



# A Time Dependent Analysis of Protein Homeostasis Stability

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## 1. Introduction

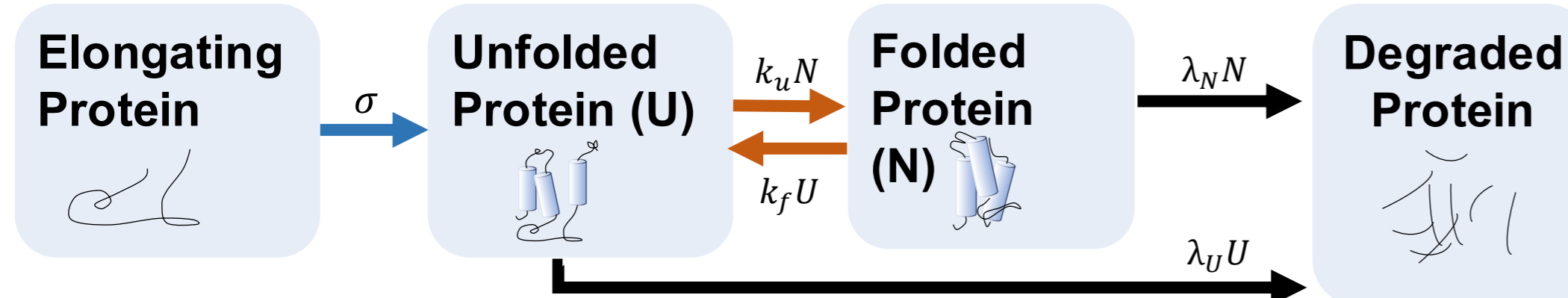
Protein homeostasis (proteostasis) depends on coordinated protein synthesis, folding, and degradation—processes that are energetically costly and vulnerable to metabolic stress [1].

Under stress, feedback mechanisms can qualitatively alter proteostasis dynamics:

- Stress can amplify unfolded protein accumulation
- Feedback may introduce bistability, separating healthy and collapsed states [2]

We propose a minimal kinetic model to establish stable baseline behavior and then introduce stress-dependent feedback to identify kinetic structures that permit instability and define boundaries between resilience and collapse [3].

## 2. Preliminary Two-state Proteostasis Model

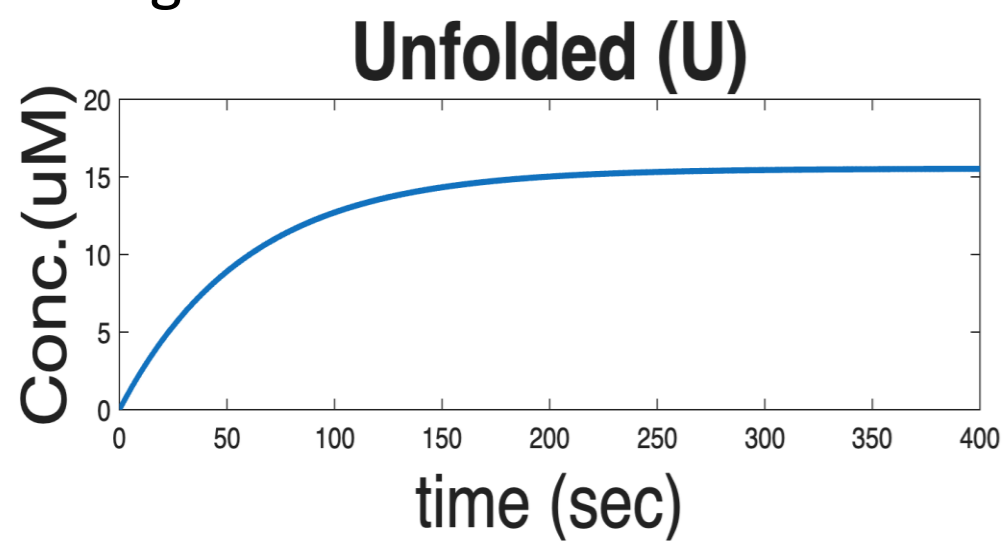


- **Goal:** establish a baseline two-state proteostasis model to identify parameter values: unfolded (U) and native (N) proteins exchange via synthesis, folding/unfolding, and degradation

