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Effects of Small Random Perturbations in the Extended Glass–Kauffman Model of Gene Regulatory Networks

Arcady Ponosov ^{1,*}, Irina Shlykova ^{1,†} and Ramazan I. Kadiev ^{2,†}¹ Department of Mathematics, Norwegian University of Life Sciences, 1432 Aas, Norway² Dagestan Research Center of the Russian Academy of Sciences, Department of Mathematics, Dagestan State University, 367005 Makhachkala, Russia; kadiev@mail.ru

* Correspondence: arkadi@nmbu.no

† These authors contributed equally to this work.

Abstract: A mathematical justification of some basic structural properties of stochastically perturbed gene regulatory networks, including those with autoregulation and delay, is offered in this paper. By using the theory of stochastic differential equations, it is, in particular, shown how to control the asymptotic behavior of the diffusion terms in order to not destroy certain qualitative features of the networks, for instance, their sliding modes. The results also confirm that the level of randomness is gradually reduced if the gene activation times become much smaller than the time of interaction of genes. Finally, the suggested analysis explains why the deterministic numerical schemes based on replacing smooth, steep response functions by the simpler yet discontinuous Heaviside function, the well-known simplification algorithm, are robust with respect to uncertainties in data. The main technical difficulties of the analysis are handled by applying the uniform version of the stochastic Tikhonov theorem in singular perturbation analysis suggested by Yu. Kabanov and S. Pergamentshchikov.

Keywords: gene regulation; stochastic differential equations; singular perturbation analysis; delay effects

MSC: 34D15; 60H10; 60H30; 92D10



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1. Introduction

Simplification frameworks in systems biology are widely used in theoretical and numerical analysis, as realistic biological models may be very complicated. Typical examples are calculations in the Heaviside limit, when one replaces steeply sloped functions by the Heaviside (step) functions. This results in hybrid models that combine the so-called ‘Boolean networks’ with a continuous-time description. Mathematically, it leads to a system of piecewise-linear differential equations, which, however, has all the properties of highly nonlinear dynamics. This idea has been successfully utilized in the neural field modeling, where the step firing rate functions are known to be very close to the Heaviside functions, this approach is known as the Amari simplification of the Wilson–Cowan model [1,2]. Another prominent example, which is studied in this paper, is motivated by analysis of gene regulatory networks (GRNs), where the expression of genes is also close to a jump-like process in a vicinity of the thresholds.

In most cases, calculations with simplified models are a priori assumed to be reliable, even if no proper mathematical justification is used. This may lead to ignoring many important features of the real-world models.

In this paper, we consider one popular model of GRNs, which is described by a system of ordinary differential equations of the form

$$\dot{x}_i(t) = F_i(Z) - G_i(Z)x_i(t), \quad i = 1, \dots, n, \quad (1)$$

or by delay differential equations, see (3) below. Here, the production and relative degradation rate functions F_i and G_i , respectively, depend on the vector $Z = (Z_1, \dots, Z_n)$, where

$Z_i = Z_i(x_i)$ are steep response (or regulation) functions, called *sigmoids* in the literature. System (1) reflects the effect of the different transcription factors regulating the expression of genes occurring when gene concentrations x_i exceed certain threshold values θ_i [3–5].

To analyze this model, one conveniently replaces the sigmoids by their limits, the Heaviside functions with the jump at the threshold. This converts System (1) into a system with Boolean-like switchings. Moreover, in the limit $Z_i = Z_i^m$ for any $m > 0$, so that the functions F_i, G_i may be assumed to be linear with respect to each Z_i , which considerably simplifies the models. This simplification is, indeed, necessary, as the amount of interacting genes appears to be quite large (up to ten thousand). This approach was originally proposed by L. Glass and S.A. Kauffman [6] and has since become very popular, see, e.g., the review paper [5]. Numerical similarity between the dynamics of the sigmoid-based model and its Heaviside limit, observed in many cases, may or may not be an indication that the simplified analysis is reliable, and indeed, it was noticed in the paper [3] that the Glass–Kauffmann model is too coarse to describe the so-called ‘sliding motions’ when the trajectories slide along the thresholds for some time without crossing them. Biologically, it reflects the situations where one or several gene concentrations can stay close to their respective thresholds without being expressed. This effect can, in particular, be observed for GRNs with autoregulation [4]. Analysis offered in [3] shows how to calculate sliding trajectories using the simplified model and to justify the preservation of sliding modes under small perturbations, which ensures efficiency of a network in regulation of gene expression and, therefore, contributes to the overall functionality of the network. Such calculations are important to uncover and analyze singular stationary points of GRNs, which belong to the discontinuity sets of the Boolean model and which represent states where some variables are actively regulated by sigmoid interactions.

