Fluctuations in chemical reactions in a large volume

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1   Introduction

Chemical reactions are very often modelled by ordinary differential equations, where the concentration of a particular particle evolves according to a deterministic law. But, in order to be able to answer several questions where the discreteness, hence the intrinsic fluctuations play a role, one needs to describe the system by a stochastic model. We assume the chemical system to be well-stirred, so that all the particles are distributed in space appropriately uniformly. Also we assume the number of reactions occurred to be Poisson-distributed, i.e. the waiting times between different reactions are distributed exponentially with given rates. This is, in a nutshell, the essence of the *Kinetic Monte Carlo (KMC)* models of chemical reactions. These models are discrete and non-deterministic, as opposed to the deterministic, continuous models governed by Ordinary Differential Equations (ODE), and the non-deterministic, continuous ones, governed by Stochastic Differential Equations (SDE). The last two models, are simpler and can be obtained from the KMC in certain limits.

The drawbacks of the deterministic description are well-known. It leads to no fluctuations, a very important characteristics in certain cases. The model governed by SDE is the so-called diffusion approximation of the original system. It is a non-deterministic model, hence it detects the intrinsic fluctuations. However, it may not be good enough, if we are concerned in the exponentially large (small) variables and/or we deal with exponentially unlikely events. We will consider the Schlögl model as the simplest model with bistability (two stable equilibriums predicted by the deterministic description) and, as an example of an exponentially large observable, we will consider the switching times between two stable states. On that example it will become clear why the diffusion approximation governed by SDE is not satisfactory.

This report is organized as follows: first, in Sec. 2 the Schlögl model is introduced as a deterministic one. Next, in Sec. 3, we will introduce the KMC model, where the number of particles evolves as a Markov jump process. In the Sec. 4 we will show how to get the simpler descriptions (ODE and SDE) as large system volume limits of the Markov jump process. Also, in order two motivate the use of the exponentially large observables, we will introduce the simplest theorem in the large deviations theory, in Sec. 5. Afterwards, in Sec. 6, we will apply the introduced ideas to the Schlögl model, emphasizing the calculations of

the mean first passage times, that are exponentially large, hence reveal the the drawbacks of the diffusion approximation. Finally, the Sec. 7 will be devoted to a short discussion and conclusions, as well as future work.

2   The Schlögl model and its deterministic description

Consider the following chemical reaction, introduced by Schlögl [1] as a catalysis model:

$$2X + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 3X$$

$$X \underset{k_4}{\overset{k_3}{\rightleftharpoons}} B. \tag{1}$$

We denote the number of particles X, A and B by the corresponding letters. Then, keeping A and B fixed and of the order of the system volume V, we are interested in the evolution of X. k_i are the rates of the corresponding reactions in (1).

The simplest description of the system is the deterministic one, where the concentration $x = X/V$ is a deterministic, continuous variable, time evolution of which is governed by the ODE:

$$\frac{dx}{dt} = u(x) - d(x). \tag{2}$$

Here we denoted $u(x) = k_1 x^2 + k_4$ and $d(x) = k_2 x^3 + k_3 x$.

For appropriate choice of parameters, the function $f(x) = u(x) - d(x)$ has three real roots: the middle one corresponds to the unstable equilibrium, while two others are the stable equilibrium values. See Fig. 1. Hence, depending on the initial value, x will exponentially approach to one of the two stable equilibriums, see Fig. 2. In a certain sense, the Schlögl model is the simplest one that leads to the bistability. Third order polynomial is normally the first choice, if we want to have a function of three real roots.

