Predicting rare events in chemical reactions: application to skin cell proliferation

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In a well-stirred system undergoing chemical reactions, fluctuations in the reaction propensities are approximately captured by the corresponding chemical Langevin equation. Within this context, we discuss in this work how the Kramers escape theory can be used to predict rare events in chemical reactions. As an example, we apply our approach to a recently proposed model on cell proliferation with relevance to skin cancer [P. B. Warren, Phys. Rev. E 80, 030903 (2009)]. In particular, we provide an analytical explanation for the form of the exponential exponent observed in the onset rate of uncontrolled cell proliferation.

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I. INTRODUCTION

Noise is ubiquitous in systems undergoing chemical reactions. In a well-stirred system, the source of noise comes from the probabilistic nature of the reactions, and can be analyzed by employing the Chemical Master Equation (CME) \[1,2\]. With the help of the Kramers-Moyal expansion, a Chemical Langevin Equation (CLE) can be formulated to approximate the CME \[2,4\]. When the number of molecules in the system is small, the limitations of the approximation have been explored in \[5,6\]. On the other hand, when the numbers of molecules of the different chemical species in the system are greater than certain thresholds, the CLE constitutes a reasonable approximation to the CME \[4\]. One big advantage of the CLE is the well developed analytical tools available. For instance, thermally activated escape theory (see, e.g., \[7,8\]), such as Kramers escape theory, serves as a natural platform for the studies of extinction rate of chemical species \[9-13\], and transition rates between two metastable states of the system concerned \[14\]. This is the approach adopted in this work. Besides being of general interest to chemical systems, the method discussed here is also relevant to cellular processes. One interesting example is the recent proposal that metastability in skin cell proliferation constitutes a component in the pathogenesis of cancer \[15\]. In particular, the author in \[15\] observed numerically that the rate for the onset of uncontrolled cell proliferation has an exponential component that scales in a specific manner with the model parameters. As an illustration, we shall demonstrate how the form of the exponent observed can be explained analytically within the context of Kramers escape theory.

II. A SIMPLE EXAMPLE

We will first start by considering a simple example to set up the formalism. Consider the following set of chemical reactions:

\[ A \xrightarrow[\lambda]{\lambda} A + A \quad , \quad A + A \xrightarrow[\Gamma]{\Gamma} A \] (1)

where \(\lambda\) depends on the number of A molecules, \(n_A\), in the following manner:

\[ \lambda(n_A) = \begin{cases} M\Gamma & , \quad \text{if } n_A < N \\ 2\Gamma n_A & , \quad \text{otherwise} \end{cases} \] (2)

where \(M\) and \(\Gamma\) are constant. In a deterministic system, the above scenario is governed by the following equation:

\[ \dot{n}_A = [\lambda(n_A) - \Gamma n_A] n_A . \] (3)

In other words, if 0 < \(n_A(t = 0) < N\), then \(n_A(t \to \infty) = M\). On the other hand, if \(n_A(t = 0) \geq N\), then \(n_A(t \to \infty)\) diverges (c.f. the phase portrait under the plot in Fig. 1).

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This deterministic picture is of course incomplete due to the neglect of the intrinsic fluctuations from the reaction propensities. Such fluctuations are approximately captured by the following CLE:

\[
\dot{n}_A = \left[ \lambda(n_A) - \Gamma n_A \right] n_A + \sqrt{\lambda(n_A) n_A} w + \sqrt{\Gamma n_A^2} w',
\]

where \( w, w' \) are Gaussian noises with zero means and unit standard deviations. Since \( w \) and \( w' \) are uncorrelated, we have

\[
\dot{n}_A = \gamma f + \sqrt{2\gamma} w
\]

where we have introduced the following functions:

\[
\gamma = \frac{[\lambda(n_A) + \Gamma n_A]}{2}, \quad f = \frac{2[\lambda(n_A) - \Gamma n_A]}{\lambda(n_A) + \Gamma n_A}.
\]

Note that the form of Eq. (5) corresponds to a Langevin equation describing a particle in a potential well under thermal perturbations in the non-inertia regime. Specifically, \( n_A \) can be treated as the coordinate of the particle, \( f \) as the force exerted on the particle due to an underlying potential, and \( \gamma \) as the position-dependent damping coefficient of the system.