Traditionally, one assumes the response functions Z_i to be the Hill function [3–5]

$$Z_i = \Sigma(x_i, \theta_i, q_i) := \begin{cases} 0 & \text{if } x_i < 0, \\ \frac{x_i^{1/q_i}}{x_i^{1/q_i} + \theta_i^{1/q_i}} & \text{if } x_i \geq 0, \end{cases} \quad (2)$$

where $q_i > 0$ are the steepness parameters and $\theta_i > 0$ are the threshold values for the respective gene concentrations (by technical reasons we assume Z_i to be defined for negative x_i , even if this is not biologically significant). It is straightforward to see that if $q_i \rightarrow 0$, then the functions Z_i approach the shifted Heaviside functions $\Sigma(x_i, \theta_i, 0)$, see Figure 1.

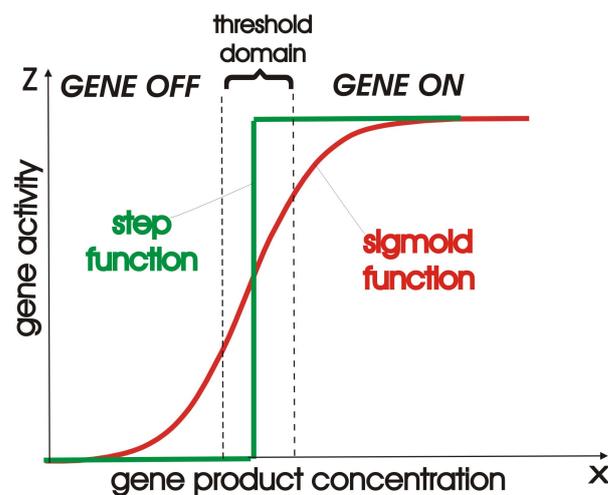


Figure 1. The Hill function $Z_i = \Sigma(x_i, \theta_i, q_i)$ ($q_i > 0$) becomes the shifted Heaviside function $\Sigma(x_i, \theta_i, 0)$ as $q_i \rightarrow 0$.

As $Z_i = 0$ or 1 in the limit, i.e., it becomes the Boolean function, the complex nonlinear system (1) splits locally into 2^n decoupled linear equations, the solutions of which can be

calculated explicitly, and the global solutions can be then obtained by simply merging these local solutions.

However, this technique is only applicable if the solution trajectories travel through the discontinuity hyperplanes $x_i = \theta_i$, while possible sliding trajectories, even if they are of generic nature and can be observed for $q_i > 0$, are simply invisible in the Heaviside limit, because System (1) and its solutions are not defined along the discontinuities. In [3] it was, therefore, proposed to extend the Glass–Kauffman framework by adding a complementary system of equations, which is used to calculate all trajectories of the sigmoid-based system in the Heaviside limit, also including possible sliding trajectories. This construction was based on Tikhonov’s singular perturbation theory.

Another method to treat sliding trajectories, which is, e.g., described in [5], goes back to Filippov’s theory of piecewise continuous dynamical systems and the theory of differential inclusions [7]. This method is not considered in the present paper.

The effect of stochasticity is indisputably important for any reasonable model of GRNs. This effect may be caused by uncertainty in data, random fluctuations in the system, or simply may be due to a large number of interacting genes [5,8–10]. Analysis of stability under small random perturbations of the system provide, therefore, valuable information about the system’s robustness. Most publications on the subject concentrate on stochastic Boolean networks, see e.g., the monograph [11], or the more recent overview offered in [12]. This approach, being highly computation-oriented, is based on the classical theory of Markov chains, but ignores, however, the time-continuous component, which is essential for qualitative and quantitative analysis.

One may try to grasp the stochastic time-continuous dynamics using time-dependent distribution functions satisfying certain partial differential equations. This approach, despite of its advantages described in the review paper [5] and in the more recent publication [13], has also several disadvantages. For instance, numerical analysis, based on partial differential equations, is more expensive and time-consuming. Also some qualitative features of GRNs may be hardly recognizable within this approach. One of them is explicitly mentioned in [5]: if the gene activation times are small compared to the time of interaction of genes (i.e., if the response functions are sufficiently steep), then stochastic effects become less visible and even may level out, which means that a purely deterministic model should actually dominate in the limit. This feature can hardly be traced up in the model based on the distribution functions.

In our scheme, we incorporate stochastic noises not as distributions, but in a dynamical way, i.e., by taking advantages of the theory of stochastic differential equations, a powerful modeling tool which efficiently captures stochastic effects of various nature. By implementing this, we achieve several gains. In particular, we can prove that deterministic GRNs do dominate stochastic models when stochastic noises are small and the response functions are steep. Furthermore, our approach is completely based on ordinary differential equations (even in the case of delays), so that the numerical analysis of such GRNs becomes easier. Moreover, the uniform convergence of solutions justified in the paper ensures the robustness property of the deterministic numerical schemes with respect to small random perturbations.

