

Michaelis-Menten theory

The Michaelis-Menten reaction models the kinetics of enzyme E reacting with substrate S to form complex ES and release product P and the enzyme:



In this analysis, it is assumed that:

- There is a single molecule enzyme in either E or ES form and the number of molecules of S and P is large enough to not be affected by the reaction.
- The reactions are modeled as random interactions in an environment at temperature T in contact with a thermal reservoir which is assumed to be in equilibrium.⁹

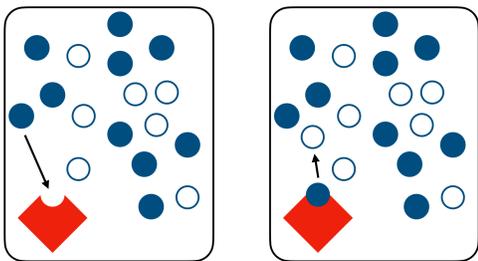


Figure 1. Figure adapted from Seifert (2010),⁹ where the solution is composed by substrate (filled circle), product (empty circle) and single enzyme (red square). The single enzyme interacts with the solution and changes its state.

The system consists of n_E molecules of E and n_{ES} molecules of ES , being the system states $\{x \in \mathcal{X} | x = (x_i, x_j)\}$ with $\mathcal{X} = \{0, \dots, n_E\} \times \{0, \dots, n_{ES}\}$.

- The evolution of the system is modeled as a Markov jump process between states x whose probability $p_x(t)$ solves the following **master equation**^{10,3}

$$\frac{dp_x(t)}{dt} = \sum_{\mathcal{X}} W_{xx'} p_{x'}(t) - W_{x'x} p_x(t) \quad (1)$$

- $W_{xx'}$ (k_ν) is the **probability transition rate** from a state x to state x' , it depends on the kinetics, and it is an element of the $|\mathcal{X}| \times |\mathcal{X}|$ rate transition matrix W equal to:⁵

$$-\sum_{\nu} a_{\nu}(x, k_{\nu}) \delta(x - x') + a_{\nu}(x - s_{\nu}, k_{\nu}) \delta(x - x' + s_{\nu}),$$

where the following terms were defined:

- $a_{\nu}(x, k_{\nu}) = \prod_{x_i \in x} k_{\nu} \frac{x_i!}{(x_i - s_{i,\nu})!}$ is the propensity function for the ν -th reaction with rate k_{ν} ;
- $s_{\nu} = (s_{i,\nu}, s'_{i,\nu})$ is the change in the number of molecules of $x_i \in x$ participating in the ν -th reaction;
- $\delta(x) = 1$ only if $x \equiv (0, 0)$, otherwise is 0.

Considering the system with $n_E + n_{ES} = 1$, it can be verified that the states $(0, 0)$ and $(1, 1)$ have no transitions coming to or leaving them, thus W can be reduced to 2×2 and set $p_x(t) = 0$ for those states.

Stochastic Thermodynamics (ST)

The energy transfer in systems modeled at the mesoscopic scale with stochastic dynamics which are open and out-of-equilibrium is the subject of Stochastic Thermodynamics.^{6,2}

- Systems at equilibrium are **reversible**, i.e. the transition $x \rightarrow x'$ occurs with rate $W_{xx'}$, and its reversed transition $x' \rightarrow x$ has the rate $W_{x'x} = W_{xx'}$.
- At **nonequilibrium** a system is kept at steady-state by exchanging an entropy to the reservoir (local detailed balance, LDB) which is proportional to $\ln(W_{xx'}/W_{x'x})$.⁴
- The transition $x' \rightarrow x$ exchanges with the reservoir an amount of entropy equal to

$$s_{x' \rightarrow x}^{flu} = k_B T \ln \frac{W_{xx'}}{W_{x'x}}. \quad (2)$$

- In the same transition, the system produces an amount of entropy equal to

$$s_{x' \rightarrow x}^{prod} = k_B T \ln \frac{W_{xx'} p_{x'}(t)}{W_{x'x} p_x(t)}.$$

- The entropy balance during the transition is

$$s_{x' \rightarrow x}^{bal} = k_B T \ln \frac{p_{x'}(t)}{p_x(t)}$$

which is equal to $s_{x' \rightarrow x}^{prod} - s_{x' \rightarrow x}^{flu}$.

