

Reproducibility Statement for “Thermodynamic Guardrails: A Bond Graph-Based Method for Self-Correcting Model Reduction in Autonomous Scientific Discovery”

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1 Overview

This document provides all necessary information to reproduce the simulations, figures, and key findings presented in the main paper. The experiments involve the simulation of a Michaelis-Menten enzymatic reaction using three different models: the full Stochastic Simulation Algorithm (SSA) as the ground truth, the stochastic total quasi-steady-state approximation (stQSSA), and our proposed hybrid model that uses a thermodynamic guardrail to switch between stQSSA and SSA. All code is provided in the supplementary materials, and a detailed step-by-step guide for running the simulations is available in the README.md file.

2 Hardware

All simulations were performed on a standard consumer-grade laptop. The computational cost is negligible (in minutes) in `run_ground_truth.py`, `run_hybrid.py`, `process_data.py`, and `run_sweep_heatmap.py`. However, it is acknowledged that `run_sweep_heatmap.py` may take several hours to complete in larger scale due to the extensive parameter sweeps involved. The specific hardware components used are listed below.

- **CPU:** Apple M4, 10-core.
- **RAM:** 16GB.
- **Operating System:** MacOS Sequoia 15.6.1.

3 Numerical Values

This section details the kinetic, concentration, and thermodynamic parameters required to replicate the results.

3.1 Kinetic and Concentration Parameters

The initial concentrations and kinetic rate constants for the Michaelis-Menten model ($E + S \rightleftharpoons ES \rightleftharpoons P$) are explicitly defined in Section 3.4 of the main paper. For clarity, they are:

- $[E_T] = 10$ (Total Enzyme)
- $[S_0] = 10$ (Initial Substrate)
- $k_1 = 100$
- $k_{-1} = 1$
- $k_2 = 1$
- $k_{-2} = 0.01$

3.2 Thermodynamic Calculations and Constants

The thermodynamic guardrail relies on calculating the net thermodynamic affinity (A_{net}) of the overall reaction $S \rightleftharpoons P$. The affinity serves as the driving force for the reaction.

The chemical potential, μ_i , for a given species i is calculated as:

$$\mu_i = \mu_i^0 + RT \ln[i] \quad (1)$$

where μ_i^0 is the standard chemical potential, R is the ideal gas constant, T is the temperature, and $[i]$ is the concentration of the species.

The net affinity is the difference between the chemical potential of the reactant (S) and the product (P):

$$A_{\text{net}} = \mu_S - \mu_P \quad (2)$$

By substituting Equation 1 into Equation 2, the expression becomes:

$$A_{\text{net}} = (\mu_S^0 - \mu_P^0) + RT \ln \left(\frac{[S]}{[P]} \right) \quad (3)$$

For the simulations presented in this work, the standard Gibbs free energies (g_S and g_E) are assumed to be zero. This simplifies the calculation, since $g_P = -\ln(10000)$:

$$A_{\text{net}} = RT \ln \left(10000 \cdot \frac{[S]}{[P]} \right) \quad (4)$$

The specific physical constants used in the simulation code (`run_hybrid.py`) are:

- **Ideal Gas Constant (R):** 8.314 J K⁻¹mol⁻¹
- **Temperature (T):** 310.15 K