In addition, we demonstrate how our analysis can be extended to GRNs with delay effects. It is well-known that time delay is a quite important characteristic of real GRNs (see e.g., [14,15]). Deterministic GRNs with delay were rigorously treated in [16,17] by introducing the hereditary system

$$\begin{aligned} \dot{x}_i(t) &= F_i(Z) - G_i(Z)x_i(t), \\ Z_i &= \Sigma(y_i, \theta_i, q_i), \\ y_i(t) &= (\mathfrak{R}_i x_i)(t), \quad t \geq 0, \quad i = 1, \dots, n, \end{aligned} \quad (3)$$

where the linear operators \mathfrak{R}_i represent delay effects in the model (see Section 5 for more details). A generic simplification procedure can be applied to (3), which is based on the

so-called ‘linear chain trick’ (in a slightly modified form) and which converts the hereditary system (3) into a (larger) system of ordinary differential equations (see [16,17]). This framework ensures, in particular, an analytical assessment of when the dynamics of GRNs are sensitive to time delays and when it is not. It also explains how one can calculate the trajectories of GRNs with delay in the Heaviside limit.

GRNs as stochastically perturbed systems with fast and slow dynamics simultaneously pose extra technical challenges because traditional perturbation methods may not adequately capture the resulting dynamics. To study such GRNs, one needs a specially designed theoretical framework. The technique, which we apply to control the stochastic perturbations around discontinuities, goes back to the monograph [18], where a stochastic version of the classical Tikhonov theorem in singular perturbation analysis is offered, see also Appendix B. To incorporate stochasticity into System (3), this version of stochastic singular perturbation analysis, together with the modified linear chain trick from [16,17] in the delay case, is utilized in the paper.

Although System (1) is a particular case of System (3), we will treat them separately. Detailed calculations are offered in the non-delay case, as this explains the main ideas and techniques in a more refined way and without additional, and sometimes cumbersome, notation, which is necessary to formalize the delay model. On the other hand, the techniques in the delay and non-delay settings are very similar. Therefore, we only briefly outline the proofs in the former case.

The main hypothesis of our analysis states that only one variable may approach its threshold value at a time, i.e., different types of genes cannot be activated simultaneously. In some sense, it may be regarded as a generic case, yet the framework elaborated for deterministic GRNs covers more general situations [3,19]. The full stochastic analogue of the deterministic results would require generalizations of the theory presented in the monograph [18] and is beyond the scope of our report.

The paper is organized as follows: Section 2 contains an example explaining the deterministic model. In Section 3, we formulate the problem in the stochastic non-delay case and list the main assumptions. Section 4 provides a detailed analysis of the non-delayed stochastic model in the Heaviside limit. In Section 5, we introduce stochastically perturbed GRNs with delay and give a short description of the modified linear chain trick to be applied in Section 6. Notice that in this section, we use the techniques developed in Section 4. In Appendix A, we formulate some known definitions and results from the theory of stochastic differential equations [20], while a brief description of the stochastic Tikhonov theorem from the monograph [18] is provided in Appendix B.

2. A Short Overview of the Deterministic Model

Let us start with an explanatory example (see [3] for the idea).

Example 1. Consider the system

$$\begin{aligned} \dot{x}_1 &= Z_1 + Z_2 - 3Z_1Z_2 - \gamma_1x_1, \\ \dot{x}_2 &= 1 - Z_1Z_2 - \gamma_2x_2, \end{aligned} \tag{4}$$

where Z_1, Z_2 are given by (2), $\theta_1 = \theta_2 = 1$ and $0 < \gamma_i < 1$. In the Heaviside limit ($q_1, q_2 = 0$), the response functions Z_i are Boolean, i.e., only assume the values 0 and 1.

If $Z_1 = 0, Z_2 = 0$, then System (4) becomes $\dot{x}_1 = -\gamma_1x_1, \dot{x}_2 = 1 - \gamma_2x_2$, and we assume that $x_1 \rightarrow 0, x_2 \rightarrow \frac{1}{\gamma_2} > 1$.

If $Z_1 = 0, Z_2 = 1$ or $Z_1 = 1, Z_2 = 0$, then (4) converts to $\dot{x}_1 = 1 - \gamma_1x_1, \dot{x}_2 = 1 - \gamma_2x_2$, while $x_1 \rightarrow \frac{1}{\gamma_1} > 1, x_2 \rightarrow \frac{1}{\gamma_2} > 1$.

Finally, if $Z_1 = 1, Z_2 = 1$, then we obtain $\dot{x}_1 = -1 - \gamma_1x_1, \dot{x}_2 = -\gamma_2x_2$, while $x_1 \rightarrow -\frac{1}{\gamma_1} < 0, x_2 \rightarrow 0$.