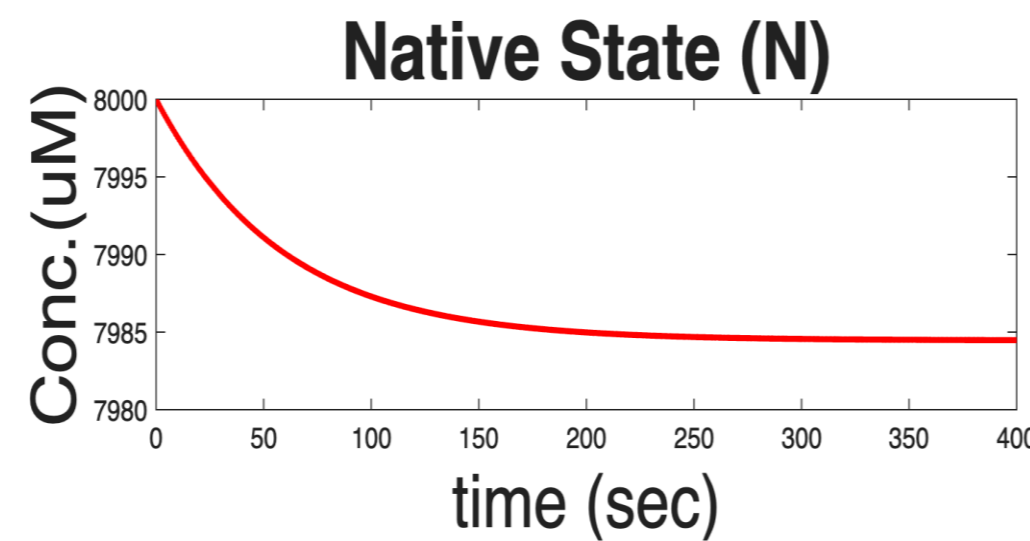
$$\frac{dU}{dt} = \sigma - k_f U + k_u N - \lambda_U U$$

$$\frac{dN}{dt} = k_f U - k_u N - \lambda_N N$$

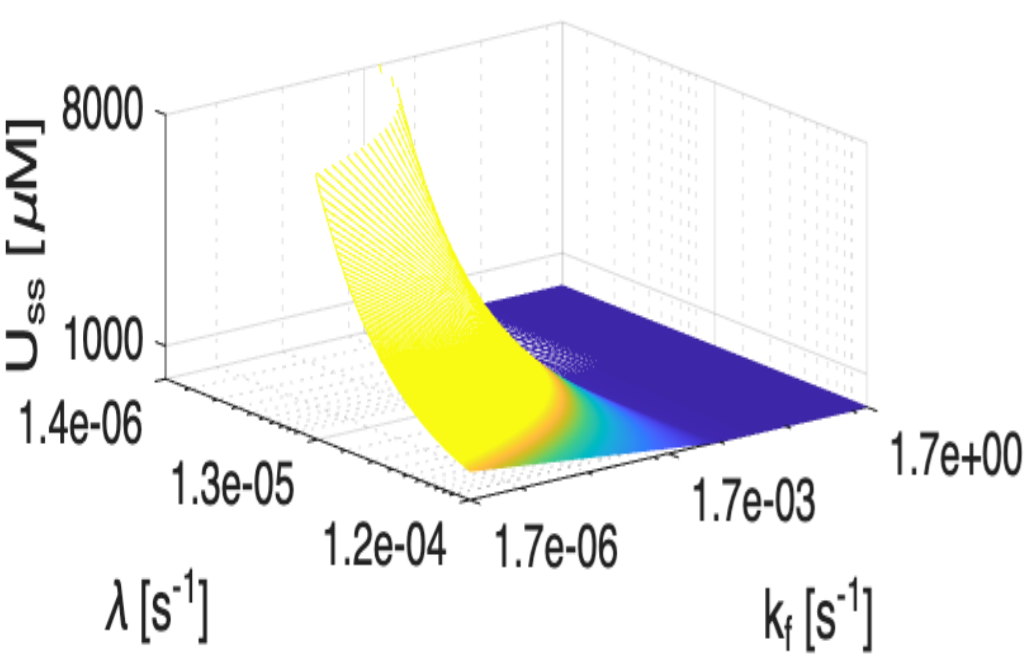
For simplicity,  $\lambda_U = \lambda_N = \lambda$  and  $\sigma = [U + N]\lambda$  when coupled



