Most Probable Evolution Trajectories in a Genetic Regulatory System Excited by Stable Lévy Noise *

Xiujun Cheng¹, Hui Wang⁴,a), Xiao Wang², Jinqiao Duan³, Xiaofan Li³

Abstract

We study the most probable trajectories of the concentration evolution for the transcription factor activator in a genetic regulation system, with non-Gaussian stable Lévy noise in the synthesis reaction rate taking into account. We calculate the most probable trajectory by spatially maximizing the probability density of the system path, i.e., the solution of the associated nonlocal Fokker-Planck equation. We especially examine those most probable trajectories from low concentration state to high concentration state (i.e., the likely transcription regime) for certain parameters, in order to gain insights into the transcription processes and the tipping time for the transcription likely to occur. This enables us: (i) to visualize the progress of concentration evolution (i.e., observe whether the system enters the transcription regime within a given time period); (ii) to predict or avoid certain transcriptions via selecting specific noise parameters in particular regions in the parameter space. Moreover, we have found some peculiar or counter-intuitive phenomena in this gene model system, including (a) a smaller noise intensity may trigger the transcription process, while a larger noise intensity can not, under the same asymmetric Lévy noise. This phenomenon does not occur in the case of symmetric Lévy noise; (b) the symmetric Lévy motion always induces transition to high concentration, but certain asymmetric Lévy motions do not trigger the switch to transcription.

These findings provide insights for further experimental research, in order to achieve or to avoid specific gene transcriptions, with possible relevance for medical advances.

Key words: Most probable trajectories; Stable Lévy motion; Nonlocal Fokker-Planck equation; Stochastic genetic regulation system

* ¹ Center for Mathematical Sciences & School of Mathematics and Statistics & Hubei Key Laboratory of Engineering Modeling and Scientific Computing, Huazhong University of Science and Technology, Wuhan 430074, China. ² School of Mathematics and Statistics, Henan University, Kaifeng 475000, China. ³ Department of Applied Mathematics, Illinois Institute of Technology, Chicago 60616, USA. ⁴School of Mathematics and Statistics, Zhengzhou University, Zhengzhou 450001, China. a) Author to whom correspondence should be addressed: huiwheda@hust.edu.cn
1 Introduction

Random fluctuations have been extensively considered in the modeling and analysis of genetic regulatory systems [1–18]. These fluctuations may lead to switching between gene expression states [3, 19–28]. To characterize this switching behaviour, researchers have been developing stochastic models [18, 22, 24, 29] by taking noises into account in deterministic differential equations. Noisy fluctuations are mostly considered as Gaussian white noise in terms of Brownian motion [6, 14, 21, 22, 30]. But it has been observed that the transcriptions of DNA from genes and translations into proteins occur in an intermittent, bursty way [9, 10, 31–37]. This evolutionary manner [38–44] resembles the features of trajectories or solution paths of a stochastic differential equation with a Lévy motion. In contrast to the (Gaussian) Brownian motion, Lévy motion is a non-Gaussian process with heavy tails and occasional jumps.

In this present paper, we consider a genetic regulatory model for the evolution of the concentration for a transcription factor activator (TF-A), developed by Smolen et al. [45], with the synthesis reaction rate perturbed by stable Lévy fluctuations. Liu and Jia [22] investigated the effect of fluctuations arise from the Gaussian noise in the degradation and the synthesis reaction rate of the transcription factor activator, and found that a successive switch process occurred with the increase of the cross-correlation intensity between noises. In addition, Zheng et al. [24] used the mean first exit time and the first escape probability to examine the mean time scale and the likelihood for the concentration profile to evolve from low concentration regime to high concentration regime (indicating the transcription status).

Unlike the existing works in examining transition possibility and time scales under noises (e.g., [22, 24]), the objective of this present paper is to study the most probable trajectories (or orbits) for concentration states themselves of the transcription factor activator (a protein) as time goes on. This offers the following information for the gene regulation system:

(i) The concentration evolution trajectories from low concentration to high concentration, indicating the evolutionary routes to transcription.
(ii) The tipping time for the most likely orbits to pass the barrier between the low concentration state and the high concentration state.

To this end, we compute the most probable phase portrait for this stochastic gene model, in order to gain insights into the concentration trajectories from the low concentration state to the high concentration state (i.e., the likely transcription regime), and the tipping time for these trajectories passing a threshold state between low and high concentration. Especially, we try to characterize the dependence of these dynamical behaviors on the noise parameters.

This paper is organized as follows. In Section 2, we introduce the TF-A monomer concentration model in a gene regulation system excited by a stable Lévy noise and present our method on most probable evolution trajectories. In Section 3, we present the most probable evolution trajectories for the gene system under various noise parameters. We examine which kind of stable noise is more beneficial for transcription. Finally, we summarize the above results in Section 4. The Appendix contains basic facts about a stable Lévy motion, and the nonlocal Fokker-Planck equation formulation for a stochastic differential equation.
Fig 1: Genetic regulatory model with a feedforward (Eq (1)).

with a stable Lévy motion.

