

# van't Hoff-Arrhenius Analysis of Mesoscopic and Macroscopic Dynamics of Simple Biochemical Systems: Stochastic vs. Nonlinear Bistabilities

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Multistability of mesoscopic, driven biochemical reaction systems has implications to a wide range of cellular processes. Using several simple models, we show that one class of bistable chemical systems has a deterministic counterpart in the nonlinear dynamics based on the Law of Mass Action, while another class, widely known as noise-induced stochastic bistability, does not. Observing the system's volume ( $V$ ) playing a similar role as the inverse temperature ( $\beta$ ) in classical rate theory, an van't Hoff-Arrhenius like analysis is introduced. In one-dimensional systems, a transition rate between two states, represented in terms of a barrier in the landscape for the dynamics  $\Phi(x, V)$ ,  $k \propto \exp\{-V\Delta\Phi^\ddagger(V)\}$ , can be understood from a decomposition  $\Delta\Phi^\ddagger(V) \approx \Delta\phi_0^\ddagger + \Delta\phi_1^\ddagger/V$ . Nonlinear bistability means  $\Delta\phi_0^\ddagger > 0$  while stochastic bistability has  $\Delta\phi_0^\ddagger < 0$  but  $\Delta\phi_1^\ddagger > 0$ . Stochastic bistabilities can be viewed as remnants (or "ghosts") of nonlinear bifurcations or extinction phenomenon, and  $\Delta\phi_0^\ddagger$  and  $\Delta\phi_1^\ddagger$  as "enthalpic" and "entropic" barriers to a transition.

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Biochemical reaction dynamics in a small volume on the order of a cell is stochastic. For a given spatially homogeneous biochemical kinetic mechanism, be it a gene regulatory network or an intracellular signaling pathway, the stochastic trajectories of the chemical compositions of a mesoscopic, nonlinear reaction system can be computationally modelled via the Gillespie algorithm, and its probability distribution follows the chemical master equation (CME) first studied by Delbrück [1]. The Delbrück-Gillespie process (DGP) is a multi-dimensional birth-and-death process [2], with the system's volume,  $V$ , as a key parameter. In the limit of infinite large  $V$ , a macroscopic nonlinear dynamical system emerges [3]. This is precisely the system of ordinary differential equations (ODEs) following the classic Law of Mass Action (LMA) for chemical kinetics.

Bistability in terms of two stable fixed points is one of the salient features of many nonlinear chemical reaction systems [4]. The stationary distribution of a DGP that corresponds to a macroscopic bistable nonlinear chemical reaction system is bimodal [5]. Recently, it also has been discovered that certain nonlinear reaction system with small  $V$  can exhibit bimodal stationary distribution which has no macroscopic bistable counterpart. This phenomenon has been called *noise-induced bistability* and *stochastic bifurcation* [6, 7]. Recent experiments in synthetic biological systems have partially confirmed the theoretical insights [8].

One of us has proposed the notion of *nonlinear bistability* and *stochastic bistability* to distinguish the two dif-

ferent scenarios [2]. In particular, it was suggested that there is a distinct difference in the volume dependence of the transition rates between states. While the transition rate of a state decreases with increasing  $V$  for the nonlinear bistability, it actually increases for stochastic bistability. A van't Hoff-Arrhenius-like analysis with respect to system size  $V$  seems possible [9].

For a large class of DGP, the stationary probability distribution with increasing  $V$  has the asymptotic expression [10]

$$p_n^{st}(V) \approx e^{-V\phi_0(x) - \phi_1(x)} \quad (1)$$

where  $x = n/V$  is the concentration(s) of the chemical species, and the  $\phi$ 's are independent of  $V$ . Furthermore, it can be shown that if  $\phi_0(x)$  exists and is differentiable, then it is a Lyapunov function for the macroscopic ODE dynamics  $dx/dt = F(x)$  [11]:

$$\frac{d}{dt}\phi_0(x(t)) = \nabla\phi_0(x) \cdot \left(\frac{dx}{dt}\right) \leq 0. \quad (2)$$

Therefore, the stable fixed points of the ODE are located at the minima of  $\phi_0(x)$ , and the leading term in the exponent in Eq. (1) indicates that the "barrier" between two stable fixed points increases with  $V$ . In the limit of  $V = \infty$ , ergodicity breaks down and there will be no transitions between stable fixed points (attractors).

