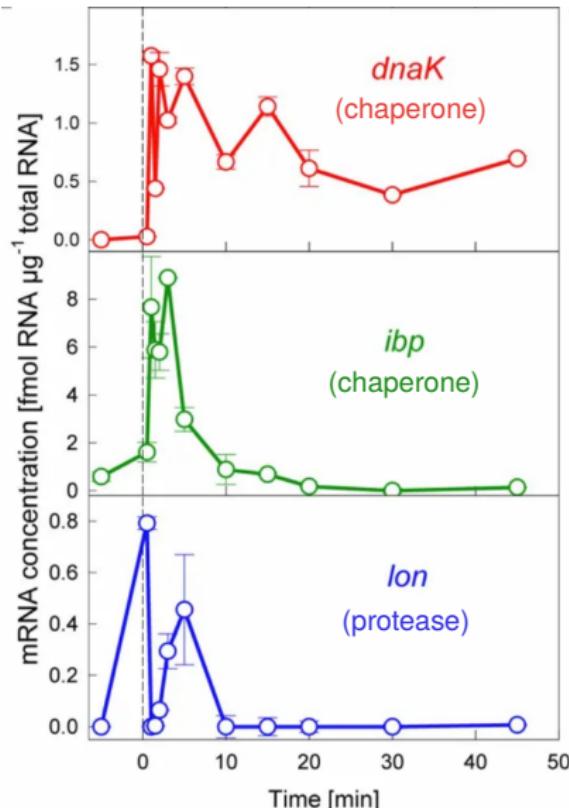
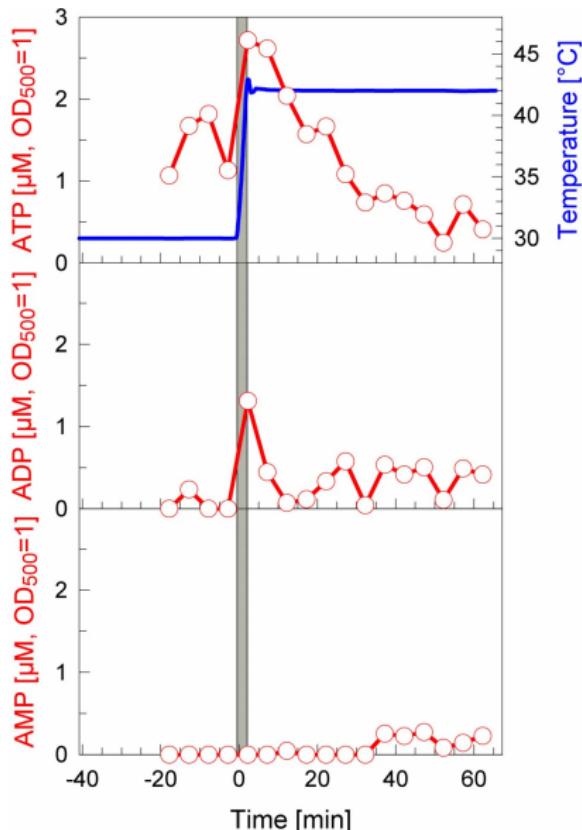


# CD protocols for different $\tau$



# Experimental data: *E. coli* heat shock response

Data from: Soini *et al.*, *Microb. Cell Fact.* (2005)



## Extension: from discrete states to the continuum

$\cdots \rightleftharpoons O \rightleftharpoons O \rightleftharpoons O \rightleftharpoons O \rightleftharpoons \cdots$

Markov dynamics on chain of states  
⇒ continuum Fokker-Planck description

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⇒ continuum Fokker-Planck description

- We can recover Fokker-Planck counterdiabatic solution of Patra & Jarzynski, New J. Phys. (2017).