2 Model and Method

2.1 Model: Stochastic gene regulation

We consider a model for the transcription factor activator (TF-A) of a genetic regulatory system, established by Smolen et al. [45]. A single transcriptional activator TF-A is considered as part of a pathway mediating a cellular response to a stimulus. The TF forms a homodimer bound to responsive elements (TF-REs). The TF-A gene incorporates one of these responsive elements, where binding to this element of homodimers will increase TF-A transcription. Only phosphorylated dimers can activate transcription. As shown in Fig 1, the phosphorylated (P) transcription factor activator (TF-A) activates transcription with a maximal rate $k_f$, with $k_d$ and $R_{bas}$ the degradation and synthesis rate of the TF-A monomer, respectively. The dissociation concentration of the TF-A dimer from TF-REs is denoted by $K_d$. Then the evolution of the TF-A concentration $x$ obeys the following differential equation [45]:

$$\dot{x} = \frac{k_f x^2}{x^2 + K_d} - k_d x + R_{bas}. \quad (1)$$

The system (1) may be written as $\dot{x} = -U'(x)$, with the potential $U(x) = k_f \sqrt{K_d} \arctan \frac{x}{\sqrt{K_d}} + k_d^2 x^2 - (R_{bas} + k_f) x$. It has two stable states and one unstable state, when the parameters satisfy the condition: $[-\left(\frac{k_f + R_{bas}}{3k_d}\right)^3 + \frac{K_d(k_f + R_{bas})}{6k_d} - \frac{K_dR_{bas}}{2k_d}]^2 + [K_d^3 - \left(\frac{k_f + R_{bas}}{3k_d}\right)^2]^3 < 0$. As in [22], we select suitable parameters: $k_f = 6 \text{ min}^{-1}$, $K_d = 10$, $k_d = 1 \text{ min}^{-1}$, and $R_{bas} = 0.4 \text{ min}^{-1}$. Then two stable states are $x_- \approx 0.62685 \text{ nM}$ and $x_+ \approx 4.28343 \text{ nM}$ and the unstable state (a saddle point) is $x_u \approx 1.48971 \text{ nM}$. See Fig 2.
The dynamical system (1) is a deterministic model. Some experiments indicated that basal synthesis rate $R_{bas}$ is influenced by random fluctuations arising from the biochemical reactions, the concentrations of other proteins, and gene mutations [22,35,41]. There exists powerful evidences indicating that gene expression with small diffusion and large bursting resembles the composition of systems with Lévy noise [38–41]. Zheng et al. [24] model random behaviour of the synthesis rate $R_{bas}$ on the genetic regulatory system (1) by a symmetric Lévy noise, but this symmetry is quite a idealized, special situation. We thus consider a general asymmetric stable Lévy noise. Hence, we take a stable Lévy noise as a random perturbation of the synthesis rate $R_{bas}$. Then the model (1) becomes the following scalar stochastic gene regulation model with additive stable noise:

$$
\dot{X}_t = \frac{k_f X_t^2}{X_t^2 + K_d} - k_d X_t + (R_{bas} + \tilde{L}_t^{\alpha,\beta}), \quad X_0 = x_0,
$$

(2)

where the scalar stable Lévy motion $\tilde{L}_t^{\alpha,\beta}$, with non-Gaussianity index $\alpha (0 < \alpha < 2)$, skewness index $\beta (-1 \leq \beta \leq 1)$, scaling index $\sigma (\sigma > 0)$ and shift index zero, is recalled in A1 Asymmetric stable Lévy motion at the end of this paper. We denote $\epsilon \triangleq \sigma^\alpha$ the noise intensity. It is worth noting that we concern on the internal noise [46,47], which can be realized as additive noise. In stochastic dynamical systems, it is customary to denote a system variable by a capital letter with time as subscript $(X_t)$. A stable Lévy motion is asymmetric when $\beta \neq 0$ and symmetric when $\beta = 0$. The well-known Brownian motion $B_t$ is a Gaussian process, corresponding to the special symmetric case with $\alpha = 2$ (and $\beta = 0$). A solution orbit (also called a solution trajectory) $X_t$ has occasional (up to countable) jumps for almost all samples (i.e., realizations), except in the case with Brownian motion $B_t$, for which almost all the solution trajectories are continuous in time [48].

