

LECTURE #14

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THERMODYNAMIC BEHAVIOR

Thermodynamic Systems

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- We can view a Markovian reaction network as a thermodynamic system that:
 - ▣ absorbs energy
 - ▣ produces entropy
 - ▣ dissipates heat
- This perspective can provide important insights into functional properties of the network, such as robustness and stability.
- It can also lead to a better understanding of the relationship between the network's microscopic/mesoscopic (unobservable) and macroscopic (observable) behavior.

Thermodynamic Systems

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- Consider an irreducible Markovian reaction network comprised of $M / 2$ pairs of reversible reactions $(2m-1, 2m)$.
 - ▣ $2m-1$ is the forward reaction
 - ▣ $2m$ is the reverse reaction
- This does not forbid us to consider irreversible reactions, since an irreversible reaction can be thought of as being reversible with negligible propensity in the reverse direction.
- The reaction network is characterized by a unique population probability distribution $p_{\mathbf{x}}(\mathbf{x};t)$ that is analytic for all $t \geq 0$ and converges to a stationary distribution $\bar{p}_{\mathbf{x}}(\mathbf{x})$, which does not depend on the initial state $\mathbf{x}(0)$.

Thermodynamic Systems

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- We can define the energy of a state \mathbf{x} by

$$E(\mathbf{x}) \triangleq -\frac{1}{\Omega} \ln \bar{p}_{\mathbf{x}}(\mathbf{x})$$

where Ω is an appropriately chosen size parameter.

Thermodynamic Systems

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- Here, the discussion is purely mathematical in nature and can be applied to any physical or nonphysical Markovian reaction network.
- Direct connection to thermodynamics can be made in certain physical systems, such as biochemical reaction networks, which may exchange matter, work, and heat through a well-defined boundary that separates the system from its surroundings (open system).
- In this case, we must take the size Ω to be the inverse of $k_B T$.
 - ▣ k_B is the [Boltzmann constant](https://en.wikipedia.org/wiki/Boltzmann_constant)
 - ▣ T is the system temperature.
- Since the exact value of Ω is not important here, we set $\Omega = 1$ for simplicity.

https://en.wikipedia.org/wiki/Boltzmann_constant

Fundamental Thermodynamic Quantities

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$$E(\mathbf{x}) \triangleq -\ln \bar{p}_{\mathbf{x}}(\mathbf{x}), \quad \text{for every } \mathbf{x} \quad \textbf{Energy of State}$$

$$U(t) \triangleq \sum_{\mathbf{x}} E(\mathbf{x}) p_{\mathbf{x}}(\mathbf{x};t), \quad \text{for } t \geq 0 \quad \textbf{Internal Energy}$$

$$S(t) \triangleq -\sum_{\mathbf{x}} p_{\mathbf{x}}(\mathbf{x};t) \ln p_{\mathbf{x}}(\mathbf{x};t), \quad \text{for } t \geq 0 \quad \textbf{Entropy}$$

$$F(t) \triangleq U(t) - S(t) = \sum_{\mathbf{x}} p_{\mathbf{x}}(\mathbf{x};t) \ln \frac{p_{\mathbf{x}}(\mathbf{x};t)}{\bar{p}_{\mathbf{x}}(\mathbf{x})}, \quad \text{for } t \geq 0$$

Helmholtz Free Energy

Fundamental Thermodynamic Quantities

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$$F(t) \triangleq U(t) - S(t) = \sum_{\mathbf{x}} p_{\mathbf{x}}(\mathbf{x};t) \ln \frac{p_{\mathbf{x}}(\mathbf{x};t)}{\bar{p}_{\mathbf{x}}(\mathbf{x})}, \quad \text{for } t \geq 0$$

Helmholtz Free Energy

- It measures the energy available in a thermodynamic system to do work under constant temperature and volume.
- It coincides with the [Kullback-Leibler divergence](#) of the probability distribution $p_{\mathbf{x}}(\mathbf{x};t)$ from the steady-state probability distribution $\bar{p}_{\mathbf{x}}(\mathbf{x})$.
- It provides a measure of how far a Markovian reaction network is from steady-state at time t .
- It turns out that

