Mesoscopic thermodynamics of single-particle enzymatic reactions

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Michaelis-Menten theory

The transitions in the Michaelis-Menten case represent the changes in the configuration of the single enzyme (E) to complexed with substrate (ES) and back.

- The reaction network that models the kinetics is:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E + P \tag{1}$$

where P is the product of the complete process.

- The transitions occur due to the random interactions of the enzyme with the solution, the later acting as a reservoir in equilibrium with defined temperature T.[9]

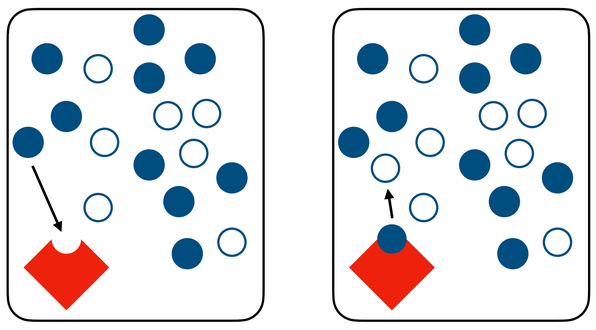

Figure 1. Figure adapted from Seifert (2010),[9] where the solution is composed by substrate (filled circle), product (empty circle) and single enzyme (red). The single enzyme is randomly interacting with the solution changing its state.

- The system performs a Markovian jump process with the states having probability[3] given by the solution of the following **Master equation**[10]

$$\frac{dp_x(t)}{dt} = \sum_x W_{x'x}p_x(t) - W_{xx'}p_{x'}(t) \tag{2}$$

- The $W_{xx'}$ is the **probability transition rate** from the state x' to x, it forms a **stochastic matrix** W dependent on the kinetics of the chemical reactions:[5]

$$W_{x'x} = -\sum_\nu a_\nu(x_\nu)\delta(x - x') + a_\nu(x_\nu)\delta(x - x' - s_\nu), \tag{3}$$

where were defined:
- The **propensity function** $a_\nu(x) = \prod_i k_\nu \frac{x_i!}{(x_i - s_{i,\nu})!}$ for each ν-th reaction, with the vector of states $x = [x_1, ..., x_i, ...]$ and state changes $s = [s_1, ..., s_i, ...]$;
- $x_{i,\nu}$ as the number of molecules in the system of the i-th reactant in the ν-th reaction;
- $s_{i,\nu}$ as the number of molecules of the i-th reactant participating in the ν-th reaction.

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Stochastic Thermodynamics (ST)

The energy transfer of systems at mesoscopic scale with stochastic dynamics which are open and out-of-equilibrium is the subject of study Stochastic Thermodynamics.[6,2]

- Systems at equilibrium have **reversible trajectory**, i.e. a transition of the system from the state $x \to x'$ at has the rate $W_{xx'}$ and its reversed transition $x' \to x$ has the rate $W_{x'x} = W_{xx'}$.
- At **non-equilibrium** a system is kept stationary by dissipating energy (local detailed balance, LDB) proportional to $\ln(W_{xx'}/W_{x'x})$ in each transition.[4]

- The transition $x \to x'$ must expel/absorb an amount of entropy equals to

$$s(t) = k_B T \ln \frac{W_{xx'}}{W_{x'x}} \tag{4}$$

- Solving (2), one obtains the probabilities to compute the **average rate entropy flux** which is expelled/absorbed by the reservoir:[6]

$$\dot{S}^{res} = k_B T \frac{1}{2} \sum_{x \neq x'} [W_{x'x}p_x(t) - W_{xx'}p_{x'}(t)] \ln \frac{W_{x'x}}{W_{xx'}} \tag{5}$$

- From the average, one obtains the relations for the **average entropy production rate** and **entropy balance rate**,[8] respectively:

$$\dot{S}^{tot} = k_B T \frac{1}{2} \sum_{x \neq x'} [W_{x'x}p_x(t) - W_{xx'}p_{x'}(t)] \ln \frac{W_{x'x}p_x(t)}{W_{xx'}p_{x'}(t)}; \tag{6a}$$

$$\dot{S}^{sys} = k_B T \frac{1}{2} \sum_{x \neq x'} [W_{x'x}p_x(t) - W_{xx'}p_{x'}(t)] \ln \frac{p_x(t)}{p_{x'}(t)}. \tag{6b}$$

The probability of the state when the system is in equilibrium p_x^{eq} gives the **generalized free energy rate**:[7]

$$\dot{F}(t) - \dot{F}^{eq}(t) = \sum_{x \neq x'} [W_{x'x}p_x(t) - W_{xx'}p_{x'}(t)] \ln \frac{p_x(t)}{p_{x'}^{eq}}, \tag{7}$$

where $\dot{F}^{eq}$ is the equilibrium free energy rate.

- The nonequilibrium free energy rate in (7) is defined as the information I needed to specify the nonequilibrium state,[1] thus

$$F(t) - F^{eq}(t) = k_B T I(t) \equiv T D_{KL}(p_x(t)||p_x^{eq}(t)) \geq 0 \tag{8}$$

where D_{KL} is the Kullback-Leibler divergence measuring the "difference" between the nonequilibrium and the equilibrium probability distributions.