Although the deterministic model is simple to analyze, it is a good approximation to the real, discrete system only in the limit of large volume and for finite time intervals [2, 3]. It is not able to answer to questions related to the stochastic behaviour of the system, namely, the intrinsic fluctuations of the system are not detected. Consequently, it leaves open the question of relative stability: near which of the two stable equilibrium states we are more likely to find the system at a randomly chosen time? The system spends most of the time near one of the equilibrium states, but fluctuations can sporadically drive it to the neighborhood of the other equilibrium. In order to analyze the intrinsic fluctuative behaviour of the system, we will next introduce the discrete stochastic model (Kinetic Monte-Carlo scheme) according to which the chemical reaction happens.
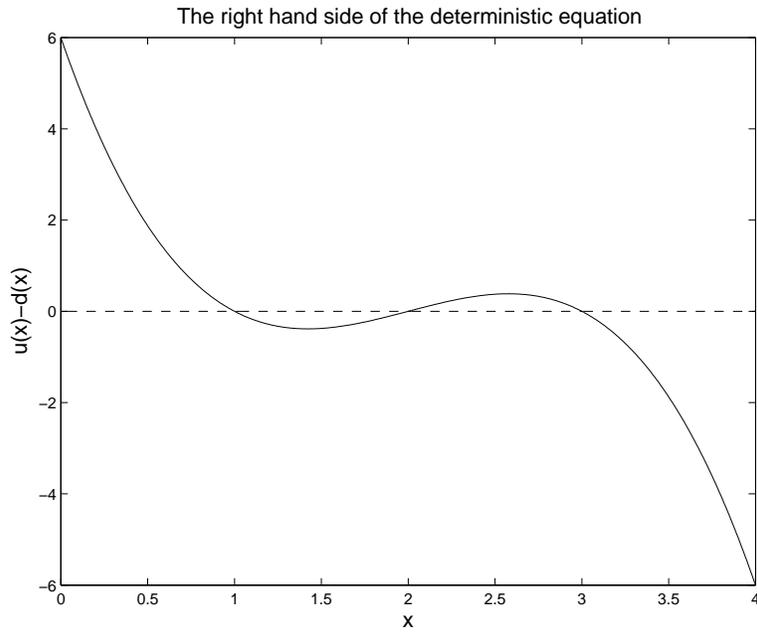
Figure 1: The deterministic rate $u(x) - d(x)$ for $u(x) = 6x^2 + 6$ and $d(x) = x^3 + 11x$, i.e. $k_1 = k_4 = 6$, $k_2 = 1$ and $k_3 = 11$.
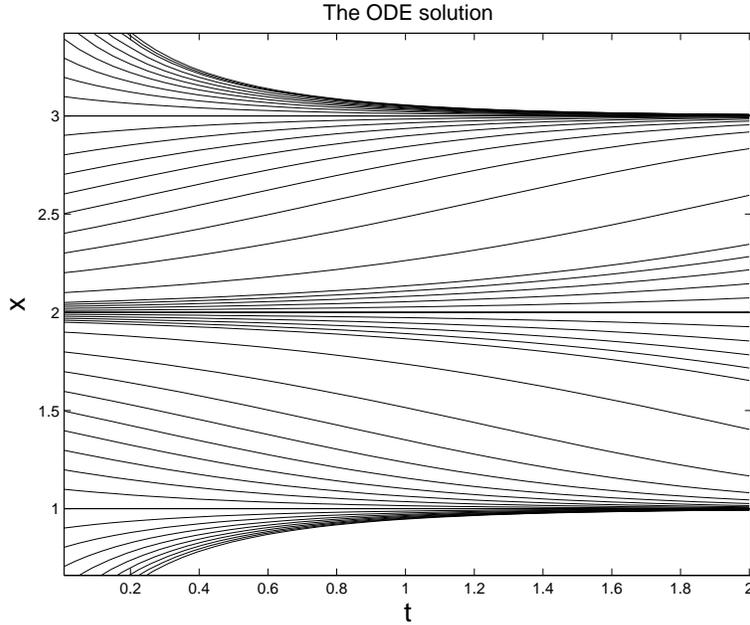

Figure 2: The time evolution of $x(t)$. Depending on the initial value, it approaches one or the other equilibrium state.

