Effect of energy expenditure on transient dynamics of gene regulation

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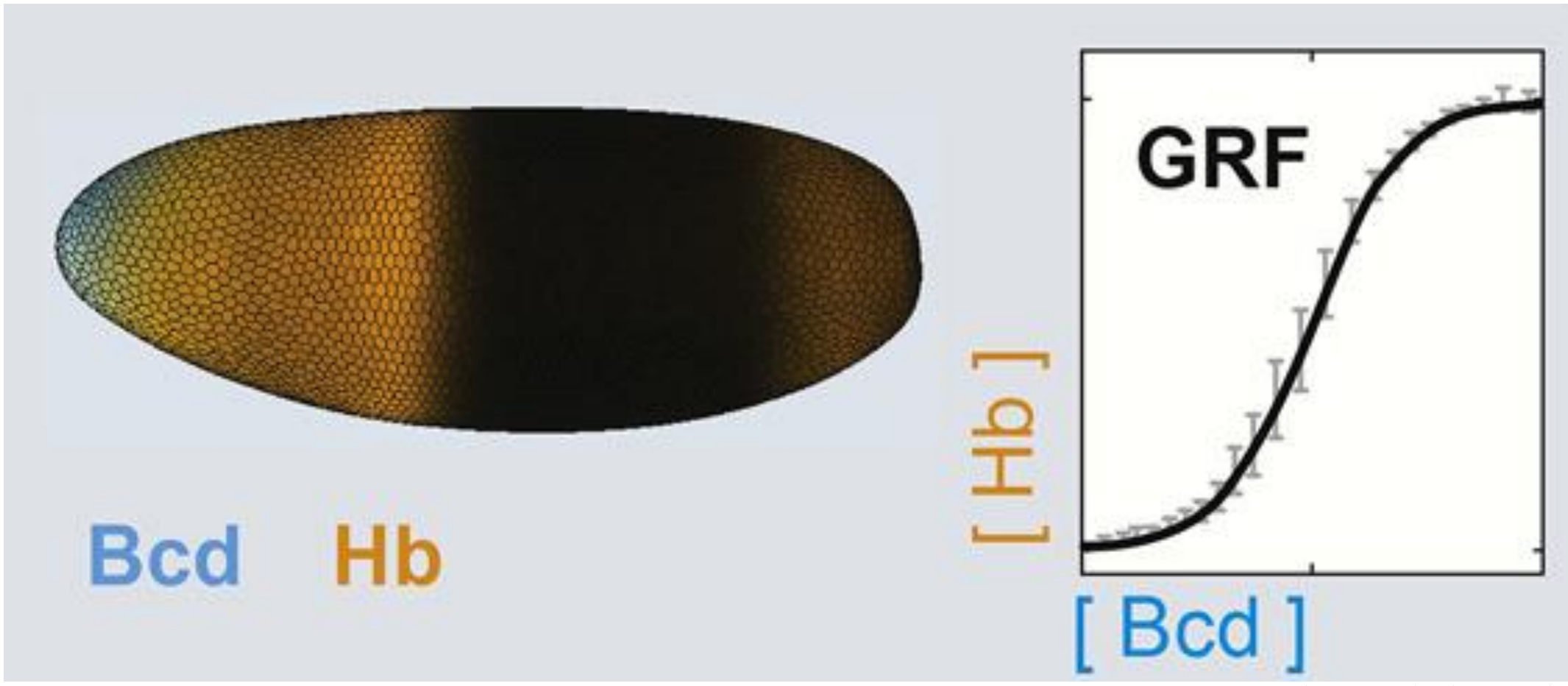
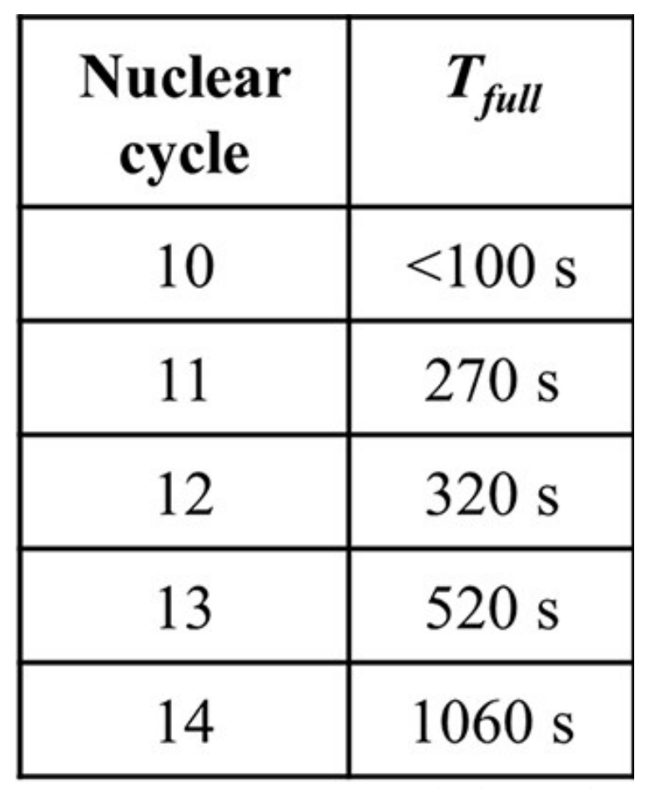
Introduction