Fluctuation theorems set constrains on the distributions of the observables above:

- The **integral** and the **detailed** fluctuation relation constrain the entropy production[6]

$$\langle e^{s(t)/k_B T} \rangle_F = 1, \quad \frac{p(s)}{p(-s)} = e^{s/k_B T}. \tag{9}$$

There are other relations as Crooks and Jarzynski relations which deal with the fluctuations in the work applied to the system. They are, respectively:

$$\langle e^{-w/k_B T} \rangle_F = e^{-\Delta F/k_B T}, \quad \frac{p(w;\lambda)}{p(-w;\hat{\lambda})} = e^{(w-\Delta F)/k_B T}.$$

But as there is no driving or control protocol λ (and its time-reversed $\hat{\lambda}$), the analysis will not be done in this work,

Results

The system was simulated using the parameters $k_1 = 0.5$, $k_{-1} = 0.005$, $k_2 = 0.1$ and $k_{-2} = 0.0$.

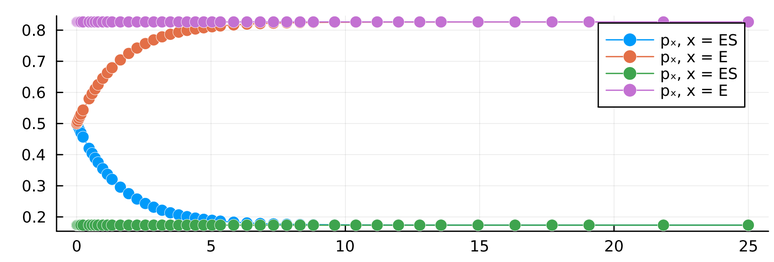

Figure 2. The time evolution of the system compared to its equilibrium probability values.

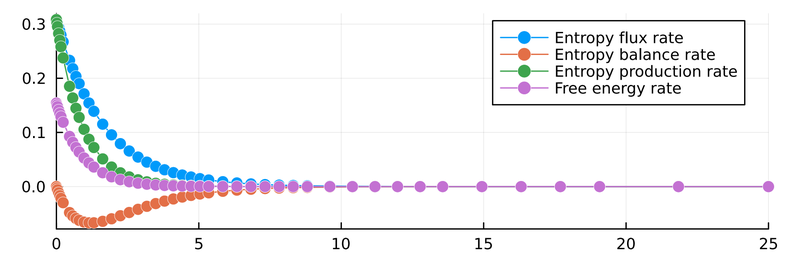

Figure 3. Average entropy flux, balance, production ans free energy rates evaluated according to ST.

Below are shown 5 different trajectories of the system and the thermodynamic observables in each one.

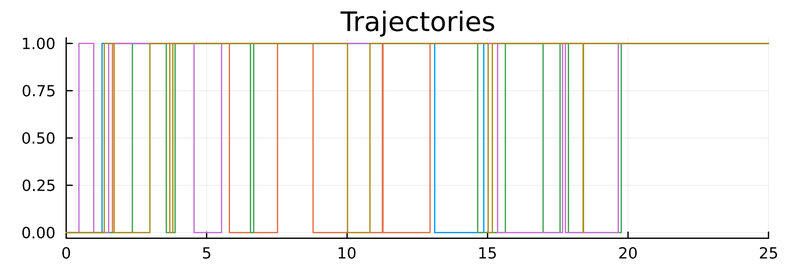

Figure 4. Simulation of the Markov jump process for the Michaelis-Menten. Each color is a different trajectory of the system. The enzyme jumps from the state E (0.00 in y-axis) to ES (1.00 in y-axis).

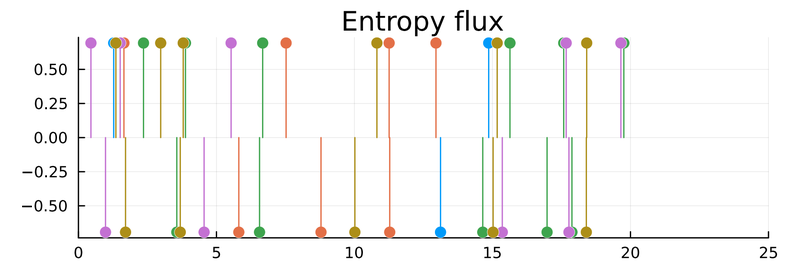

Figure 5. Stochastic entropy flux per $k_B T$ released in each transition in time. Each color is a different trajectory of the system.

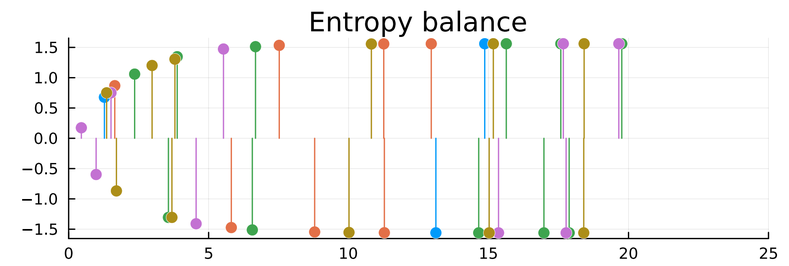

Figure 6. Stochastic entropy balance per $k_B T$ released in each transition in time. Each color is a different trajectory of the system.

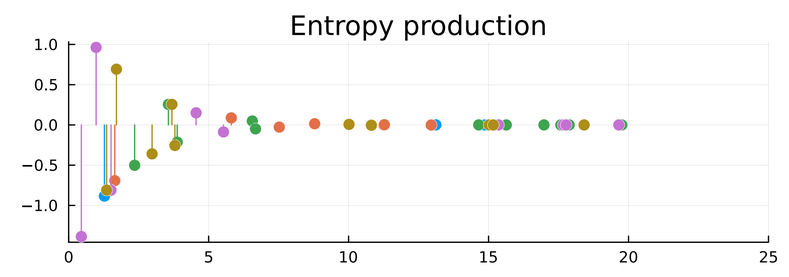

Figure 7. Stochastic entropy production per $k_B T$ released in each transition in time. Each color is a different trajectory of the system..