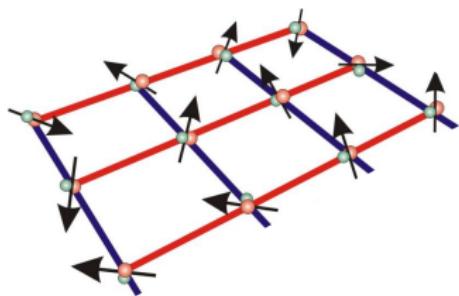


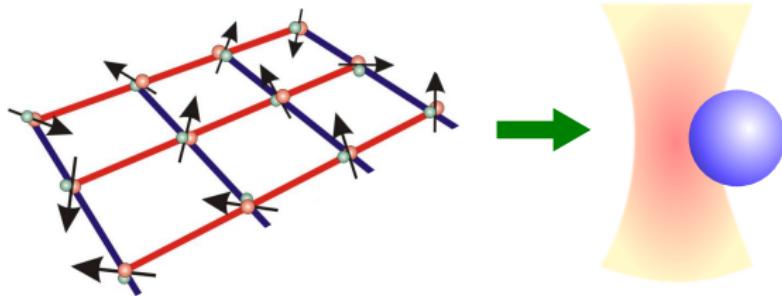
# Shortcuts to adiabaticity



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

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

# Shortcuts to adiabaticity



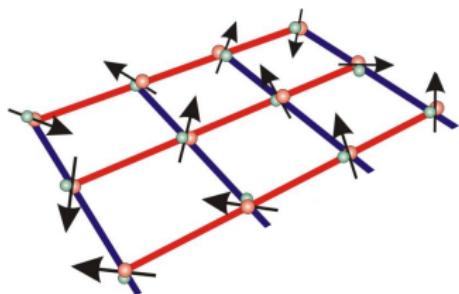
**adiabatic quantum computing:**  
maintaining ground state while  
driving a quantum system

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

**Brownian motion of  
bead in optical trap:**  
maintaining instantaneous  
equilibrium as trap changes

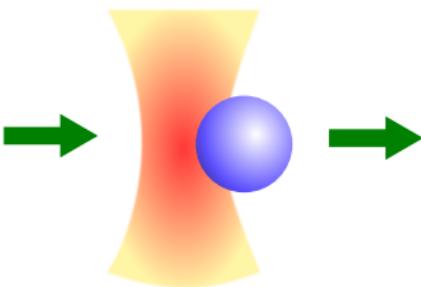
Martinez *et al* Nature Physics (2016)  
Patra, Jarzynski, New. J. Phys. (2017)

# Shortcuts to adiabaticity



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

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



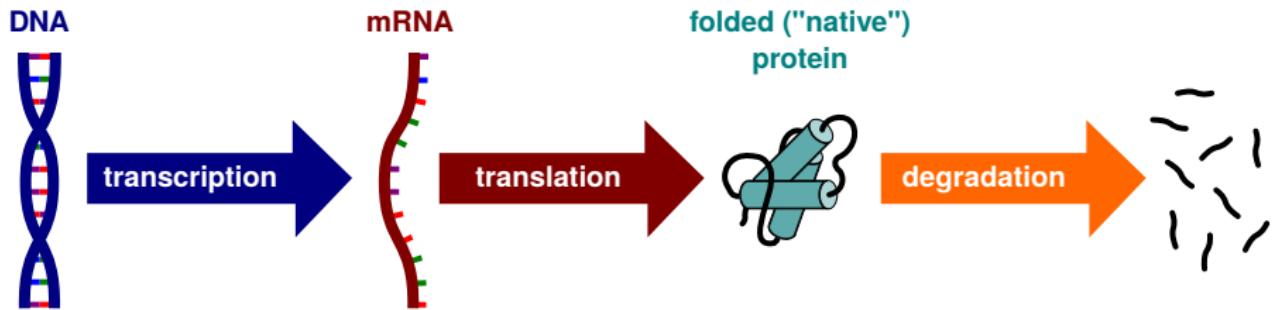
**Brownian motion of  
bead in optical trap:**  
maintaining instantaneous  
equilibrium as trap changes

Martinez *et al* Nature Physics (2016)  
Patra, Jarzynski, New. J. Phys. (2017)

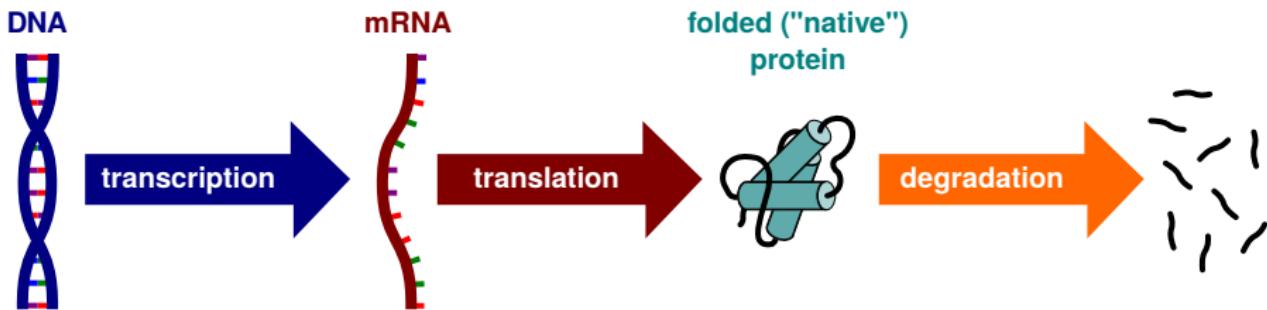


**Possible biological  
applications:**  
population genetics  
molecular chaperones  
force spectroscopy

# Traditional view of protein production



# Traditional view of protein production



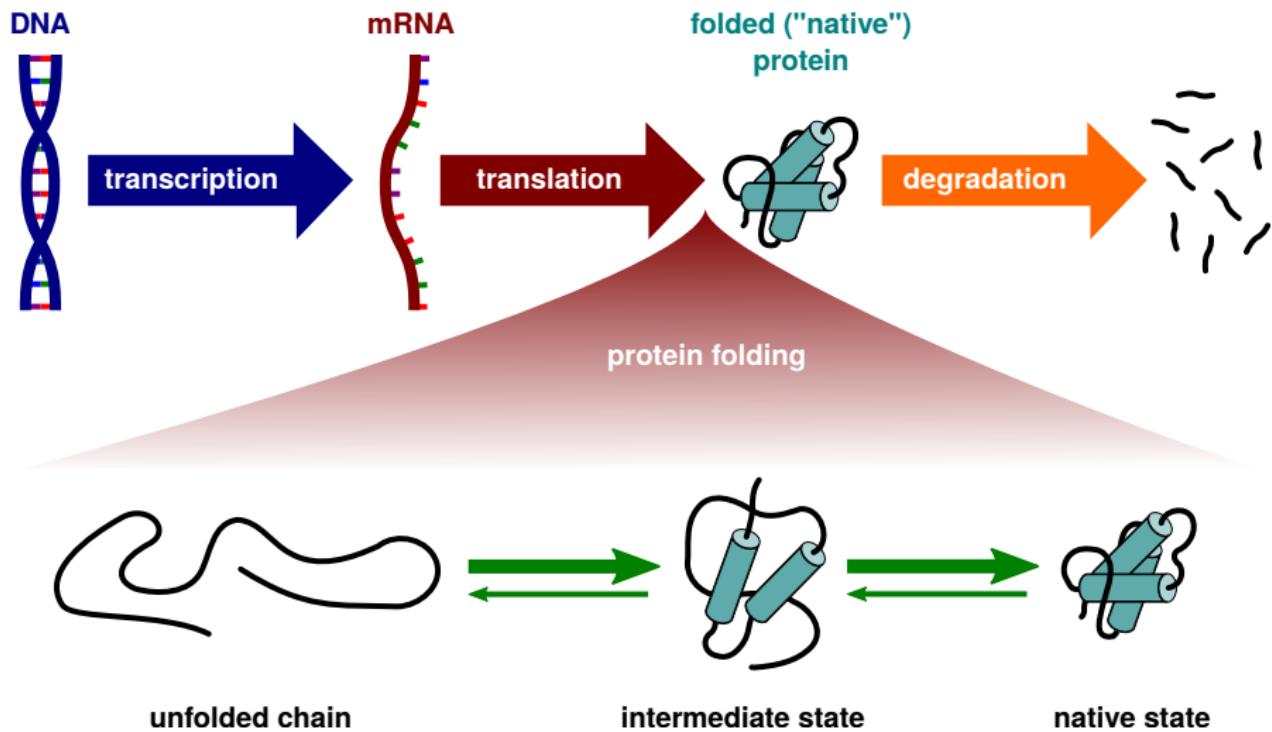
All these processes involve nonequilibrium reaction networks driven by ATP hydrolysis.