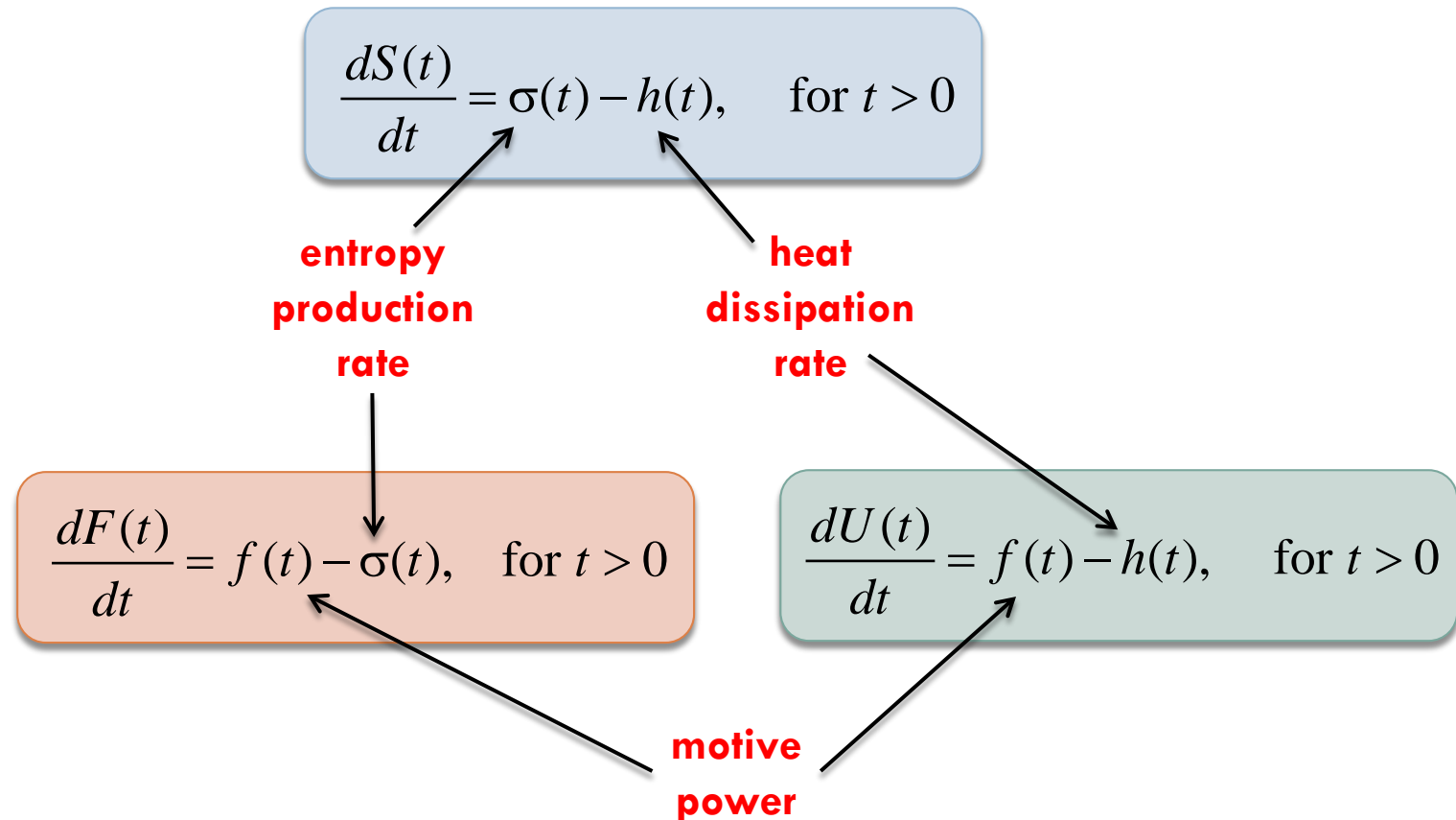
$$F(t) \geq 0, \quad t \geq 0$$

$$\frac{dF(t)}{dt} \leq 0, \quad t \geq 0$$

with equality only at steady-state.

Balance Equations

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Balance Equations

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$$\frac{dS(t)}{dt} = \sigma(t) - h(t), \quad \text{for } t > 0$$

**entropy
production
rate** **heat
dissipation
rate**

Balance Equations

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entropy production rate

$$\sigma(t) = \frac{1}{2} \sum_{m=1}^{M/2} \sum_{\mathbf{x}} [\rho_m^+(\mathbf{x};t) A_m^+(\mathbf{x};t) + \rho_m^-(\mathbf{x};t) A_m^-(\mathbf{x};t)]$$

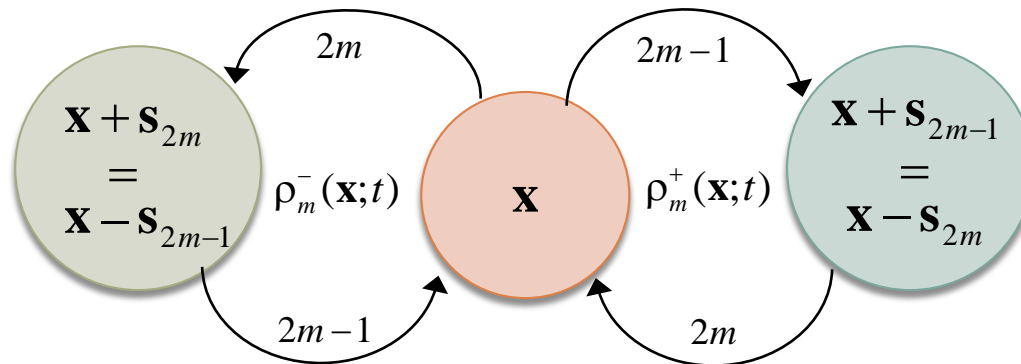
$(2m-1, 2m)$ reversible reactions $\Rightarrow \mathbf{s}_{2m} = -\mathbf{s}_{2m-1}$

net flux of m -th pair of reversible reactions transitioning between states \mathbf{x} and $\mathbf{x} + \mathbf{s}_{2m-1}$

$$\rho_m^+(\mathbf{x};t) = \pi_{2m-1}(\mathbf{x}) p_{\mathbf{x}}(\mathbf{x};t) - \pi_{2m}(\mathbf{x} + \mathbf{s}_{2m-1}) p_{\mathbf{x}}(\mathbf{x} + \mathbf{s}_{2m-1};t)$$

net flux of m -th pair of reactions transitioning between states \mathbf{x} and $\mathbf{x} + \mathbf{s}_{2m}$

$$\rho_m^-(\mathbf{x};t) = \pi_{2m}(\mathbf{x}) p_{\mathbf{x}}(\mathbf{x};t) - \pi_{2m-1}(\mathbf{x} - \mathbf{s}_{2m-1}) p_{\mathbf{x}}(\mathbf{x} - \mathbf{s}_{2m-1};t)$$



Balance Equations

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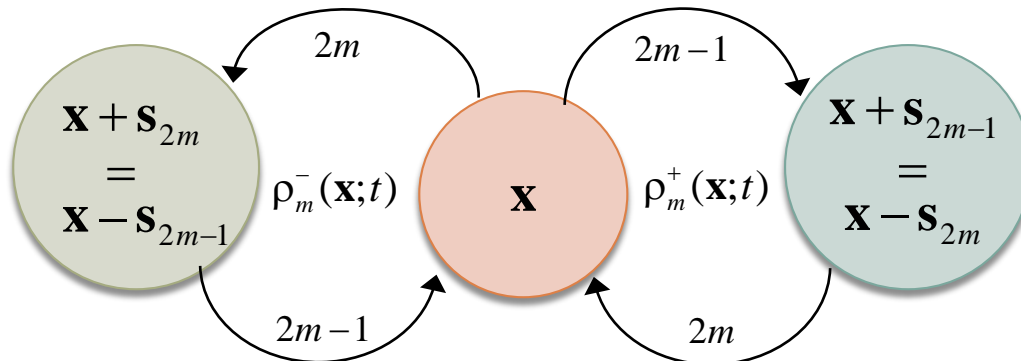
entropy production rate

$$\sigma(t) = \frac{1}{2} \sum_{m=1}^{M/2} \sum_{\mathbf{x}} [\rho_m^+(\mathbf{x}; t) A_m^+(\mathbf{x}; t) + \rho_m^-(\mathbf{x}; t) A_m^-(\mathbf{x}; t)]$$

affinities of the m -th pair of reactions

$$A_m^+(\mathbf{x}; t) \triangleq \ln \left[\frac{\pi_{2m-1}(\mathbf{x}) p_{\mathbf{x}}(\mathbf{x}; t)}{\pi_{2m}(\mathbf{x} + \mathbf{s}_{2m-1}) p_{\mathbf{x}}(\mathbf{x} + \mathbf{s}_{2m-1}; t)} \right]$$

$$A_m^-(\mathbf{x}; t) \triangleq \ln \left[\frac{\pi_{2m}(\mathbf{x}) p_{\mathbf{x}}(\mathbf{x}; t)}{\pi_{2m-1}(\mathbf{x} - \mathbf{s}_{2m-1}) p_{\mathbf{x}}(\mathbf{x} - \mathbf{s}_{2m-1}; t)} \right]$$