In the region \( n_A < M \), the force is

\[
f(n_A) = \frac{2(M - n_A)}{M + n_A}.
\]

The corresponding potential energy can thus be determined as

\[
U(n_A) = -\int_M^{n_A} dx f(x) = 2(n_A - M) - 4M \ln \frac{n_A + M}{2M}.
\]

Similarly, in the region \( n_A \geq M \), we have \( f(n_A) = \frac{2}{M} \) and \( U(n_A) = -2n_A / 3 + \) constant. The shape of the potential energy is depicted in Fig. 1

We are primarily concerned with rare escape events and we thus assume that \( N - M \gg 1 \). In this scenario, if the initial state of the system is such that \( n_A(t = 0) = M \), then the waiting time, \( \tau \), for the system to move out of the potential well, i.e., the waiting time for \( n_A \) to attain the value \( N \) is (c.f. Sect. 7.2 in [8]):

\[
\tau = \frac{2\pi}{U'(M)} \exp \left[ 2(N - M) - 4M \ln \frac{N + M}{2M} \right]
\]

\[
= 2\pi M \exp \left[ 2(N - M) - 4M \ln \frac{N + M}{2M} \right].
\]

Note that \( n_A \) will, with probability one, either go to zero or diverge [8], and so the knowledge of the escape rate is particularly important.

III. SKIN CELL PROLIFERATION

We now move onto discussing a model for skin cell proliferation. The model we study is based on the single progenitor cell model introduced in [16, 17]. This model was then generalized in [15] to account for the homeostasis of the system. Furthermore, the author in [15] suggests that the escape of the system from the homeostatic basin due to rare stochastic fluctuations plays a role in uncontrolled cell proliferation. This is of important relevance to the study of skin cancer. Specifically, there are two basal layer cell types in this model: progenitor cells \( A \) and postmitotic cells \( B \). These two types of cells proliferate according to following scheme:

\[
A \xrightarrow{\lambda_1} A + A, \quad A \xrightarrow{\lambda_2} A + B
\]

\[
A \xrightarrow{\lambda_3} B + B, \quad B \xrightarrow{\Gamma} \emptyset.
\]

The first three processes represent the different progenitor cell division pathways, and the fourth represents postmitotic cells leaving the basal layer. In the model above, \( \Gamma \) is a constant and \( \lambda_i \) are defined as follow:

\[
\lambda_1 = \lambda(n) r(1 - q(\rho))
\]

\[
\lambda_2 = \lambda(n)(1 - 2r)
\]

\[
\lambda_3 = \lambda(n) r(1 + q(\rho))
\]

where

\[
n = n_A + n_B, \quad \rho = \frac{n_A}{n}
\]
\[ \lambda(n) = \lambda_0 \left( \frac{n_0}{n} \right)^2, \quad \lambda_0 = \frac{\Gamma(1 - \rho_0)}{\rho_0} \] (19)

and

\[ q(\rho) = \tanh \left[ \frac{10 \rho_0 (1 - \rho_0) (\rho - \rho_0) (\rho_1 - \rho)}{\rho (1 - \rho) (\rho_1 - \rho_0)} \right]. \] (20)

Note that the constants \( n_0 \), \( \rho_0 \) and \( \rho_1 \) represent the initial number of cells, the fraction of progenitor cells at the stable fixed point (marked by the gray circle in Fig. 2), and the fraction of progenitor cells at the unstable fixed point (marked by the gray square in Fig. 2), respectively.

An experimentally motivated set of parameters for this model is shown in the caption of Fig. 2. We refer the readers to [13] for more detailed physiological interpretations of the different processes. Here, we will only note that a divergence of the total cell density, \( n_A + n_B \), signifies the onset of uncontrolled cell proliferation. In [15], the author employs the standard Gillespie kinetic Monte Carlo algorithm [18] to perform stochastic simulations of the model, and finds that the escape rate has an exponential component of the form \( \exp(-4.6 \times n_0 \Delta \rho^2) \) where \( \Delta \rho \equiv \rho_1 - \rho_0 \) denotes the difference in the fractions of progenitor cells at the saddle point and at the fixed point. We will now demonstrate how the Kramers escape theory accounts for the exponent observed.

We shall first look at the deterministic case, where the chemical reaction scheme in Eqs. (13) and (14) lead to the following set of ordinary differential equations:

\[ \dot{n}_A = -2 \lambda r q n_A, \quad \dot{n}_B = \lambda (1 + 2 r q) n_A - \Gamma n_B. \] (21)

Setting the L.H.S. in the equations above to zero, we find two nontrivial fixed points:

\[ X = \begin{pmatrix} n_0 \rho_0, (1 - \rho_0) n_0 \end{pmatrix} \] (22)

\[ Y = \begin{pmatrix} n_0 \sqrt{\frac{\lambda_0 \rho_0^3}{\Gamma(1 - \rho_0)}}, n_0 \sqrt{\frac{\lambda_0 \rho_1 (1 - \rho_1)}{\Gamma}} \end{pmatrix}. \] (23)

These fixed points are denoted by a gray circle and a gray square respectively in Fig. 2 along with flow lines.