Estrada et al. (2016)



Nuclear cycle	T_{full}
10	<100 s
11	270 s
12	320 s
13	520 s
14	1060 s

Tran et al. (2018)

Drosophila embryos express Hb in a steep pattern in response to Bcd gradient.

Energy expenditure could allow higher steepness to be accessed. (Estrada et al. 2016)

Drosophila embryos divide very rapidly in the early divisions, and the available time is insufficient for the observed steepness to develop based on current equilibrium models. (Tran et al. 2018)

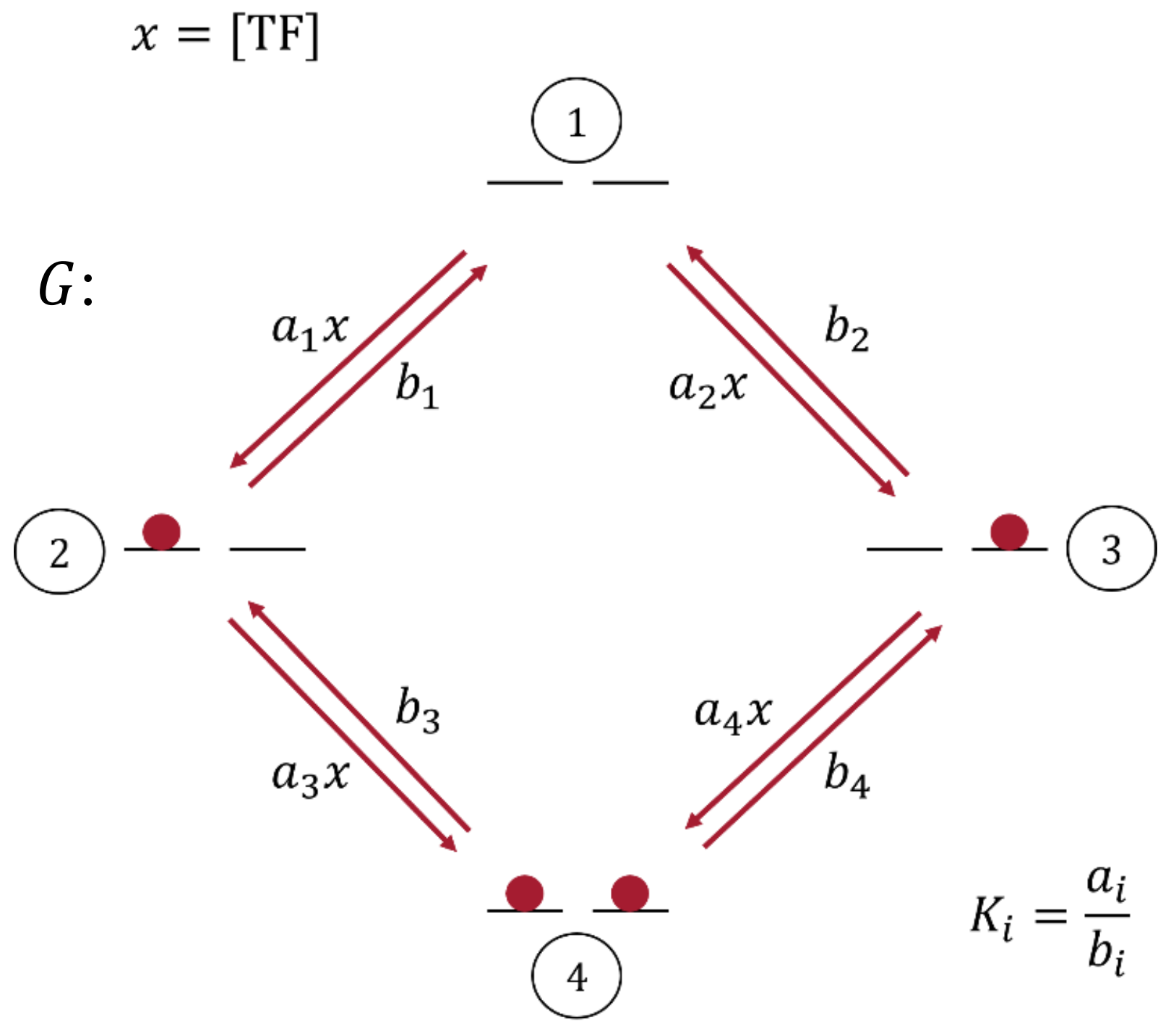
Questions

Most current models assume that gene regulation occurs at thermodynamic equilibrium (no energy is spent at steady state).

- Does spending energy hasten the time it takes for the transcription factor (TF) binding to reach a steady state, allowing a steep reproducible pattern to emerge?
- More generally, how does energy expenditure affect the transient dynamics of TF binding?

Model

$x = [\mathrm{TF}]$



$$K_i = \frac{a_i}{b_i}$$

When the product of the rates in one direction is equal to the other, i.e.,

$$a_1x \cdot a_3x \cdot b_4 \cdot b_2 = a_2x \cdot a_4x \cdot b_3 \cdot b_1$$
$$\Rightarrow \frac{K_1K_3}{K_2K_4} = 1,$$

(cycle condition), then the system is at thermodynamic equilibrium.

Moving the ratios away from this detailed balance condition results in energy expenditure at steady state, and the thermodynamic driving force (DF) measures this departure from equilibrium:

$$\mathrm{DF} = \log\frac{K_1K_3}{K_2K_4}$$

$$\mathcal{L}(G) = \begin{pmatrix} -(a_1x + a_2x) & b_1 & b_2 & 0 \\ a_1x & -(a_3x + b_1) & 0 & b_3 \\ a_2x & 0 & -(a_4x + b_2) & b_4 \\ 0 & a_3x & a_4x & -(b_3 + b_4) \end{pmatrix}$$