Balance Equations

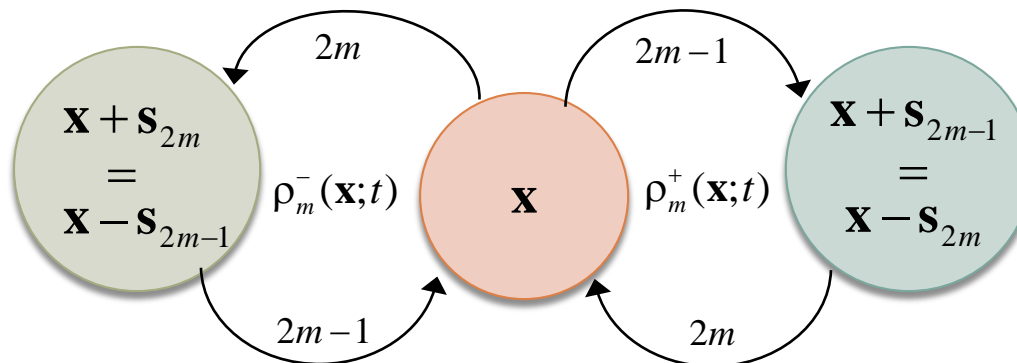
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□ The affinity

$$A_m^+(\mathbf{x};t) \triangleq \ln \left[\frac{\pi_{2m-1}(\mathbf{x}) p_{\mathbf{x}}(\mathbf{x};t)}{\pi_{2m}(\mathbf{x} + \mathbf{s}_{2m-1}) p_{\mathbf{x}}(\mathbf{x} + \mathbf{s}_{2m-1};t)} \right]$$

can be viewed as a thermodynamic force that drives a Markovian reaction network from state \mathbf{x} to state $\mathbf{x} + \mathbf{s}_{2m-1}$.

- If $A_m^+(\mathbf{x};t) > 0$, then $\pi_{2m-1}(\mathbf{x}) p_{\mathbf{x}}(\mathbf{x};t) dt > \pi_{2m}(\mathbf{x} + \mathbf{s}_{2m-1}) p_{\mathbf{x}}(\mathbf{x} + \mathbf{s}_{2m-1};t) dt$ which means that the probability of moving from state \mathbf{x} to state $\mathbf{x} + \mathbf{s}_{2m-1}$ within dt by means of the forward reaction $2m-1$ will be higher than the probability of moving from state $\mathbf{x} + \mathbf{s}_{2m-1}$ to state \mathbf{x} by means of the reverse reaction $2m$.



Balance Equations

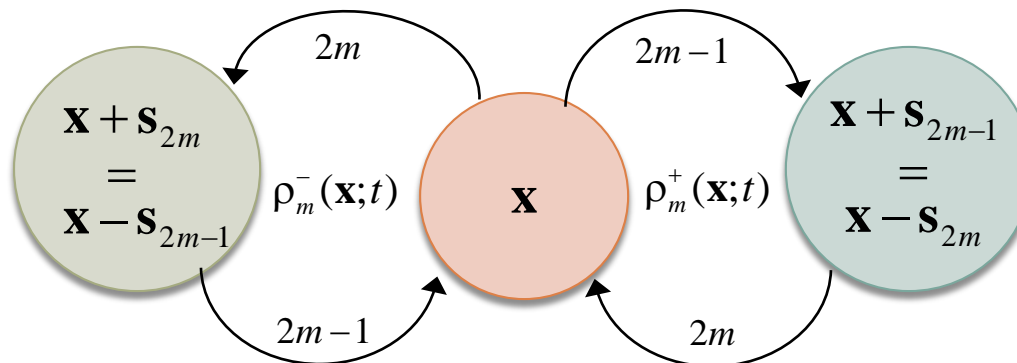
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□ The affinity

$$A_m^-(\mathbf{x};t) \triangleq \ln \left[\frac{\pi_{2m}(\mathbf{x}) p_{\mathbf{x}}(\mathbf{x};t)}{\pi_{2m-1}(\mathbf{x} - \mathbf{s}_{2m-1}) p_{\mathbf{x}}(\mathbf{x} - \mathbf{s}_{2m-1};t)} \right]$$

can be viewed as a thermodynamic force that drives a Markovian reaction network from state \mathbf{x} to state $\mathbf{x} - \mathbf{s}_{2m-1}$.

- If $A_m^-(\mathbf{x};t) > 0$, then $\pi_{2m}(\mathbf{x}) p_{\mathbf{x}}(\mathbf{x};t) dt > \pi_{2m-1}(\mathbf{x} - \mathbf{s}_{2m-1}) p_{\mathbf{x}}(\mathbf{x} - \mathbf{s}_{2m-1};t) dt$ which means that the probability of moving from state \mathbf{x} to state $\mathbf{x} - \mathbf{s}_{2m-1}$ within dt by means of the reverse reaction $2m$ will be higher than the probability of moving from state $\mathbf{x} - \mathbf{s}_{2m-1}$ to state \mathbf{x} by means of the forward reaction $2m-1$.