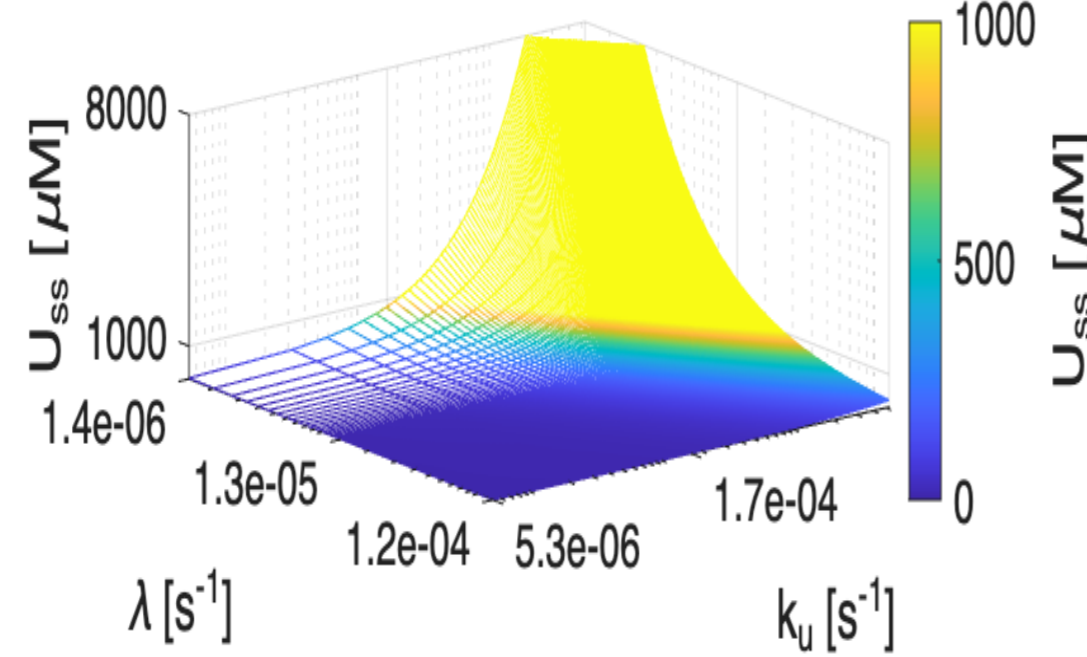
(a) Unfolded vs  $k_f$  vs  $\lambda$



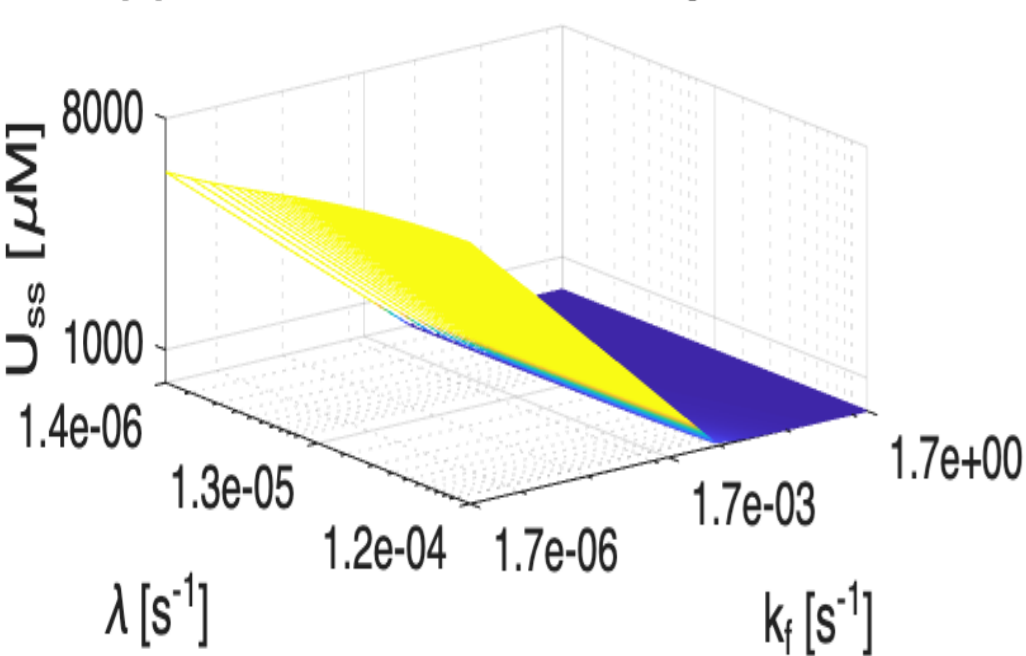
(b) Unfolded vs  $k_u$  vs  $\lambda$



(c) Unfolded vs  $k_f$  vs Coupled  $\lambda$  &  $\sigma$



(d) Unfolded vs  $k_u$  vs Coupled  $\lambda$  &  $\sigma$



- **Range Derivation:** 3D plots (a–d) helped defined parameter ranges that meet our target conditions. Ranges are presented in table.
- Baseline ranges are used to identifying drivers of bistability (Section 3)

Parameter	Values
$k_f$	$0.017 \times 10^{-4}$ to $0.17 \text{ s}^{-1}$
$k_u$	$5.3 \times 10^{-6}$ to $5.3 \times 10^{-3} \text{ s}^{-1}$
$\lambda$	$0.01/3600$ to $0.45/3600 \text{ s}^{-1}$

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## 3. Stress and Bistability

### Modeling Stress-Induced Feedback and Interaction

Extend baseline model with a generalized stress-dependent term

Introduce  $X(U, N)$  stress-driven exchange between unfolded (U) and native (N)

$$\frac{dU}{dt} = \sigma - k_f U + k_u N + k_{auto} X(U, N) - \lambda_U U$$

$$\frac{dN}{dt} = k_f U - k_u N - k_{auto} X(U, N) - \lambda_N N$$

$X(U, N)$	Stability Behavior	Interpretation
$UN^n$	Single stable equilibrium	Not enough feedback to cause instability; Increasing the degree of N stabilizes solutions
$\frac{(UN)^n}{(K + N)^n}$	Bistability possible, but restricted to narrow and hard-to-identify regions	Saturation adds some feedback, but only in small regions; increasing $n$ make the region harder to find