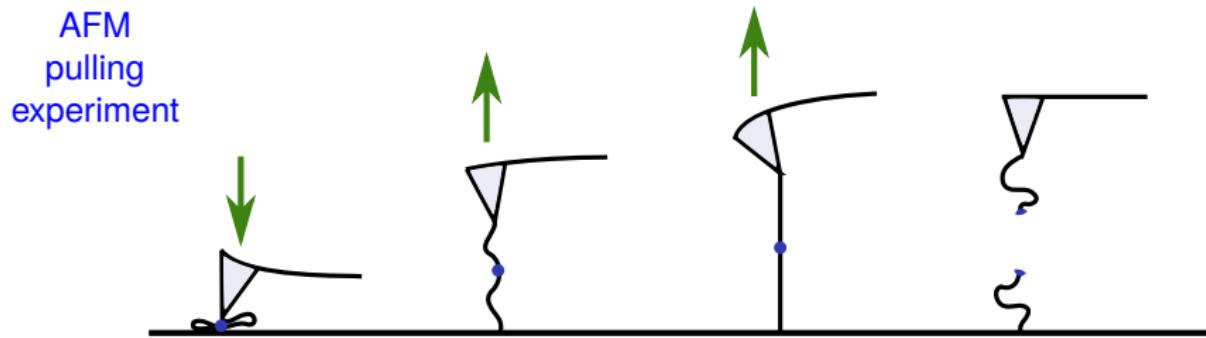
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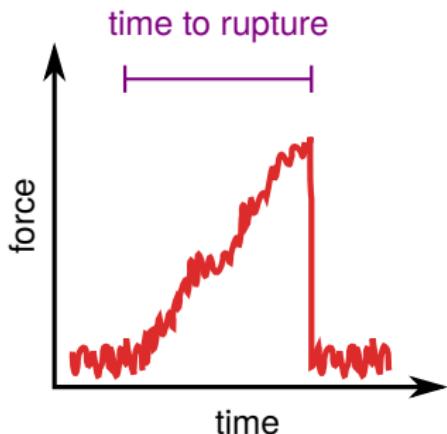
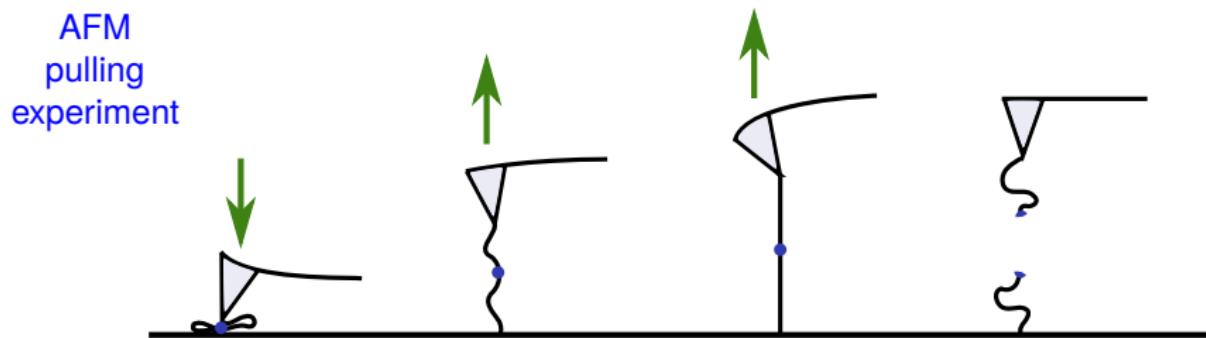
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- Generalize solution to problems with position-dependent diffusivity (i.e. population genetics, force spectroscopy)

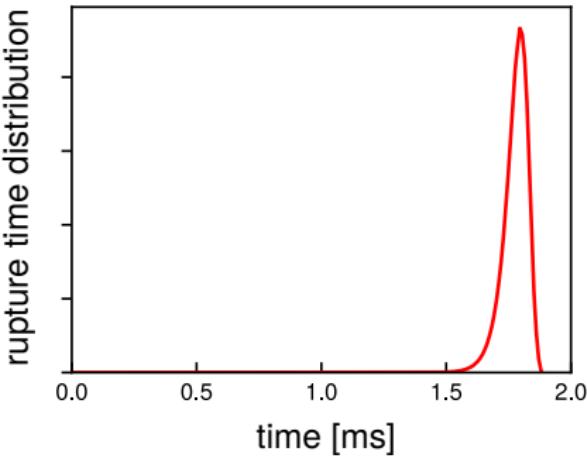
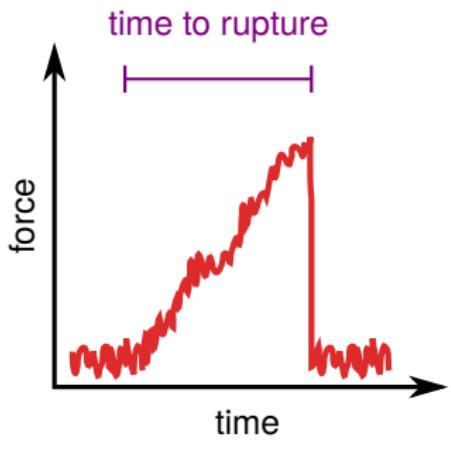
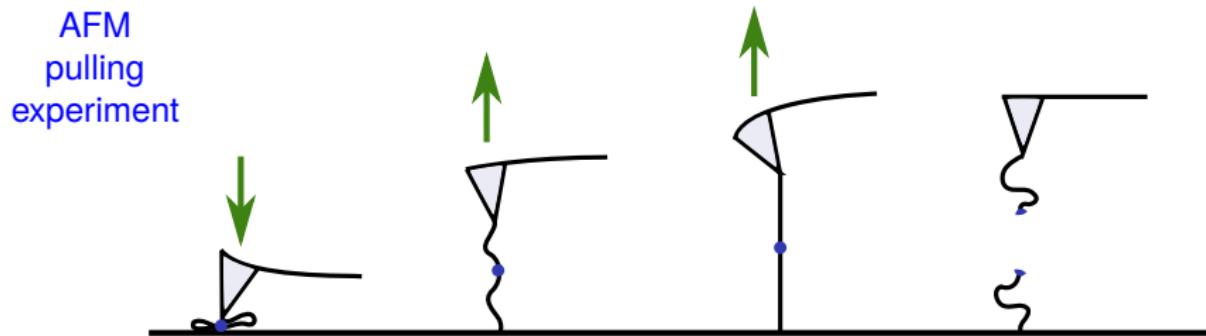
# AFM force spectroscopy to study biomolecular complexes