3 Discrete model as a Markov jump process (Kinetic Monte Carlo)

The reaction (1) can be rewritten as:

$$X \xrightarrow{U(X)} X + 1$$

$$X \xrightarrow{D(X)} X - 1. \tag{3}$$

Here the rates of moving "up" and "down" are, correspondingly,

$$U(X) = \frac{k_1}{V}X(X-1) + k_4 V \text{ and } D(X) = \frac{k_2}{V^2}X(X-1)(X-2) + k_3 X. \tag{4}$$

Recall that, without loss of generality, we absorbed A and B into the system volume V.

Hence, our model is one-step Markov jump process (see [4]) and is governed by the following *Master Equation* (forward Kolmogorov equation) for the probabilities $P(n,t) = \mathbb{P}\{X(t) = n\}$:

$$\frac{\partial P(n,t)}{\partial t} = U(n-1)P(n-1,t) + D(n+1)P(n+1,t) - (U(n) + D(n))P(n,t) =$$

$$= (\mathcal{L}^* P)(n,t), \tag{5}$$

where $\mathcal{L}^*$ is the adjoint of the *generator* $\mathcal{L}$ of the process. The generator of a Markov process $X(t)$, by definition, is the operator

$$(\mathcal{L}f)(n) = \lim_{t \to 0} \frac{\mathbb{E}\{f(X(t)) - f(X(0))|X(0) = n\}}{t}, \tag{6}$$

which for one-step Markov jump processes takes the form

$$(\mathcal{L}f)(n) = U(n)[f(n+1) - f(n)] + D(n)[f(n-1) - f(n)]. \tag{7}$$

The generator defines the Markov process completely. Also, if we define

$$v(n,t) = \mathbb{E}[f(X(t))|X(0) = n] \tag{8}$$

for any *observable* $f(n)$, then $v(n,t)$ solves the partial differential equation (backward Kolmogorov equation)

$$v_t = \mathcal{L}v \tag{9}$$

with initial condition $v(n,0) = f(n)$, see [5].

4 Large system volume limits

In order to analyze large system size limits, let us pass to *intensive variable* $x = n/V = \epsilon n$. In terms of x, the generator has the form

$$(\mathcal{L}_\epsilon f)(x) = \epsilon^{-1}u_\epsilon(x)[f(x+\epsilon) - f(x)] + \epsilon^{-1}d_\epsilon(x)[f(x-\epsilon) - f(x)]. \tag{10}$$

Here
$$u_\epsilon(x) = \epsilon U(x/\epsilon) = k_1 x(x - \epsilon) + k_4 = u(x) + \epsilon u_1(x)$$

and
$$d_\epsilon(x) = \epsilon D(x/\epsilon) = k_2 x(x - \epsilon)(x - 2\epsilon) + k_3 x = d(x) + \epsilon d_1(x) + \mathcal{O}(\epsilon^2).$$

Hence, the leading order rates are, correspondingly, $u(x) = k_1 x^2 + k_4$ and $d(x) = k_2 x^3 + k_3 x$.

The Markov process corresponding to the generator (10) is the same as in the original model, only with the rates and jump sizes rescaled by ϵ. Instead of working with the Master equation, we will explore the generator $\mathcal{L}_\epsilon$ itself, i.e. the backward form

$$v_t = \mathcal{L}_\epsilon v. \tag{11}$$

Expanding the generator (10) in the small ϵ limit leads to

$$(\mathcal{L}_\epsilon f)(x) = [u(x) - d(x)]f'(x) + \epsilon[u_1(x) - d_1(x)]f'(x) + \frac{\epsilon}{2}[u(x) + d(x)]f''(x) + o(\epsilon^2).$$

To the leading order, we get the differential operator

$$(\mathcal{L}_0 f)(x) = [u(x) - d(x))]f'(x) \tag{12}$$

corresponding to the deterministic description (2), discussed in Sec. 2.