The trajectories of (4) in the Heaviside limit are depicted in Figure 2. They travel through the ‘transparent’ (see [3]) line $x_2 = \theta_2 = 1, x_1 < \theta_1 = 1$, but stop at the ‘black’ [3] line $x_1 = \theta_1 = 1$,

$x_2 > \theta_2 = 1$. The line $x_2 = \theta_2 = 1, x_1 > \theta_1 = 1$ is also ‘black’, while the line $x_1 = \theta_1 = 1, x_2 < \theta_2 = 1$ is repellent (‘white’ according to [3]).

Summarizing, we obtain the following in the Heaviside limit:

- The system becomes piecewise linear;
- The dynamics of the system can be easily described between the thresholds lines (hyperplanes in higher dimensions);
- Some trajectories may ‘stop’ at the threshold lines (hyperplanes), as it is shown in Figure 2;
- However, the trajectories in the true model never stop, as the corresponding system is smooth. Rather, the trajectories slide along the respective threshold lines (hyperplanes), see Figure 3.

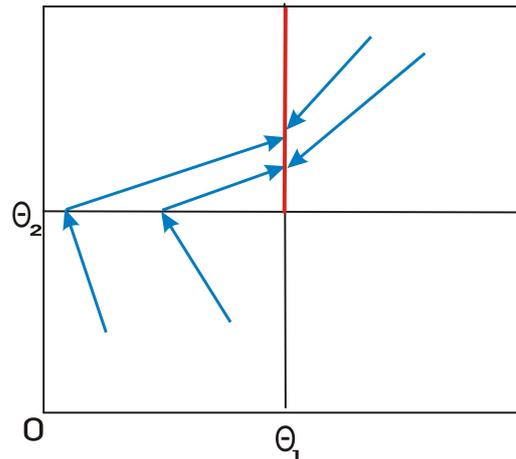


Figure 2. Some phase trajectories of System (4) with $\gamma_1 = 0.7, \gamma_2 = 0.6, q_1 = q_2 = 0$. The trajectories seem to ‘stop’ at the threshold line $x_1 = \theta_1 = 1, x_2 > \theta_2 = 1$.

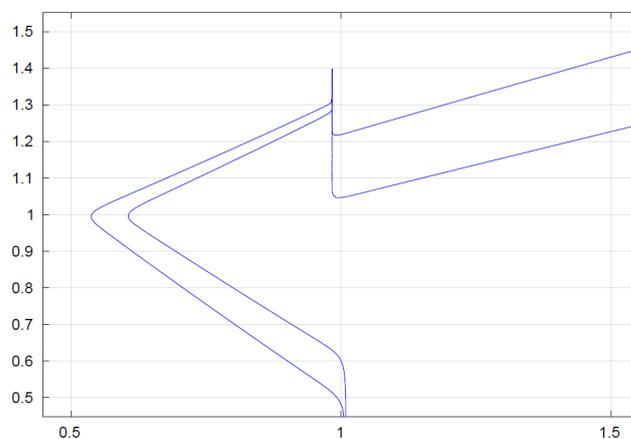


Figure 3. Some phase trajectories of System (4) with $\gamma_1 = 0.7, \gamma_2 = 0.6, q_1 = q_2 = 0.01$. The ‘true’ trajectories do not stop, but slide along the threshold line $x_1 = \theta_1 = 1, x_2 > \theta_2 = 1$ (Pplane8 [21], MATLAB R2018b).

To understand how the model in the Heaviside limit should be adjusted to cover the case of sliding trajectories, let us assume that only one of the variables, say x_1 , approaches its threshold value at a specific time t_0 , i.e., $x_1(t) \rightarrow \theta_1$ as $t \rightarrow t_0$, while the other variables stay separated from their respective thresholds $|x_i(t_0) - \theta_i| \geq \varepsilon > 0, i = 2, \dots, n$. This implies that $Z_i \rightarrow B_i$, where B_i is either 0 or 1, as $q_i \rightarrow 0$ for all $1 \leq i \leq n$. On the other hand, the behavior of the corresponding response function Z_1 may be quite irregular around t_0 ,

so that a special technique is required to perform the analysis for this quantity. As in [3], we rewrite (1) as follows:

$$\begin{aligned} \dot{x}_1 &= F_1(Z_1, Z_R) - G_1(Z_1, Z_R)x_1, \\ \dot{x}_R &= F_R(Z_1, Z_R) - G_R(Z_1, Z_R)x_R, \end{aligned}$$

where $R = \{2, \dots, n\}$, $x_R = (x_r)_{r \in R}$, $Z_R = (Z_r)_{r \in R}$, $F_R = (F_r)_{r \in R}$, $G_R = \text{diag}(G_r)_{r \in R}$, and Z_i are given by (2).