Without noise, the low concentration stable state $x_-$ and high concentration stable state $x_+$ are resilient (see Fig 2): the TF-A concentration states will locally be attracted $x_-$ or $x_+$,
as time increases for the deterministic system (1). It is known that stochastic fluctuations may induce switches between two stable states [22, 45]. The TF-A concentration, starting near the low concentration state \(x_-\) in \(D = (0, x_u)\), arrives at a high concentration state (near \(x_+\)) by passing through the unstable saddle state \(x_u\) (see Fig 2). The threshold time instant when the system passes the unstable saddle state \(x_u \approx 1.48971\) is called the ‘tipping time’ for a specific solution trajectory.

We now examine these system trajectories or orbits for the gene regulation model:

(i) How does the system evolve from low concentration (near \(x_-\)) to high concentration (near \(x_+\)), indicating the system in a transcription regime?

(ii) What is the tipping time while evolving from the low concentration state to the high concentration state?

Figs 3(a) and 3(b) show two sample paths of \(X_t\) for the stochastic gene regulation system (2), starting at low concentration state \(x_- \approx 0.62685\). Unlike the phase portraits for deterministic dynamical systems [49, 50], these sample paths (‘orbit’ or ‘trajectories’) mingled together and can not provide much information. Thus we consider most probable phase portraits [51–53] for the stochastic gene regulation system (2) in the next section.

\[\text{Fig 3: (Online color) Two stochastic TF-A concentration sample paths } X_t \text{ starting at } X_0 = x_- \approx 0.62685 \text{ with noise intensity } \epsilon = 1.\]

(a) Stochastic TF-A concentration sample paths \(X_t\) with (Gaussian) Brownian motion. (b) Stochastic TF-A concentration sample paths \(X_t\) with (non-Gaussian) Lévy motion at \(\alpha = 1.2, \beta = 0\).

### 2.2 Method: Most probable trajectories for concentration evolution

**Most probable trajectories:**

For the stochastic system (2) starting at an initial point \(x_0\), each sample path is a possible
outcome of the solution orbit $X_t$. What is the most probable or maximal likely orbit of $X_t$? In order to answer the question, we need to decide on the most probable position $x_m(t)$ of the system (starting at the initial point $x_0$) at every given future time $t$, but this is the maximizer for the probability density function $p(x, t) \triangleq p(x, t; x_0, 0)$ of solution $X_t$. We first numerically solve the nonlocal Fokker-Planck equation (A.2), which reduces to a local Fokker-Planck equation (A.4) when stable Lévy motion $L_t^{a, \beta}$ is replaced by Brownian motion $B_t$, and then we find the most probable position $x_m(t)$ as the maximizer of $p(x, t)$ at every given time $t$. The probability density function $p(x, t)$ is a surface in the $(x, t, p)$ space. At a given time instant $t$, the maximizer $x_m(t)$ for $p(x, t)$ indicates the most probable (i.e., maximal likely) location of this orbit at time $t$. The trajectory (or orbit) traced out by $x_m(t)$ is called the most probable trajectory starting at $x_0$. Thus, $x_m(t)$ follows the top ridge or plateau of the surface in the $(x, t, p)$ space as time goes on. Starting at every initial point, we may thus compute its most probable trajectory for the evolution of concentration for the transcription factor activator (and thus we occasionally call it the most probable evolution trajectory). The most probable trajectories [51,52] are also called ‘paths of mode’ in climate dynamics and data assimilation [54, 55].

Considering the movement of the peak for $p(x, t)$ at a given time instant $t$, there are two cases: (i) The only peak of $p(x, t)$ moves and the height varies as time goes on (see Fig 4(a)(d)); (ii) Two peaks for $p(x, t)$ at a given time instant $t$, and one decreases and the other increases as time goes on (see Fig 4(b)(c)). Consequently, in the case (i), the most probable trajectory is continuous. But in the case (ii), it is feasible that the most probable trajectory jumps from one location to another, when the maximal value at one time instant switches to the maximal value at the following time instant, as shown in Fig 4(b)(c). This should not be confused with the discontinuity or lack of it for the individual solution paths of the stochastic system (2). Rather, the most probable trajectory tracks the time evolution of the system state of highest likelihood, among possible states that may be assumed by all sample solution paths starting from a given deterministic initial state $x_0$.

Most probable trajectories from low to high concentration states:

As in [53], the most probable equilibrium state is a state which either attracts or repels all nearby orbits. When it attracts all nearby orbits, it is called a most probable stable equilibrium state, while if it repels all nearby orbits, it is called a most probable unstable equilibrium state. Most probable equilibrium states depend on noise parameters $\alpha, \beta$, noise intensity $\epsilon$ as well as the genetic system parameters.

Fig 5 also shows one or two most probable equilibrium states. We observe that the most probable equilibrium state $x^{high}$ in high concentration is between 4 and 5, depending on $\alpha, \beta, \epsilon$, and it differs from the deterministic stable state $x_+ \approx 4.28343$ due to the effect of noise.