One can making an analogue between  $V^{-1}$  and temperature  $T$  in the traditional rate theory [9]. Both  $V^{-1} \rightarrow 0$  and  $T \rightarrow 0$  imply a deterministic limit. In fact, Arrhenius law states that a rate constant  $k \propto e^{-\Delta G^\ddagger/k_B T}$ , where the activation free energy, according to van't Hoff analysis, has an enthalpic and an entropy part  $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$ . Therefore negative activation enthalpy leads to decreasing  $k$  with increasing temperature [12].

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Comparing the van't Hoff-Arrhenius analysis with Eq. (1), we can identify  $\phi_0$  with “enthalpy” and  $\phi_1$  with entropy. As we shall show below, stochastic bistability is associated with a negative  $\Delta\phi_0^\ddagger$ .

**The general theory**—Let us consider the 1-dimensional birth-and-death process with birth rate  $u_n(V)$  and death rate  $w_n(V)$ :

$$\frac{d}{dt}p_n(t) = p_{n-1}u_{n-1} - p_n(w_n + u_n) + p_{n+1}w_{n+1}, \quad (3)$$

( $n \geq 0, u_{-1} = w_0 = 0$ .) The unique stationary distribution of Eq. (3) is

$$p_n^{st} = p_0^{st} \prod_{\ell=0}^{n-1} \frac{u_\ell(V)}{w_{\ell+1}(V)} = p_0^{st} e^{-V\Phi(n,V)}, \quad (4)$$

where  $p_0^{st}$  is a normalization factor, and  $\Phi(n, V) =$

$$\frac{1}{V} \sum_{\ell=0}^{n-1} \ln \left[ \frac{w_{\ell+1}(V)}{u_\ell(V)} \right] = \phi_0(x) + \frac{1}{V} \psi(x, V), \quad (5)$$

here we have assumed  $n = xV$ . To obtain  $\phi_0(x)$ , we let  $V \rightarrow \infty$  while holding  $x$  constant.

To derive Eq. (5), we consider  $\ell = Vz$  and noting that functions  $u$  and  $w$  have asymptotic expansions according to the macroscopic LMA

$$\begin{aligned} V^{-1}u_{Vz}(V) &\approx \mu_0(z) + V^{-1}\mu_1(z) + \dots, \\ V^{-1}w_{Vz}(V) &\approx \lambda_0(z) + V^{-1}\lambda_1(z) + \dots. \end{aligned} \quad (6)$$

Then we have:

$$\phi_0(x) = \int_0^x \ln \left( \frac{\lambda_0(z)}{\mu_0(z)} \right) dz. \quad (7)$$

We can also obtain a leading order approximation for  $\psi(x, V) \approx \phi_1(x) + V^{-1}\phi_2(x) + \dots$ . Note that

$$\begin{aligned} &\int_0^x \ln \left( \frac{\lambda_0(z)}{\mu_0(z)} \right) dz - \frac{1}{V} \sum_{\ell=0}^{xV-1} \ln \left[ \frac{\lambda_0(\ell/V)}{\mu_0(\ell/V)} \right] \\ &= \sum_{\ell=0}^{xV-1} \frac{d}{dz} \left[ \ln \frac{\lambda_0(z)}{\mu_0(z)} \right]_{z=\frac{\ell}{V}} \int_{\frac{\ell}{V}}^{\frac{\ell+1}{V}} \left( z - \frac{\ell}{V} \right) dz + o\left(\frac{1}{V}\right) \\ &= \frac{1}{2V} \int_0^x \frac{d}{dz} \left[ \ln \frac{\lambda_0(z)}{\mu_0(z)} \right] dz + o(V^{-1}), \end{aligned}$$

and

$$\begin{aligned} &\sum_{\ell=0}^{n-1} \ln \left[ \frac{w_{\ell+1}(V)}{u_\ell(V)} \right] - \sum_{\ell=0}^{xV-1} \ln \left[ \frac{\lambda_0(\ell/V)}{\mu_0(\ell/V)} \right] \\ &= \int_0^x \left( \frac{\lambda_1(z) + \lambda_0'(z)}{\lambda_0(z)} - \frac{\mu_1(z)}{\mu_0(z)} \right) dz + o(1). \end{aligned}$$