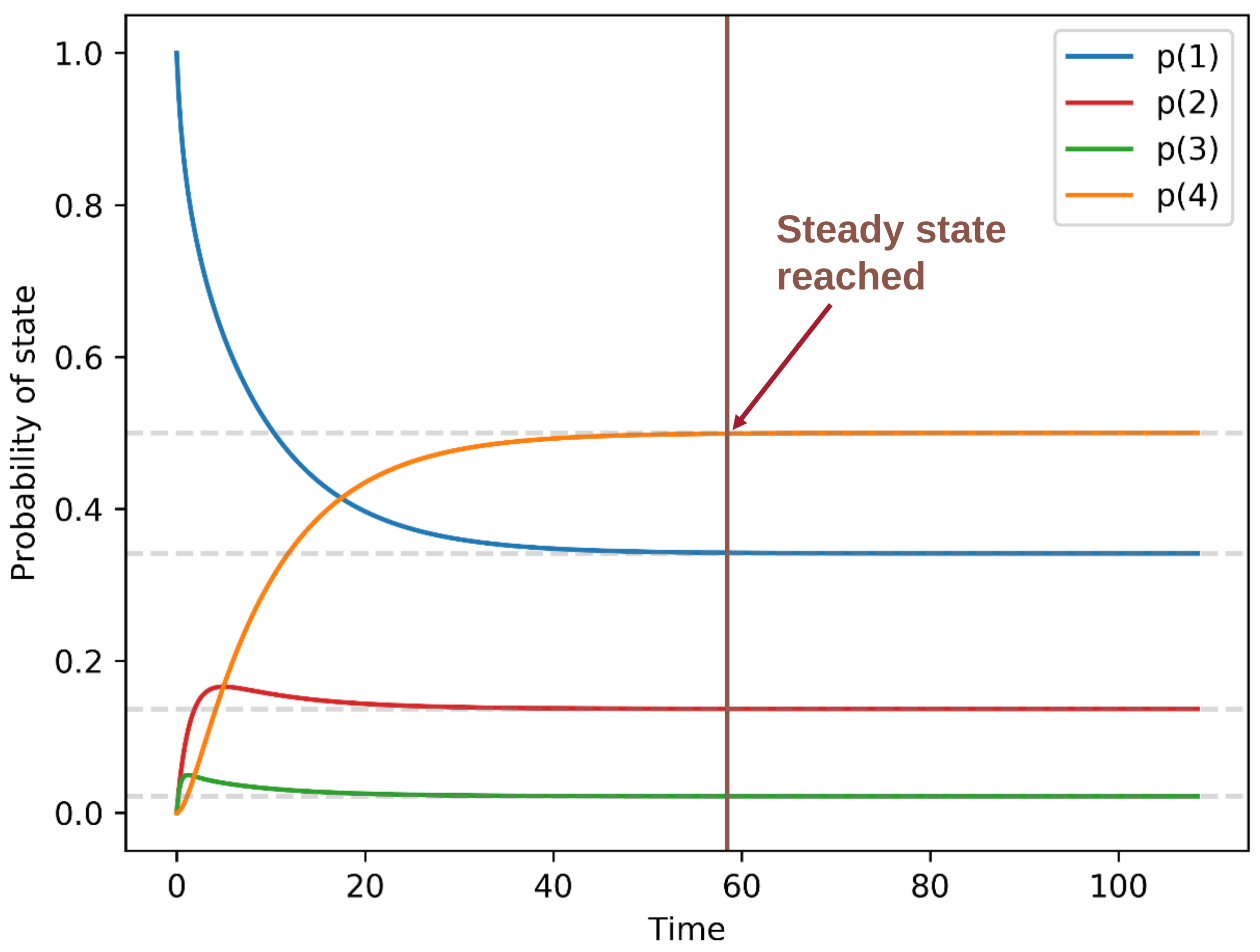
Compute eigenvalues and eigenvectors of graph Laplacian matrix to get the solution to the master equation.

$$\frac{du}{dt} = \mathcal{L}(G) \cdot u(t) \qquad (1)$$

$$u(t) = c_1e^{\lambda_1 t}v_1 + c_2e^{\lambda_2 t}v_2 + c_3e^{\lambda_3 t}v_3 + c_4e^{\lambda_4 t}v_4 \qquad (2)$$