The corresponding CLE for this system is [1]:

\[ \dot{n}_A = (\lambda_1 - \lambda_3) n_A + \sqrt{\lambda_1 n_A w_1} - \sqrt{\lambda_3 n_A w_3} \] (24)

\[ \dot{n}_B = (\lambda_2 + 2 \lambda_3) n_A - \Gamma n_B \] (25)

\[ + \sqrt{\lambda_2 n_A w_2} + 2 \sqrt{\lambda_3 n_A w_3} - \sqrt{\Gamma n_B w_4} \] (26)

where the \( w_i \) are again Gaussian noises with zero means and unit standard deviations. As among the four independent Gaussian noise terms, only \( w_3 \) are common in both equations, we can thus simplify the above equation to the followings:

\[ \dot{n}_A = (\lambda_1 - \lambda_3) n_A + \sqrt{\lambda_1 + \lambda_3} n_A w_1 \] (27)

\[ \dot{n}_B = (\lambda_2 + 2 \lambda_3) n_A - \Gamma n_B \] (28)

\[ + \sqrt{(\lambda_2 + 4 \lambda_3) n_A} + \Gamma n_B \left[ \sigma w_1 + \sqrt{1 - \sigma^2} w_2 \right] \]

\[ \sigma = \sqrt{\frac{2 \lambda_3 n_A}{\sqrt{n_A (\lambda_1 + \lambda_3)} (\lambda_2 + 4 \lambda_3) n_A + \Gamma n_B}} \] (29)

where

\[ \rho = \frac{\lambda_1 n_A + \lambda_2 n_B}{\lambda_2 n_A + \lambda_3 n_B + \Gamma n_B} \]

The magnitude of the correlation \( \sigma \) as a function of \( n_A \) and \( n_B \) around the two fixed points indicated again by the square and the circle. The broken line denotes the escape path corresponding to the analytical calculation in Eq. (38), and the solid line denotes the escape path obtained numerically (c.f. the discussion before Eq. (49)), which corresponds to the result in Eq. (10).

As aforementioned, the Gaussian noises associated to the two coordinates are correlated. In Fig. 3, we show the magnitude of \( \sigma \) around the two fixed points, which is bounded above by 0.31. The first approximation is that we will set \( \sigma \) to zero, i.e., we assume that the perturbations acting on \( n_A \) and \( n_B \) are uncorrelated. With this simplification, Eqs (24) and (25) can be written as:

\[ \dot{n}_A = \gamma_A f_A + \sqrt{2 \gamma_A w_A}, \quad \dot{n}_B = \gamma_B f_B + \sqrt{2 \gamma_B w_B} \] (30)

where

\[ \gamma_A = r \lambda n_A, \quad \gamma_B = \frac{\lambda (1 + 2 r + 4 r q) n_A + \Gamma n_B}{2} \] (31)

\[ f_A = -2 q, \quad f_B = \frac{2 \lambda (1 + 2 r + 4 r q) n_A - 2 \Gamma n_B}{\lambda (1 + 2 r + 4 r q) n_A + \Gamma n_B}. \] (32)
Fig. 4: The force vector fields, \((f_A, f_B)\), according to Eqs (32). The magnitudes of the vectors are scaled up uniformly for visual clarity.

Fig. 4 shows the force vectors \((f_A, f_B)\) around the two fixed points, which suggests that \(|f_B| \ll |f_A|\) in the region connecting \(X\) and \(Y\). In other words, it is much easier for the particle to diffuse vertically than to diffuse horizontally. We will therefore ignore the second dimension and consider purely the first coordinate. This constitutes our second approximation and effectively collapses the problem into a one-dimensional problem. As a result, we can calculate the corresponding potential by simply integrating over \(f_A\):

\[
U = \int 2q \left( \frac{x}{x + \hat{n}_B} \right) dx . \tag{33}
\]

where we will take \(\hat{n}_B = X_B\) (c.f. Eqs (20) and (22)). If the initial cell densities are in the metastable region around \(X\), the rate, \(R\), at which uncontrolled cell proliferation occurs will be of the form \(R \propto \exp(-\Delta U)\) [19], where

\[
\Delta U = \int_{X_A}^{Y_A} 2q \left( \frac{x}{x + \hat{n}_B} \right) dx . \tag{34}
\]

Note that our consideration effectively amounts to calculating the first passage time of a particle constrained to diffuse along the horizontal path depicted by the broken line in Fig. 4.