Balance Equations

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- We also we have that

heat dissipation rate

$$h(t) = \frac{1}{2} \sum_{m=1}^{M/2} \sum_{\mathbf{x}} \left\{ \rho_m^+(\mathbf{x}; t) \ln \left[\frac{\pi_{2m-1}(\mathbf{x})}{\pi_{2m}(\mathbf{x} + \mathbf{s}_{2m-1})} \right] + \rho_m^-(\mathbf{x}; t) \ln \left[\frac{\pi_{2m}(\mathbf{x})}{\pi_{2m-1}(\mathbf{x} - \mathbf{s}_{2m-1})} \right] \right\}$$

Balance Equations

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The diagram shows the balance equation for Helmholtz free energy, $\frac{dF(t)}{dt} = f(t) - \sigma(t)$, for $t > 0$. The equation is enclosed in a light blue rounded rectangle. An arrow points from the text "entropy production rate" to the term $\sigma(t)$. Another arrow points from the text "motive power" to the term $f(t)$.

$$\frac{dF(t)}{dt} = f(t) - \sigma(t), \quad \text{for } t > 0$$

The Helmholtz free energy measures the energy available in a thermodynamic system to do work under constant temperature and volume.

Balance Equations

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motive power

$$f(t) \triangleq \frac{1}{2} \sum_{m=1}^{M/2} \sum_{\mathbf{x}} [\rho_m^+(\mathbf{x}; t) \bar{A}_m^+(\mathbf{x}) + \rho_m^-(\mathbf{x}; t) \bar{A}_m^-(\mathbf{x})]$$

$$\left. \begin{aligned} \bar{A}_m^+(\mathbf{x}) &= \lim_{t \rightarrow \infty} A_m^+(\mathbf{x}; t) \\ \bar{A}_m^-(\mathbf{x}) &= \lim_{t \rightarrow \infty} A_m^-(\mathbf{x}; t) \end{aligned} \right\} \text{steady-state affinities}$$

- The motive power quantifies the rate of energy (i.e., power) supplied to the Markovian reaction network.

$$\text{since } \frac{dF(t)}{dt} \leq 0, \text{ we have that } f(t) \leq \sigma(t)$$

Balance Equations

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- From

$$\frac{dF(t)}{dt} = f(t) - \sigma(t), \quad \text{for } t > 0$$

the reactions in a Markovian reaction network can increase the Helmholtz free energy by adding “motive” energy to the system, whereas they can reduce the Helmholtz free energy due to entropy production.

- Moreover

$$\sigma(t) = f(t) - \frac{dF(t)}{dt}, \quad \text{for } t > 0$$

which implies that entropy production comes from two sources:

- ▣ from supplying motive power $f(t)$
- ▣ from a spontaneous decrease $dF(t)/dt$ in Helmholtz free energy.

Balance Equations

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$$\frac{dU(t)}{dt} = f(t) - h(t), \quad \text{for } t > 0$$

heat
dissipation
rate

motive
power

The diagram shows a light blue rounded rectangle containing the differential equation $\frac{dU(t)}{dt} = f(t) - h(t)$ for $t > 0$. An arrow points from the term $f(t)$ to the text 'motive power' below the rectangle. Another arrow points from the term $h(t)$ to the text 'heat dissipation rate' above the rectangle.

Balance Equations

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- The equation

$$\frac{dU(t)}{dt} = f(t) - h(t), \quad \text{for } t > 0$$

expresses the [first law of thermodynamics](#) (energy conservation):

- A change $\Delta U(t) = U(t + dt) - U(t)$ in internal energy within an infinitesimal time interval $[t, t + dt)$ must equal the amount of motive energy $f(t)dt$ added to the system minus the dissipated heat $h(t)dt$.

https://en.wikipedia.org/wiki/First_law_of_thermodynamics

Balance Equations

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□ From

$$\sigma(t) = \frac{1}{2} \sum_{m=1}^{M/2} \sum_{\mathbf{x}} [\rho_m^+(\mathbf{x};t) A_m^+(\mathbf{x};t) + \rho_m^-(\mathbf{x};t) A_m^-(\mathbf{x};t)]$$

note that

$$\sigma(t) \geq 0, \quad \text{for every } t \geq 0$$

with equality if and only if

$$A_m^+(\mathbf{x};t) = A_m^-(\mathbf{x};t) = 0, \quad \text{for every } m = 1, 2, \dots, M/2$$

- This is a direct consequence of the fact that $(x_1 - x_2) \ln(x_1 / x_2) \geq 0$ with equality if and only if $x_1 = x_2$.
- It agrees with the [second law of thermodynamics](https://en.wikipedia.org/wiki/Second_law_of_thermodynamics) which postulates that the rate of entropy production must always be nonnegative.

https://en.wikipedia.org/wiki/Second_law_of_thermodynamics

Balance Equations

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□ Equations

$$\frac{dS(t)}{dt} = \sigma(t) - h(t) \quad \text{and} \quad \frac{dF(t)}{dt} = f(t) - \sigma(t)$$

lead to

$$0 \leq \bar{\sigma} = \bar{h} = \bar{f}$$

- This result implies that, at steady-state, the amount of motive power supplied to the system must be equal to the rate of heat dissipation, in agreement with the first law of thermodynamics.
- Moreover, the rate of heat dissipation must be equal to the rate of entropy production.
- It also implies that the steady-state entropy production, heat dissipation and motive power must all be nonnegative, in agreement with the second law of thermodynamics.

Thermodynamic Equilibrium

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- A Markovian reaction network at thermodynamic equilibrium at steady-state if and only if

$$\bar{A}_m^+(\mathbf{x}) = \bar{A}_m^-(\mathbf{x}) = 0, \quad \text{for every } m = 1, 2, \dots, M / 2$$

- The affinities $\bar{A}_m^+(\mathbf{x})$ and $\bar{A}_m^-(\mathbf{x})$ can be viewed as thermodynamic forces that drive a Markovian reaction network at steady-state away from thermodynamic equilibrium.

Thermodynamic Equilibrium

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□ Note that

$$\bar{A}_m^+(\mathbf{x}) = \bar{A}_m^-(\mathbf{x}) = 0, \quad \text{for every } m = 1, 2, \dots, M / 2$$

is equivalent to the following equations:

$$\begin{aligned} \pi_{2m-1}(\mathbf{x}) \bar{p}_{\mathbf{x}}(\mathbf{x}) &= \pi_{2m}(\mathbf{x} + \mathbf{s}_{2m-1}) \bar{p}_{\mathbf{x}}(\mathbf{x} + \mathbf{s}_{2m-1}) \\ \pi_{2m-1}(\mathbf{x} - \mathbf{s}_{2m-1}) \bar{p}_{\mathbf{x}}(\mathbf{x} - \mathbf{s}_{2m-1}) &= \pi_{2m}(\mathbf{x}) \bar{p}_{\mathbf{x}}(\mathbf{x}) \\ &\text{for every } m = 1, 2, \dots, M / 2, \text{ and } \mathbf{x} \end{aligned}$$

known as detailed balance equations.