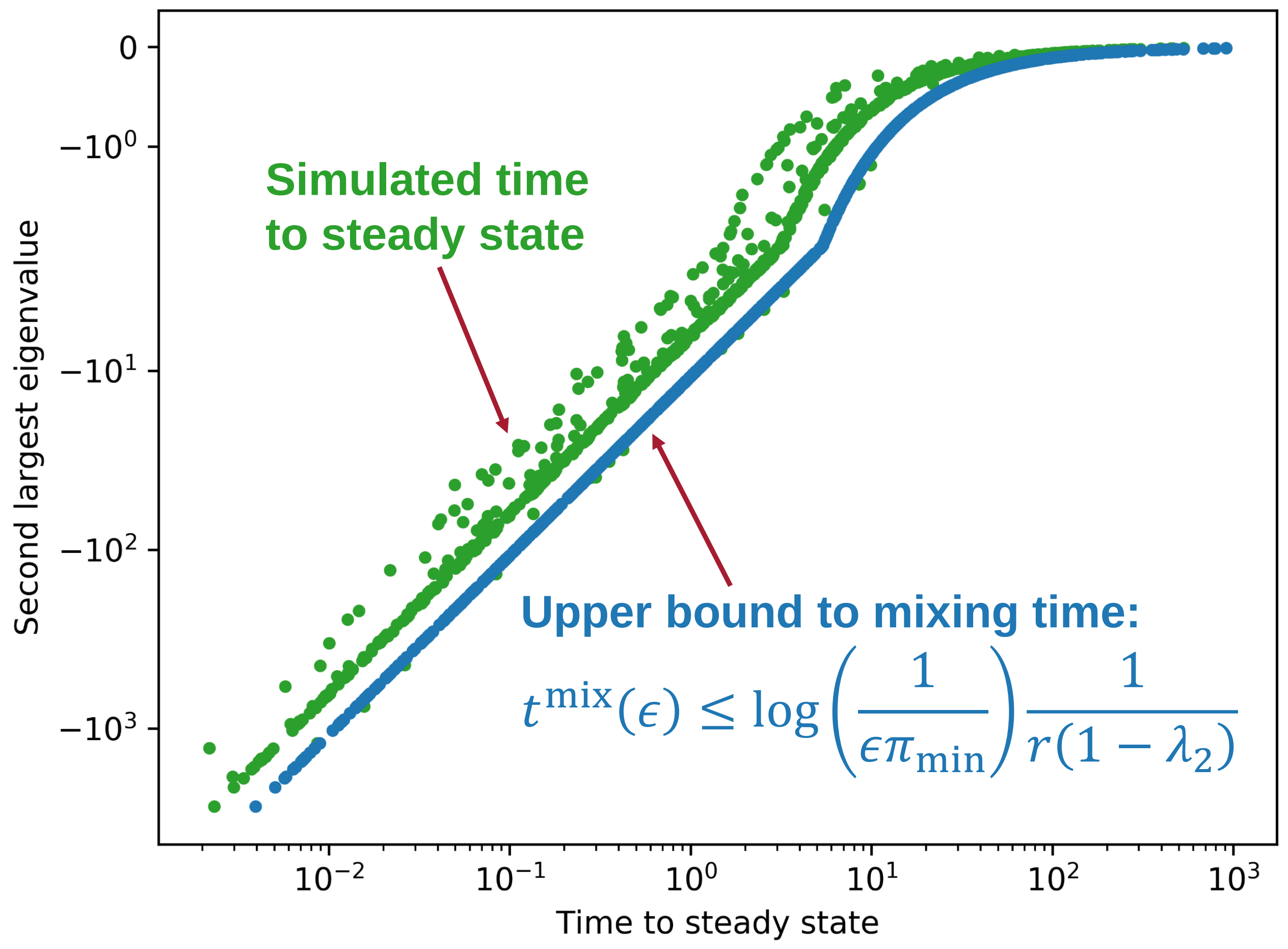
Results

One example of a simulation



Solution to equation (2) for one set of randomly chosen rates