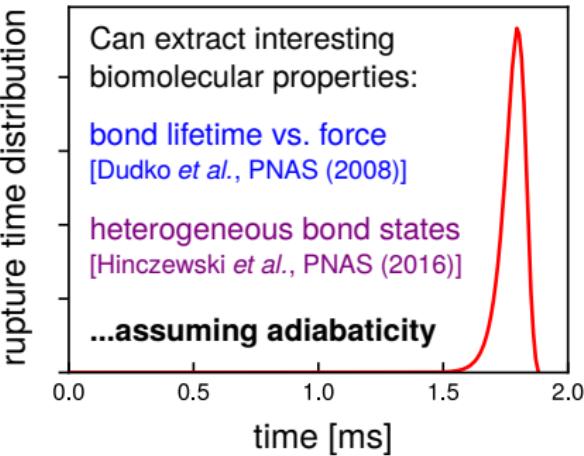
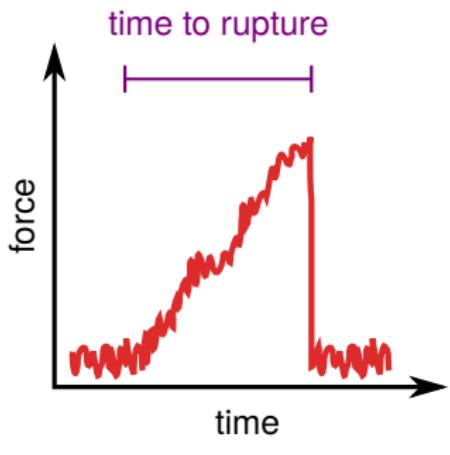
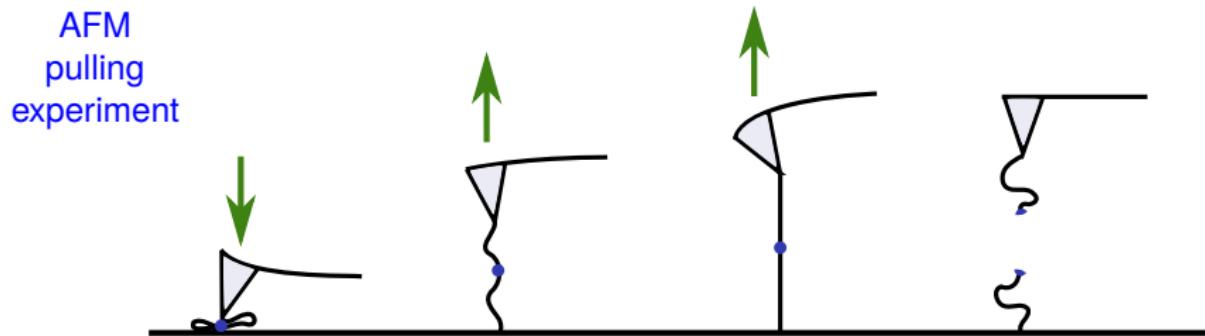
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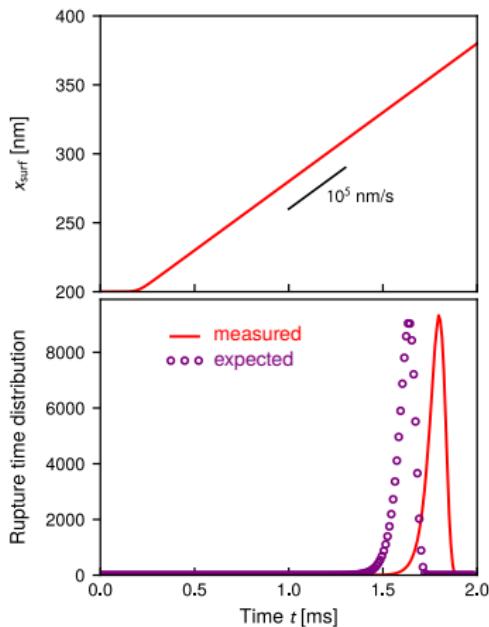
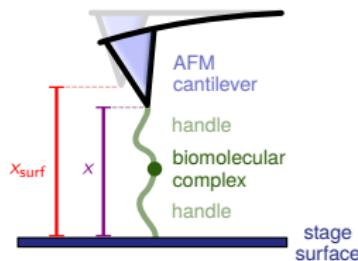
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# Counterdiabatic driving to correct nonadiabatic artifacts



