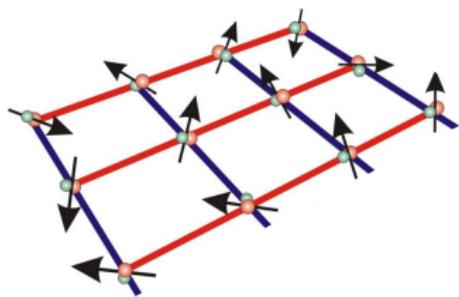


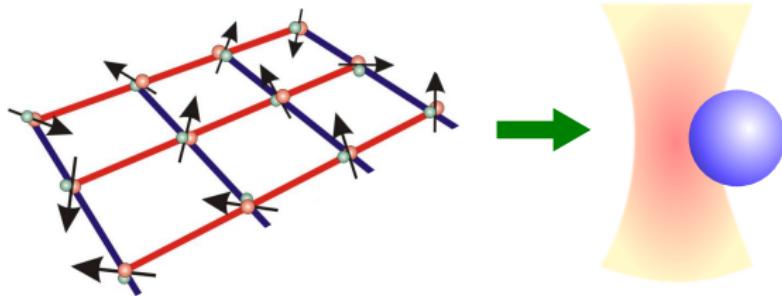
Shortcuts to adiabaticity



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

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

Shortcuts to adiabaticity



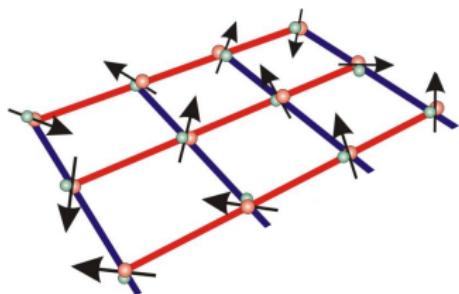
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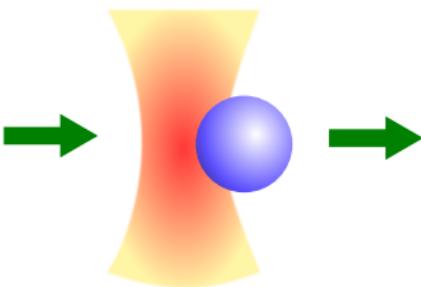
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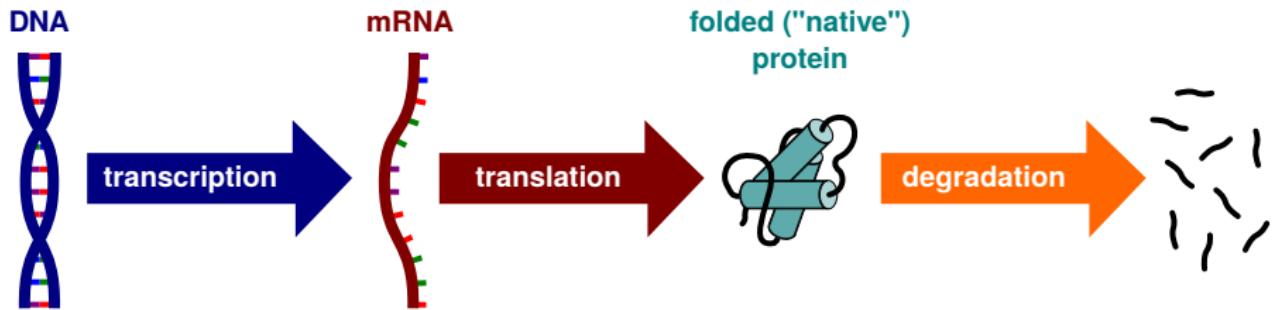
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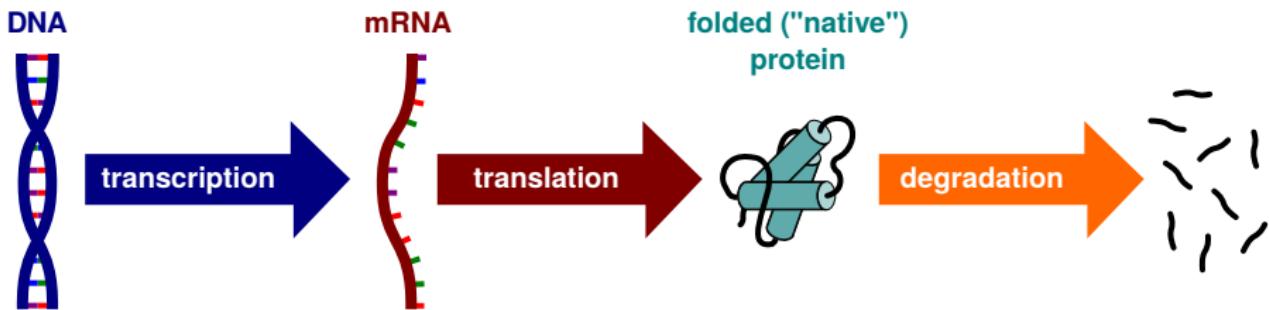


**Possible biological
applications:**
population genetics
molecular chaperones
force spectroscopy

Traditional view of protein production



Traditional view of protein production



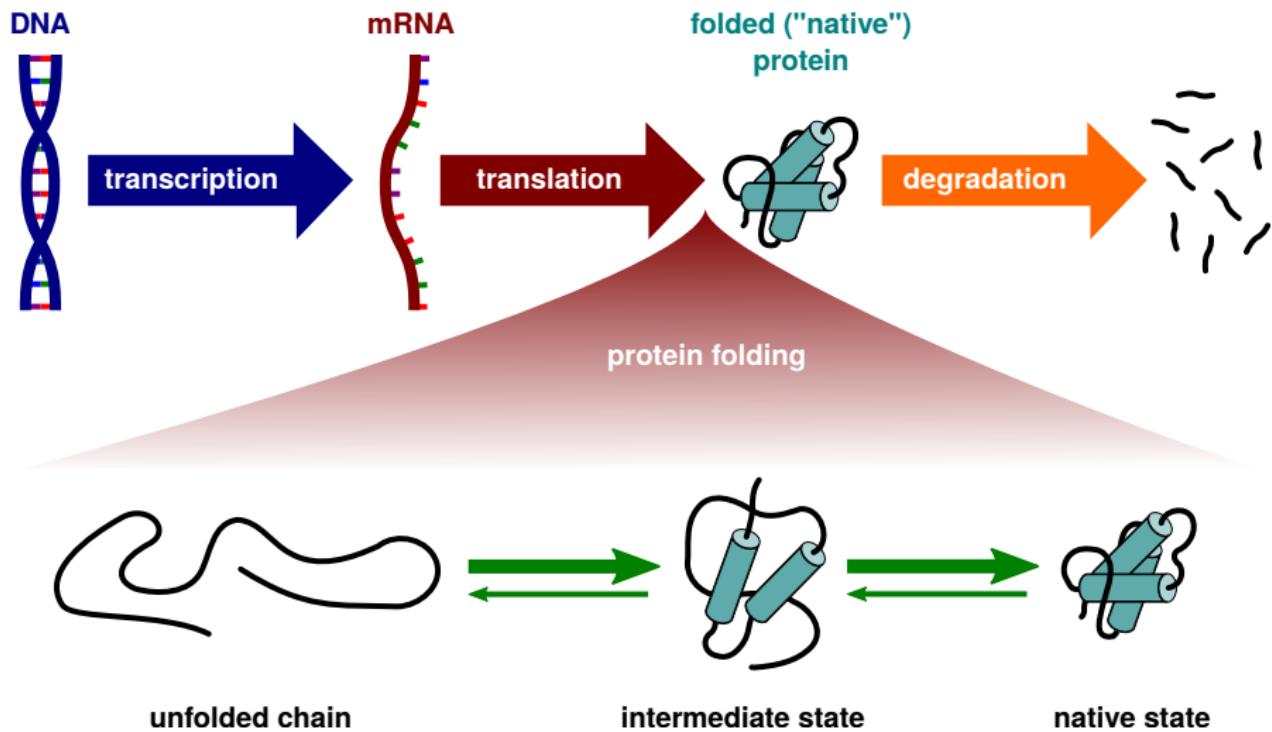
All these processes involve nonequilibrium reaction networks driven by ATP hydrolysis.