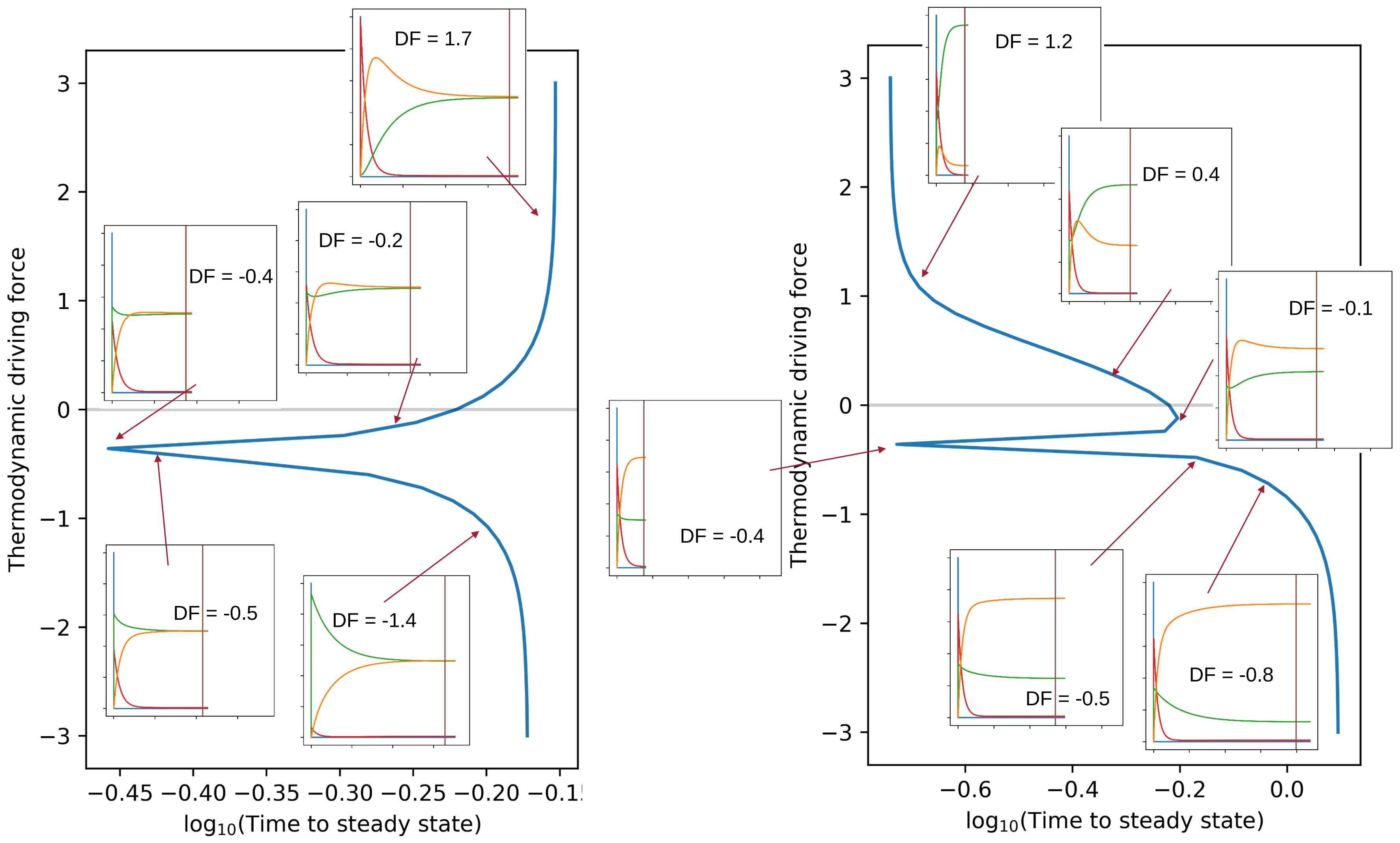
Is the second largest eigenvalue of $\mathcal{L}(G)$ a good proxy for the time to steady state?