Thermodynamic Equilibrium

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- The detailed balance equations

$$\begin{aligned}\pi_{2m-1}(\mathbf{x})\bar{p}_{\mathbf{x}}(\mathbf{x}) &= \pi_{2m}(\mathbf{x} + \mathbf{s}_{2m-1})\bar{p}_{\mathbf{x}}(\mathbf{x} + \mathbf{s}_{2m-1}) \\ \pi_{2m-1}(\mathbf{x} - \mathbf{s}_{2m-1})\bar{p}_{\mathbf{x}}(\mathbf{x} - \mathbf{s}_{2m-1}) &= \pi_{2m}(\mathbf{x})\bar{p}_{\mathbf{x}}(\mathbf{x}) \\ &\text{for every } m = 1, 2, \dots, M / 2, \text{ and } \mathbf{x}\end{aligned}$$

imply that the net fluxes $\bar{\rho}_m^+(\mathbf{x}) = \lim_{t \rightarrow \infty} \rho_m^+(\mathbf{x}; t)$ and $\bar{\rho}_m^-(\mathbf{x}) = \lim_{t \rightarrow \infty} \rho_m^-(\mathbf{x}; t)$ at steady-state will be zero for all reactions.

- A Markovian reaction network at steady-state is at thermodynamic equilibrium if and only if all net fluxes are zero.

Thermodynamic Equilibrium

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□ Since

$$f(t) \triangleq \frac{1}{2} \sum_{m=1}^{M/2} \sum_{\mathbf{x}} [\rho_m^+(\mathbf{x}; t) \bar{A}_m^+(\mathbf{x}) + \rho_m^-(\mathbf{x}; t) \bar{A}_m^-(\mathbf{x})]$$

we have that

$$\bar{f} = 0$$

when a Markovian reaction network at steady-state is at thermodynamic equilibrium.

Thermodynamic Equilibrium

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- From $0 \leq \bar{\sigma} = \bar{h} = \bar{f}$, we now have that

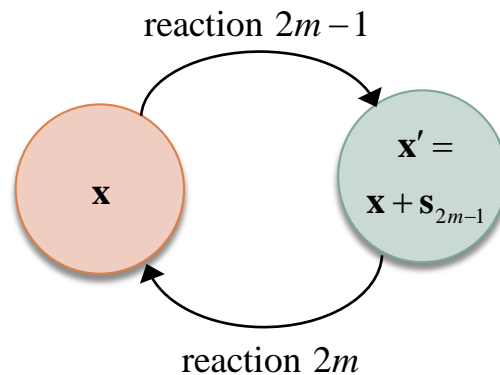
$$\bar{\sigma} = \bar{h} = \bar{f} = 0$$

- This shows that a Markovian reaction network that is at thermodynamic equilibrium at steady-state will not produce entropy or dissipate heat.
- This system “dies” at steady-state.
- In most cases of interest, a useful Markovian reaction network at steady-state must operate away from thermodynamic equilibrium.
- We can make sure that this is the case by including nonreversible reactions that transfer mass between the system and its surroundings (open system), thus breaking detailed balance by supplying motive power to the network using non-zero thermodynamic forces (i.e., non-zero affinities).

Reaction Cycles

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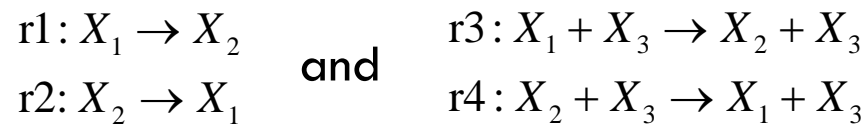
- A useful representation of the state-space of a Markovian reaction network is by means of a graph \mathcal{G} .
- Its nodes are the population states, and its edges connect pairs of population states $(\mathbf{x}, \mathbf{x} + \mathbf{s}_{2m-1})$ when $\pi_{2m-1}(\mathbf{x}), \pi_{2m}(\mathbf{x} + \mathbf{s}_{2m-1}) > 0$.
- An edge connecting two states \mathbf{x}, \mathbf{x}' indicates that these states can “reach” each other using a pair of reversible reactions.



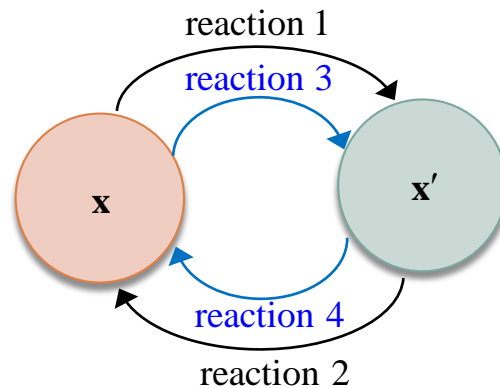
Reaction Cycles

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- There might be several distinct edges (corresponding to different reversible reactions) connecting a given pair of nodes, in which case \mathcal{G} is a multi-graph.
- **Example:** the reversible reactions



are characterized by the same net stoichiometry and will therefore connect the same pair of nodes in \mathcal{G} .



Reaction Cycles

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- An ordered chain (m_1, m_2, \dots, m_L) of reactions will produce a path

$$(\mathbf{x}_0, \mathbf{x}_0 + \mathbf{s}_{m_1}, \dots, \mathbf{x}_0 + \sum_{l=1}^L \mathbf{s}_{m_l})$$

in \mathcal{G} of length L , provided that each reaction can occur with positive probability.

- When

$$\sum_{l=1}^L \mathbf{s}_{m_l} = \mathbf{0}$$

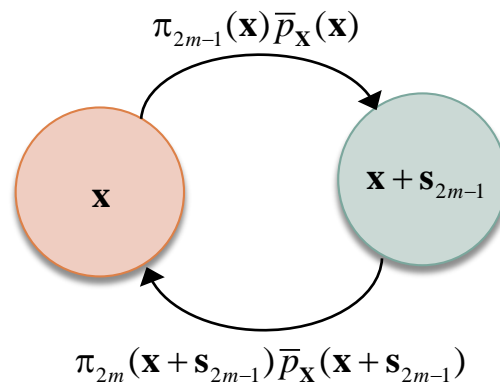
the reactions (m_1, m_2, \dots, m_L) will produce a reaction cycle C in \mathcal{G} of length L that ends in the same state as the starting state.