To the next order $\mathcal{O}(\epsilon)$ we obtain the *backward form of the Fokker-Planck equation* (see [6])

$$(\mathcal{L}_{FP} f)(x) = [u(x) - d(x)]f'(x) + \epsilon[u_1(x) - d_1(x)]f'(x) + \frac{\epsilon}{2}[u(x) + d(x)]f''(x), \tag{13}$$

which leads to a stochastic differential equation for $x(t)$:

$$dx = [u(x) - d(x) + \epsilon(u_1(x) - d_1(x))]dt + \sqrt{\epsilon(u(x) + d(x))}dW. \tag{14}$$

This corresponds to the *diffusion approximation* of the process, with *drift* $u(x) - d(x) + \epsilon(u_1(x) - d_1(x))$ and *diffusion* $\epsilon[u(x) + d(x)]/2$.

In contrast with the deterministic description, the diffusion approximation takes the fluctuations into account, but it is not good enough if we are dealing with rare events, that arise when we calculate exponentially large (small) observables. In the next section we will introduce basic large deviations ideas, in order to qualify "rare events" in a more formal way.

5 Large deviations principles

5.1 Large deviations principle for random variables

Let us start off with the large deviations principle for the random variables. Suppose we have independent, identically distributed random variables x_i with the common mean $\mathbb{E}x_i = m$ and moment generating function $M(\theta) = \mathbb{E}\,e^{\theta x_i}$.

The well-known law of large numbers states that the average of these variables goes to m in probability as the ensemble size goes to infinity:

$$\frac{x_1 + ... + x_n}{n} \xrightarrow{\mathbb{P}} m \qquad \text{as} \qquad n \to \infty, \tag{15}$$

hence, for any $a > m$,

$$\mathbb{P}\left\{\frac{x_1 + ... + x_n}{n} > a\right\} \longrightarrow 0 \qquad \text{as} \qquad n \to \infty. \tag{16}$$

The natural question arises: what is the convergence rate in (16)? Since $e^{\theta x}$ is a monotone function, we have

$$\mathbb{P}\left\{x_1 + ... + x_n > na\right\} = \mathbb{P}\left\{e^{\theta(x_1 + ... + x_n)} > e^{\theta na}\right\} \le e^{-\theta na}\mathbb{E}\, e^{\theta(x_1 + ... + x_n)}. \tag{17}$$

The last step is just an application of the Chebyshev's inequality. By independence, we get

$$\mathbb{P}\left\{x_1 + ... + x_n > na\right\} \le e^{-\theta na}M(\theta)^n = e^{-n(\theta a - \log M(\theta))} \qquad \text{for all } \theta. \tag{18}$$

Since (18) works for all θ we can define the *action (rate) function* $l(a) = \sup_{\theta}\{\theta a - \log M(\theta)\}$ to obtain a stronger inequality:

$$\mathbb{P}\left\{x_1 + ... + x_n > na\right\} \le e^{-nl(a)}. \tag{19}$$

The basic theorem in the large deviations theory states that the bound in (19) is sharp, namely,

$$\frac{1}{n}\log \mathbb{P}\left\{\frac{x_1 + ... + x_n}{n} > a\right\} \sim -l(a) \tag{20}$$

as $n \to \infty$. See, say, [7, 8]. We say that the exponentially unlikely event $\{x_1 + ... + x_n > na\}$ satisfies the large deviations principle with the action function $l(a)$.

5.2 Large deviations expansion

We will look at an observable $v(x,t) = \mathbb{E}[f(X(t))|X(0) = x]$ with $f(x) = e^{g(x)/\epsilon}$ for some function $g(x)$. This motivates the ansatz $v(x,t) = e^{\phi(x,t)/\epsilon}$. We plug it into (11) and expand the nearby values of the exponent $\phi(x,t)$ to obtain, in the highest order ϵ^{-1}, the partial differential equation

$$\phi_t = u(x)(e^{\phi_x} - 1) + d(x)(e^{-\phi_x} - 1) \tag{21}$$

with initial condition $\phi(x,0) = g(x)$.