We are especially interested in the most probable trajectory starting at the low concentration stable state $x_- \approx 0.62685$ and approaching (or arriving in a small neighborhood of) the most probable equilibrium stable state in the high concentration regime (more likely for transcription). It is a deterministic estimator for the most likely orbit with these features.
Fig 4: (Online color) The probability density function $p$ of stochastic system (2) starting at $x_0 = x_- \approx 0.62685$. (a) Under Gaussian noise with $\epsilon = 1$ at $t = 2, 3, 4, 5$. (b) Under Gaussian noise with $\epsilon = 0.5$ at $t = 6, 10, 11, 12$. (c) Under symmetric ($\beta = 0$) Lévy noise $\alpha = 1$ with $\epsilon = 1$ at $t = 4, 5, 6, 7$. (d) Under asymmetric Lévy noise $\alpha = 1.5, \beta = -0.5$ with $\epsilon = 1$ at $t = 2, 2.3, 2.7, 5$.

Fig 5 also shows the most probable evolution trajectories for certain parameters. This definition of most probable evolution trajectories is based on maximizing the solution’s probability density at every time instant.

We use a similar efficient numerical finite difference method developed by us in Gao et al. [56] to simulate the nonlocal Fokker-Planck equation (A.2) and use the standard finite difference method to simulate the local Fokker-Planck equation (A.4). This applies to stochastic systems with finite as well as small noise intensity.

In the following, we compute the most probable evolution trajectories, in order to analyze how the TF-A concentration evolves from the low concentration state to the high concentra-
Fig 5: (Online color) Most probable evolution trajectories of stochastic system (2) starting at various initial concentration \( x_0 \). (a) With Brownian motion: \( \epsilon = 0.02 \). (b) With Brownian motion: \( \epsilon = 0.4 \). (c) With Lévy motion: \( \alpha = 1.5, \beta = 0, \epsilon = 0.02 \). (d) With Lévy motion: \( \alpha = 1.5, \beta = 0, \epsilon = 0.4 \).

...tion state. The most probable orbits \( x_m(t) \), starting at \( x_- \), is a deterministic estimator as time goes on. The tipping time is the time needed (counting from the start) for this most probable evolution trajectories \( x_m(t) \) to pass through the saddle point \( x_u \). The tipping time for the most probable orbit provides the threshold time instant at which the system enters the high concentration regime.
3 Results

3.1 Gene regulation under Gaussian noise

Now, we discuss the influence of the Gaussian noise on the most probable evolution trajectories. As seen in Fig 6 as time goes on, for four different noise intensities $\epsilon = 0.25, 0.5, 0.75, 1$, the most probable concentration increases, and then remains a nearly constant high concentration near $x_+$ (interpreted as in the transcription regime). Moreover, we clearly observe that the most probable concentration reaches $x_u \approx 1.48971$ faster for larger $\epsilon$, that is, the tipping time is shorter. Besides, there exists a great jump on the most probable orbit with $\epsilon = 0.25$, which is explained by Fig 4.

![Fig 6: (Online color) Most probable evolution trajectories under Gaussian noise for different $\epsilon$.](image)

In the (Gaussian) Brownian noise case, we observe that the most probable concentration always maintains a nearly constant concentration level for sufficiently long time (we computed up to $t = 50$). Moreover, we find that a shorter tipping time can be achieved under a larger noise intensity $\epsilon$.

3.2 Gene regulation under non-Gaussian Lévy noise

We now discuss the influence of symmetric (see Fig 7(a)) and asymmetric (see Fig 7(b)) Lévy noise on most probable evolution trajectories. In Fig 7(a), as time increases, for four different noise intensities $\epsilon = 0.25, 0.5, 0.75, 1$, the most probable concentration decreases a bit at the beginning, increases to the high concentration quickly, and finally remains a nearly constant level (in transcription regime). These dynamical behaviors, in the symmetric noise case, may appear intuitively correct, but this is not true in the asymmetric noise case as we now discuss.
In Fig 7(b), we notice that the most probable concentration goes through the saddle state \(x_u\) and arrives at the high concentration state for smaller noise intensities \(\epsilon = 0.25, 0.5, 0.75\), but counter-intuitively decrease to a nearly constant low concentration for larger noise intensity \(\epsilon = 1\). In this work, we take time \(t = 50\) as the tipping time if the most probable concentration does not pass through the saddle point \(x_u\) by time \(t = 50\). This suggests that the asymmetric Lévy noise with \(\alpha = 0.5, \beta = -0.5\), and \(\epsilon = 1, x_0 = 0.62685\), does not induce the switch mechanism for transcription.

![Fig 7](image-url)  
**Fig 7:** (Online color) Most probable evolution trajectories under symmetric (\(\beta = 0\)) and asymmetric (\(\beta \neq 0\)) Lévy noise for various parameters. (a) Dependence on \(\epsilon\): \(\alpha = 0.5, \beta = 0\). (b) Dependence on \(\epsilon\): \(\alpha = 0.5, \beta = -0.5\).