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

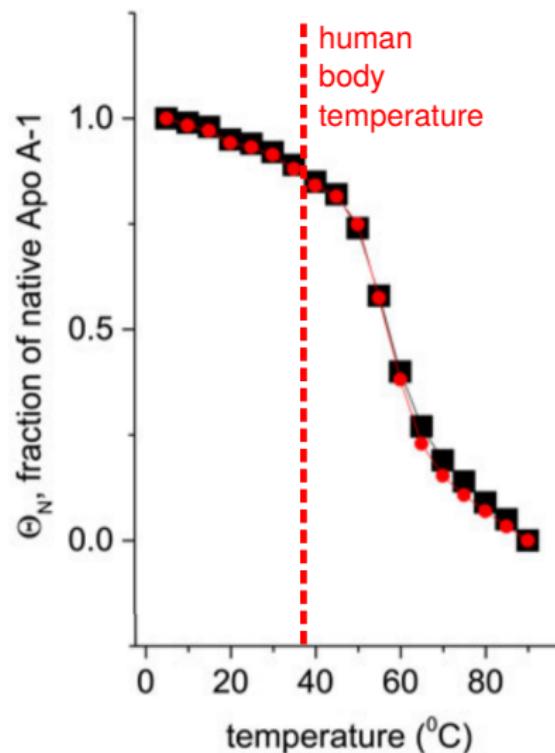
Ilker & Hinczewski, Phys. Rev. Lett. (2019)

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

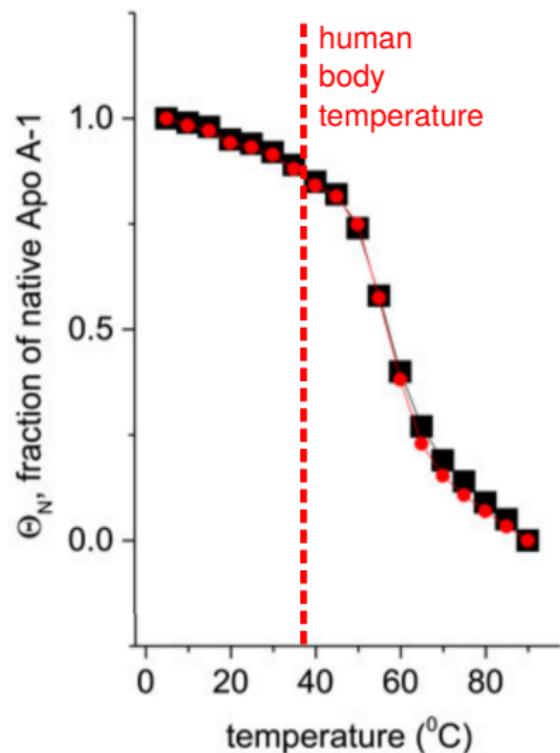
Traditional view of protein production



Proteins function at the cliff edge of unfolding

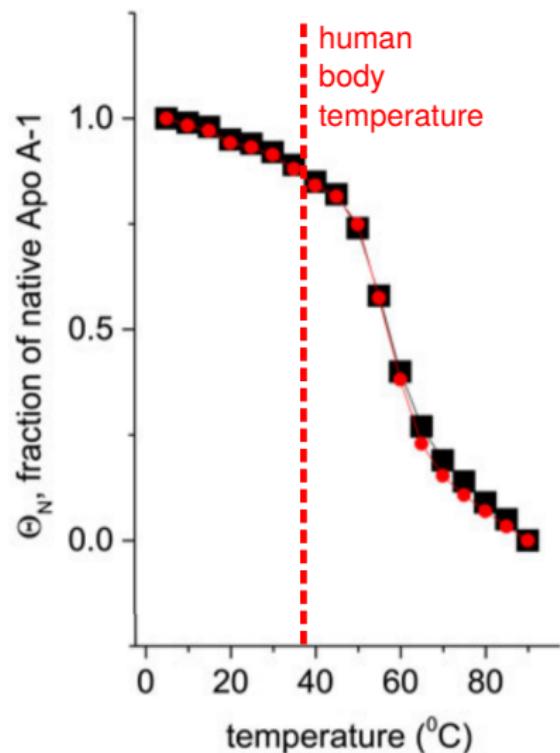


Proteins function at the cliff edge of unfolding



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

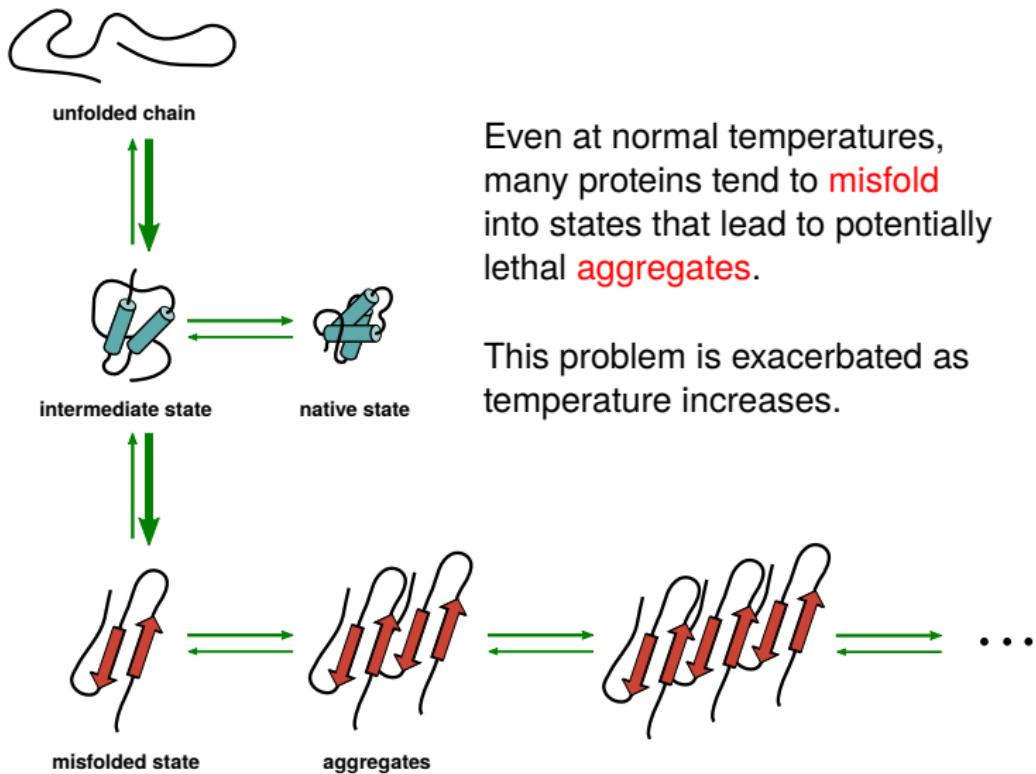
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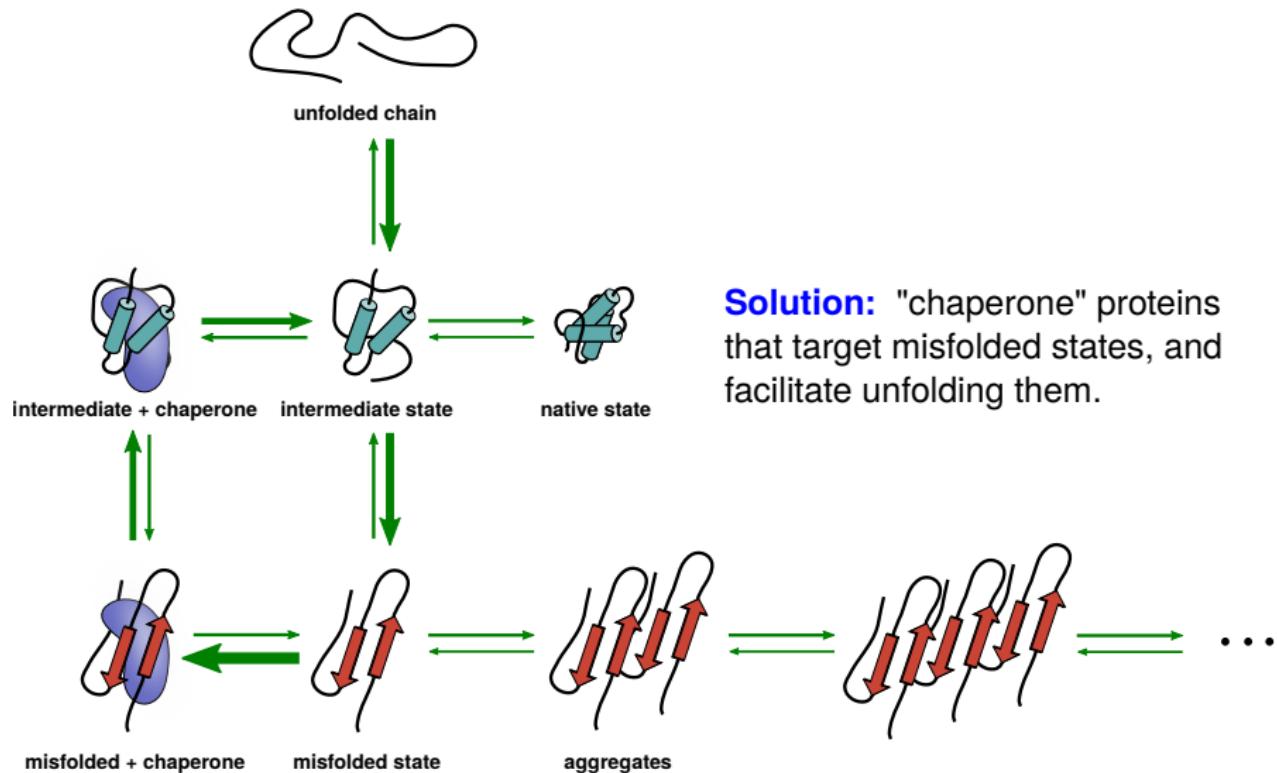
Being on the verge of melting gives proteins the **dynamical flexibility** essential for their diverse roles as enzymes.