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

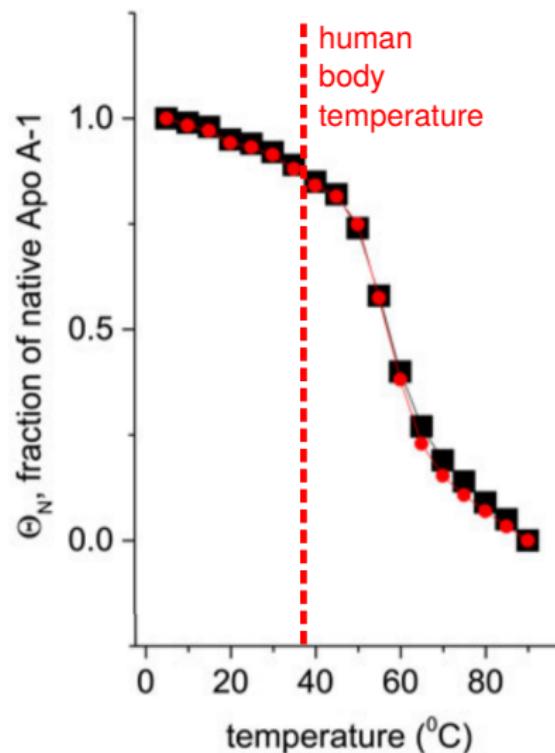
Ilker & Hinczewski, Phys. Rev. Lett. (2019)

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

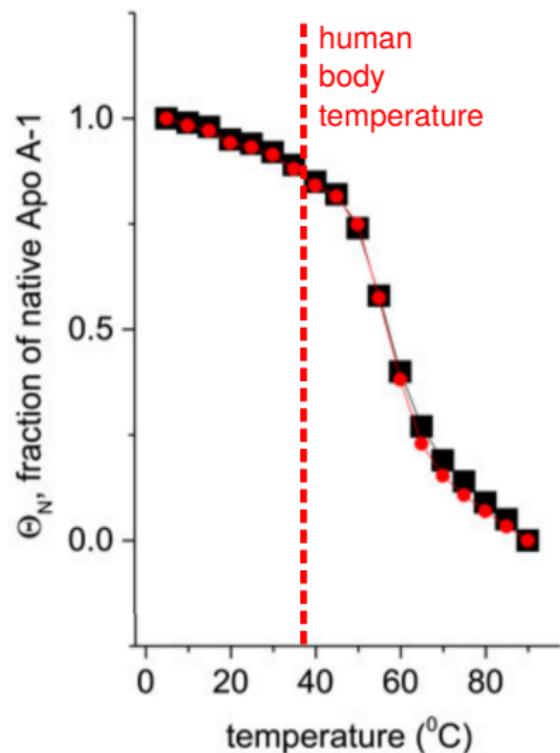
# Traditional view of protein production



# Proteins function at the cliff edge of unfolding

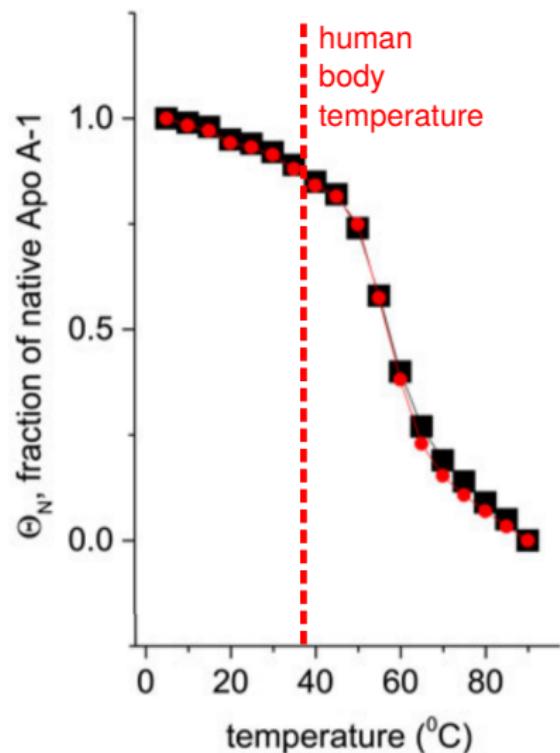


# Proteins function at the cliff edge of unfolding



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

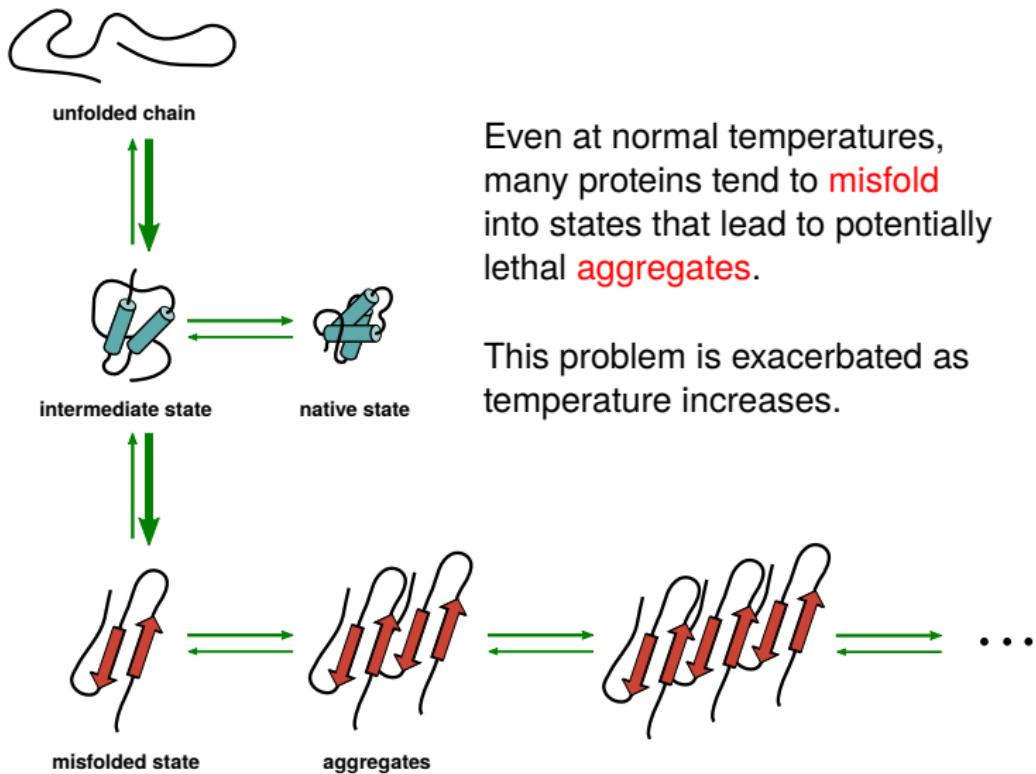
# Proteins function at the cliff edge of unfolding