The reason for no possible transcription may be explained by the stability of two deterministic stable states \(x_-, x_+\) in system \(\Pi\), under the influence of noise. As shown in Fig 8(a), the state near \(x_-\) is attracted to the most probable equilibrium stable state in high concentration domain and thus we have possible transcription for the smaller noise intensity \(\epsilon = 0.25\). But in Fig 8(b), the state near \(x_-\) is attracted to the most probable equilibrium stable state in the low concentration state, and this offers an explanation for the counter-intuitive phenomenon of no possible transcription for the larger noise intensity \(\epsilon = 1\).

In summary, by examining the transition orbits in the most probable phase portraits, we have thus found that although the symmetric (\(\beta = 0\)) Lévy noise (including the special case Brownian noise) appears to induce transition to transcription, asymmetric (\(\beta \neq 0\)) Lévy noise with certain parameters do not trigger the switch to transcription. Furthermore, we have explained the reason for no apparent transcription, due to the system stability change for some asymmetric stable Lévy noise. In the next section, we will further show effects of stable Lévy noise by computing the tipping time and the concentration values for most
Fig 8: (Online color) Most probable evolution trajectories starting at various initial concentration $x_0$. (a) With Lévy motion: $\alpha = 0.5, \beta = -0.5, \epsilon = 0.25$. (b) With Lévy motion: $\alpha = 0.5, \beta = -0.5, \epsilon = 1$.

probable evolution trajectories at the end of computation ($t = 50$).

### 3.3 Most probable transcription and tipping time

In this subsection, we investigate which kind of stable Lévy noise has a significant impact on the transcriptional activities, via the most probable concentration state value at $t = 50$ (see Fig 8(a)) on the most probable evolution trajectories and the tipping time (see Fig 8(b)) for these trajectories.

The red region in Fig 8(a) presents the valid transcription region corresponding to the gene regulation system with the noise within the parameter plane $(\beta, \alpha)$, as it shows the high concentration values (indicating transcription). Note that the symmetric ($\beta = 0$) Lévy noise (including the special case Brownian noise) induces transition to transcription, but asymmetric ($\beta \neq 0$) Lévy noise with certain parameters do not trigger the switch to transcription.

The dark blue region indicates the situation with no transcription.

Likewise, as seen in Fig 8(b) about tipping time in the noise case in the parameter plane $(\beta, \alpha)$, the red region illustrates that no transcription has occurred by the time $t = 50$ as there is no tipping from the low concentration to the high concentration state (i.e., the most probable orbit does not pass through the saddle state $x_u$).

In addition, the critical line $\alpha = 1$ helps form a part of the boundary between the transcription and no-transcription regions in the parameter plane. With this divided parameter plane, we can select combined parameters $\alpha$ and $\beta$, in order to achieve transcription within an appropriate time scale.
The tipping time

4 Conclusion

In this work, we have investigated the transcription factor activator’s concentration evolution in a prototypical gene regulation model, focusing on the effects of Gaussian noise and non-Gaussian Lévy noise in the synthesis reaction rate. We examine the most probable concentration trajectory, i.e., we visualize the trajectories from low concentration to high concentration. We also compute the tipping time from the low concentration state to the high concentration state. The most probable evolution trajectories are calculated via numerically solving the nonlocal Fokker-Planck equation for the stochastic gene regulation model, and they form the most probable phase portrait for this model.

For initial concentration \( x_0 \) at the lower stable concentration state, we compute the most probable evolution trajectory \( x_m(t) \) and this enables us to visualize the progress of concentration evolution as time goes on (i.e., observe whether the system enters the transcription regime).

We have further characterized the concentration evolution with varying noise parameters: non-Gaussianity index \( \alpha \), skewness index \( \beta \) and noise intensity \( \epsilon \). Therefore, we can predict the concentration level (or an appropriate transcription status) at a given future time, depending on the specific noise parameters in divided regions in the parameter plane (see Fig 9). We have also noticed some peculiar or counter-intuitive phenomena. For example, a smaller noise intensity may trigger the transcription process, while a larger noise intensity can not, in this gene system with the same asymmetric Lévy noise (see Fig 7(b)). This phenomenon
does not occur in the case of symmetric Lévy noise. Moreover, the symmetric ($\beta = 0$) Lévy noise (including the special case Brownian noise) induces transition to transcription for all non-Gaussianity index $\alpha$, but asymmetric ($\beta \neq 0$) Lévy noise with certain non-Gaussianity index $\alpha$ do not trigger the switch to transcription.

These findings may provide helpful insights for further experimental research, in order to achieve or to avoid specific gene transcriptions.