Kolmogorov Cyclic Conditions

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- For a Markovian reaction network at steady state containing only reversible reactions that is at thermodynamic equilibrium, the flux of a forward reaction will be equal to the flux of the corresponding reverse reaction (detailed balance).
- In this case, and for every pair m of reactions, we must have


$$\pi_{2m-1}(\mathbf{x}) \bar{p}_{\mathbf{x}}(\mathbf{x}) = \pi_{2m}(\mathbf{x} + \mathbf{s}_{2m-1}) \bar{p}_{\mathbf{x}}(\mathbf{x} + \mathbf{s}_{2m-1}), \text{ for every } \mathbf{x}$$



Kolmogorov Cyclic Conditions

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- For an ordered chain (m_1, m_2, \dots, m_L) of forward reactions, detailed balance leads to (see slide 32 for an example)

$$\bar{p}_{\mathbf{x}}(\mathbf{x}_0 + \sum_{l=1}^L \mathbf{s}_{m_l}) = \bar{p}_{\mathbf{x}}(\mathbf{x}_0) \prod_{l=1}^L \frac{\pi_{m_l}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k})}{\pi_{m_l^*}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k})}$$


pair of forward/reverse reactions

- This implies that (see slides 33 and 34 for an example)

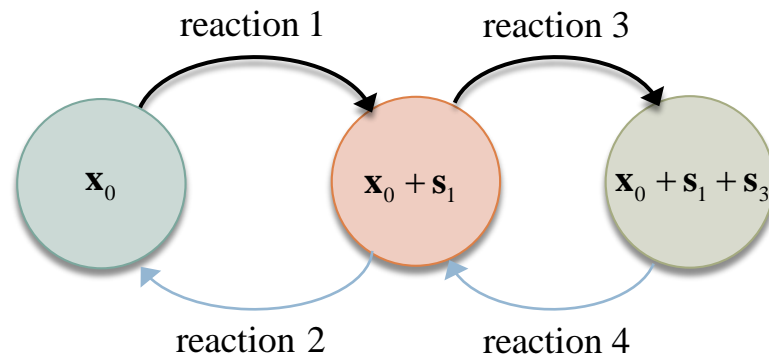
$$K(C) \triangleq \prod_{l=1}^L \frac{\pi_{m_l}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k})}{\pi_{m_l^*}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k})} = 1$$

if the ordered chain produces a reaction cycle C , which is known as the Kolmogorov cyclic condition.

Kolmogorov Cyclic Conditions – Example 1

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- Let us consider two reversible reactions $(2m-1, 2m), m=1, 2$.
- The ordered chain $(1, 3)$ of forward reactions produces a path $(\mathbf{x}_0, \mathbf{x}_0 + \mathbf{s}_1, \mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3)$ of length 2.

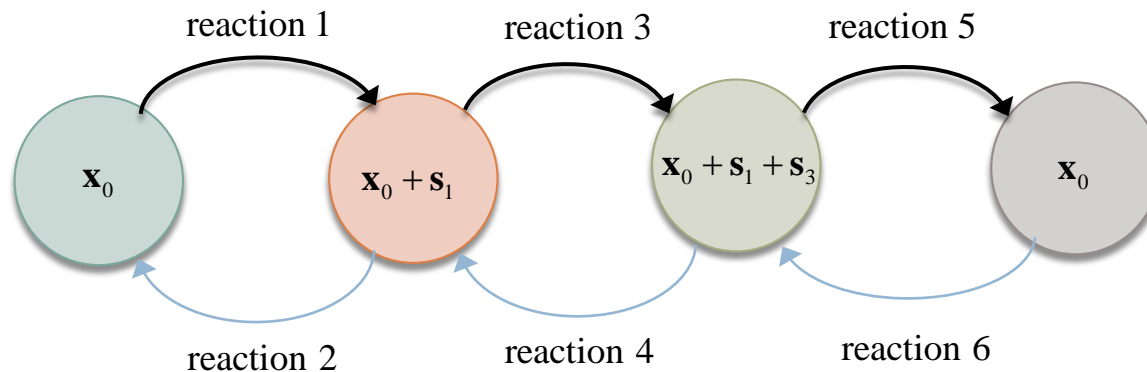


$$\begin{aligned}
 \bar{p}_{\mathbf{x}}(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3) &= \frac{\pi_3(\mathbf{x}_0 + \mathbf{s}_1)}{\pi_4(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3)} \bar{p}_{\mathbf{x}}(\mathbf{x}_0 + \mathbf{s}_1) \\
 &= \frac{\pi_3(\mathbf{x}_0 + \mathbf{s}_1)}{\pi_4(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3)} \frac{\pi_1(\mathbf{x}_0)}{\pi_2(\mathbf{x}_0 + \mathbf{s}_1)} \bar{p}_{\mathbf{x}}(\mathbf{x}_0)
 \end{aligned}$$

Kolmogorov Cyclic Conditions – Example 2

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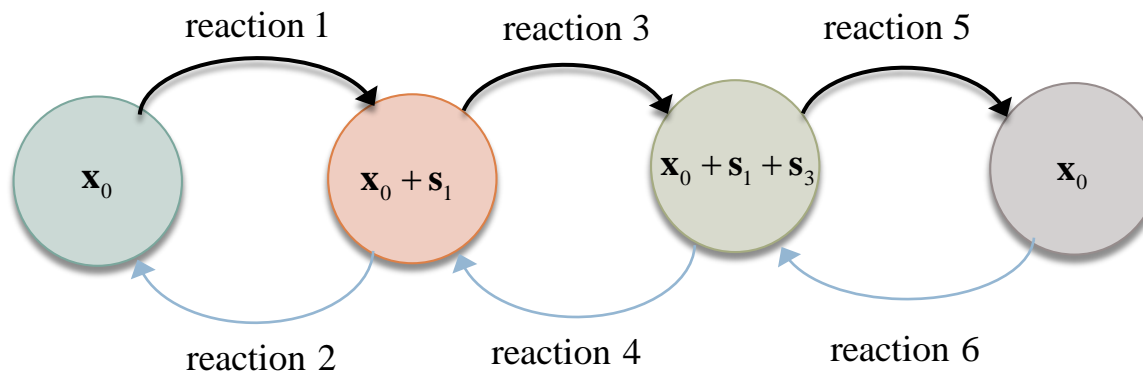
- Let us now consider three reversible reactions $(2m-1, 2m), m=1, 2, 3$, such that $\mathbf{s}_5 = -(\mathbf{s}_1 + \mathbf{s}_3)$.
- The ordered chain $(1, 3, 5)$ of forward reactions produces a reaction cycle $C = (\mathbf{x}_0, \mathbf{x}_0 + \mathbf{s}_1, \mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3, \mathbf{x}_0)$ of length 3.