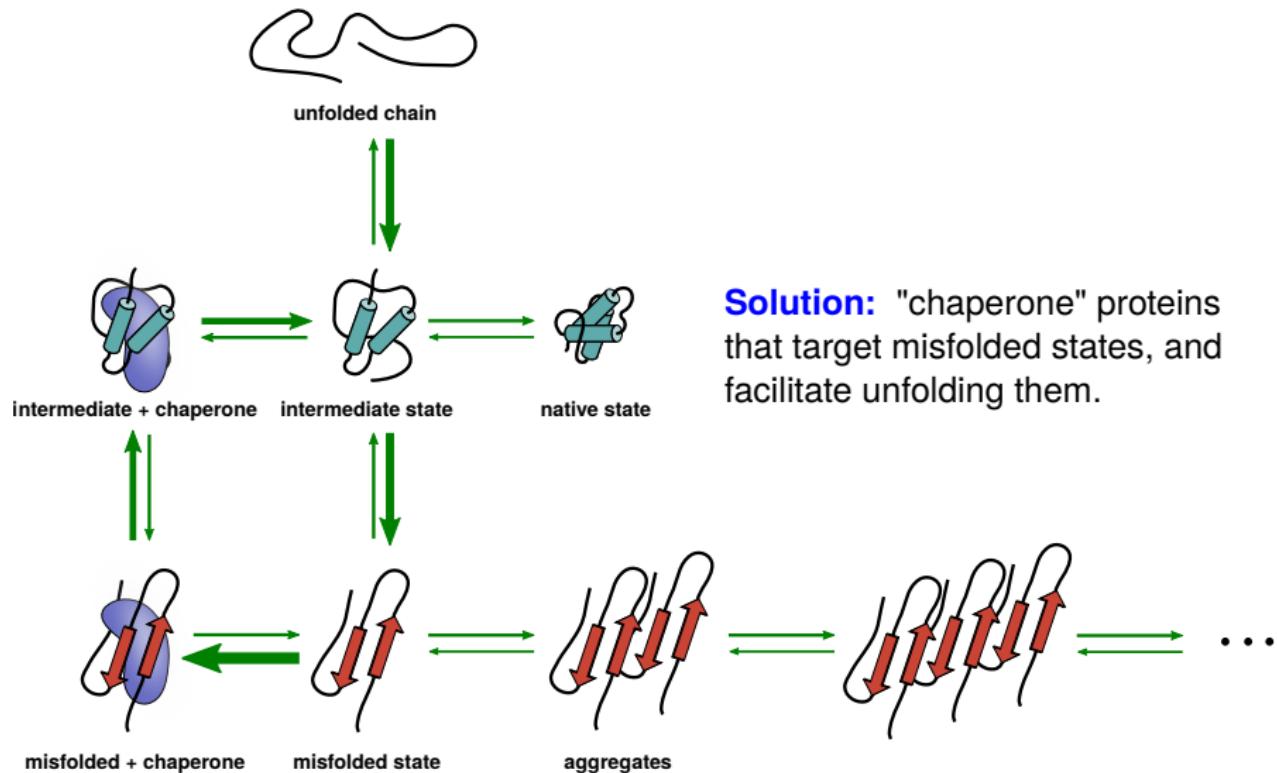
Being on the verge of melting gives proteins the **dynamical flexibility** essential for their diverse roles as enzymes.

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

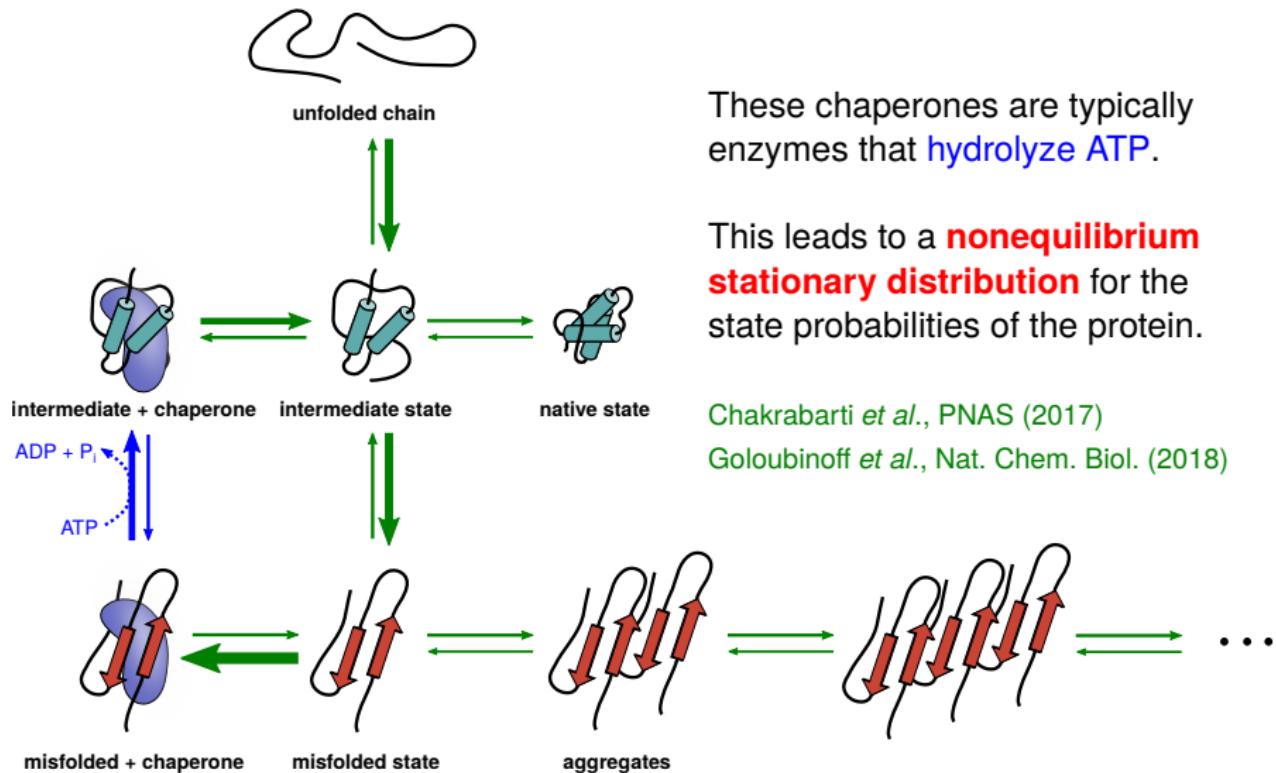
# Constant threats: misfolding and aggregation