**Acknowledgments**

We would like to thank Yayun Zheng, Jintao Wang, Xu Sun, Ziyi He and Rui Cai for helpful discussions. This work was partly supported by the National Science Foundation Grant No. 1620449, the National Natural Science Foundation of China Grant Nos. 11531006 and 11771449, and the Fundamental Research Funds for the Central Universities, HUST, No. 0118011075.

**Appendix**

We recall the definition of a scalar stable Lévy motion $L_t^{\alpha,\beta}$ and the nonlocal Fokker-Planck equation for the probability density evolution of the solution to the stochastic system $[2]$.

**A1 Asymmetric stable Lévy motion $L_t^{\alpha,\beta}$** A scalar stable Lévy motion $L_t^{\alpha,\beta}$ is a stochastic process with the following properties $[48, 51, 57, 58]$:

(i) $L_0^{\alpha,\beta} = 0$, almost surely (a.s.);

(ii) $L_t^{\alpha,\beta}$ has independent increments;

(iii) $L_t^{\alpha,\beta}$ has stationary increments: $L_t^{\alpha,\beta} - L_s^{\alpha,\beta} \sim S_\alpha((t-s)^{\frac{1}{\alpha}}, \beta, 0)$, for all $s$ and $t$ with $0 \leq s \leq t$;

(iv) $L_t^{\alpha,\beta}$ has stochastically continuous sample paths, i.e., for every $s > 0$, $L_t^{\alpha,\beta} \rightarrow L_s^{\alpha,\beta}$ in probability, as $t \rightarrow s$.

Here $S_\alpha(\sigma, \beta, \mu)$ is the so-called stable distribution $[51,58]$ and is determined by four indexes: non-Gaussianity index $\alpha (0 < \alpha < 2)$, skewness index $\beta (-1 \leq \beta \leq 1)$, shift index $\mu (-\infty < \mu < +\infty)$ and scale index $\sigma (\sigma > 0)$. A stable Lévy motion has jumps and its probability density function has heavy-tails (i.e., the tails decrease for large spatial variable like a power function $[51,57,58]$). The non-Gaussianity index $\alpha$ decides the thickness of the tail, as shown in Fig A.1(a). In contrast, Brownian motion $B_t$ (corresponding to $\alpha = 2, \beta = 0$) has light tails (i.e., the tails decrease exponentially fast). As seen in Fig A.1(b), the skewness index $\beta$ measures the asymmetry (i.e., non-symmetry) of the probability density function. The distribution is right-skewed if $\beta > 0$, left-skewed if $\beta < 0$, and symmetric for $\beta = 0$ $[51,57,58]$. 


A path for $L_t^{\alpha,\beta}$, although stochastically continuous, has occasional (up to countable) jumps for almost all samples (i.e., realizations), while almost all paths of Brownian motion $B_t$ are continuous in time.

(a) Non-Gaussianity indexes $\alpha = 0.4$, 1.2, 2 for $\beta = 0$. (b) Skewness indexes $\beta = -0.9$, 0, 0.9 for $\alpha = 0.5$.

**A2 Nonlocal Fokker-Planck equation**  For the stochastic gene regulation system (2), let us recall the Fokker-Planck equation for the probability density function $p(x, t) \triangleq p(x; t; x_0,0)$ of its solution $X_t$, with initial condition $X_0 = x_0$. The generator $A$ for the solution process $X_t$ is (45, 48, 51)

$$Ap(x, t) = (f(x) + \epsilon M_{\alpha,\beta}) \partial_x p(x, t)$$

$$+ \epsilon \int_{\mathbb{R}^1 \setminus \{0\}} \left[ p(x + y, t) - p(x, t) - I_{\{|y|<1\}}(y) y \partial_x p(x, t) \right] \nu_{\alpha,\beta}(dy), \quad (A.1)$$

where $I$ is the indicator function and

$$M_{\alpha,\beta} = \begin{cases} \frac{C_1 - C_2}{1 - \alpha}, & \alpha \neq 1, \\ \left( \int_1^{\infty} \frac{\sin(x)}{x^2} dx + \int_0^1 \frac{\sin(x) - x}{x^2} dx \right) (C_2 - C_1), & \alpha = 1. \end{cases}$$

Then the nonlocal Fokker-Planck equation is

$$\frac{\partial}{\partial t} p(x, t) = A^* p(x, t), \quad p(x, 0) = \delta(x - x_0), \quad (A.2)$$
where $A^*$ is the adjoint operator of $A$ and $\delta$ is the Dirac function. The adjoint operator $A^*$ can be further written as

$$A^* p(x, t) = -\partial_x ((f(x) + \epsilon M_{\alpha, \beta}) p(x, t)) + \epsilon \int_{\mathbb{R}^1 \setminus \{0\}} \left[ p(x + y, t) - p(x, t) - I_{\{|y|<1\}}(y) y \partial_x p(x, t) \right] \nu_{\alpha,-\beta}(dy),$$