Kolmogorov Cyclic Conditions – Example 2

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□ In this case, we have that



$$\begin{aligned}
 & \bar{p}_X(\mathbf{x}_0) \\
 &= \frac{\pi_5(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3)}{\pi_6(\mathbf{x}_0)} \bar{p}_X(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3) \Rightarrow \frac{\pi_5(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3)}{\pi_6(\mathbf{x}_0)} \frac{\pi_3(\mathbf{x}_0 + \mathbf{s}_1)}{\pi_4(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3)} \frac{\pi_1(\mathbf{x}_0)}{\pi_2(\mathbf{x}_0 + \mathbf{s}_1)} = 1 \\
 &= \frac{\pi_5(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3)}{\pi_6(\mathbf{x}_0)} \frac{\pi_3(\mathbf{x}_0 + \mathbf{s}_1)}{\pi_4(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3)} \bar{p}_X(\mathbf{x}_0 + \mathbf{s}_1) \\
 &= \frac{\pi_5(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3)}{\pi_6(\mathbf{x}_0)} \frac{\pi_3(\mathbf{x}_0 + \mathbf{s}_1)}{\pi_4(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3)} \frac{\pi_1(\mathbf{x}_0)}{\pi_2(\mathbf{x}_0 + \mathbf{s}_1)} \bar{p}_X(\mathbf{x}_0)
 \end{aligned}$$

Kolmogorov Cyclic Conditions

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- In addition to being necessary, the Kolmogorov cyclic conditions

$$K(C) \triangleq \prod_{l=1}^L \frac{\pi_{m_l}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k})}{\pi_{m_l^*}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k})} = 1$$

can be shown to be sufficient for a Markovian reaction network to reach thermodynamic equilibrium at steady-state.

Kolmogorov Cyclic Conditions

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$$K(C) \triangleq \prod_{l=1}^L \frac{\pi_{m_l}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k})}{\pi_{m_l^*}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k})} = 1$$

- For thermodynamic consistency, the Kolmogorov cyclic conditions must always be satisfied, even if the system operates away from thermodynamic equilibrium.
- This is because a system with fixed propensity functions that operates away from thermodynamic equilibrium may reach thermodynamic equilibrium in the absence of motive power.
- Consequently, the propensity function of a Markovian reaction network cannot be chosen arbitrarily, since they are constrained by Kolmogorov's cyclic conditions.

Net Affinity of a Cycle

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- The net affinity (i.e., the net thermodynamic force) of a cycle C of length L is defined by:

$$A(t; C) \triangleq A_{m_1}^+(\mathbf{x}_0; t) + A_{m_2}^+(\mathbf{x}_0 + \mathbf{s}_{m_1}; t) + \cdots + A_{m_L}^+(\mathbf{x}_0 + \sum_{k=1}^{L-1} \mathbf{s}_{m_k}; t)$$

$$= \sum_{l=1}^L \ln \frac{\pi_{m_l}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k}) p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k}; t)}{\pi_{m_l^*}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k}) p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k}; t)}, \quad \text{for every } t \geq 0$$

pair of forward/reverse reactions

$$A_m^+(\mathbf{x}; t) \triangleq \ln \left[\frac{\pi_{2m-1}(\mathbf{x}) p_{\mathbf{x}}(\mathbf{x}; t)}{\pi_{2m}(\mathbf{x} + \mathbf{s}_{2m-1}) p_{\mathbf{x}}(\mathbf{x} + \mathbf{s}_{2m-1}; t)} \right]$$

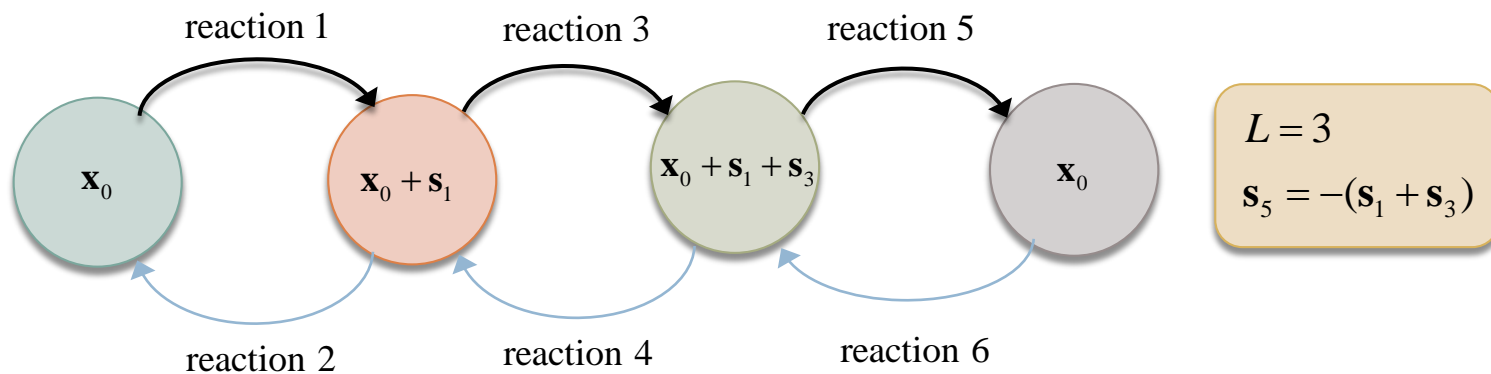
Net Affinity of a Cycle

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□ **Example (from slide 33):**