Since throughout the range of the integration, the argument in \(q\) is bounded above by 0.12, \(q\) is well approximated by \(\hat{q}\) where (c.f. Eq. (20))

\[
\hat{q}(\rho) = \frac{10\rho_0(1 - \rho_0)(\rho - \rho_0)(\rho_1 - \rho)}{\rho(1 - \rho)(\rho_1 - \rho)} . \tag{35}
\]

This simplification allows us to perform the integration in Eq. (34) analytically, and we find that for small \(\Delta \rho\),

\[
\Delta U = \frac{5\rho_0(3 - 2\rho_0)^2}{3(1 - \rho_0)} n_0 \Delta \rho^2 + \mathcal{O}(\Delta \rho^3) . \tag{36}
\]

\[
\approx 3.1 \times n_0 \Delta \rho^2 , \tag{37}
\]

where the second approximated equality comes from substituting in the numerical values of the parameters shown in the caption of Fig. 2. Recall that the exponent is found numerically to be \((4.6 \times n_0 \Delta \rho^2)\) [15]. We have therefore recovered the scaling of the exponent with respect to \(\Delta \rho\). On the other hand, the prefactor we obtained is about two thirds of that observed from simulations.

We will now try to incorporate the second dimension and the correlation in the fluctuations into the picture. Our strategy is to find a path that better represents the escape route. In the weak noise limit, such an optimal escape path encapsulates the information on the asymptotic behavior of the escape process, and in principle, can be obtained by solving a set Hamiltonian equations with the appropriate end points. 7, 21, 22. We find the application of the numerical procedure to the problem concerned challenging as the corresponding set of Hamiltonian equations are higher sensitive to the initial conditions chosen. Hence, we will instead make a crude estimate on the escape path that connects the metastable state to the saddle point [24]. Specifically, as we have argued that the particle diffuses more easily along the vertical direction, we reason that as the particle goes upward in the \(nA\) direction, it should stay at the bottom of the valley with respect to the force fields along the \(nA\). We therefore start at the metastable point, \(X\), and find the \(nA\) that minimizes \(|f_A|\) as we move up in the \(nA\) dimension. We find that such a path corresponds to a slanted as depicted by the solid line in Fig. 3. While the path reaches \(Y_B\) in the \(nB\) coordinate, we simply connects it horizontally with the saddle point \(Y\) (c.f. Fig. 3). We denote this escape path by \(z(s)\), where \(0 \leq s \leq L\) corresponds to the parametrization of the curve such that \(z(0) = X, z(L) = Y\) and \(|z'(s)| = 1\) for all \(s\). Now we collapse the problem into one dimension by considering only fluctuation processes along this path. The time evolution of the particle along the path can be expressed as:

\[
\dot{s} = w\gamma_A f_A + v\gamma_B f_B + \left[2(u^2\gamma_A + v^2\gamma_B + 2\sigma w^2\sqrt{\gamma_A\gamma_B})\right]^{1/2} w , \tag{38}
\]

where the \(\gamma_A/B\) and \(f_{A/B}\) are as expressed in Eqs (31) and (32), \(\sigma\) is defined in Eq. (29), and \((u, v)\) denotes the unit tangent of the curve \(z\) at the point \((nA, nB)\). As a result, the exponent in the rate describing the escape process from \(s = 0\) to \(s = L\) is:

\[
\Delta U = -\int_0^L \frac{w\gamma_A f_A + v\gamma_B f_B}{w^2\gamma_A + v^2\gamma_B + 2\sigma w^2\sqrt{\gamma_A\gamma_B}} ds . \tag{39}
\]

The numerical value is found to be

\[
\Delta U = 2.05 = 6.4 \times n_0 \Delta \rho^2 , \tag{40}
\]

which is greater than the simulation results by about 39%. The discrepancy here is likely an outcome of the approximation of the correlation in the fluctuations into the picture.
our crude way of estimating the escape path. To improve upon this result, more sophisticated numerical approaches would be required, which is beyond the scope of this work.

IV. CONCLUSION

In summary, we have discussed how the Kramers escape theory can be used to predict rare events in chemical reactions due to stochastic fluctuations. As an application, we have considered a model on cell proliferation and explained analytically the observed rate for the onset of uncontrolled cell growth.

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