The change of the variable $Z_1 = \Sigma(x_1, \theta_1, q_1)$ yields

$$\begin{aligned} q_1 \dot{Z}_1 &= \frac{Z_1(1 - Z_1)}{x_1} (F_1(Z_1, Z_R) - G_1(Z_1, Z_R)x_1), \\ \dot{x}_R &= F_R(Z_1, Z_R) - G_R(Z_1, Z_R)x_R, \end{aligned}$$

where

$$x_1 = \Sigma^{-1}(Z_1, \theta_1, q_1) = \theta \left(\frac{Z_1}{1 - Z_1} \right)^{q_1}.$$

The stretching transformation $\tau = t/q_1$ in the first equation and $q_1 \rightarrow 0$ results in the boundary layer equation

$$\frac{dZ_1}{d\tau} = \frac{Z_1(1 - Z_1)}{\theta_1} (F_1(Z_1, B_R) - G_1(Z_1, B_R)\theta_1). \tag{5}$$

It was shown in [3], by virtue of the singular perturbation analysis, that if $\hat{Z}_1 \in (0, 1)$ is an asymptotically stable point of (5), then the trajectories of System (1) slide along the hyperplane $x_1 = \theta_1$, and the changing part x_R of the limit solution obeys the reduced system

$$\dot{x}_R = F_R(\hat{Z}_1, B_R) - G_R(\hat{Z}_1, B_R)x_R. \tag{6}$$

If the stable stationary point \hat{Z}_1 of the boundary layer Equation (5) is outside the interval $(0, 1)$, then no sliding motion can occur. In particular, if $\hat{Z}_1 = 0$ or 1 , then the trajectories in the Heaviside limit will travel through the threshold hyperplane $x_1 = \theta_1$.

In Example 1, we obtain no sliding motion along the line $x_2 = \theta_2 = 1$, $x_1 < \theta_1 = 1$, as the boundary layer Equation (5) is equal to $\frac{dZ_2}{d\tau} = Z_2(1 - Z_2)(1 - \gamma_2)$, where $\hat{Z}_2 = 1$ is asymptotically stable. On the other hand, we do obtain sliding trajectories along the line $x_2 > \theta_2 = 1$, $x_1 = \theta_1 = 1$, as the boundary layer Equation (5) becomes in this case $\frac{dZ_1}{d\tau} = Z_1(1 - Z_1)(1 - \gamma_1 - 2Z_1)$, where $\hat{Z}_1 = \frac{1 - \gamma_1}{2} \in (0, 1)$ is asymptotically stable. The sliding trajectory in the Heaviside limit will be governed by $\dot{x}_2 = \frac{1 + \gamma_1}{2} - \gamma_2 x_2$.

3. Formulation of the Stochastic Problem in the Non-Delay Case

Consider the system

$$\begin{aligned} \dot{x}_i &= F_i(Z) - G_i(Z)x_i + \sigma_i(q_i)\mathcal{B}_i, \\ Z_i &= \Sigma(x_i, \theta_i, q_i), \quad q_i \geq 0, \quad i = 1, \dots, n, \end{aligned} \tag{7}$$

with the initial conditions

$$x(0) = x^0. \tag{8}$$

Here, $\mathcal{B} = (\mathcal{B}_1, \dots, \mathcal{B}_n)$ is the standard n -dimensional Brownian motion, and $\sigma = (\sigma_1, \dots, \sigma_n)$ is a vector of diffusion parameters. The functions F_i and G_i stand for the production rate and the relative degradation rate of the product of gene i , respectively, and x_i denotes the gene product concentration. Both functions are assumed to be linear in each Z_i (see Section 1 for the explanation) and satisfy the natural positivity conditions $F_i(Z_1, \dots, Z_n) \geq 0$, $G_i(Z_1, \dots, Z_n) > 0$ for $0 \leq Z_i \leq 1$, $i = 1, \dots, n$. Each response function

$Z_i = \Sigma(x_i, \theta_i, q_i)$ is the Hill function (2) if the steepness parameter $q_i > 0$ and converts into the shifted Heaviside function with the unit jump at $x_i = \theta_i$ if $q_i = 0$.

For $q_i > 0, i = 1, \dots, n$, the right-hand sides $F_i(Z_1, \dots, Z_n) - G_i(Z_1, \dots, Z_n)x_i$ of System (7) are smooth, therefore locally Lipschitz. Since all response functions Z_i are bounded ($0 \leq Z_i \leq 1$), then $|F_i| \leq M_i$ and $0 < \delta \leq G_i \leq M_i$. Therefore, the right-hand sides of (7) grow linearly. By the existence and uniqueness theorem for stochastic differential equations (see Appendix A) there exists a unique solution of the initial value problem (7)–(8), which is defined for all $t \geq 0$. This fact is important for justifying the calculations below.