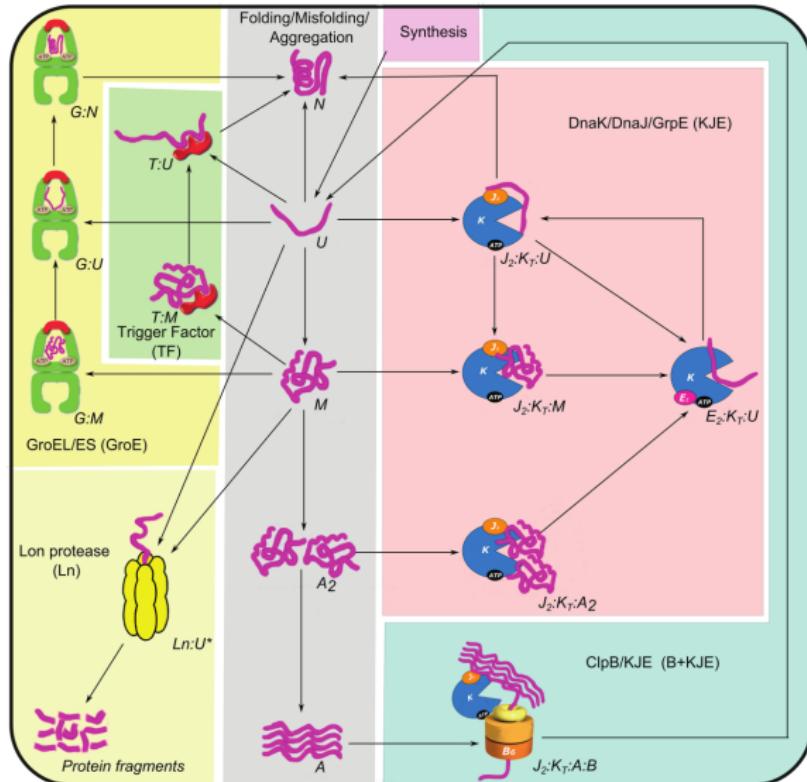
# Constant threats: misfolding and aggregation



# Constant threats: misfolding and aggregation



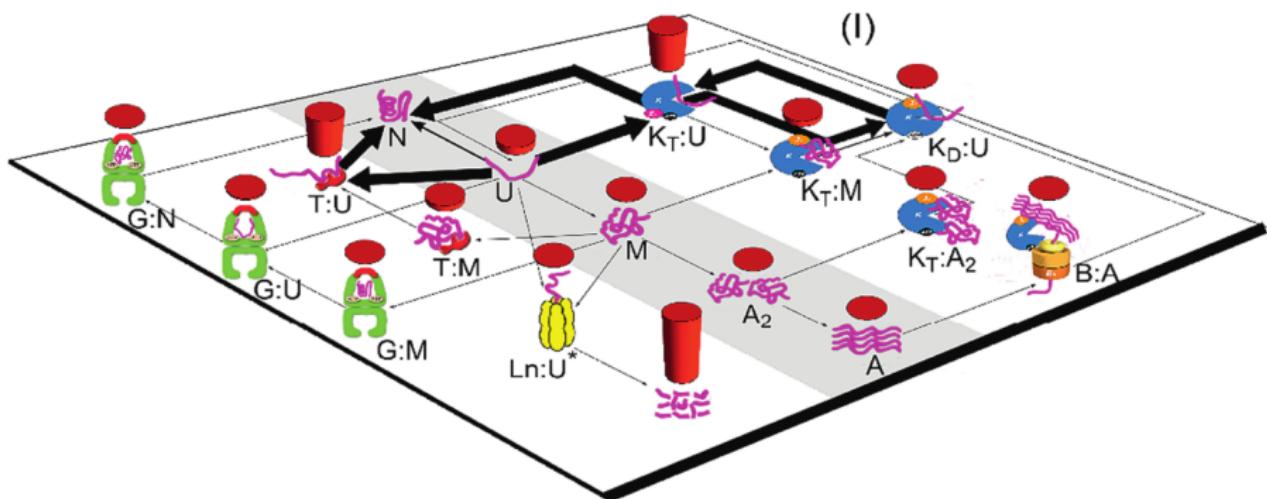
# The protein “hospital”: possible chaperone pathways



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

# The protein “hospital”: possible chaperone pathways

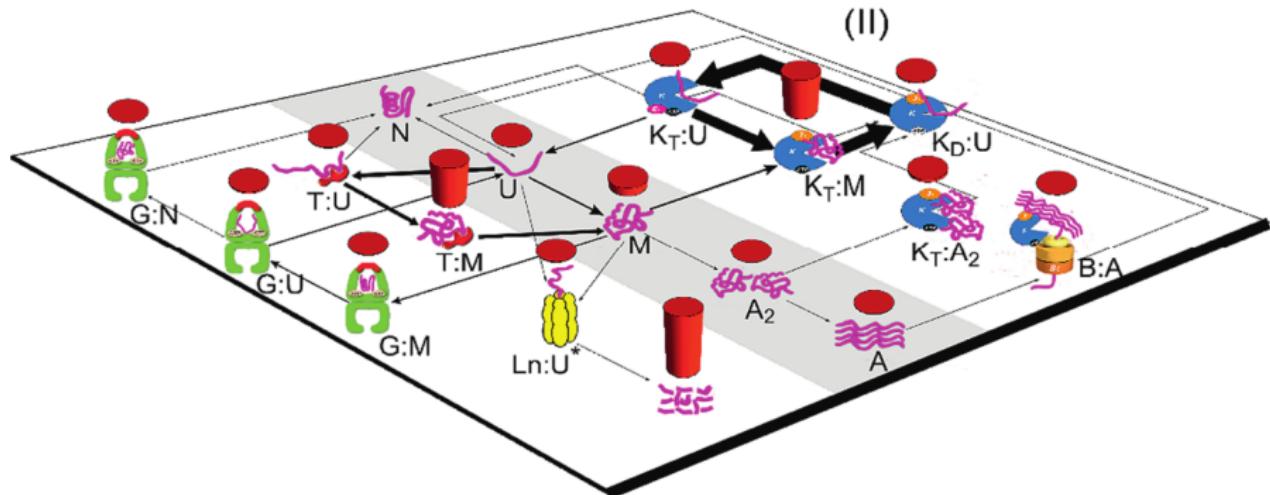
Different classes of proteins interact primarily with different chaperone sub-systems:



Santra *et al.*, PNAS (2017)

# The protein “hospital”: possible chaperone pathways

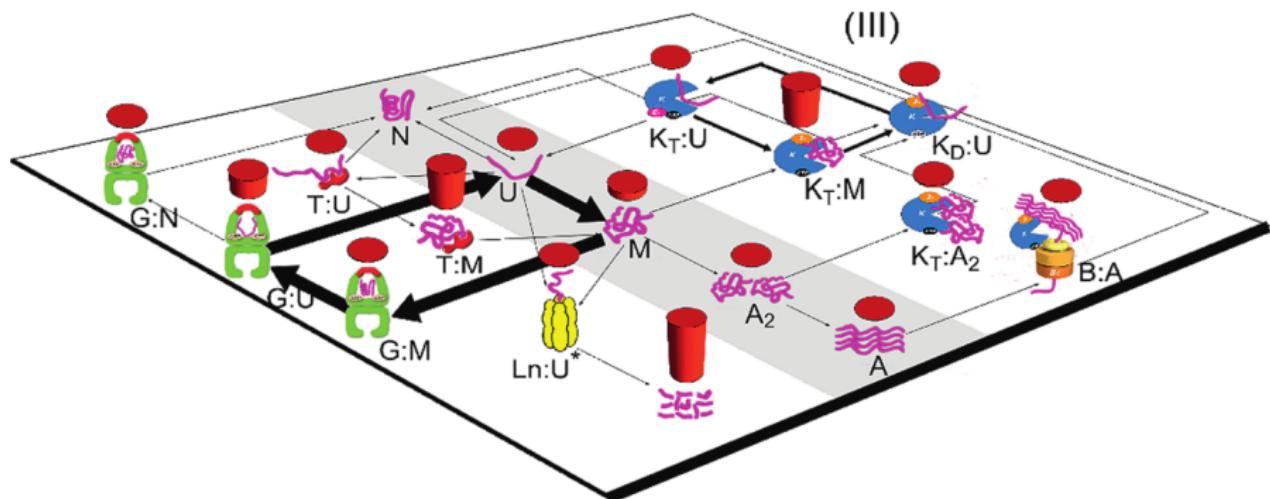
Different classes of proteins interact primarily with different chaperone sub-systems:



Santra *et al.*, PNAS (2017)

# The protein “hospital”: possible chaperone pathways

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



Santra et al., PNAS (2017)

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

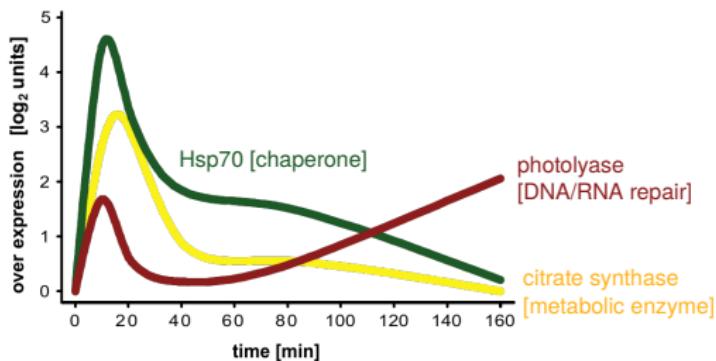
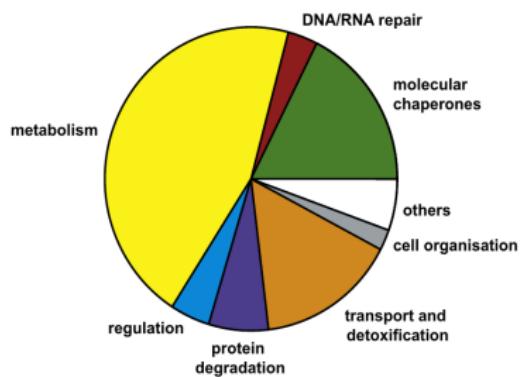
## Heat shock

What happens when the cell enters a higher temperature environment?

# Heat shock

What happens when the cell enters a higher temperature environment?

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):

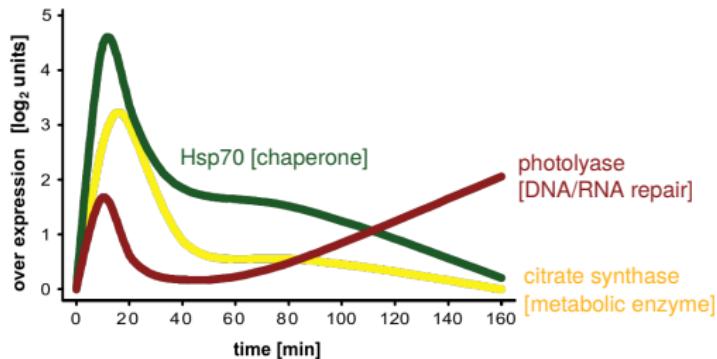
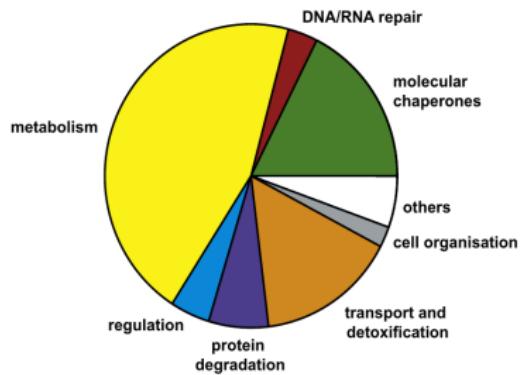


[Richter *et al.*, Molec. Cell (2010)]

# Heat shock

What happens when the cell enters a higher temperature environment?

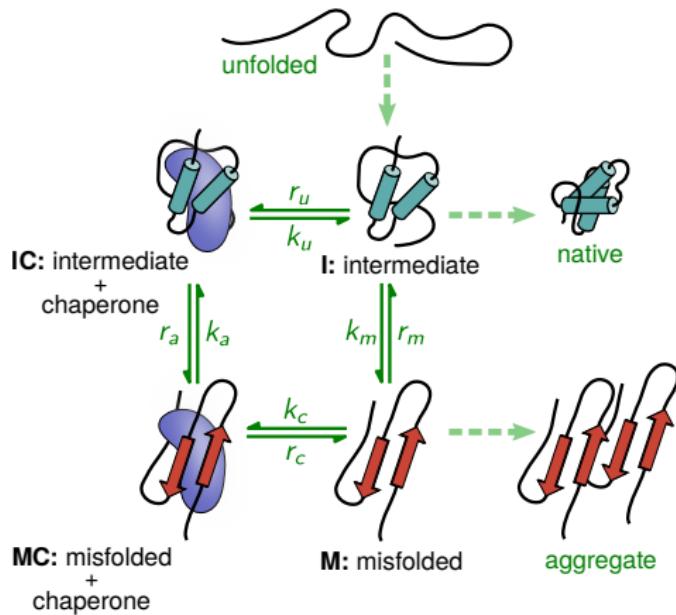
Functional classes of upregulated genes in yeast after a heat shock from 25°C to 35°C over 10 min (out of total of 91 genes upregulated by more than 2.8x):



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

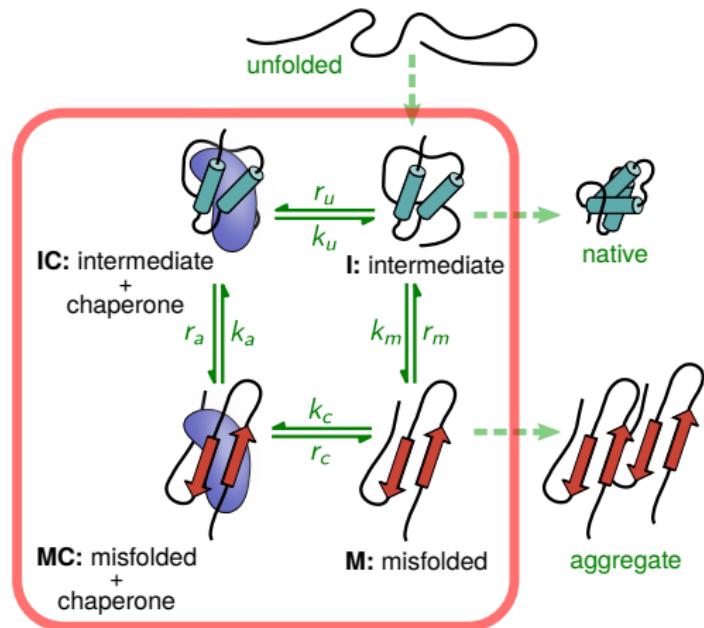
Can we understand this upregulation of chaperones using ideas from thermodynamic control?