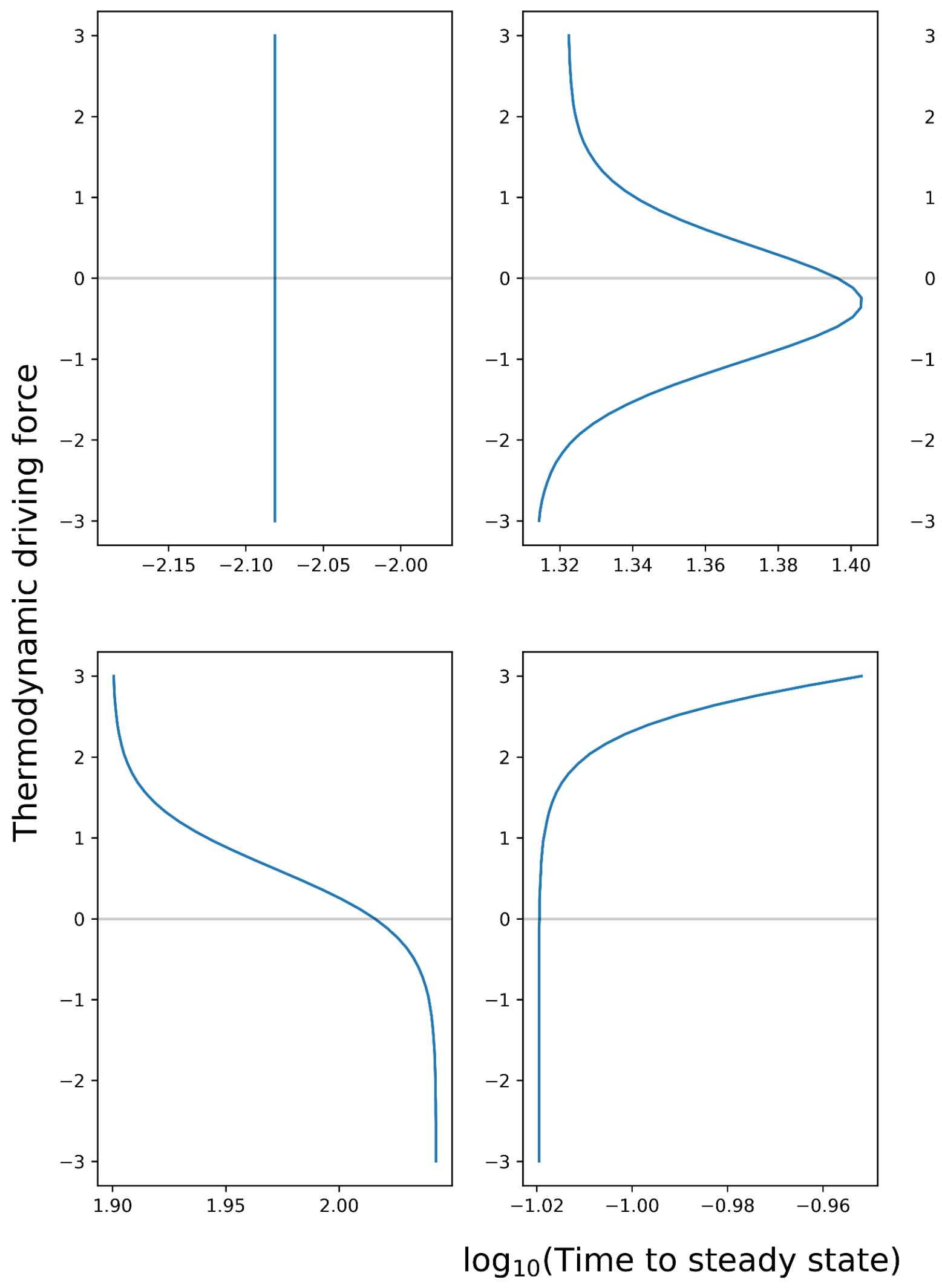


$$t^{\mathrm{mix}}(\epsilon) \leq \log\left(\frac{1}{\epsilon\pi_{\min}}\right)\frac{1}{r(1-\lambda_2)}$$

Using the second largest eigenvalue as a proxy for the time to steady state would remove the need to use simulations and avoid the resulting numerical inaccuracy, but the second largest eigenvalue only describes an upper bound, and is not a good estimate of the actual time.

Examples of different patterns for time to steady state vs. thermodynamic driving force (DF)





For different choices of rates, the energy spent vs time to steady state adopts different patterns. A few examples are shown.

Conclusion and Next Steps

The relationship between energy expenditure and time to steady state is not straightforward. Spending energy does not necessarily speed up the dynamics, and there are different patterns depending on the individual rates for each graph. Further directions to explore include:

- using more concrete measures of distance from equilibrium such as internal entropy production
- looking at the relationship between first passage times/residence times and energy expenditure
- decomposing the different parts of the response (slow vs. fast)
- studying systems with more constraints to understand the basis for different patterns.

Acknowledgments

I would like to thank the members of the Gunawardena lab, including Rosa Martinez-Corral, Pencho Yordanov, Ugur Cetiner, and Jeremy Gunawardena for their guidance on this project. I would also like to thank the Department of Systems Biology, HMS, for making this internship possible.

References

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