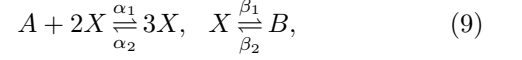
Therefore,

$$\phi_1(x) = \int_0^x \left( \frac{\lambda_1(z)}{\lambda_0(z)} - \frac{\mu_1(z)}{\mu_0(z)} \right) dz + \frac{\ln(\mu_0(x)\lambda_0(x))}{2}. \quad (8)$$

Therefore,  $\Phi(x) \approx \phi_0(x) + \phi_1(x)/V$ .

**Stochastic bistability**—Stochastic bistability means for a finite  $V$ , the  $\Phi(x, V)$  has a minimum at  $x = x^*$  and a maximum (or saddle point in multi-dimensional problems) at  $x^\ddagger$ , with  $\Phi(x^\ddagger, V) > \Phi(x^*, V)$ , but  $\phi_0(x^\ddagger) < \phi_0(x^*)$ . Noting the relation  $\Phi(x, V) \approx \phi_0(x) + V^{-1}\phi_1(x)$ , this indicates that  $\phi_1(x^\ddagger) - \phi_1(x^*) = \Delta\phi_1^\ddagger > 0$ .

We illustrate the theory by an example. The Schlögl model of nonlinear chemical reactions with autocatalysis,



has recently found wide applications in cellular biochemistry [2]. With appropriate parameters it is well-known to exhibit bistability. We now consider this model outside but near its bistable regime. The stochastic DGP has birth and death rates [5]:

$$\begin{aligned} u_n(V) &= \frac{k_1 n(n-1)}{V} + k_{-2}V, \\ w_n(V) &= \frac{k_{-1} n(n-1)(n-2)}{V^2} + k_2 n, \end{aligned} \quad (10)$$

in which  $k_1 = \alpha_1[A]$ ,  $k_{-1} = \alpha_2$ ,  $k_2 = \beta_1$  and  $k_{-2} = \beta_2[B]$ . Then,  $\mu_0(z) = k_1 z^2 + k_{-2}$ ,  $\mu_1(z) = -k_1 z$ ,  $\lambda_0(z) = k_{-1} z^3 + k_2 z$ ,  $\lambda_1(z) = -3k_{-1} z^2$ . Then,

$$\begin{aligned} \phi_0(x) &= x \ln \frac{(\theta x^2 + \nu\gamma)x}{\nu\gamma(\theta x^2 + \nu)} - 2\sqrt{\frac{\nu}{\theta}} \arctan \left( \sqrt{\frac{\theta}{\nu}} x \right) \\ &\quad + 2\sqrt{\frac{\nu\gamma}{\theta}} \arctan \left( \sqrt{\frac{\theta}{\nu\gamma}} x \right) - x, \end{aligned} \quad (11)$$

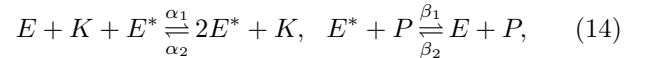
$$\phi_1(x) = \frac{1}{2} \ln \left[ \frac{x(\theta x^2 + \nu)^2}{(\theta x^2 + \nu\gamma)^2} \right], \quad (12)$$

in which

$$\theta = k_1/k_2, \quad \nu = k_{-2}/k_2, \quad \gamma = k_1 k_2 / (k_{-1} k_{-2}). \quad (13)$$

Fig. 1 shows that with increasing  $V$ , the bistability disappears in the deterministic limit. Furthermore, it shows that the “activation enthalpy”  $\Delta\phi_0^\ddagger$  has a negative value, and the barrier at finite  $V$  is an “entropic” one. This is the origin of the stochastic bistability.