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

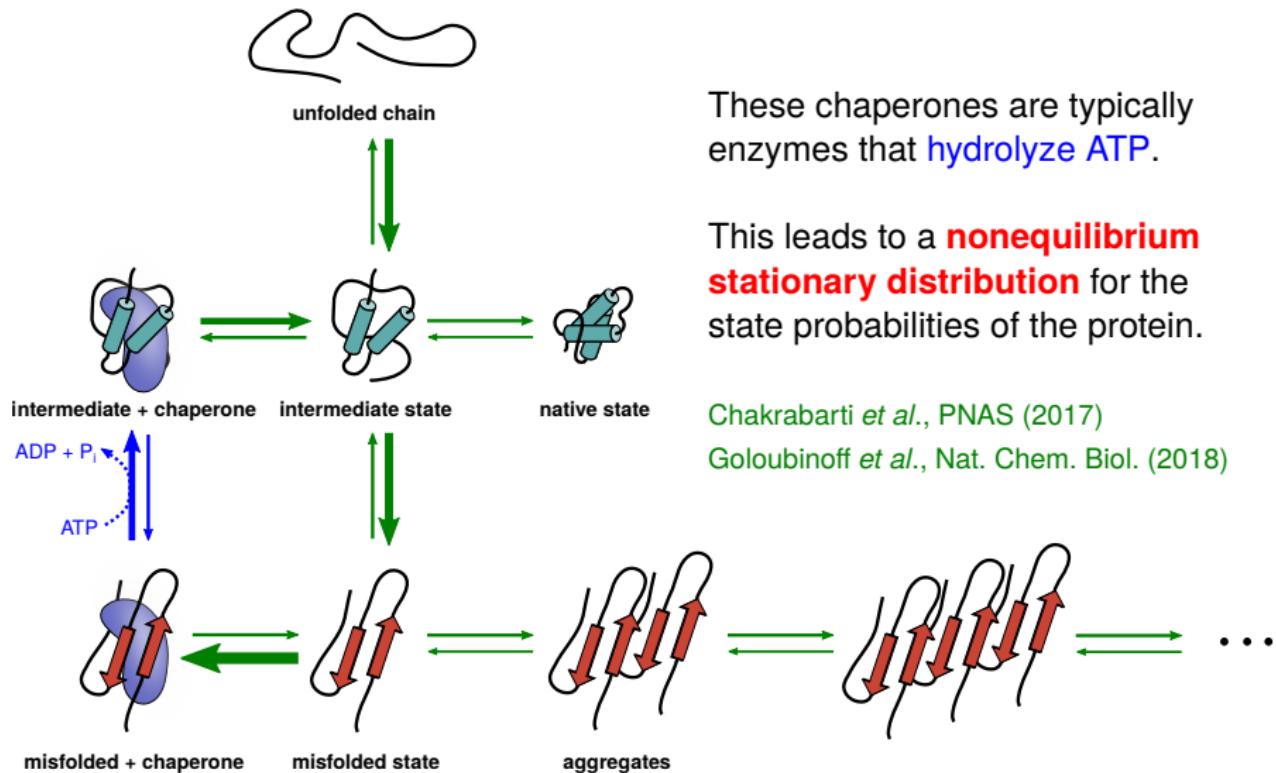
Constant threats: misfolding and aggregation



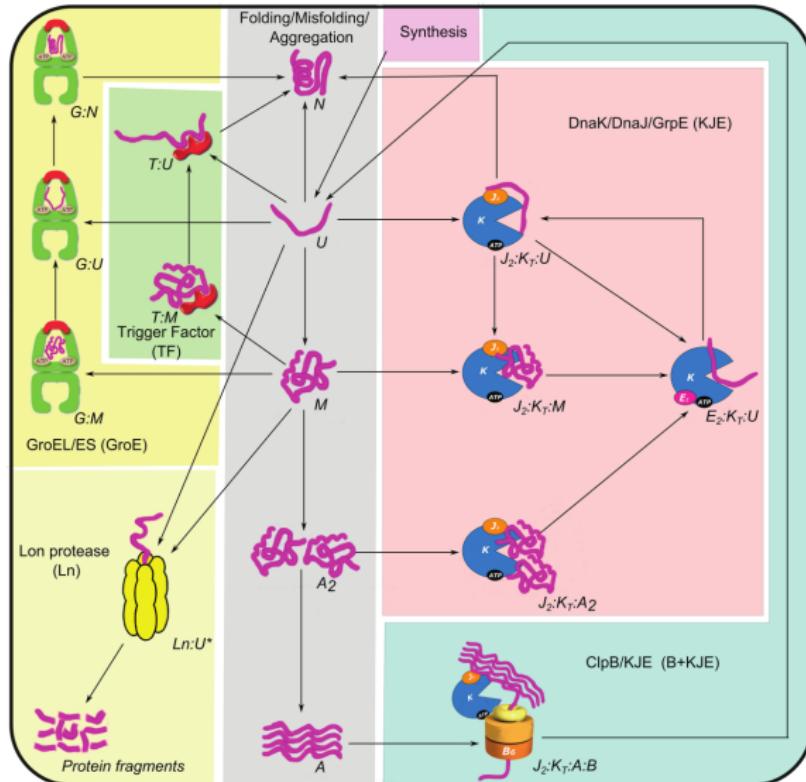
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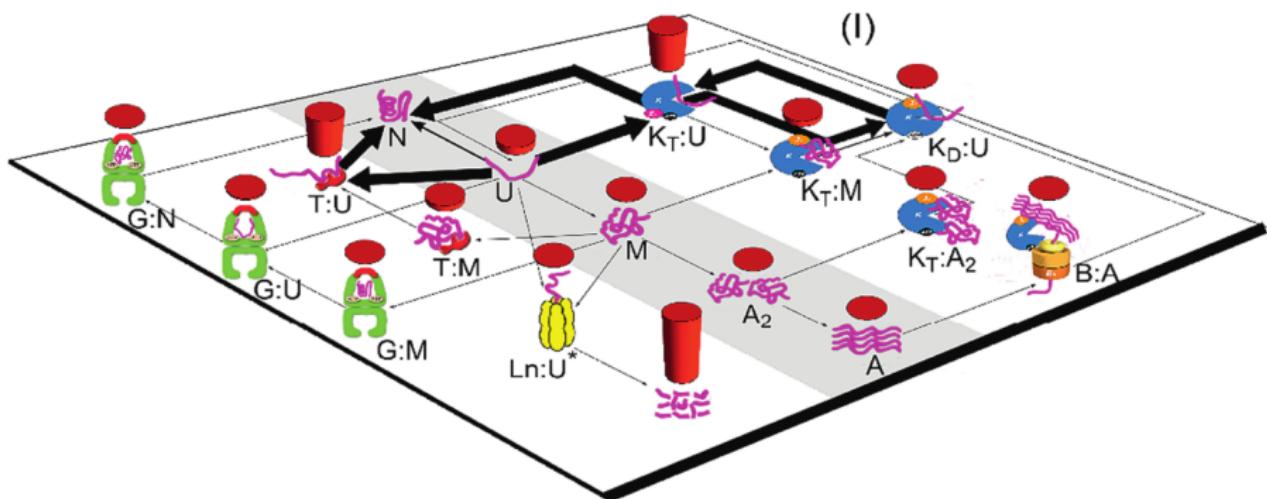
The protein “hospital”: possible chaperone pathways