¿From the other hand, if we used the diffusion approximation with its generator $\mathcal{L}_{FP}$ *before* applying the WKB ansatz above, then we would get, again in the leading order ϵ^{-1}, a *wrong* PDE for the exponent function $\phi(x,t)$, namely,

$$\phi_t = [u(x) - d(x)]\phi_x + \frac{u(x) + d(x)}{2}\phi_x^2. \tag{22}$$

Therefore, if we are interested in exponentially large observables with the exponent of $\mathcal{O}(\epsilon^{-1}) = \mathcal{O}(V)$, then the diffusion approximation, hence the corresponding SDE (14) lead to a systematic error in the exponent function $\phi(x,t)$.

We may go to the next order by taking $\phi(x,t) = \phi_0(x,t) + \epsilon\phi_1(x,t)$. Then $\phi_0(x,t)$ satisfies (21), whereas $\phi_1(x,t)$ can be expressed as $\phi_1(x,t) = \ln z(x,t)$ with $z(x,t)$ satisfying

$$z_t = z_x(u(x)e^{(\phi_0)_x} + d(x)e^{-(\phi_0)_x}) + \frac{z\,(\phi_0)_{xx}}{2}(u(x)e^{(\phi_0)_x} - d(x)e^{-(\phi_0)_x}), \qquad (23)$$

which can be solved, as soon as $\phi_0(x,t)$ is found explicitely.

5.3 Moderate deviations expansion

Let us now look at an observable of the form $f(x) = e^{g(x)/\delta}$ with $1 \gg \delta \gg \epsilon$, so we are dealing with *moderate deviations*, as opposed to the large deviations, where we had $\delta = \epsilon$. One can think of $\delta = \epsilon^\alpha$ with $0 < \alpha < 1$. This will motivate the moderate deviation ansatz $v(x,t) = e^{\phi(x,t)/\delta}$ which, with both the correct generator $\mathcal{L}_\epsilon$ and the Fokker-Planck generator $\mathcal{L}_{FP}$ in the backward equation, leads, in the first two orders, to the *same* equation for the exponent function $\phi(x,t)$

$$\phi_t + (u(x) - d(x))\phi_x + \frac{\epsilon}{\delta}\frac{u(x) + d(x)}{2}\phi_x^2 = 0 \qquad (24)$$

with initial condition $\phi(x,0) = g(x)$, as before.

Therefore, we can claim that the diffusion approximation is good enough in describing up to moderate deviation events. At least, it gives the correct exponent (action) function.

6 Solving for the action function

6.1 Classical mechanics interpretation

We will focus on the large deviations case $v(x,t) = e^{\phi(x,t)/\epsilon}$ leading to the equation for the action function $\phi(x,t)$

$$\phi_t = u(x)(e^{\phi_x} - 1) + d(x)(e^{-\phi_x} - 1) \qquad (25)$$

with initial condition $\phi(x,0) = g(x)$.

Notice that this equation is of the Hamilton-Jacobi form $\phi_t + H(x,\phi_x) = 0$, hence can be solved by the method of characteristics. The (x,t)-plane is being covered by the characteristics (rays), and the evolution of $\phi(x,t)$, as well as x, is tracked along these characteristics according to a system of ODE, see [9, 10].