Recall that our main hypothesis says that at most one of the variables x_i in (7) is *singular* at any time t_0 , i.e., approaches its threshold value θ_i if $q_i \rightarrow 0, i = 1, \dots, n$ and $t \rightarrow t_0$, while the others are *regular*, i.e., they must stay away from their respective thresholds in the limit, i.e., $|x_j(t_0) - \theta_j| \geq \varepsilon > 0$ if $j \neq i$. Renumbering the variables, we can always assume, without loss of generality, that the singular variable is x_1 . In the Heaviside limit, i.e., as $q_i \rightarrow 0, i = 1, \dots, n$, we obtain that $x_1 = \theta_1$, while $Z_i(x_i) = B_i$, where $B_i = 0$ or 1 for $i = 2, \dots, n$. Adopting the notation from [3,16] we can equivalently say that if $q_i \rightarrow 0, i = 1, \dots, n$, and $t \rightarrow t_0, t \neq t_0$, then the trajectory evolves towards *the singular domain*

$$SD(\theta_1, B_R) = \{(x_1, \dots, x_n) : x_1 = \theta_1, Z_i(x_i) = B_i, i \geq 2\}. \tag{9}$$

As in the deterministic case, the challenge is to calculate the limit behavior of the solutions of the stochastic system (7) in its sliding modes, i.e., when the trajectory hits the singular domain (9). To be able to do it, we proceed, as in Section 2, with replacing the singular variable x_1 by the corresponding response function Z_1 . In the stochastic setting, the resulting calculations, which are offered in the next section, will be based on the celebrated Itô formula (see e.g., [20]) instead of the standard differentiation rules. To this end, we will use the standard Itô representation of stochastic differential equations, which are based on the differentials rather than the derivatives (which do not exist in the stochastic case). In addition, we will take advantage of the notation introduced in Section 2 and rewrite (7) in a more suitable form. More precisely, we will deal with the following system of Itô equations:

$$\begin{aligned} dx_1 &= (F_1(Z_1, Z_R) - G_1(Z_1, Z_R)x_1)dt + \sigma_1(q_1)d\mathcal{B}_1, \\ dx_R &= (F_R(Z_1, Z_R) - G_R(Z_1, Z_R)x_R)dt + \sigma_R(q_R)d\mathcal{B}_R \end{aligned} \tag{10}$$

with the initial conditions

$$(x_1(0), x_R(0)) \in SD(\theta_1, B_R), \text{ i.e., } x_1(0) = \theta_1, x_R(0) = x_R^0, \tag{11}$$

where $Z_i(x_R^0) = B_R$.

Here, $x_R = (x_2, \dots, x_n), F_R = (F_2, \dots, F_n), G_R$ is the diagonal $(n - 1) \times (n - 1)$ matrix with the diagonal elements $G_2, \dots, G_n, Z_R = (Z_2, \dots, Z_n), \theta_R = (\theta_2, \dots, \theta_n), q_R = (q_2, \dots, q_n), \mathcal{B}_R = (\mathcal{B}_2, \dots, \mathcal{B}_n), \sigma_R(q_R) = (\sigma_2(q_2), \dots, \sigma_n(q_n))$.

4. Analysis in the Non-Delay Case

The substitution $Z_1 = \Sigma(x_1, \theta_1, q_1)$, or equivalently,

$$x_1 = \Sigma^{-1}(Z_1, \theta_1, q_1) = \theta_1 \left(\frac{Z_1}{1 - Z_1} \right)^{q_1}$$

requires the calculation of the differential dZ_1 , which will be completed with the help of Itô's formula

$$df(x_1) = f'(x_1)dx_1 + \frac{f''(x_1)}{2!} \sigma_1^2(q_1)dt, \tag{12}$$

where $f(x_1) = \Sigma(x_1, \theta_1, q_1)$ and $q_1 > 0$. Thus,

$$dZ_1 = d\Sigma(x_1, \theta_1, q_1) = \frac{\partial \Sigma(x_1, \theta_1, q_1)}{\partial x_1} dx_1 + \frac{1}{2} \frac{\partial^2 \Sigma(x_1, \theta_1, q_1)}{\partial x_1^2} \sigma_1^2(q_1) dt.$$

It is readily seen that

$$\frac{\partial \Sigma(x_1, \theta_1, q_1)}{\partial x_1} = \frac{Z_1(1 - Z_1)}{q_1 \Sigma^{-1}(Z_1, \theta_1, q_1)} \quad \text{and} \quad \frac{\partial^2 \Sigma(x_1, \theta_1, q_1)}{\partial x_1^2} = \frac{Z_1(1 - Z_1)(1 - 2Z_1 - q_1)}{q_1^2 (\Sigma^{-1}(Z_1, \theta_1, q_1))^2}.$$