(A.3)

where $\nu_{\alpha,\beta}(dy) = \frac{C_1 I_{\{0<y<\infty\}}(y) + C_2 I_{\{-\infty<y<0\}}(y)}{|y|^{1+\alpha}} dy$, $C_1 = \frac{H_{\alpha}(1+\beta)}{2}$, $C_2 = \frac{H_{\alpha}(1-\beta)}{2}$. Here,

$$H_{\alpha} = \begin{cases} \frac{\alpha(1-\alpha)}{\Gamma(2-\alpha) \cos(\frac{\pi \alpha}{2})}, & \alpha \neq 1, \\ \frac{2}{\pi}, & \alpha = 1. \end{cases}$$

For a symmetric stable Lévy motion ($\beta = 0$), the jump measure is $\nu_{\alpha,0}(dy) = \frac{H_{\alpha}}{2|y|^{1+\alpha}} dy$.

This nonlocal equation can be numerically solved by a similar finite difference method as in [56].

In particular, when the Lévy motion is replaced by Brownian motion $B_t$, the Fokker-Planck equation becomes

$$\frac{\partial}{\partial t} p(x, t) = -\frac{\partial}{\partial x} (f(x) p(x, t)) + \frac{\epsilon}{2} \frac{\partial^2}{\partial x^2} p(x, t).$$

(A.4)

References

1. J. M. Raser, and E. K. O’Shea, *Science* 309(5743):2010, (2005).
2. N. Maheshri, and E. K. O’Shea, *Annu. Rev. Biophys. Biomolec. Struct.* 36(36):413, (2007).
3. P. S. Swain, M. B. Elowitz, and E. D. Siggia, *Proc. Natl. Acad. Sci.* 99(20):12795, (2002).
4. M. Kittisopikul, and G. M. Süel, *Proc. Natl. Acad. Sci.* 107(30):13300, (2010).
5. P. C. Bressloff, *Stochastic Processes in Cell Biology.* (Springer, New York, 2014).
6. R. Gui, Q. Liu, Y. Yao, H. Deng, C. Ma, Y. Jia, and M. Yi, *Front. Physiol.* 7, (2016).
7. G. M. Süel, R. P. Kulkarni, J. Dworkin, J. Garcia-Ojalvo, and M. B. Elowitz, *Science* 315(5819):1716, (2017).
8. M. Turcotte, J. Garcia-Ojalvo, and G. M. Süel, *Proc. Natl. Acad. Sci.* 105(41):15732, (2008).
9. N. Friedman, L. Cai, and X. S. Xie, *Phys. Rev. Lett.* 97(16):168302, (2006).

10. Y. T. Lin, and C. R. Doering, *Phys. Rev. E* 93(2):022409, (2016).

11. P. J. Choi, L. Cai, K. Frieda, and X. S. Xie, *Science* 322(5900):442, (2008).

12. J. J. Tabor, T. S. Bayer, Z. B. Simpson, M. Levy, and A. D. Ellington, *Mol. Biosyst.* 4(7):754, (2008).

13. B. Munsky, G. Neuert, and A. V. Oudenaarden, *Science* 336(6078):183, (2012).

14. G. M. Süel, J. Garcia-Ojalvo, L. M. Liberman, and M. B. Elowitz, *Nature* 440(7083):545, (2006).

15. S. Ciuchi, F. de Pasquale, and B. Spagnolo, *Phys. Rev. E* 47:3915, (1993).

16. S. Ciuchi, F. de Pasquale, and B. Spagnolo, *Phys. Rev. E* 54:706, (1996).

17. D. Li, J. Zhang, and Z. Zhang, *J. Sci. Comput.* 76:848, (2018).

18. G. Augello, D. Valenti, and B. Spagnolo, *Eur. Phys. J. B* 78:225, (2010).

19. M. Assaf, E. Roberts, and Z. Luthey-Schulten, *Phys. Rev. Lett.* 106(24):248102, (2011).

20. J. Hasty, J. Pradines, M. Dolnik, and J. J. Collins, *Proc. Natl. Acad. Sci.* 97(5):2075, (2000).

21. J. Hasty, J. Pradines, M. Dolnik, and J. J. Collins, *Stochastic & Chaotic Dynamics in the Lakes: S. American Institute of Physics*, 502:191, (2000).