**The ghost of extinction**—A canonical phosphorylation-dephosphorylation signaling with positive feedbacks exhibits stochastic bistability [7]:



in which  $K$  is a kinase that catalyzes the phosphorylation reaction  $E \rightarrow E^*$ , and  $P$  is a phosphatase that catalyzes the dephosphorylation reaction. The  $K$  is only active, however, after binding an  $E^*$  [13]. The rates of the DGP are

$$u_n = \frac{k_1 n(N-n)}{V} + k_{-2}(N-n), \quad w_n = \frac{k_{-1} n(n-1)}{V} + k_2 n, \quad (15)$$

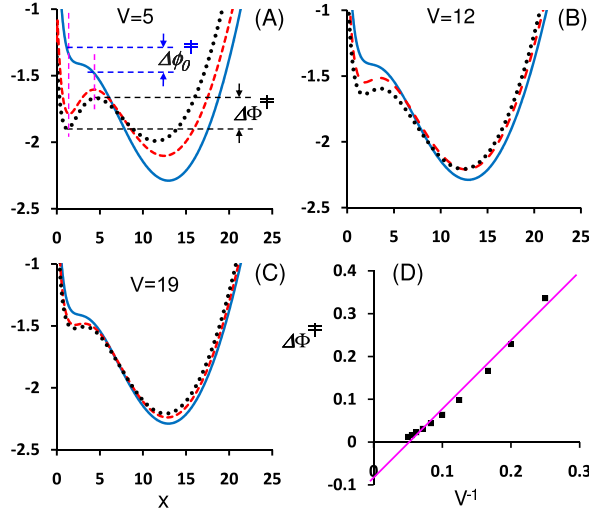


FIG. 1: Stochastic bistability has a barrier height  $\Delta\Phi^\ddagger(V)$  which decreases with increasing  $V$ , as revealed by the van't Hoff-Arrhenius analysis  $\Delta\Phi^\ddagger = \Delta\phi_0^\ddagger + V^{-1}\Delta\phi_1^\ddagger$ . (A-C): Blue solid line:  $\phi_0(x)$  where  $x = n/V$  is concentration of  $X$  in (9); Black dots: exact  $\Phi(x, V)$ ; Red dashed line:  $\phi_0(x) + V^{-1}\phi_1(x)$  according to Eqs.(11,12) with  $\theta = 0.25, \nu = 1.2, \gamma = 15$ , and different  $V$ s shown in the figures. (D) van't Hoff-Arrhenius plot, with filled squares for  $\Delta\Phi^\ddagger(V)$ , shows a slope  $\sim \Delta\phi_1^\ddagger > 0$  and an interaction  $\sim \Delta\phi_0^\ddagger < 0$ .

where  $k_1 = \alpha_1[K]$ ,  $k_{-1} = \alpha_2[K]$ ,  $k_2 = \beta_1[P]$ ,  $k_{-2} = \beta_2[P]$  and  $N$  is the total copy number of  $E$  and  $E^*$  molecules together. We have  $\mu_0(z) = (k_1 z + k_{-2})(e_t - z)$ ,  $\mu_1(z) = 0$ ,  $\lambda_0(z) = k_{-1}z^2 + k_2 z$ , and  $\lambda_1(z) = -k_{-1}z$ , where  $e_t = N/V$ . Therefore,

$$\phi_0(x) = \frac{\theta x + \nu\gamma}{\theta} \ln\left(\frac{\theta}{\nu\gamma}x + 1\right) + x \ln x \quad (16)$$

$$- \frac{\theta x + \nu}{\theta} \ln(\theta x + \nu) + (e_t - x) \ln(e_t - x),$$

$$\phi_1(x) = \frac{1}{2} \ln\left[\frac{x(\theta x + \nu)(e_t - x)}{\theta x + \nu\gamma}\right], \quad (17)$$

in which  $\theta, \nu, \gamma$  are again given in Eq. (13).

