SUPPORTING INFORMATION

Lyapunov Functions, Stationary Distributions, and Non-equilibrium Potential for Reaction Networks

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Example 13 in the Main text

In Example 13 in the main text we consider the following reaction network:

$$X \xrightarrow{\kappa_1} \emptyset, \qquad \emptyset \xrightarrow{\kappa_2} 2X. \tag{1}$$

The network is not weakly reversible, hence it cannot be complex balanced. Furthermore, the model is not a birth-death process as the 'birth event' creates two copies of X. Consequently, we cannot use the theory developed in the main text to determine whether the non-equilibrium potential converges to a Lyapunov function and in case it does, the form of the Lyapunov function.

Here we prove the claims made in the main text about the network. To be precise we will show that an equilibrium distribution exists and show that it can be given as the sum of two independent Poisson distributions. We will use this representation to argue that the non-equilibrium potential converges to a Lyapunov function and state its form.

Proposition 1. *Let N_t be the number of X molecules at time t in the network $\mathcal{N}$. Then the distribution of N_t is given as the convolution of two independent random variables,*

$$N_t = N_{1,t} + 2N_{2,t}, \qquad N_{1,t} \sim Po\left(2\alpha V(1-e^{-k_1 t})^2\right), \quad and \quad N_{2,t} \sim Po\left(\alpha V(1-e^{-2k_1 t})\right).$$

Letting $t \to \infty$, we obtain the equilibrium distribution of X,

$$N = N_1 + 2N_2, \qquad N_1 \sim Po(2\alpha V), \quad and \quad N_2 \sim Po\left(\alpha V\right),$$

where N_1 and N_2 are independent random variables.

Proof of Proposition 1. Let $\lambda = Vk_2$ and $\mu = k_1$ for convenience. Fix $t > 0$. The number of birth events that has occured before time t is Poisson with rate λt. Assume a birth event happens at time $0 < u < t$. Then either zero, one or two of the X molecules might survive until time t, each with death rate μ. The probabilities of these events are

$$p_u(2) = e^{-2\mu(t-u)}, \quad p_u(1) = 2e^{-\mu(t-u)}(1 - e^{-\mu(t-u)}), \quad \text{and} \quad p_u(0) = 1 - p_u(1) - p_u(2), \qquad (2)$$

where $p_t(i)$, $i = 0, 1, 2$, is the probability that i lineages survive. Given that N_t birth events have happened, each of the N_t events occur at a uniform random time in $(0, t)$. Hence, the probabilities in equation (2), averaged over time, become

$$P_t(i) = \frac{1}{t} \int_0^t p_u(i) du,$$

or

$$P_t(2) = \frac{1}{2\mu t}(1 - e^{-2\mu t}), \quad P_t(1) = \frac{1}{\mu t}(1 - e^{-\mu t})^2, \quad \text{and} \quad P_t(0) = 1 - P_t(1) - P_t(2).$$

It follows that the number of birth events for which both molecules survive is $N_{2,t} \sim \text{Po}(\lambda t P_t(2))$ and the number of birth events for which only one of the two molecules survive is $N_{1,t} \sim \text{Po}(\lambda t P_t(1))$, which coincide with those stated in the lemma. Since birth events occur independently of each other, $N_{1,t}$ and $N_{2,t}$ are independent random variables. Further, the number of molecules at time t is $N_t = N_{1,t} + 2N_{2,t}$, which proves the first part.

To obtain the equilibrium distribution we let $t \to \infty$ and obtain $N_1 \sim \text{Po}(2\alpha V)$ and $N_2 \sim \text{Po}(\alpha V)$, where α is as defined in the lemma. □

The probability distribution of N in Lemma 1 is given by

$$\begin{aligned} P(N = n) &= \sum_{k,m:\, k+2m=n} \frac{(2V\alpha)^k}{k!} e^{-2V\alpha} \frac{(V\alpha)^m}{m!} e^{-V\alpha} \\ &= e^{-3V\alpha} \sum_{k,m:\, k+2m=n} \frac{(2V\alpha)^k}{k!} \frac{(V\alpha)^m}{m!}, \end{aligned} \qquad (3)$$

where the sum is over all positive integers k, m such that $k + 2m = n$. The sum does not seem easy to manipulate further.

To evaluate $\frac{1}{V}\ln(P(N = n))$ as $V \to \infty$ and $n/V \to x$, we need a version of Laplace's method for approximating integrals of the form $\int e^{Vf(x)} dx$. To state the method, we first look at the sum in (3). Each term is rewritten by taking the exponential and the logarithm to the term, and subsequently applying Stirling's approximation,

$$\sqrt{2\pi}\, n^{n+\frac{1}{2}} e^{-n} \le n! \le e\, n^{n+\frac{1}{2}} e^{-n} \quad \text{for} \quad n \ge 1 \quad (e \approx 2.71),$$

to provide an upper and a lower bound:

$$\begin{aligned} \frac{(2V\alpha)^k}{k!} \frac{(V\alpha)^m}{m!} &= \exp\{k \ln(2V\alpha) - \ln(k!) + m \ln(V\alpha) - \ln(m!)\} \ge \frac{\sqrt{2\pi}}{V} \frac{1}{u^{1/2}(x - 2u)^{1/2}} e^{V f_x(u)} \\ \frac{(2V\alpha)^k}{k!} \frac{(V\alpha)^m}{m!} &= \exp\{k \ln(2V\alpha) - \ln(k!) + m \ln(V\alpha) - \ln(m!)\} \le \frac{e}{V} \frac{1}{u^{1/2}(x - 2u)^{1/2}} e^{V f_x(u)}, \end{aligned} \qquad (4)$$

where $x = \frac{n}{V}$, $u = \frac{m}{V}$, and $k, m > 0$, such that $u > 0$ and $x - 2u > 0$, and

$$f_x(u) = -u\ln(u) - (x-2u)\ln(x-2u) + (x-u)(\ln(\alpha)+1) + (x-2u)\ln(2).$$

Note that $x - 2u = \frac{k}{V}$, $x - u = \frac{k+m}{V}$ and $0 < u < \frac{x}{2}$. Only the cases $m = 0$ and $k = 0$ cannot be bound in this way.

Consider $f_x(u)$ as a function on the open interval $(0, \frac{x}{2})$ into $\mathbb{R}$. The derivative of $f_x(u)$ with respect to u is

$$f_x'(u) = -\ln(u) + 2\ln(x-2u) - 2\ln(2) - \ln(\alpha),$$

which is decreasing in u. The function $f_x(u)$ attains its maximum for

$$u^* = \frac{1}{2}(x + \alpha - \sqrt{\alpha(\alpha+2x)}),$$

which fulfills

$$0 < u^* < \frac{x}{2} \quad \text{for} \quad x > 0.$$

The second derivative of $f_x(u)$ is always negative; hence $f_x(u)$ is convex and strictly increasing for $u < u^*$ and strictly decreasing for $u > u^*$.

Let (a, b) be an open interval in $\mathbb{R}$ with a, b potentially infinite.

Theorem 1. (Laplace's method) *Assume $h\colon (a,b) \to \mathbb{R}$ and $f(u)\colon (a,b) \to \mathbb{R}$ are two functions, such that $h(u)$ is continuous and $h(z) > 0$ for all $u \in (a,b)$, and $f(u)$ is twice continuously differentiable with a unique (global) maximum $u^* \in (a,b)$, such that $f''(u^*) < 0$. Further, assume $h(u)e^{Vf(u)}$ is integrable on (a,b) for all $V \geq 0$.*

Then,

$$\int_a^b h(u)e^{Vf(u)}du \approx \sqrt{\frac{2\pi}{V|f''(u^*)|}}\,h(u^*)e^{Vf(u^*)} \quad as \quad V \to \infty,$$

where the approximation means that the ratio of the two terms goes to one.

Lemma 1. *Let $P(N = n)$ be the probability in (3). Then*

$$\lim_{V\to\infty} -\frac{1}{V}\ln(P(N = xV)) = 3\alpha - f_x(u^*),$$

where u^*, which depends on u, is the unique maximum of $f_x(u)$.

Proof of Lemma 1. We assume the notation and definitions introduced above. Consider the sum over all k, m, such that $k + 2m = n$ and $k, m > 0$:

$$S = \sum_{u=\frac{1}{V}}^{\frac{n'}{V}} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{Vf_x(u)},$$

where $n' = \frac{n-1}{2}$, if n is odd and $n' = \frac{n}{2} - 1$, if n is even. We split the sum S into three parts:

$$\sum_{u<\epsilon} + \sum_{\frac{x}{2}-\epsilon<u} + \sum_{\epsilon\leq u\leq\frac{x}{2}-\epsilon} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{V\tilde{f}_x(u)}$$

for some (small) $\epsilon > 0$. The sum of the first two terms can be bounded downwards by 0 and upwards by

$$d_1 V^{\frac{1}{2}} e^{V d_2},$$

where $d_1 > 0$ and $d_2 \in \mathbb{R}$. Indeed, using the properties of $f_x(u)$, we have $d_2 = \max(f_x(\epsilon), f_x(\frac{x}{2} - \epsilon))$, and d_1 is a number such that $d_1 V^{\frac{1}{2}} > \max\left(\frac{1}{u^{1/2}(x-2u)^{1/2}} | u \leq \epsilon \text{ or } \frac{x}{2} - \epsilon \leq u\right)$.