$$A(t; C) \triangleq \sum_{l=1}^L \ln \frac{\pi_{m_l}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k}) p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k}; t)}{\pi_{m_l^*}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k}) p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k}; t)}, \text{ for every } t \geq 0$$

$$A_m^+(\mathbf{x}; t) \triangleq \ln \left[\frac{\pi_{2m-1}(\mathbf{x}) p_{\mathbf{x}}(\mathbf{x}; t)}{\pi_{2m}(\mathbf{x} + \mathbf{s}_{2m-1}) p_{\mathbf{x}}(\mathbf{x} + \mathbf{s}_{2m-1}; t)} \right]$$



$$A(t; C) = A_1^+(\mathbf{x}_0; t) + A_2^+(\mathbf{x}_0 + \mathbf{s}_1; t) + A_3^+(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3; t)$$

$$= \ln \left[\frac{\pi_1(\mathbf{x}_0) p_{\mathbf{x}}(\mathbf{x}_0; t)}{\pi_2(\mathbf{x}_0 + \mathbf{s}_1) p_{\mathbf{x}}(\mathbf{x}_0 + \mathbf{s}_1; t)} \right] + \ln \left[\frac{\pi_3(\mathbf{x}_0 + \mathbf{s}_1) p_{\mathbf{x}}(\mathbf{x}_0 + \mathbf{s}_1; t)}{\pi_4(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3) p_{\mathbf{x}}(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3; t)} \right] + \ln \left[\frac{\pi_5(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3) p_{\mathbf{x}}(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3; t)}{\pi_6(\mathbf{x}_0) p_{\mathbf{x}}(\mathbf{x}_0; t)} \right]$$

Net Affinity of a Cycle

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□ Note that

$$\begin{aligned}
 A(t; C) &\triangleq \sum_{l=1}^L \ln \frac{\pi_{m_l}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k}) p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k}; t)}{\pi_{m_l^*}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k}) p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k}; t)} \\
 &= \ln \prod_{l=1}^L \frac{\pi_{m_l}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k})}{\pi_{m_l^*}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k})} + \ln \prod_{l=1}^L \frac{p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k}; t)}{p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k}; t)} \\
 &= \ln K(C) + \ln P(C) \\
 &= \ln K(C)
 \end{aligned}$$

$$\begin{aligned}
 K(C) &\triangleq \prod_{l=1}^L \frac{\pi_{m_l}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k})}{\pi_{m_l^*}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k})} \\
 P(C) &\triangleq \prod_{l=1}^L \frac{p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k}; t)}{p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k}; t)}
 \end{aligned}$$

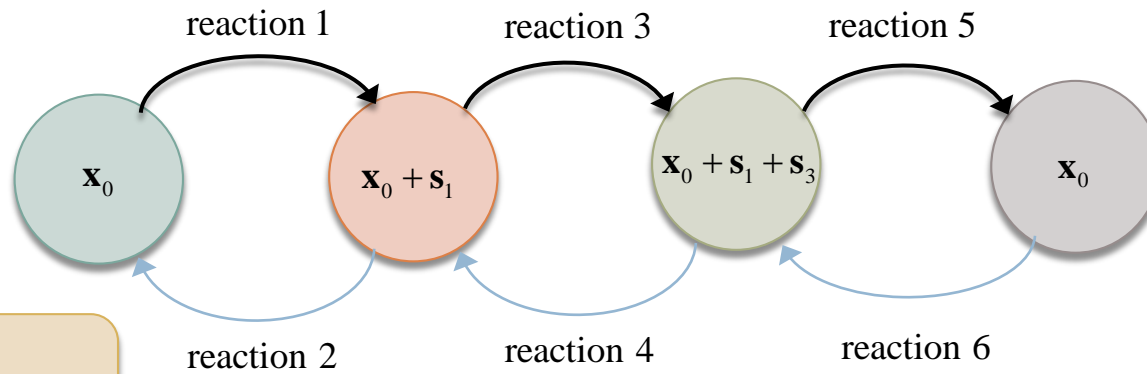
since, in a reaction cycle C , we always have (see slide 40 for an example)

$$P(C) \triangleq \prod_{l=1}^L \frac{p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k}; t)}{p_{\mathbf{x}}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k}; t)} = 1, \quad \text{for every } t \geq 0$$

Net Affinity of a Cycle

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Example (from page 33):



$$L = 3$$

$$\mathbf{s}_5 = -(\mathbf{s}_1 + \mathbf{s}_3)$$

$$\begin{aligned}
 P(C) &\triangleq \prod_{l=1}^L \frac{p_{\mathbf{X}}(\mathbf{x}_0 + \sum_{k=1}^{l-1} \mathbf{s}_{m_k}; t)}{p_{\mathbf{X}}(\mathbf{x}_0 + \sum_{k=1}^l \mathbf{s}_{m_k}; t)} \\
 &= \frac{p_{\mathbf{X}}(\mathbf{x}_0; t)}{p_{\mathbf{X}}(\mathbf{x}_0 + \mathbf{s}_1; t)} \frac{p_{\mathbf{X}}(\mathbf{x}_0 + \mathbf{s}_1; t)}{p_{\mathbf{X}}(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3; t)} \frac{p_{\mathbf{X}}(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3; t)}{p_{\mathbf{X}}(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3 + \mathbf{s}_5; t)} \\
 &= \frac{p_{\mathbf{X}}(\mathbf{x}_0; t)}{p_{\mathbf{X}}(\mathbf{x}_0 + \mathbf{s}_1; t)} \frac{p_{\mathbf{X}}(\mathbf{x}_0 + \mathbf{s}_1; t)}{p_{\mathbf{X}}(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3; t)} \frac{p_{\mathbf{X}}(\mathbf{x}_0 + \mathbf{s}_1 + \mathbf{s}_3; t)}{p_{\mathbf{X}}(\mathbf{x}_0; t)} = 1
 \end{aligned}$$

Net Affinity of a Cycle

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- Recall that $K(C) = 1$ for thermodynamic consistency.
- Therefore, for a Markovian reaction network that contains only reversible reactions, we must have

$$A(t; C) = \ln K(C) = 0, \text{ at any time } t$$

- This implies that the net affinity (i.e., the net thermodynamic force) applied on a reaction cycle C will be zero at any time point !