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

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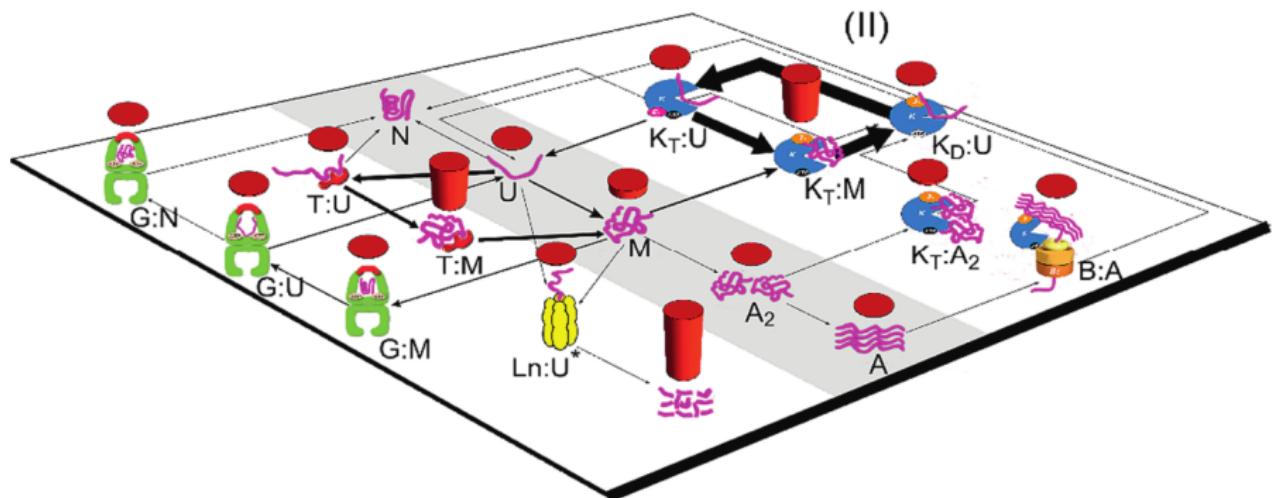
Different classes of proteins interact primarily with different chaperone sub-systems:



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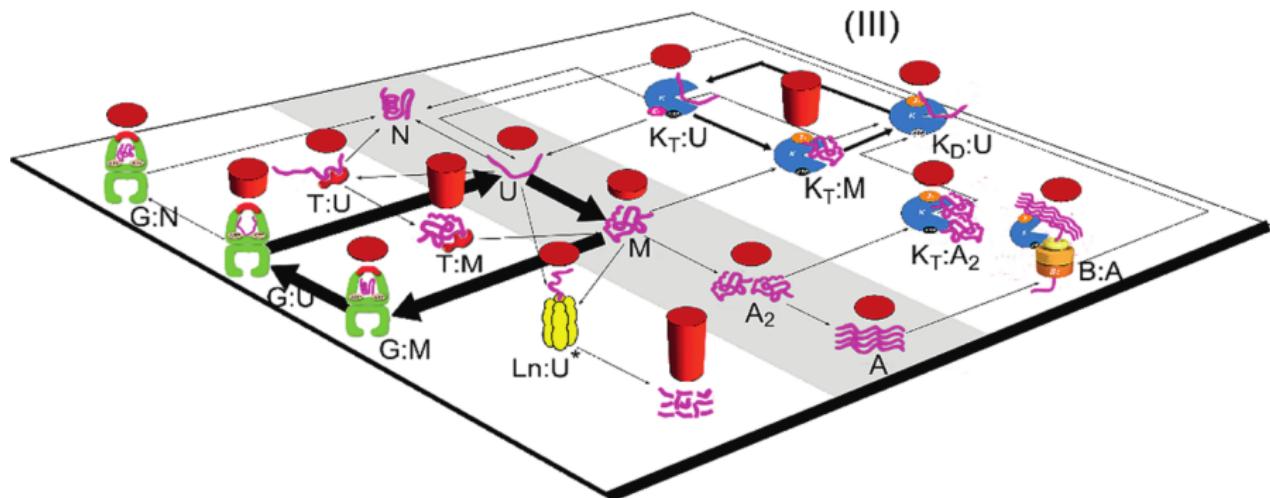
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Under optimal growth conditions, chaperones are nearly fully occupied by “patient” proteins: spare capacity is too energetically costly.

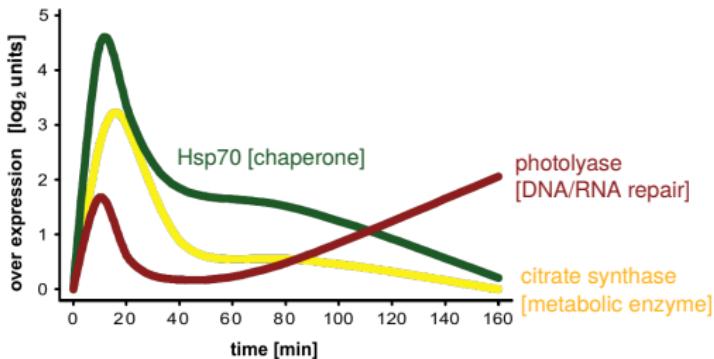
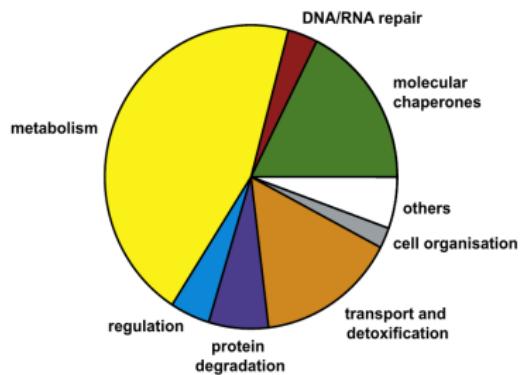
Heat shock

What happens when the cell enters a higher temperature environment?

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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):

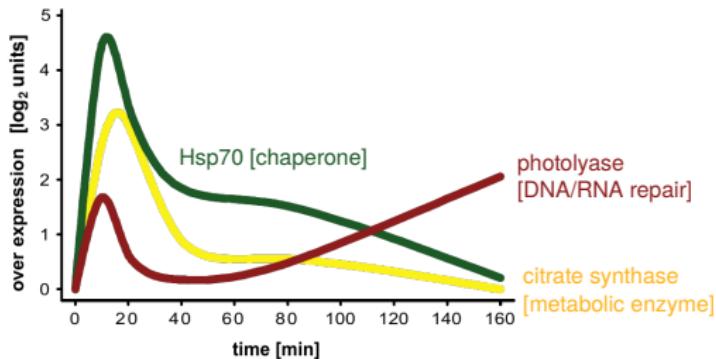
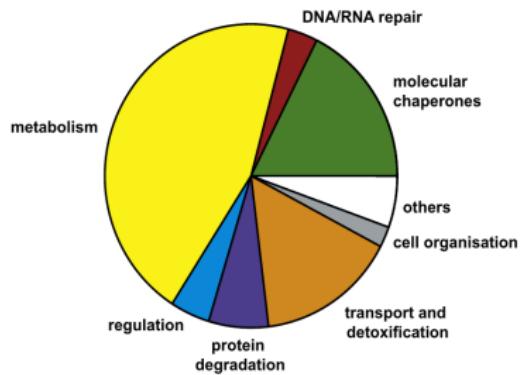


[Richter *et al.*, Molec. Cell (2010)]