The average of (2) over the probability of the system to transition to x gives the **average entropy flux rate**.⁶

$$\dot{S}^{flu} = k_B T \frac{1}{2} \sum_{x \neq x'} [W_{xx'} p_{x'}(t) - W_{x'x} p_x(t)] \ln \frac{W_{xx'}}{W_{x'x}}$$

- The **average entropy production rate** and the **average entropy balance rate**⁸ are, respectively:

$$\dot{S}^{prod} = k_B T \frac{1}{2} \sum_{x \neq x'} [W_{xx'} p_{x'}(t) - W_{x'x} p_x(t)] \ln \frac{W_{xx'} p_{x'}(t)}{W_{x'x} p_x(t)},$$

$$\dot{S}^{bal} = k_B T \frac{1}{2} \sum_{x \neq x'} [W_{xx'} p_x(t) - W_{x'x} p_{x'}(t)] \ln \frac{p_{x'}(t)}{p_x(t)}$$

The **nonequilibrium free energy** $F(t)$ is the information I needed to specify the nonequilibrium system at time t ¹

$$F(t) - F^{eq} = k_B T I(t) \equiv k_B T D_{KL}(p(t) || p^{eq}) \quad (4)$$

where F^{eq} is the time-independent **equilibrium free energy**.

- D_{KL} is the Kullback-Leibler divergence measuring the "difference" between the nonequilibrium probability $p(t)$ and the equilibrium probability p^{eq} , mathematically:

$$D_{KL}(p(t) || p^{eq}) = \sum_{\mathcal{X}} p_x(t) \ln \frac{p_x(t)}{p_x^{eq}}.$$

- The **nonequilibrium free energy rate** is given by the derivative of (4) with respect to time

$$\dot{F}(t) = k_B T \sum_{x \neq x'} [W_{xx'} p_{x'}(t) - W_{x'x} p_x(t)] \ln \frac{p_x(t)}{p_x^{eq}}.$$

Results

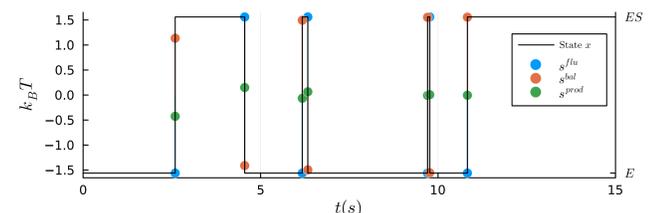


Figure 2. Single trajectory of the Markov jump process for the Michaelis-Menten with $k_1 = 0.5$, $k_{-1} = 0.005$, $k_2 = 0.1$ and $k_{-2} \approx 0.0$, and entropy exchange/balance/production for that trajectory.

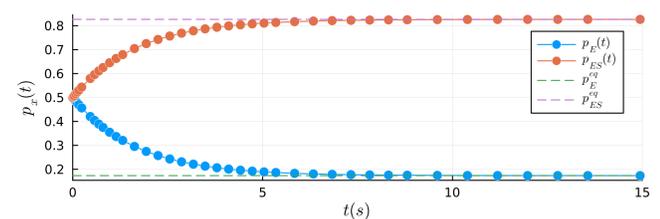


Figure 3. Time evolution of the probability of the states of the system, p_E and p_{ES} , and the probability of the states for the system in equilibrium, p_E^{eq} and p_{ES}^{eq} .

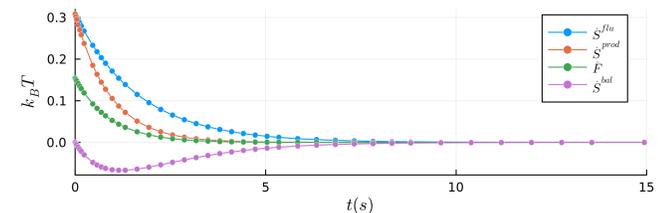


Figure 4. Average entropy flux rate, average entropy production rate, free energy rate and average entropy balance rate.

Some conclusions are:

- The system relaxes to the equilibrium and, once there, it stabilizes at reservoir properties (e.g. intensive quantities as temperature, chemical potential, etc.);
- The nonequilibrium free energy of the system is greater than the equilibrium one, thus indicating that work can be exchanged between the system and the reservoir before it gets equilibrated;
- To sustain the nonequilibrium, work must be applied to the system, which is object of future investigations;
- The evaluation of the quantities \dot{S}^{prod} , \dot{S}^{bal} , their respective average rates \dot{S}^{flu} , \dot{S}^{prod} , and \dot{S}^{bal} is only possible because of the numerical solution of (1), which is hard to solve for systems with large number of particles. The conventional approach is to use Gillespie algorithm to obtain an ensemble of trajectories;
- Future explorations are needed to compare the results of the entropies evaluated with the ensemble of trajectories and the numerical integration of (1).

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