22. Q. Liu, and Y. Jia, *Phys. Rev. E* 70:041907, (2004).

23. Y. Xu, J. Feng, J. Li, and H. Zhang, *Chaos* 23(1):013110, (2013).

24. Y. Zheng, L. Serdukova, J. Duan, and J. Kurths, *Sci. Rep.* 6:29274, (2016).

25. W. Horsthemke, and R. Lefever, *Noise-Induced Transitions*, Springer-Verlag, Berlin, 1984.

26. A. Fiasconaro, J.J. Mazo, and B. Spagnolo, *Phys. Rev. E* 82:041120, (2010).

27. D. Valenti, C. Guarcello, and B. Spagnolo, *Phys. Rev. B* 89:214510, (2014).

28. N.V. Agudov, A.A. Dubkov, and B. Spagnolo, *Physica A* 325(1-2):144-151, (2003).

29. A. La Cognata, D. Valenti, A.A. Dubkov, and B. Spagnolo, *Phys. Rev. E* 82:011121, (2010).
30. Y. Li, M. Yi, and X. Zou, *Sci. Rep.* 4(4):5764, (2014).

31. R. D. Dar, B. S. Razooky, A. Singh, T. V. Trimeloni, J. M. McCollum, C. D. Cox, M. L. Simpson, and L. S. Weinberger, *Proc. Natl. Acad. Sci.* 109(43):17454, (2012).

32. W. J. Blake, M. Kærn, C. R. Cantor, and J. J. Collins, *Nature* 422(6932):633, (2003).

33. A. Sanchez, and I. Golding, *Science* 342(6163):1188, (2013).

34. E. M. Ozbudak, M. Thattai, I. Kurtser, A. D. Grossman, and A. V. Oudenaarden, *Nature Genet.* 31(1):69, (2012).

35. A. Raj, and A. V. Oudenaarden, *Ann. Rev. Biophys.* 38(1):255, (2009).

36. N. Kumar, A. Singh, and R. V. Kulkarni, *PLoS Comput. Biol.* 11(10):e1004292, (2015).

37. D. M. Holloway, and A. V. Spirov, *PLoS One* 12(4):e0176228, (2017).

38. I. Golding, J. Paulsson, S. M. Zawilski, and E. C. Cox, *Cell* 123(6):1025, (2005).

39. C. H. Bohrer, and E. A. Roberts, *BMC Biophys.* 9(1):1, (2016).

40. T. Muramoto, D. Cannon, M. Gierlinski, A. Corrigan, G. J. Barton, and J. R. Chubb, *Proc. Natl. Acad. Sci.* 109(19): 7350, (2012).

41. A. Raj, C. Peskin, D. Tranchina, D. Vargas, and S. Tyagi, *PLoS Biol.* 4:1707, (2006).

42. D. Alexander, and B. Spagnolo, *Acta Phys. Pol. B* 38:1745, (2007).

43. A.A. Dubkov, B. Spagnolo, and V.V. Uchaikin, *Int. J. Bifurcation Chaos* (18):2649, (2008).

44. A. A. Dubkov, A. La Cognata, and B. Spagnolo, *J. Stat. Mech.-Theory Exp.* P01002, (2009).

45. P. Smolen, D. A. Baxter, and J. H. Byrne, *Am. J. Physiol.* 274(1):531, (1998).

46. X. Liu, H. Xie, L. Liu, and Z. Li, *Physica A* 338:392, (2009).

47. M. Thattai, and A.V. Oudenaarden, *Proc. Natl. Acad. Sci. U. S. A.* 98:8614, (2001).

48. D. Applebaum, *Lévy Processes and Stochastic Calculus*, 2nd Edition. (Cambridge University Press, New York, 2009).

49. J. Guckenheimer, and P. Holmes, *Nonlinear Oscillations, Dynamical Systems and Bifurcations of Vector Fields* (Springer, New York, 1983).
50. S. Wiggins, *Introduction to Applied Nonlinear Dynamical Systems and Chaos*, 2nd Edition. (Springer, New York, 2003).

51. J. Duan, *An Introduction to Stochastic Dynamics* (Cambridge University Press, New York, 2015).

52. Z. Cheng, J. Duan, and L. Wang, *Commun. Nonlinear Sci. Numer. Simulat.* 30:108, (2016).

53. H. Wang, X. Chen, and J. Duan, *Int. J. Bifurcation Chaos*. arXiv:1801.03739 [math.DS]. To appear, 2018.

54. R. N. Miller, E. F. Carter, and S. T. Blue, *Tellus Ser. A-Dyn. Meteorol.* 51:167, (1999).

55. T. Gao, J. Duan, X. Kan, and Z. Cheng, *J. Phys. A-Math. Theor.* 49:294002, (2016).

56. T. Gao, J. Duan, and X. Li, *Appl. Math. Comput.* 278:1, (2016).

57. K. Sato, *Lévy Processes and Infinitely Divisible Distributions* (Cambridge University Press, New York, 1999).

58. G. Samorodnitsky and M. S. Taqqu, *Stable Non-Gaussian Random Processes* (Chapman and Hall, New York, 1994).