First, we read off the formal Hamiltonian $H(x,p) = u(x)(e^p - 1) + d(x)(e^{-p} - 1)$, and the momentum is introduced by $p = \phi_x$ The corresponding Lagrangian can also be calculated:

$$L\left(x, \frac{dx}{dt}\right) = \frac{dx}{dt}\log\frac{\frac{dx}{dt} + \sqrt{\left(\frac{dx}{dt}\right)^2 + 4u(x)d(x)}}{2u(x)} + u(x) + d(x) - \sqrt{\left(\frac{dx}{dt}\right)^2 + 4u(x)d(x)}. \quad (26)$$
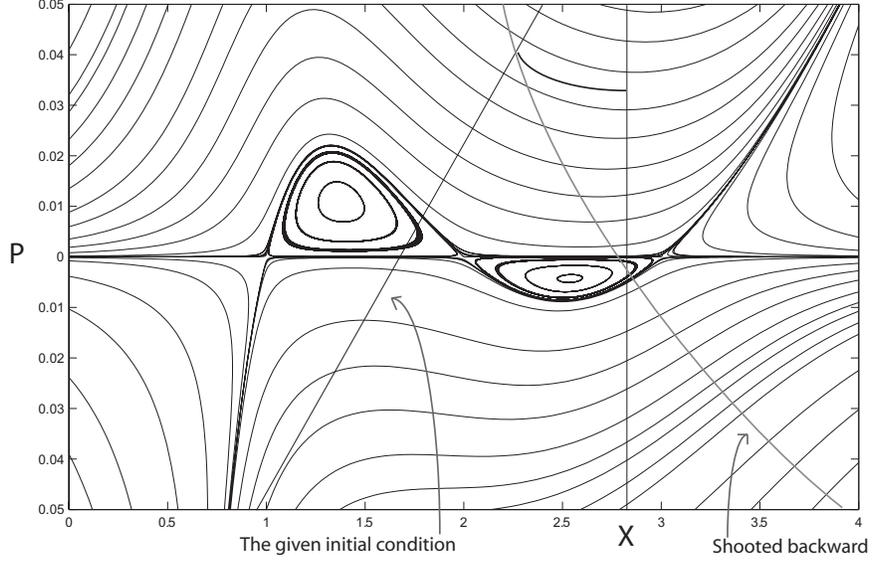
Figure 3: The phase portrait of the Hamiltonian system corresponding to the Hamilton-Jacobi equations for the action function $\phi(x,t)$.

The system evolves along the characteristics $H = \text{const}$ according to the Hamiltonian system of ODE

$$
\begin{cases}
\frac{dx}{dt} = u(x)e^p - d(x)e^{-p} \\[2mm]
\frac{dp}{dt} = -u'(x)(e^p - 1) - d'(x)(e^{-p} - 1)
\end{cases}
\tag{27}
$$

while $\phi(x,t)$ evolves by

$$
\frac{d\phi}{dt} = \phi_t + \phi_x \frac{dx}{dt} = -H(x,p) + p\frac{dx}{dt} =
$$

$$
= L\left(x, \frac{dx}{dt}(x,p)\right) = u(x)(pe^p - e^p + 1) - d(x)(pe^{-p} + e^{-p} - 1).
\tag{28}
$$

Also, by Hamilton's principle, $\phi(x,t)$ solves the variational problem

$$
\phi(x,t) = \inf\left\{ \int_0^t L(x, dx/ds)ds + g(x(0)) \right\},
\tag{29}
$$

where the infimum is taken over all $C^1[0,t]$ functions $x(\cdot)$ with $x(t) = x$.

6.2 Switching times in the Schlögl model

For the Schlögl model, $H = \text{const}$ paths are shown in Fig. 3. Using the phase portrait of the corresponding Hamiltonian system, the solution $\phi(X,T)$ of Hamilton-Jacobi equation with an initial condition $\phi(x,0) = g(x)$ is obtained in the following way. We take the vertical line $x = X$ and trace all the points backward for time T. That will give an "initial" profile $f(x,p) = 0$ of the points that lead to X at time T. The intersection of this profile with the

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real initial curve $p = g'(x)$ will give the initial value (in fact, there could be more than one intersection points), therefore, the correct characteristics, leading to the point X in time T. This is the essence of the "shooting" method [9].