# Markov model for chaperone-protein interaction



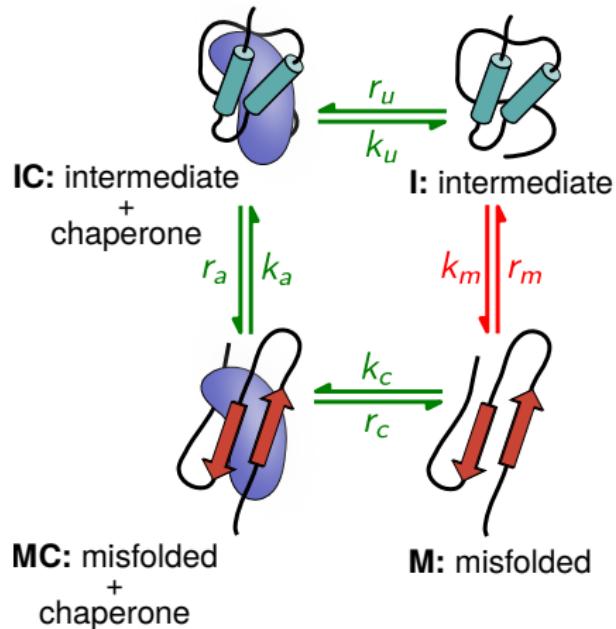
Using separation of timescales we can construct a simplified **Markov model** for a protein that tends to misfold under heat shock, focusing on four key states.

# Markov model for chaperone-protein interaction



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



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

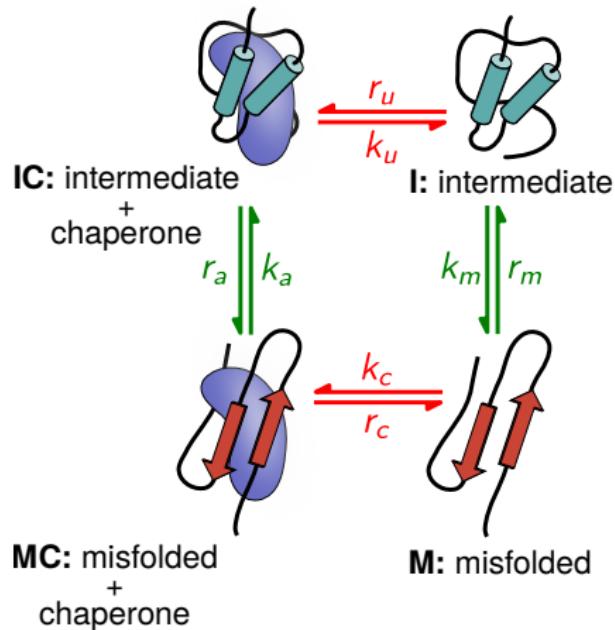
$$\frac{k_m}{r_m} = e^{\beta\epsilon} \gg 1$$

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  $C$ :

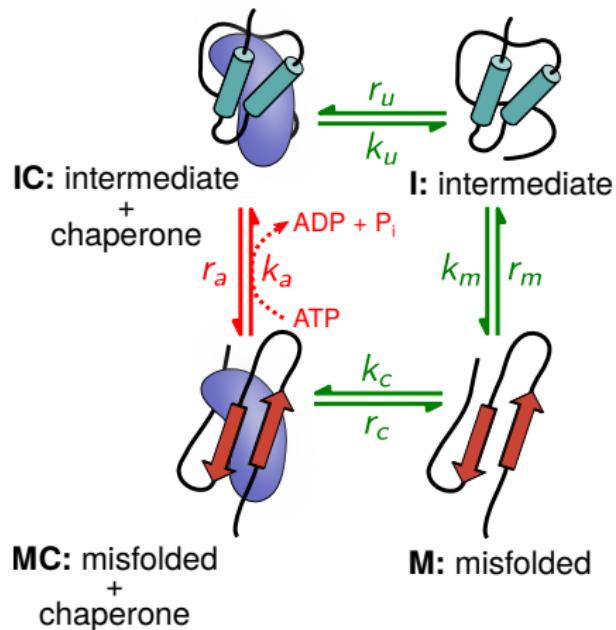
$$k_c = \gamma_c C, \quad r_u = \gamma_u C$$

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



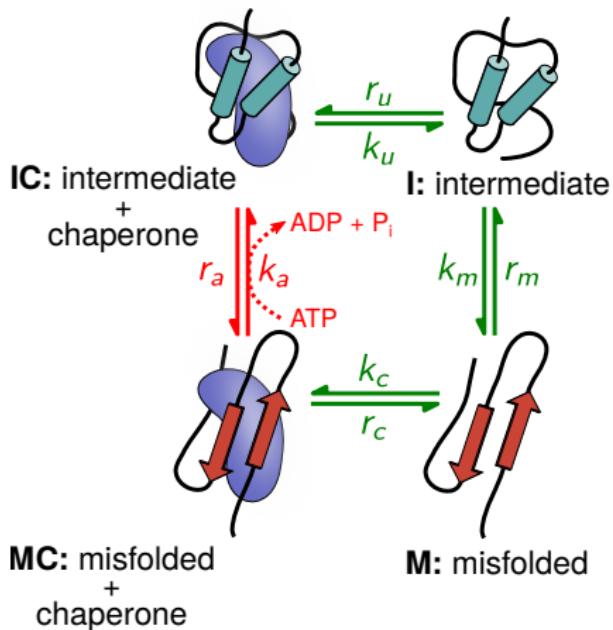
Chaperone-catalyzed reactions follow Michaelis-Menten kinetics that depend on **ATP concentration  $A$**  and **ADP concentration  $B$** :

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

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



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

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

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

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

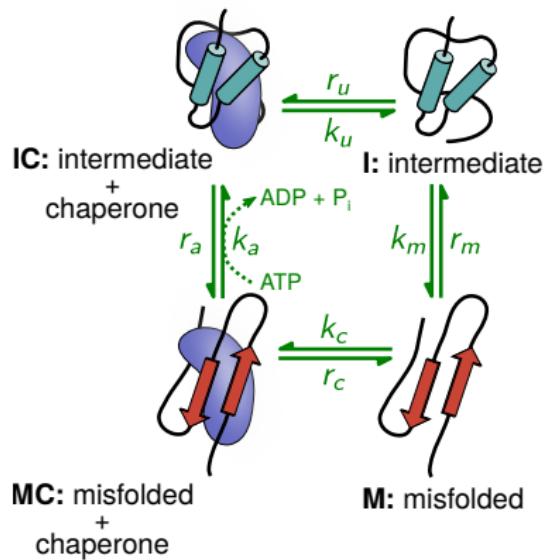
$$\frac{k_{f,cat}K_{r,M}\gamma_c k_u}{k_{r,cat}K_{f,M}\gamma_u r_c} = e^{-\beta\epsilon}$$

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

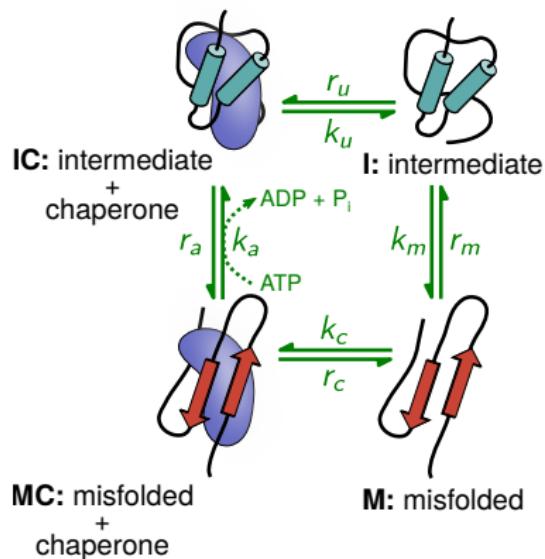
$$\dot{\mathbf{p}}(t) = \Omega \mathbf{p}(t)$$