Heat shock

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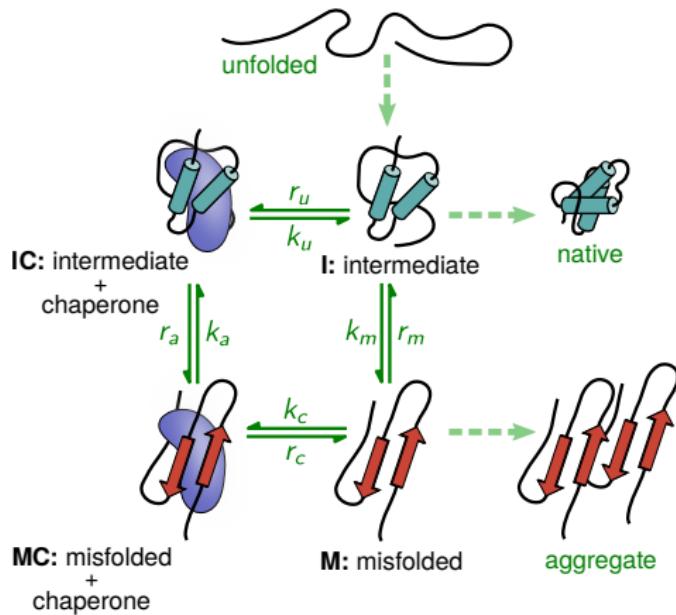
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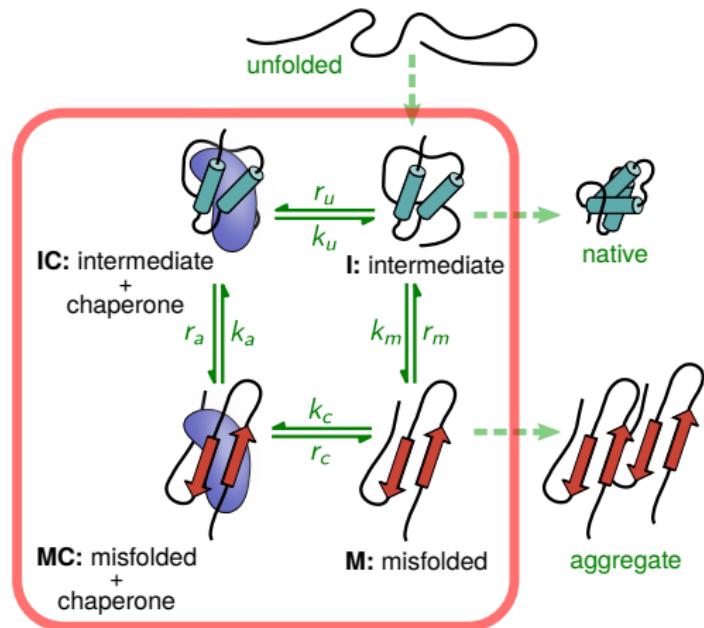
Can we understand this upregulation of chaperones using ideas from thermodynamic control?

Markov model for chaperone-protein interaction



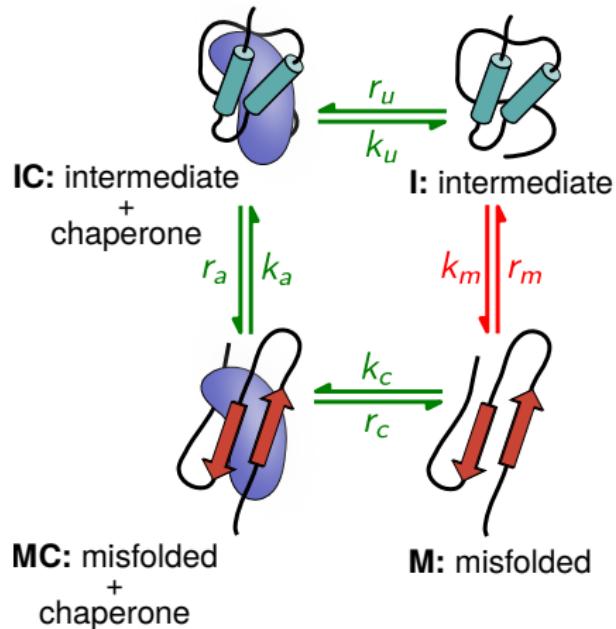
Using separation of timescales we can construct a simplified **Markov model** for a protein that tends to misfold under heat shock, focusing on four key states.

Markov model for chaperone-protein interaction



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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:

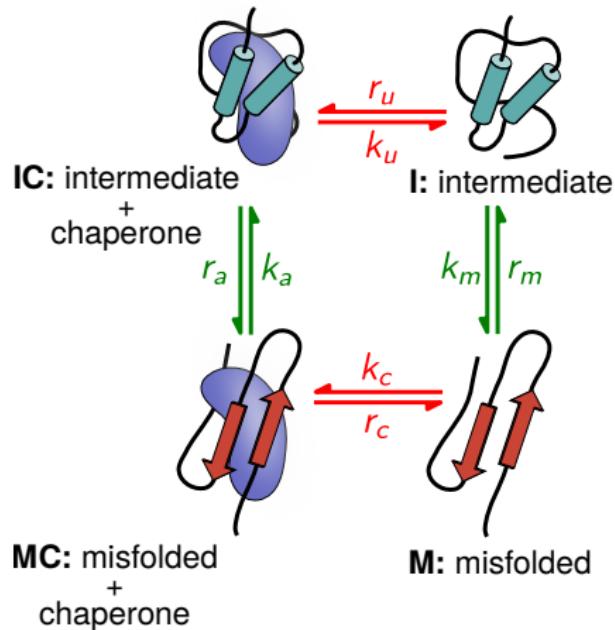
$$\frac{k_m}{r_m} = e^{\beta\epsilon} \gg 1$$

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 :

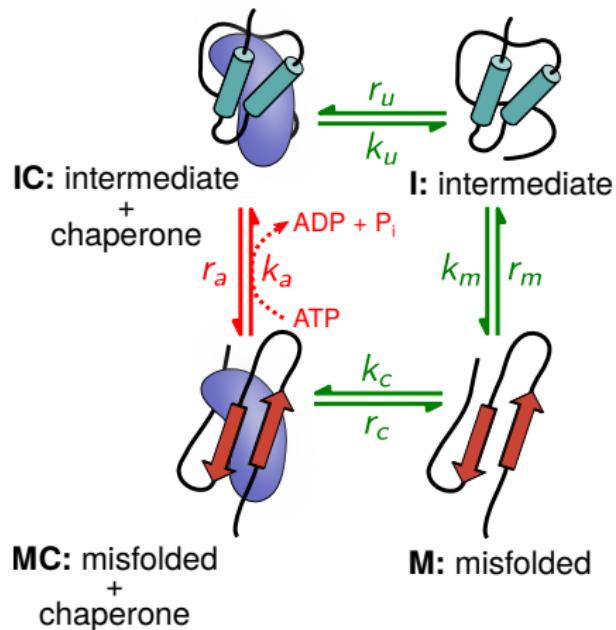
$$k_c = \gamma_c C, \quad r_u = \gamma_u C$$

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



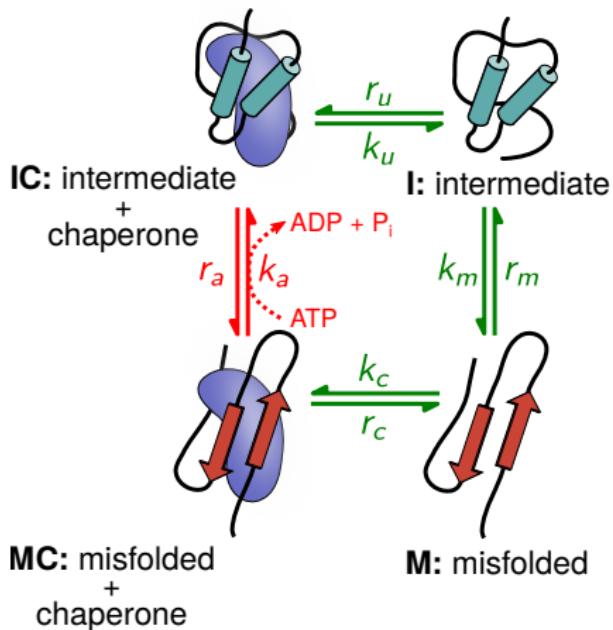
Chaperone-catalyzed reactions follow Michaelis-Menten kinetics that depend on **ATP concentration A** and **ADP concentration B** :

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

Typical parameter values:

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

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

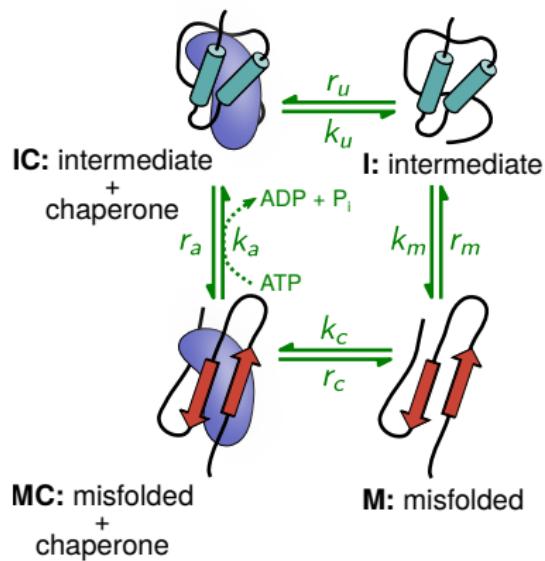
$$\frac{k_{f,cat}K_{r,M}\gamma_c k_u}{k_{r,cat}K_{f,M}\gamma_u r_c} = e^{-\beta\epsilon}$$