As mentioned in Sec. 2, one of the most important questions for bistable systems is: which of the stable states is more stable? To answer it, we should compare the mean first passage times (called switching times) from one stable state to the other.

Mean first passage time $T(x)$ from a state x to a fixed state x_f solves the backward equation $-1 = \mathcal{L}T(x)$ with the appropriate boundary conditions [4, 5]. For the one-step jump Markov processes the mean first passage times can be calculated exactly from the backward master equation and it leads to the large deviations asymptotics of the form $e^{\phi(x)/\epsilon}$ for some action function $\phi(x)$. In general, deterministically forbidden switches between two states (in the deterministic case, see Fig. 2, switches that have to pass through $x = 2$ are not allowed) are large deviation events. The large deviation analysis applied to the $-1 = \mathcal{L}T(x)$ (as opposed to (9), discussed above) now will lead to the time-independent Hamilton-Jacobi equation

$$0 = u(x)(e^{\phi_x} - 1) + d(x)(e^{-\phi_x} - 1) = H(x, \phi_x). \tag{30}$$

Therefore, large deviation paths on the phase portrait are the ones corresponding to $H(x, p) = 0$. These are the heteroclinic connections, and they correspond to $p = 0$ and $p = \log \frac{d(x)}{u(x)}$, as can be seen in Fig. 4. From (27) one can see that $p = 0$ leads to the deterministic description $\dot{x} = u(x) - d(x)$, where the switches between the first and third equilibria x_1 and x_3 are not allowed (in order to go from one to the other, the path necessarily leaves the axis $p = 0$). To switch from x_1 to x_3, while staying on the $H = 0$ curves, the system has to "climb" the non-deterministic path x_1-to-x_2 and then follow the deterministic one, x_2-to-x_3 on the x-axis. Similarly, the switch from x_3 to x_1 has to go through the "valley" x_3-to-x_2 and then follow the deterministically allowed path on the x-axis, x_2-to-x_1.

By (28), the exponent (action) $\phi_{13} = \epsilon \log T_{13}$ for the switching time T_{13} from x_1 to x_3 can be found by

$$\phi_{13} = \int \left(-H + p\frac{dx}{dt} \right) dt = \int_{x_1}^{x_2} p \, dx = \int_{x_1}^{x_2} \log \frac{d(x)}{u(x)} \, dx = \text{ the area } S_1, \tag{31}$$

since $p = 0$ on the second part of the path and $H = 0$ throughout the whole path. Similarly,

$$\phi_{31} = \int_{x_3}^{x_2} p \, dx = \int_{x_2}^{x_3} \log \frac{u(x)}{d(x)} \, dx = \text{ the area } S_2. \tag{32}$$

For instance, from the Fig. 4 we can see that in this particular parameter regime $S_1 > S_2$, hence $T_{13} > T_{31}$. Since it takes longer to switch from x_1 to x_3 than vice-versa, we can conclude that the first equilibrium is the more stable one.

The important point here is that if we used SDE to model the chemical reaction (or, equivalently, if we used the diffusion approximation *before* the large deviation ansatz), it would not give the correct Hamiltonian, hence the switching times would be miscalculated.