with transition matrix

$$\Omega =$$

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

# 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

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

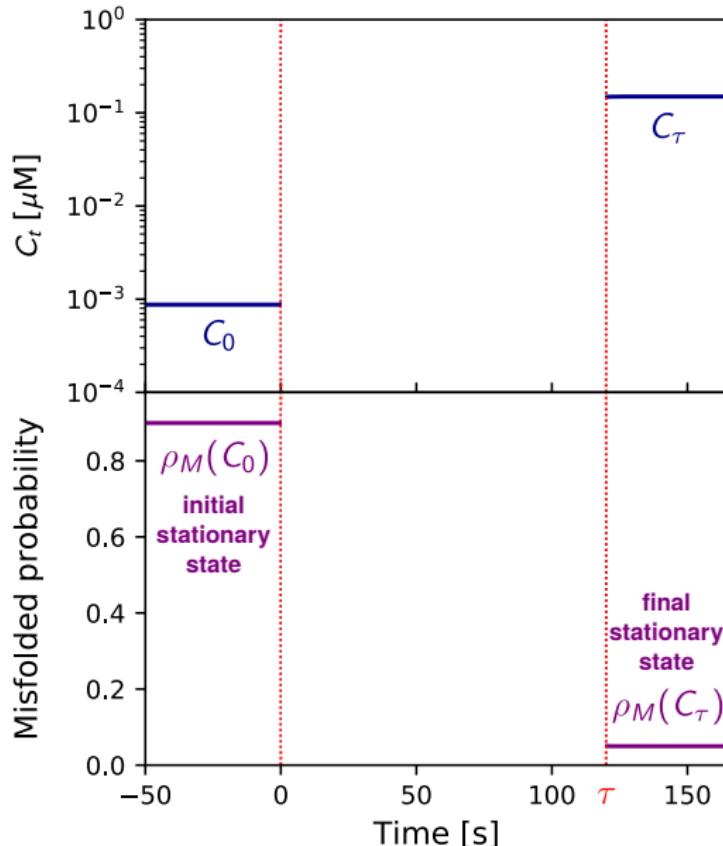
with transition matrix

$$\Omega =$$

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

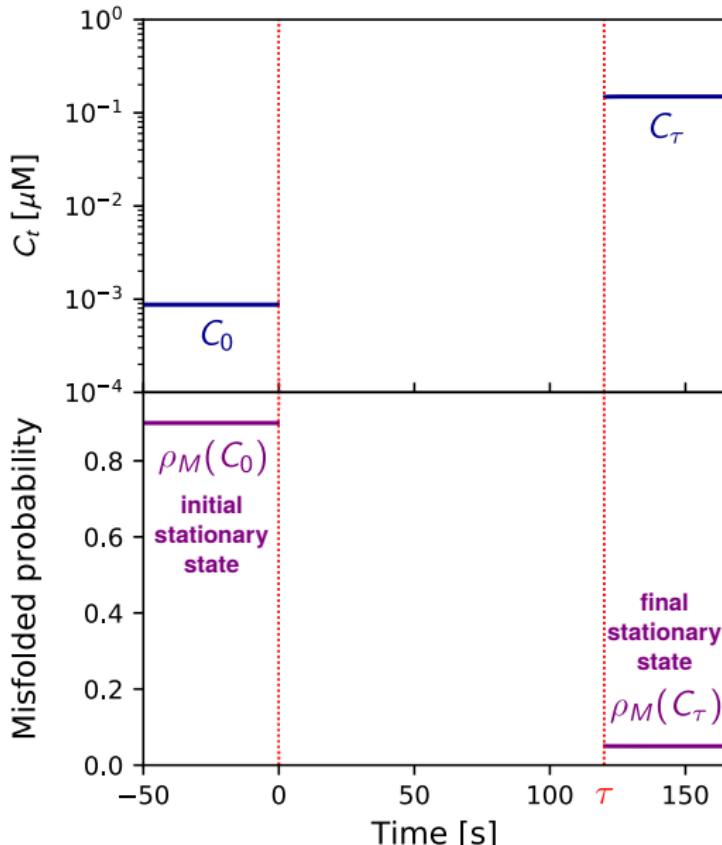
For given  $A, B, C$ , the **stationary distribution**  $\rho$  satisfies:  $\Omega\rho = 0$ .

# Chaperone upregulation as a control problem



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

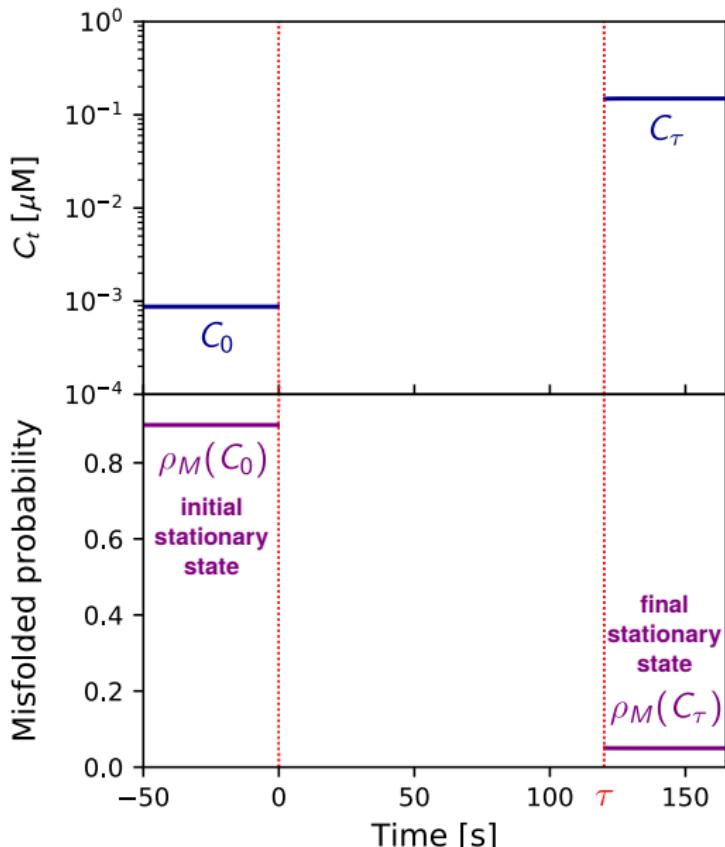
# Chaperone upregulation as a control problem



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

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

# Chaperone upregulation as a control problem

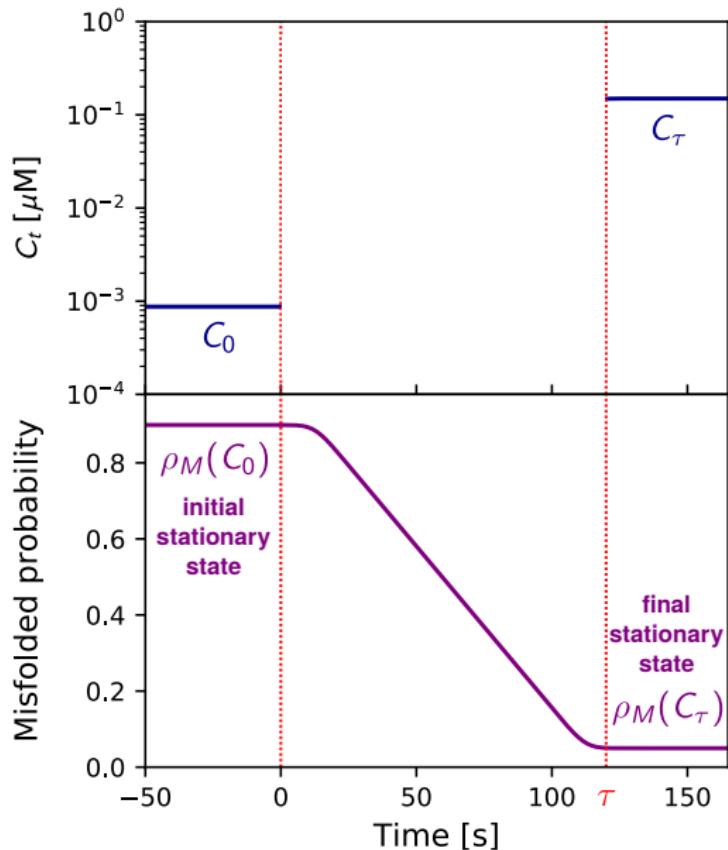


Right after heat shock, system relaxes quickly to stationary state for free chaperone concentration  $C_0$ .