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

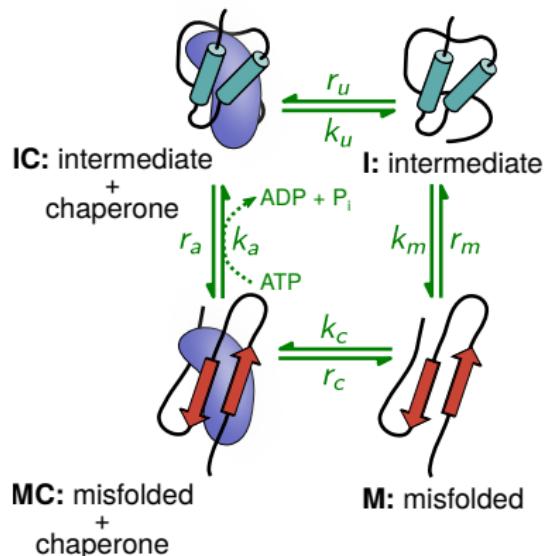
$$\dot{\mathbf{p}}(t) = \Omega \mathbf{p}(t)$$

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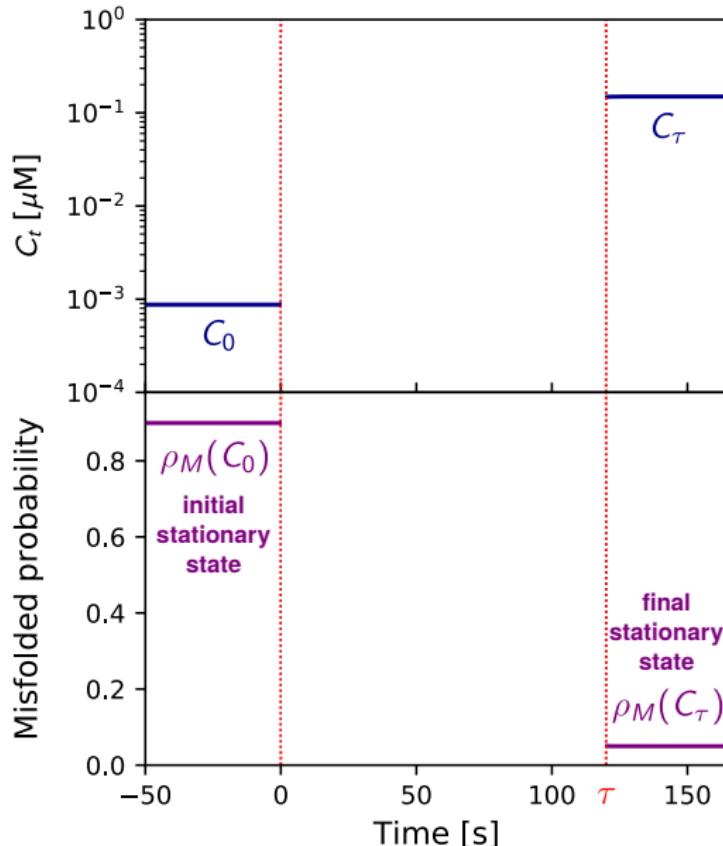
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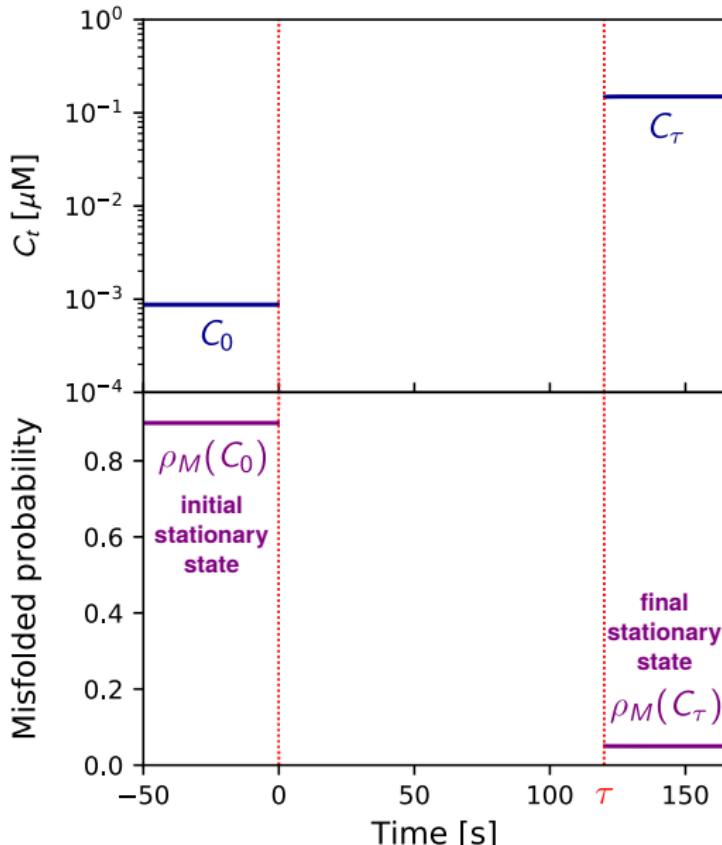
For given A, B, C , the **stationary distribution** ρ satisfies: $\Omega\rho = 0$.

Chaperone upregulation as a control problem



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

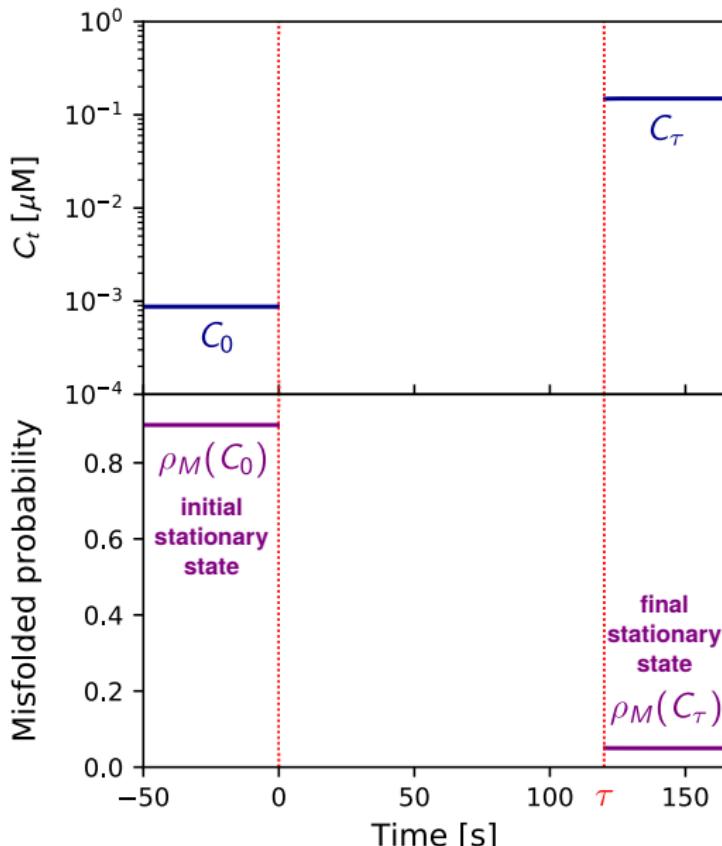
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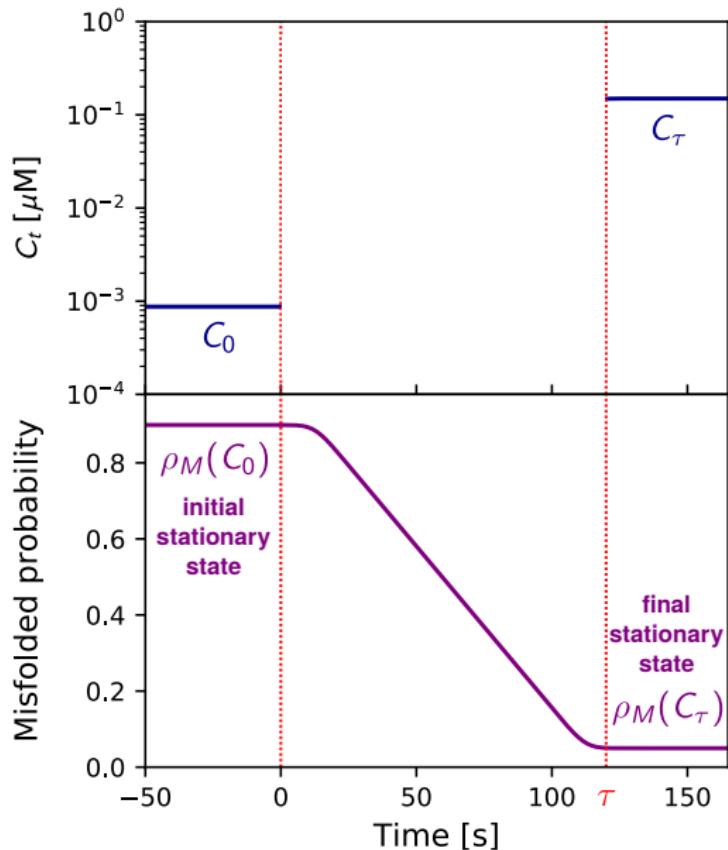