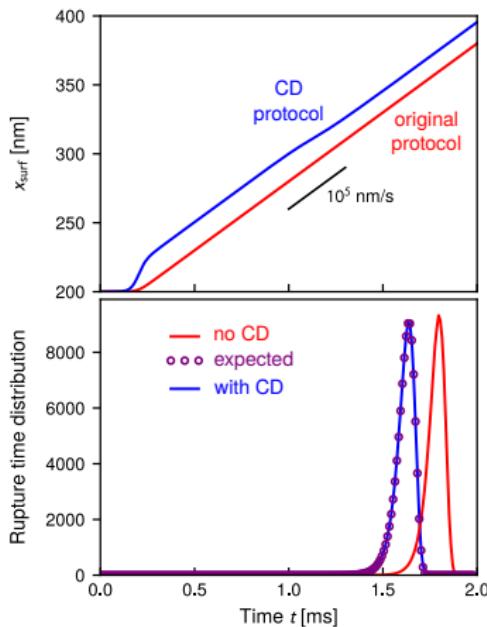
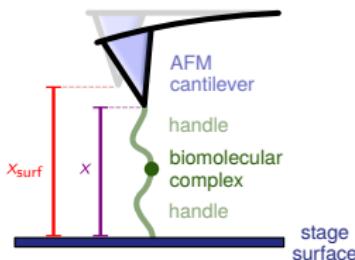
Fast pulling leads to rupture distributions far from those predicted by adiabatic theories.

Parameter extraction for bond lifetime vs. force:

$$\tau(F) = \tau_0 \exp(-dF)$$

	$\tau_0$ [s]	$d$ [nm]
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with CD:	9.74	0.40

CD protocol just depends on measurable properties of the AFM cantilever and handles, independent of the complex.

## Future work

Testing these ideas out experimentally:

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Testing these ideas out experimentally:

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- ▶ Analogous methods should work for any enzymatic reaction cycle: a “straightforward” proof-of-principle experiment?
- ▶ Validating the AFM pulling CD protocol.

# Counterdiabatic protocols for Markov models

Solution:

$$\tilde{\Omega}_{ij}(\lambda_t, \dot{\lambda}_t) = \hat{\Omega}_{ij}(\lambda_t, \dot{\lambda}_t) \Gamma_j(\lambda_t, \dot{\lambda}_t)$$

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**Step 1:** Construct  $\hat{\Omega}_{ij}$ ,

$$\hat{\Omega}_{ij}(\lambda_t, \dot{\lambda}_t) = \tilde{M}_{ij}(\lambda_t, \dot{\lambda}_t) / \rho_j(\lambda_t)$$

where  $\tilde{M}$  is an arbitrary matrix with positive off-diagonal elements where each row and each column sum to zero. Each choice of  $\tilde{M}$  corresponds to a distinct CD protocol.

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Here  $\hat{\Omega}^\times$  is the Drazin pseudoinverse of  $\hat{\Omega}$ , which satisfies:

$$\hat{\Omega}^\times(\lambda_t, \dot{\lambda}_t) \hat{\Omega}(\lambda_t, \dot{\lambda}_t) = I - \rho(\lambda_t) \mathbf{e}^T$$

where  $I$  is the identity matrix and  $\mathbf{e}_i = 1$  for all  $i$ .  $\Gamma_0$  is uniquely specified by enforcing the condition:

$$\sum_{i=1}^N \frac{\rho_i(\lambda_t)}{\Gamma_i(\lambda_t, \dot{\lambda}_t)} = 1$$

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- **Controllability:** some elements of  $\tilde{M}_{ij}$  may not be amenable to external control (i.e. the corresponding elements  $\tilde{\Omega}$  cannot be varied).