Also, the parameters k_i can be tuned so that the two stable equilibriums are equally stable, and there are certain parameter regimes where the diffusion approximation gives the opposite, wrong answer to the relative stability question.
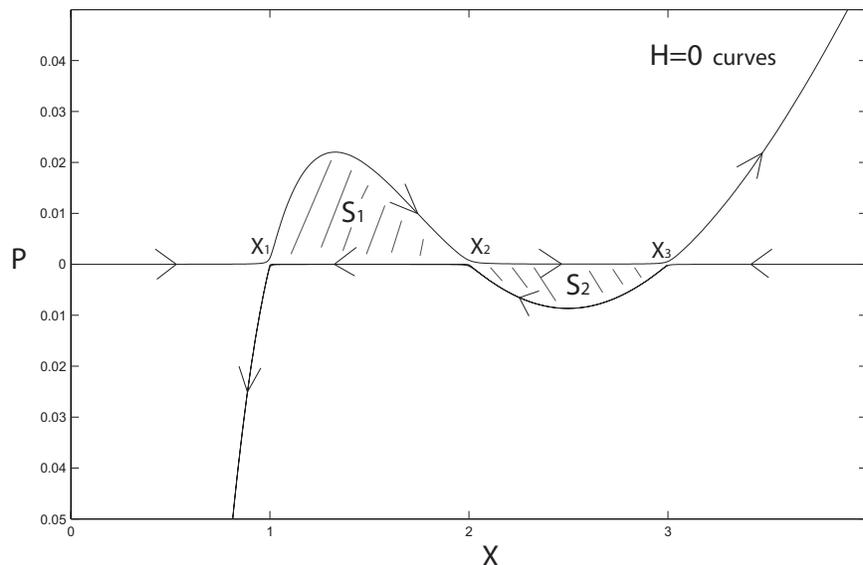
Figure 4: The $H = 0$ curves are heteroclinic connections. They correspond to $p = 0$ and $p = \log \frac{d(x)}{u(x)}$. Parameters are picked so that $x_i = i$ for i=1,2,3 are the equilibrium states.

7   Conclusion and future work

In this report we have introduced the Kinetic Monte Carlo modeling of chemical reactions, paying particular attention to the benchmark bistable system - the Schlögl model. The main reason of using KMC is that the simplest, deterministic model of a chemical reaction is not satisfactory at all as we are interested in fluctuations in concentrations. We have also discussed the SDE approach to the problem and have shown that it is not able to correctly answer questions concerning large deviation events/observables. If we are interested in exponentially large observables (e.g., switching times between two states that are nor reachable from each other in the deterministic case) with the exponent proportional to the volume of the system, then SDE approach gives a systematic error in the exponent function. The reason is hidden in (10): we need to plug the exponential ansatz into it *first* and then expand the exponent function, as opposed to the SDE approach, where we expanded (10) to arrive to (13), and then plugged in the exponential ansatz.

In fact, the work can be carried out for general Markov jump processes with generator

$$(\mathcal{L}f)(n) = \sum_{i=1}^{k} \lambda_i(n)[f(n + e_i) - f(n)] \tag{33}$$

and its rescaled version

$$(\mathcal{L}_\epsilon f)(x) = \sum_{i=1}^{k} \epsilon^{-1} \lambda_i(x)[f(x + \epsilon e_i) - f(x)], \tag{34}$$

where e_i are the jump sizes (there are k possible ones) and $\lambda_i(n)$ are the ϵ-independent *propensity functions* (rates) corresponding to these jumps. Then the deterministic generator is $(\mathcal{L}_0 f)(x) = \left[\sum_{i=1}^{k} \lambda_i(x)e_i\right] f'(x)$ and the Fokker-Planck one is $(\mathcal{L}_{FP}f)(x) = \left[\sum_{i=1}^{k} \lambda_i(x)e_i\right] f'(x) + \frac{\epsilon}{2}\left[\sum_{i=1}^{k} \lambda_i(x)e_i^2\right] f''(x)$. Finally, the Hamilton-Jacobi equation (25) will be generalized as

$$\phi_t = \sum_{i=1}^{k} \lambda_i(x)(e^{e_i \phi_x} - 1). \tag{35}$$

For the particular model, the Schlögl's bistable system, we answered the question of relative stability, pointing out again, that SDE approach does not answer it correctly, while the deterministic description can not address that question at all. We have found the exact formulae for the switching times from one stable state to the other and vice versa.

Similar questions may be posed for 2D models. The further work may include exploring the competition models from population dynamics in a manner of KMC. Here, the SDE approach is even more widely used, hence it is important to understand that it may not be good enough explaining the rare events, such as, in some cases, the competitive exclusion of one species.

8 Acknowledgements

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