Therefore, System (10) becomes

$$q_1 dZ_1 = \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)} \left[F_1(Z_1, Z_R) - G_1(Z_1, Z_R) \Sigma^{-1}(Z_1, \theta_1, q_1) + \frac{1 - 2Z_1 - q_1}{2q_1 \Sigma^{-1}(Z_1, \theta_1, q_1)} \sigma_1^2(q_1) \right] dt + \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)} \sigma_1(q_1) d\mathcal{B}_1, \tag{13}$$

$$dx_R = [F_R(Z_1, Z_R) - G_R(Z_1, Z_R)x_R]dt + \sigma_R(q_R)d\mathcal{B}_R, \quad q_i > 0, \quad i = 1, \dots, n,$$

where the initial conditions are given by

$$\begin{aligned} x_R(0) &= x_R^0, \\ Z_1(0) &= \Sigma(\theta_1, \theta_1, q_1) = 0.5. \end{aligned} \tag{14}$$

The following hypotheses are used in the analysis below:

Hypothesis 1. The functions F_1 and G_1 have the property.

$$\begin{cases} F_1(1, B_R) - G_1(1, B_R)\theta_1 < 0, \\ F_1(0, B_R) - G_1(0, B_R)\theta_1 > 0. \end{cases} \tag{15}$$

Hypothesis 2. The diffusion coefficient $\sigma_1(q_1)$ satisfies.

$$\sigma_1(q_1) = o\left(\sqrt{\left|\frac{q_1}{\ln q_1}\right|}\right) \quad \text{as } q_1 \rightarrow 0$$

and all other diffusion coefficients satisfy

$$\sigma_i(q_i) \rightarrow 0 \quad \text{as } q_i \rightarrow 0, \quad i \in R.$$

Remark 1. Hypothesis H1 simply means that the boundary layer Equation (5) has an asymptotically stable stationary point $\hat{Z}_1 \in (0, 1)$, which indicates that the system should possess a sliding trajectory along the singular domain (9). Hypothesis H2 reflects the experimental fact [5] that stochastic noise diminishes if the gene activation times become small compared to the time of interaction of genes. The asymptotic formula for the diffusion coefficient σ_1 of the singular variable is, however, more subtle, as convergence at a coarser scale may result in an erratic behavior of the solution x in the limit [18].

Let us now verify that Conditions B1–B5 of the stochastic Tikhonov theorem listed in Appendix B are fulfilled for the initial value problem (13)–(14).

Verification of B1.

First, let us prove the continuity of the right-hand side of (13) in (q_1, Z_1, x_R) , $q_1 \in [0, q']$, $q' < 1$, $Z_1 \in [0, 1]$, $x_r \in [0, \infty)$, $r \in R$.

Evidently, the terms $1 - q_1 - 2Z_1, F_1(Z_1, Z_R) - G_1(Z_1, Z_R)\Sigma^{-1}(Z_1, \theta_1, q_1)$ and the right-hand sides of the equations corresponding to x_R are continuous in all variables (q_1, Z_1, x_R) . Therefore, it remains to check this property for two problematic terms

$$P_1 = \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)} \quad \text{and} \quad P_2 = \frac{Z_1(1 - Z_1)(1 - 2Z_1 - q_1)}{q_1[\Sigma^{-1}(Z_1, \theta_1, q_1)]^2} \sigma_1^2(q_1).$$

We start with P_1 . If $Z_1 \in (0, 1)$, then only letting $q_1 \rightarrow 0$ may cause problems in the limit. However, in this case $\Sigma^{-1}(Z_1, \theta_1, q_1) \rightarrow \theta_1 > 0$, so that continuity at this point is verified.

If $Z_1 = 0$ or $Z_1 = 1$, then

$$\Sigma^{-1}(Z_1, \theta_1, q_1) \rightarrow \pm\infty \text{ (by definition)} \quad \text{and} \quad \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)} \rightarrow 0$$

as $q_1 \rightarrow 0$. Therefore, P_1 is continuous on $[0, 1] \times [0, q'], q' < 1$.

For the term P_2 , let us notice that since

$$\frac{\sigma_1^2(q_1)|\ln(q_1)|}{q_1} \rightarrow 0 \text{ (by H2)} \quad \text{and} \quad |\ln(q_1)| \rightarrow \infty \text{ as } q_1 \rightarrow 0,$$

then

$$\sigma_1^2(q_1) = o\left(\frac{q_1}{|\ln(q_1)|}\right) \quad \text{and} \quad \frac{\sigma_1^2(q_1)}{q_1} \rightarrow 0 \text{ as } q_1 \rightarrow 0.$$

On the other hand,

$$[\Sigma^{-1}(Z_1, \theta_1, q_1)]^2 = \left[\theta_1 \left(\frac{Z_1}{1 - Z_1}\right)^{q_1}\right]^2 = \theta_1^2 \left(\frac{Z_1}{1 - Z_1}\right)^{2q_1} = \Sigma^{-1}(Z_1, \theta_1^2, 2q_1).$$

Therefore,

$$\frac{Z_1(1 - Z_1)}{[\Sigma^{-1}(Z_1, \theta_1, q_1)]^2} = \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1^2, 2q_1)},$$

and hence P_2 , are continuous on $[0, 1] \times [0, q'/2], q' < 1$.