The stochastic bistability in (9) and Fig. 1 occurs when the system is near its deterministic bistable regime. Therefore, one can consider the stochastic bistability as a “ghost” of the saddle-node bifurcation [14]. In the present case,  $\phi_0(x)$  in Eq. (16) is a convex function with a single minimum on  $[0, e_t]$  for all parameters. Therefore, the deterministic dynamics of (14) can not have bistability or bifurcation. It however, can have a unstable fixed point at  $x = 0$  when  $\beta_2 = 0$ . This is the case of “extinction”. Even though the  $x = 0$  is unstable to the ODE, the stationary distribution for the CME is  $p_n^{st} = \delta_{n0}$ : The stochastic dynamics goes extinct with probability 1. As a “ghost” of the extinction, this system can also exhibit stochastic bistability if  $\beta_2$  is nonzero but sufficiently small [7]. Fig. 2 shows that while  $\phi_0(x)$  is convex. However, for finite  $V$  there is a *stochastic stable state* at  $x = 0$ .

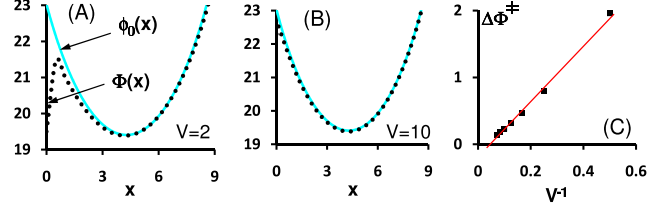


FIG. 2: Solid blue lines show  $\phi_0(x)$  according to Eq. (16). Black dots are  $\Phi(x, V)$  following Eq. (5). Parameters used are  $\theta = 0.7, \nu = 0.001, \gamma = 1000, e_t = 10$ , with (A)  $V = 2$  and (B)  $V = 10$ .  $x = 0$  is a stochastic stable state which disappears in the deterministic limit. (C) van't Hoff-Arrhenius plot with filled squares for  $\Delta\Phi^\ddagger$  showing a negative  $\Delta\phi_0^\ddagger$ , as expected for stochastic bistability.

**System with single molecules and stochastic bistability**—We have so far assumed that each term in the rates  $u_n(V)$  and  $w_n(V)$  corresponds to a term in  $\mu_0(x)$  and  $\lambda_0(x)$ . However, if a chemical reaction system at finite volume contains a term  $O(1)$ , then in the limit of  $V^{-1}u_{Vx}(V) \sim \mu_0(x) + V^{-1}\mu_1(x) + \dots$ , the term only contributes to  $\mu_1(x)$ . This is in fact the so-called “single-molecule effect”. [15]

**DGP with Lewis’ chemical detailed balance**—For chemical system with a single dynamical species, the DGP predicts that chemical equilibrium has either a binomial distribution (canonical ensemble) or Poisson distribution (grand canonical ensemble) following G.N. Lewis’ principle of chemical detailed balance [16].

The canonical ensemble has  $u_n = k_+(N - n), w_n = k_-n$  ( $n \leq N$ ),  $\phi_0(x) = x \ln(k_-x/k_+) + (e_t - x) \ln(e_t - x)$ , and  $\phi_1(x) = \frac{1}{2} \ln(x(e_t - x))$ , with  $x \leq e_t = N/V$ .  $\phi_0(x)$  is convex with a minimum at  $\hat{x} = k_+e_t/(k_+ + k_-)$ . More importantly,  $V\phi_0(x) + \phi_1(x)$  is convex for  $x \in (\frac{1}{2V}, e_t - \frac{1}{2V})$ . Note that the asymptotic expansion  $\psi(x, V) = \phi_1(x) + O(V^{-1})$  is not uniformly valid at  $x = 0, e_t$ . The existence of the ghost of extinction can not be determined by  $\phi_1(x)$ .

The grand canonical ensemble has  $u_n = jV, w_n = kn$ ,  $\phi_0(x) = x \ln(x/x^*) - x$ , and  $\phi_1(x) = \frac{1}{2} \ln x$ , where  $x^* = j/k$ . Again, convex  $\phi_0(x)$  has a minimum at  $x^*$ , and  $\phi_1(x)$  is concave. Still  $V\phi_0(x) + \phi_1(x)$  is convex when  $(\frac{1}{2V}, \infty)$ .