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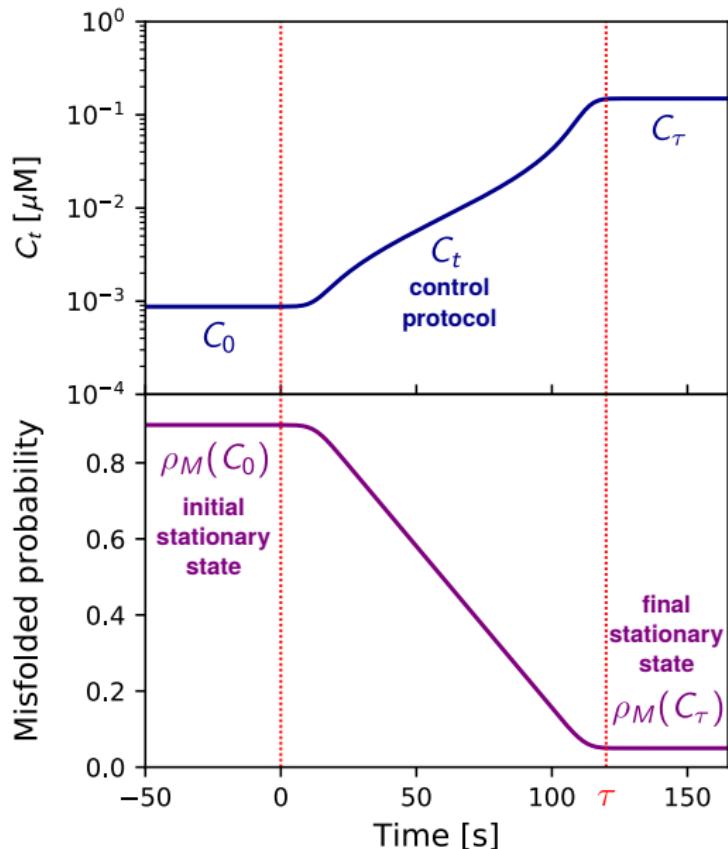
There are insufficient chaperones available, so probability of being misfolded is high.

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

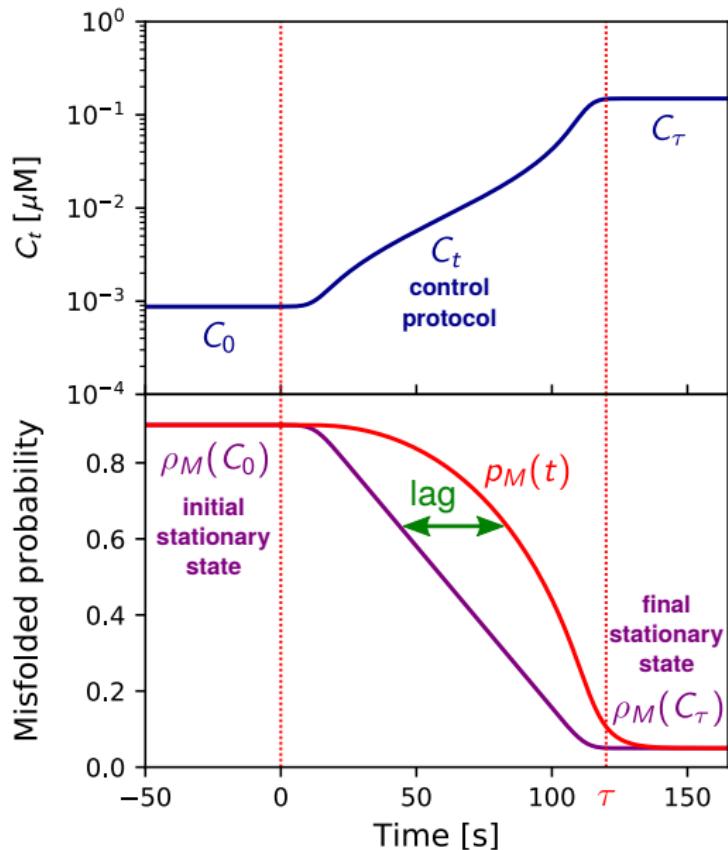
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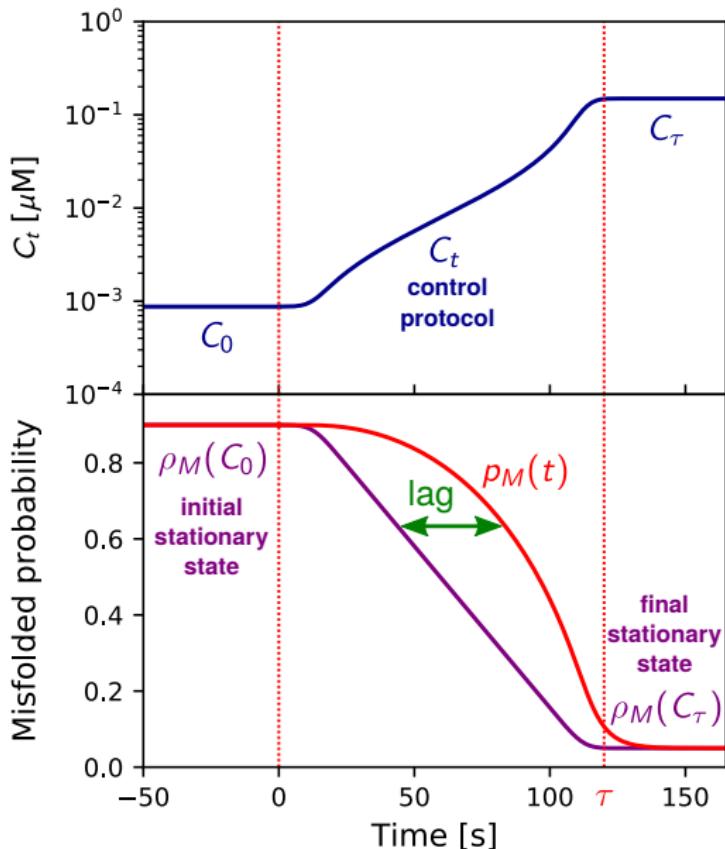
Chaperone upregulation as a control problem



Chaperone upregulation as a control problem



Chaperone upregulation as a control problem



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) λ_t for $0 \leq t \leq \tau$

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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:

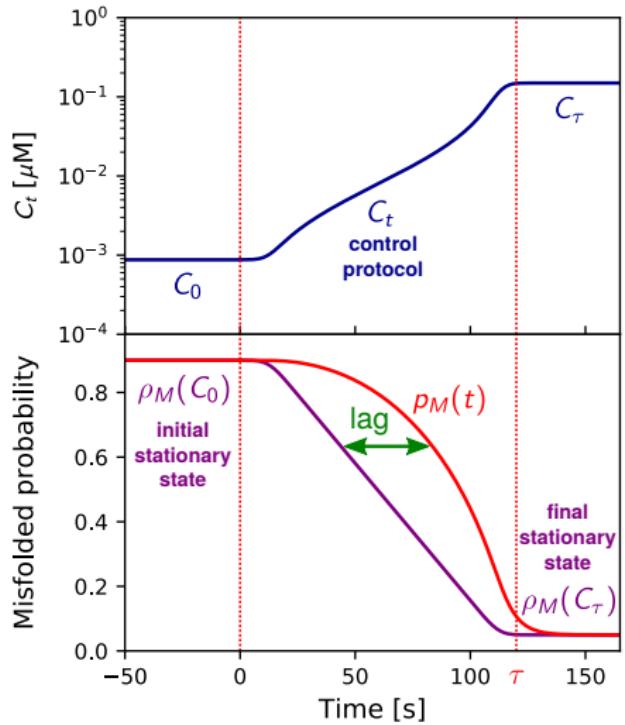
$$\tilde{\Omega}(C_t, \dot{C}_t) \approx \begin{pmatrix} -k_c(\tilde{C}_t) - r_m & r_c & 0 & k_m \\ k_c(\tilde{C}_t) & -r_c - k_a(\tilde{A}_t) & 0 & 0 \\ 0 & k_a(\tilde{A}_t) & -k_u & r_u(\tilde{C}_t) \\ r_m & 0 & k_u & -k_m - r_u(\tilde{C}_t) \end{pmatrix}$$