### Bistability Requires Significant Interaction with Multiple Saturation Terms and Incorporating Biological Features

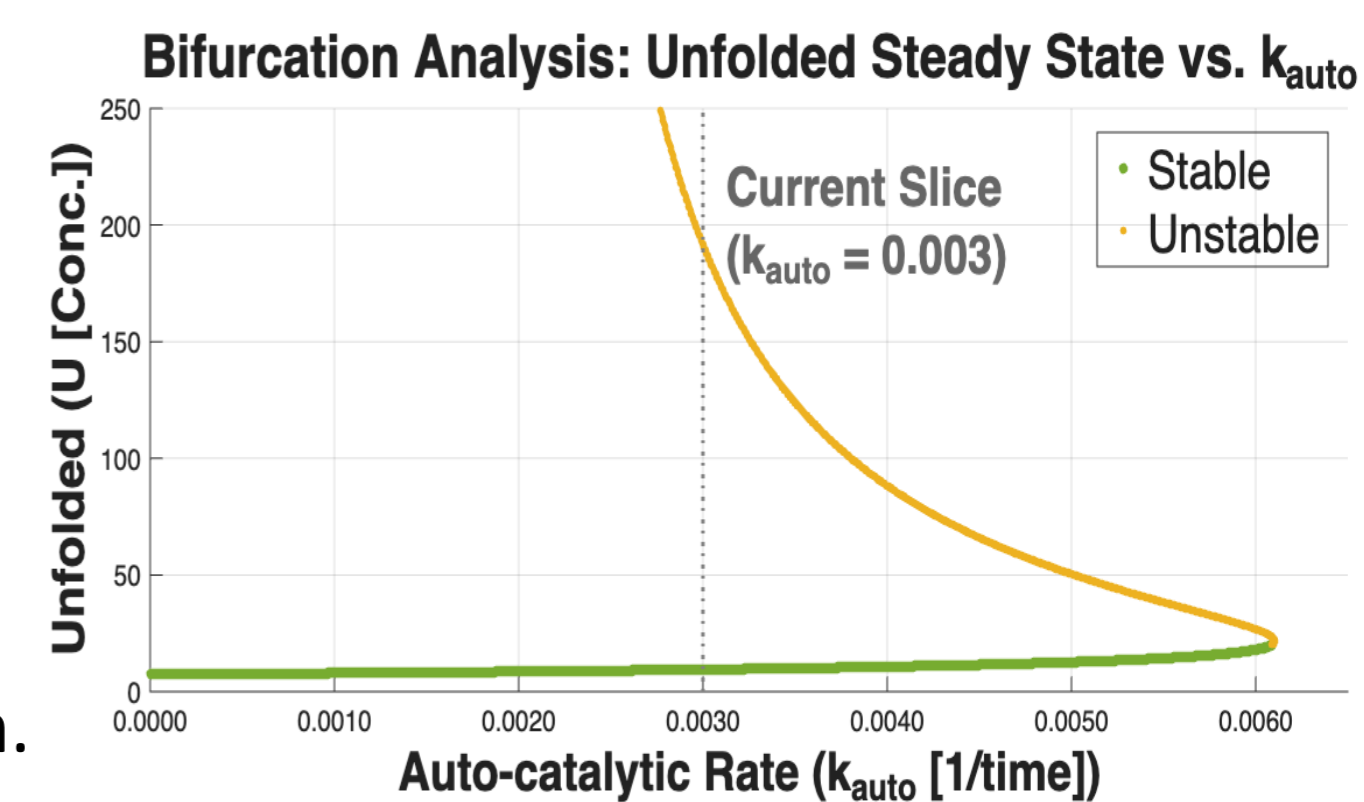
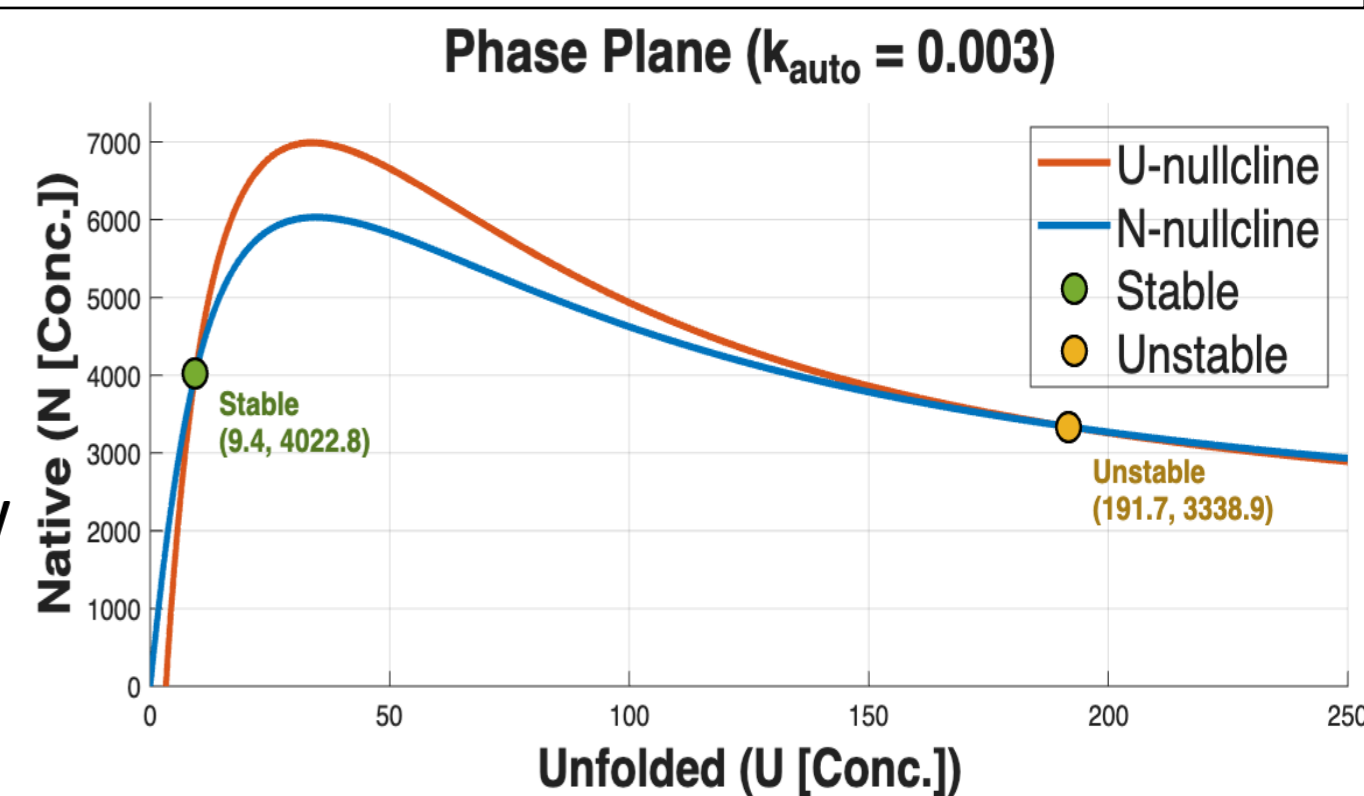
Saturation is modeled by Michaelis-Menten formation