The last sum can be approximated by an integral. For this, consider the function

$$h(u) = \frac{1}{u^{1/2}(x - 2u)^{1/2}}$$

and let u_0 be given. Since $f_x\left(u_0 + \frac{1}{V}\right) \approx f_x(u_0) + \frac{1}{V} f_x'(u_0)$ to order $\frac{1}{V}$, we have

$$a_1 V \int_{u_0}^{u_0 + \frac{1}{V}} \frac{1}{u^{1/2}(x - 2u)^{1/2}} e^{V f_x(u)} du \leq h(u_0) e^{V f_x(u_0)} \leq a_2 V \int_{u_0}^{u_0 + \frac{1}{V}} \frac{1}{u^{1/2}(x - 2u)^{1/2}} e^{V f_x(u)} du,$$

for two constants $a_1, a_2 > 0$. The functions $h(u)$, $f_x(u)$ and $f_x'(u)$ are continuous and bounded on $[\epsilon, \frac{x}{2} - \epsilon]$, hence a_1, a_2 can be chosen such that they are independent of $u \in [\epsilon, \frac{x}{2} - \epsilon]$. Consequently, the bounds hold for all $u \in [\epsilon, \frac{x}{2} - \epsilon]$ and we obtain

$$a_1 V \int_{\epsilon}^{\frac{x}{2} - \epsilon} \frac{1}{u^{1/2}(x - 2u)^{1/2}} e^{V f_x(u)} du \leq \sum_{\epsilon \leq u \leq \frac{x}{2} - \epsilon} \frac{1}{u^{1/2}(x - 2u)^{1/2}} e^{V f_x(u)}$$

$$\leq a_2 V \int_{\epsilon}^{\frac{x}{2} - \epsilon} \frac{1}{u^{1/2}(x - 2u)^{1/2}} e^{V f_x(u)} du.$$

Using Theorem 1, the sum can further be approximated by a single term for large V. Since $h(u) e^{V f_x(u)}$ is bounded on $[\epsilon, \frac{x}{2} - \epsilon]$ for fixed V, the conditions for using Theorem 1 are fulfilled and we obtain,

$$b_1 V^{\frac{1}{2}} e^{V f_x(u^*)} \leq \sum_{\epsilon \leq u \leq \frac{x}{2} - \epsilon} \frac{1}{u^{1/2}(x - 2u)^{1/2}} e^{V f_x(u)} \leq b_2 V^{\frac{1}{2}} e^{V f_x(u^*)}.$$

for some new constants $b_1, b_2 > 0$.

Consider now $P(N = n)$. We have from the equation (3) and the definition of S that

$$P(N = n) = S e^{-3\alpha V} + P(N = n, N_1 = 0) + P(N = n, N_2 = 0).$$

Depending on whether n is odd or even, $P(N = n, N_1 = 0)$ might be zero. Using Stirling's approximation we obtain

$$P(N = n, N_2 = 0) \approx e^{-3\alpha V} e^{V f_x(0)} x^{-\frac{1}{2}} V^{-\frac{1}{2}},$$

and

$$P(N = n, N_2 = 0) \approx e^{-3\alpha V} e^{V f_x(\frac{x}{2})} \left(\frac{x}{2}\right)^{-\frac{1}{2}} V^{-\frac{1}{2}},$$

where the $\approx$ means the ratio of the two terms goes to one as $V \to \infty$.

Putting all terms in $P(N = n)$ together, using that $S e^{-3\alpha V}$ is to a higher power in V than the other terms, yields

$$\lim_{V \to \infty} -\frac{1}{V} \ln(P(N = xV)) = \lim_{V \to \infty} -\frac{1}{V} \ln(S e^{-3\alpha V}) = 3\alpha - f_x(u^*),$$

which proves the claim of the lemma. □

Proposition 2. *The function*

$$g(x) = 3\alpha - f_x(u^*), \quad \textit{with} \quad u^* = \frac{1}{2}(x + \alpha - \sqrt{\alpha(\alpha + 2x)})$$

is a Lyapunov function for the network in (1)*. Further,* $g(x)$ *might be written as*

$$g(x) = \int_0^x \ln\left(\sqrt{1 + \frac{2u}{\alpha}} - 1\right) du - \ln(2)x,$$

as stated in the main text.

Proof of Proposition 2. From (1) we have $\dot{x} = 2k_2 - k_1 x$. Recall that $\alpha = \frac{k_2}{2k_1}$, hence the sign of $\dot{x}$ is the same as the sign of

$$\frac{\dot{x}}{k_1} = 4\alpha - x. \tag{5}$$

We consider the function $g(x)$ as a function $\tilde{g}(x, u) = -3\alpha + f_x(u)$ of two variables (x, u) evaluated in (x, u^*). Hence the derivative of $g(x)$ with respect to x is

$$g'(x) = \frac{\partial \tilde{g}}{\partial u}(x, u^*)\frac{du^*}{dx} + \frac{\partial \tilde{g}}{\partial x}(x, u^*) = -\frac{\partial f_x}{\partial u}(u^*)\frac{du^*}{dx} - \frac{\partial f_x}{\partial x}(u^*).$$

The first term on the right side is 0 by definition of u^*. Evaluating the second term yields

$$g'(x) = \ln\left(\sqrt{1 + \frac{2x}{\alpha}} - 1\right) - \ln(2),$$

which fulfills

$$g'(x) > 0 \quad \text{if and only if} \quad 4\alpha < x,$$

and zero only when $4\alpha = x$. Comparing with (5) gives

$$g'(x)\dot{x} \leq 0 \quad \text{for all} \quad x > 0,$$

and equality only if $x = 4\alpha$. Hence $g(x)$ is a Lyapunov function for the network (1). □