where

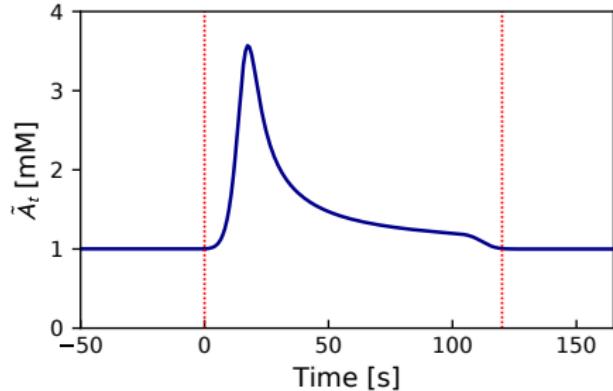
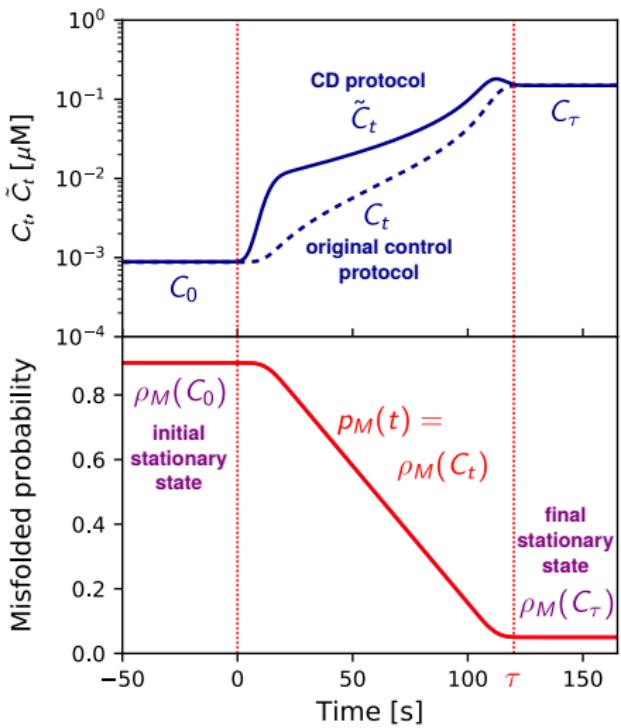
$$\tilde{C}_t \approx C_t - \underbrace{\frac{\dot{C}_t}{\gamma_c} \frac{d}{dC_t} \ln \rho_M(C_t)}_{\text{CD correction term}}$$

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

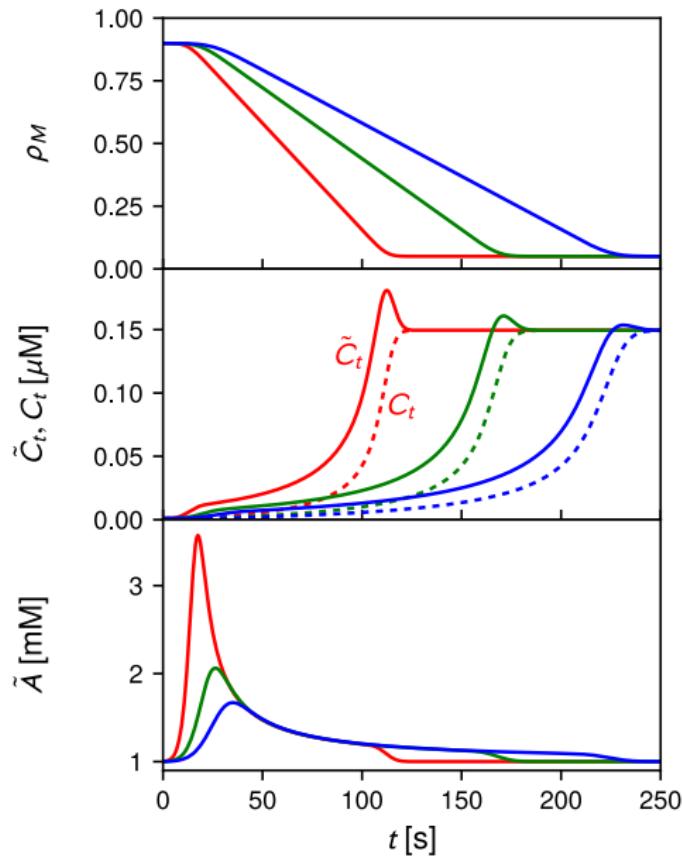
CD protocol



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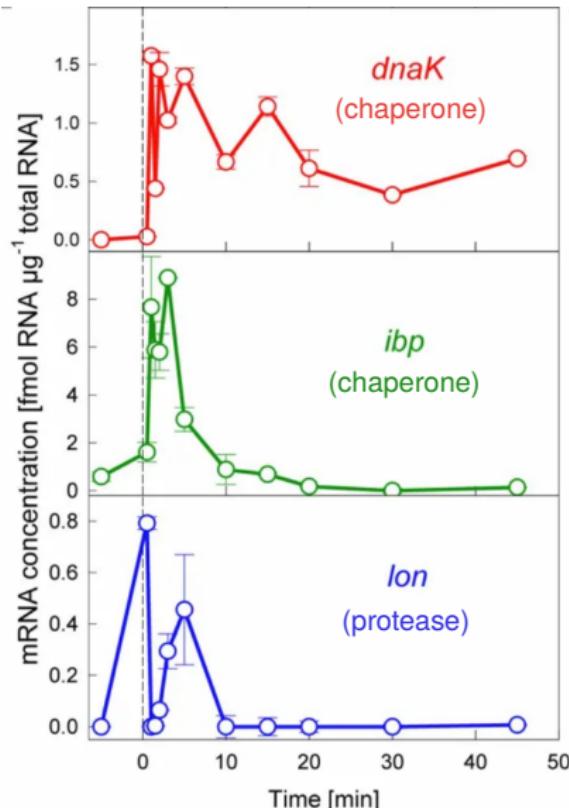
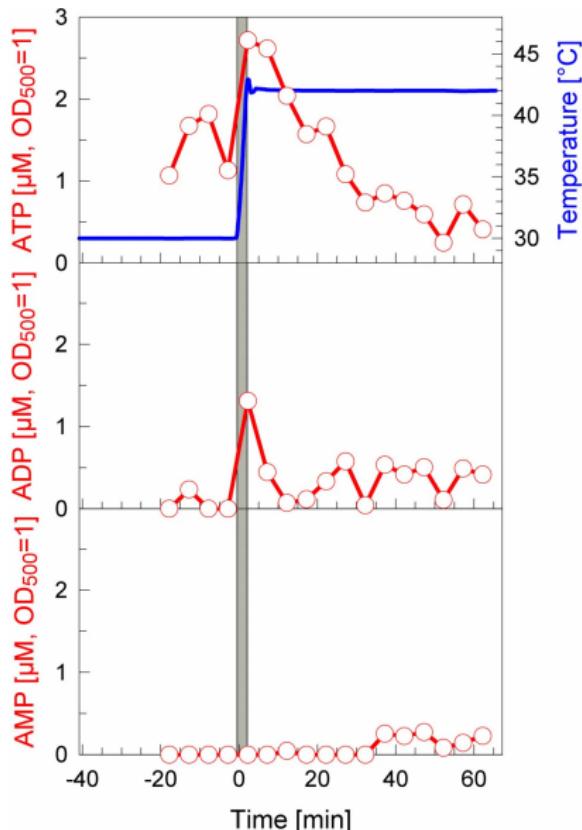


CD protocols for different τ



Experimental data: *E. coli* heat shock response

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



Counterdiabatic protocols for Markov models

Solution:

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

where one constructs the matrix $\hat{\Omega}_{ij}$ and vector Γ_i as follows:

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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.

Counterdiabatic protocols for Markov models

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where one constructs the matrix $\hat{\Omega}_{ij}$ and vector Γ_i as follows:

Step 2: Construct $\Gamma_i(\lambda_t, \dot{\lambda}_t)$,

$$\Gamma_i(\lambda_t, \dot{\lambda}_t) = \frac{(\hat{\Omega}^\times(\lambda_t, \dot{\lambda}_t) \dot{\rho}(\lambda_t))_i}{\rho_i(\lambda_t)} + \Gamma_0(\lambda_t, \dot{\lambda}_t)$$

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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 . Γ_0 is uniquely specified by enforcing the condition:

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

Constraints on possible CD protocols

Arbitrary \tilde{M} \Rightarrow infinitely many CD protocols!

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Typical constraints:

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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).