Added  $k_s$  for spontaneous folding and separate degradation rates,  $\lambda_U \neq \lambda_N$

$$\frac{dU}{dt} = \sigma - k_s U - V_f \frac{U}{K_1 + U} + k_u N + k_{auto} U \frac{N}{K_2 + N} - V_{\lambda_U} \frac{U}{K_3 + U}$$

$$\frac{dN}{dt} = k_s U + k_f \frac{U}{K_1 + U} - k_u N - k_{auto} U \frac{N}{K_2 + N} - V_{\lambda_N} \frac{N}{K_4 + N}$$

- The system features two steady states and exhibits bistability.
- Bistable behavior still occurs within a narrow parameter window.
- Small perturbations near unstable point triggers massive shifts in protein balance.
- We were able to find bistability in biological reasonable ranges through nondimensionalization.



## 4. Conclusion

Our model shows metabolic stress shifts proteostasis stability:

- Stable baseline without strong feedback,
- Feedback can induce bistability and abrupt collapse,
- Instability occurs in specific parameter regimes.

We identify parameter regions where feedback drives the transition from resilience to collapse.

**Future Directions:** We will connect model stability thresholds to *C. elegans* biology and incorporate energy dynamics to determine whether cellular collapse is driven by proteostasis failure or energetic stress.

### References:

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- [4] Santra M., Farrell D.W., Dill K.A. *Bacterial proteostasis balances energy and chaperone use*. PNAS, 2017.
- [5] Milo R. *Protein molecules per cell volume*. BioEssays, 2013.