Therefore, with detailed balance in a chemical reaction system, the equilibrium distribution is always unimodal. The  $\gamma$  parameter in the previous sections represents the energy dissipation of open chemical systems. One can verify that when  $\gamma = 1$ , the results in the previous two sections are reduced to what we have here.

**Exit rate of a stochastic stable state**—So far we have exclusively discussed the stationary distribution in the form of  $e^{-V\Phi(x, V)}$  and its relation to the stochastic bistability. We now establish the relation between the transition rate from one stable state to another and the function  $\Phi(x, V)$ . In a 1d birth-and-death process, the mean time of the first arrival at  $n_2^*$  starting at  $n_1^*$ , with

reflection at 0 ( $0 < n_1^* < n_2^*$ ), has been widely used in the various lattice hopping models [17]:

$$T_{n_1^* \rightarrow n_2^*} = \sum_{m=n_1^*+1}^{n_2^*} \sum_{n=0}^{m-1} \frac{p_n^{st}(V)}{w_m(V)p_m^{st}(V)} \quad (18)$$

in which  $p_n^{st}$  is the stationary distribution to Eq. (3). Let  $n_1^* = Vx_1^*$ ,  $n_2^* = Vx_2^*$ , then we found the asymptotic expansion formula  $T_{x_1^* \rightarrow x_2^*} =$

$$V \int_{x_1^*}^{x_2^*} \frac{1}{\Lambda(x)} e^{V\tilde{\Phi}(x,V)} dx \int_0^x e^{-V\tilde{\Phi}(z,V)} dz \left[ 1 + O\left(\frac{1}{V}\right) \right], \quad (19)$$

in which, the modified  $\tilde{\Phi}(x, V) =$

$$\phi_0(x) + \frac{1}{V} \left\{ \phi_1(x) + \ln \frac{\mu_0(x)/\lambda_0(x) - 1}{\ln(\mu_0(x)/\lambda_0(x))} \right\}, \quad (20)$$

and  $\Lambda(x) =$

$$\frac{1}{\mu_0(x)} \left( \frac{\lambda_0(x) - \mu_0(x)}{\ln \lambda_0(x) - \ln \mu_0(x)} \right)^2. \quad (21)$$

Noting  $\Lambda(x)$  playing the role of diffusion coefficient. Eq. (19) is the same as Kramers' theory for the rate of crossing a continuous energy barrier located at  $x^\ddagger \in (x_1^*, x_2^*)$  [17]. Applying Laplace's method leads

$$T_{x_1^* \rightarrow x_2^*} \approx \frac{2\pi e^{V[\Phi(x^\ddagger, V) - \Phi(x_1^*, V)]}}{\lambda_0(x^\ddagger) \sqrt{|\phi_0''(x_1^*)| |\phi_0''(x^\ddagger)|}}. \quad (22)$$

This simple relation between transition rate and  $\Phi(x, V)$  are unique for 1-d system. While the concept we developed here will be valid in higher dimensional systems with saddle point, computation will be demanding [9].

**Summary**—Nonlinear biochemical reaction systems can have bi- or multi-stable behavior, which has implications to a wide range of biological processes such as epigenetic inheritance, cell differentiation, and cancer oncogenesis [2, 18]. The nature and the existence of the multiple states are in the nonlinear biochemical reaction schemes and rates. For a traditional nonlinear bistable system in a small volume, the transition rates decreases with increasing system size. In the deterministic limit, these rates become zero. However, small systems can also exhibit bistable phenomenon which has no deterministic counterpart. In the latter case, the bistability is due to the presence of “noise”, “stochasticity”, or “entropic barrier”. This class of bistable cellular systems can be quantitatively characterized by an van't Hoff-Arrhenius like analysis on the volume dependence of the transition rate(s). With increasing volume, the barrier diminishes. Mathematically, the transition rate is related to the landscape of the stochastic dynamics,  $k \propto e^{-V\Phi(x,V)}$  where  $\Phi(x, V)$  can be decomposed into  $\phi_0(x) + \phi_1/V$ . Nonlinear bistable system has barrier  $\Delta\phi_0^\ddagger > 0$  while stochastic bistability has  $\Delta\phi_0^\ddagger < 0$  but  $\Delta\phi_1^\ddagger > 0$ .

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