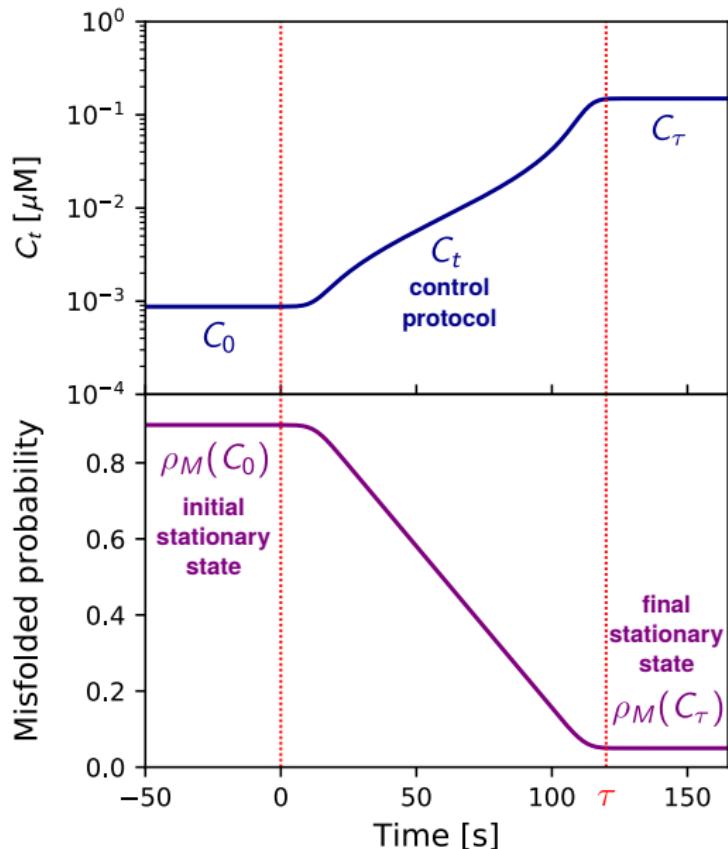
There are insufficient chaperones available, so probability of being misfolded is high.

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

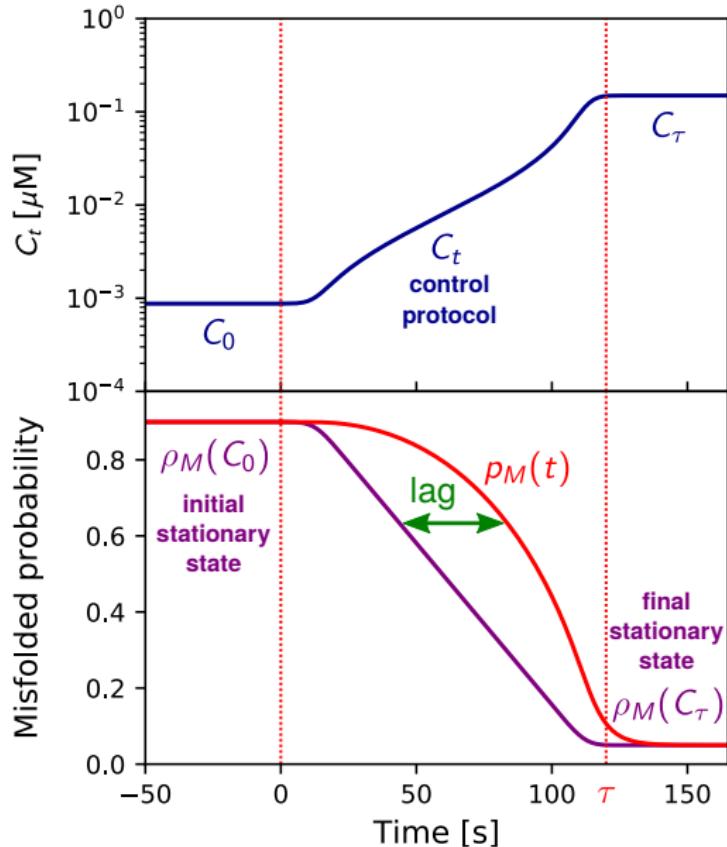
# Chaperone upregulation as a control problem



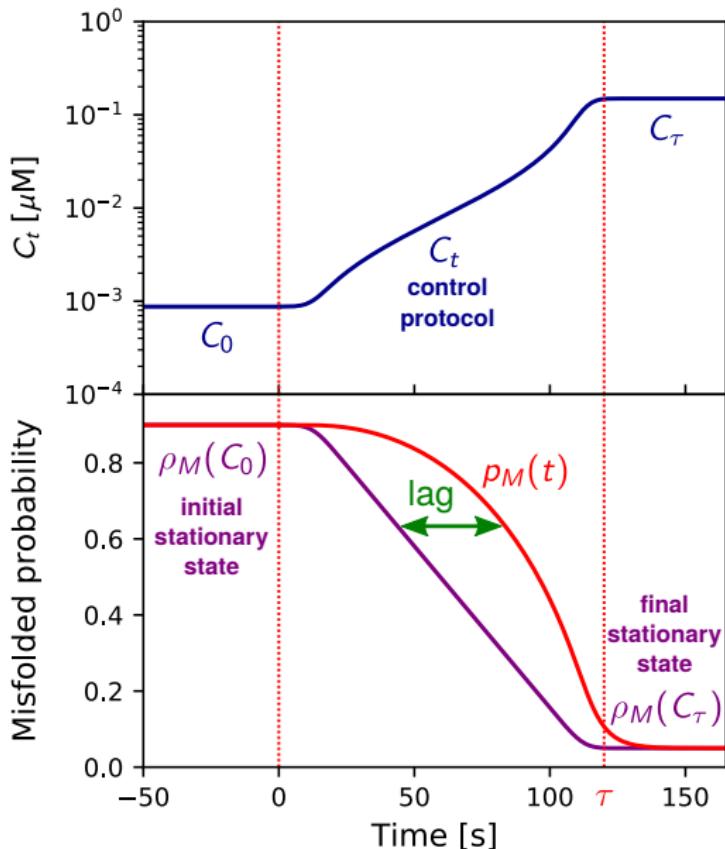
# Chaperone upregulation as a control problem



# 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)  $\lambda_t$  for  $0 \leq t \leq \tau$

# 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  $0 \leq t \leq \tau$
- ▶ Master equation for state probabilities  $\mathbf{p}(t)$ :

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

# 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  $0 \leq t \leq \tau$
- ▶ Master equation for state probabilities  $\mathbf{p}(t)$ :

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

- ▶ Instantaneous stationary state  $\rho(\lambda_t)$  defined via:

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

# 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  $0 \leq t \leq \tau$
- ▶ Master equation for state probabilities  $\rho(t)$ :

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

- ▶ Instantaneous stationary state  $\rho(\lambda_t)$  defined via:

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

**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:

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