By this, the property of continuity of the right-hand side of System (13) is checked.

It was already mentioned in Section 3 that the right-hand side of System (7) is locally Lipschitz and has a linear growth. Evidently, this also holds true for (13).

Verification of B2.

By Hypothesis H2, the diffusion coefficients $\sigma_1(q_1)$ and $\sigma_R(q_R)$ go to 0 as $q_1 \rightarrow 0$ and $q_R \rightarrow \bar{0}$. By Hypothesis H1, the equation

$$\frac{Z_1(1 - Z_1)}{\theta_1} (F_1(Z_1, B_R) - G_1(Z_1, B_R)\theta_1) = 0$$

has a solution $Z_1 = \hat{Z}_1 \in (0, 1)$ satisfying Condition B2.

Verification of B3.

The boundary layer equation is the same as in the deterministic case, i.e., (5). In the notation of Appendix B, we have

$$A(0, Z_1) := \frac{Z_1(1 - Z_1)}{\theta_1} (MZ_1 + N)$$

for some constants M and N . From Hypothesis H1, we deduce that $N > 0$, $M + N < 0$ and $M < 0$. Minding that $\hat{Z}_1 = -\frac{N}{M}$, we obtain

$$\frac{\partial A(0, Z_1)}{\partial Z_1} = \frac{1 - 2Z_1}{\theta_1}(MZ_1 + N) + \frac{Z_1(1 - Z_1)}{\theta_1}M \Rightarrow \frac{\partial A(0, \hat{Z}_1)}{\partial Z_1} = \frac{\hat{Z}_1(1 - \hat{Z}_1)}{\theta_1}M < 0.$$

By this, the estimate in Condition B3 is satisfied with $k_N = -\frac{\hat{Z}_1(1 - \hat{Z}_1)}{\theta_1}M$. In particular, the isolated stationary point $\hat{Z}_1 \in (0, 1)$ of (5) is asymptotically stable.

Verification of B4.

Evidently, the attraction domain of the isolated stationary point \hat{Z}_1 of the boundary layer Equation (5) is the interval $(0, 1)$, while the initial value $Z_1(0) = 0.5$ always belongs to this interval.

Verification of B5.

This readily follows from Hypothesis H2.

Thus, we have proven

Theorem 1. Under Hypotheses H1 and H2

$$\begin{aligned} P\text{-}\lim_{\bar{q} \rightarrow \bar{0}} \sup_{0 \leq t \leq T} |x_1(t, \bar{q}) - \theta_1| &= 0, \\ P\text{-}\lim_{\bar{q} \rightarrow \bar{0}} \sup_{0 \leq t \leq T} |x_R(t, \bar{q}) - x_R(t, \bar{0})| &= 0, \\ P\text{-}\lim_{\bar{q} \rightarrow \bar{0}} \sup_{\delta \leq t \leq T} |Z_1(x_1, \theta_1, q_1) - \hat{Z}_1| &= 0 \end{aligned}$$

for each δ , $0 < \delta < T$. Here $(x_1(t, \bar{q}), x_R(t, \bar{q}))$ ($\bar{q} = (q_1, \dots, q_n)$) is the solution of (10) and $x_R(t, \bar{0})$ ($\bar{0}$ is the n -dimensional zero vector) is its solution in the Heaviside limit satisfying the reduced system (6) equipped with the initial condition $x_R(0) = x_R^0$.

Remark 2. The interval of convergence $[0, T]$ in Theorem 1 can be calculated explicitly, as the convergence holds true as long as the solution $(\theta_1, x_R(t, \bar{0}))$ belongs to the singular domain $SD(\theta, B_R)$. Let us illustrate this fact by using the system from Example 1. Assume that $x_1^0 = 1$, $x_2^0 > 1$. As $\hat{Z}_1 = \frac{1 - \gamma_1}{2}$, Equation (6) becomes

$$\dot{x}_2 = \frac{1 + \gamma_1}{2} - \gamma_2 x_2.$$

The solution $x_2(t, \bar{0})$ satisfies the initial condition $x_2(0, \bar{0}) = x_2^0 > 1$. Therefore the time T must satisfy $x_2(T, \bar{0}) = 1$. It is straightforward to check that $T = \frac{1}{\gamma_2} \ln \frac{2\gamma_2 x_2^0 - 1 - \gamma_1}{2\gamma_2 - 1 - \gamma_1}$. Of course, the interval of convergence depends on the initial value x_2^0 .

5. Formulation of the Stochastic Problem in the Delay Case

The delay system, which is studied in this section,

$$\begin{aligned} \dot{x}_i &= F_i(Z) - G_i(Z)x_i + \sigma_i(q_i)\dot{B}_i, \\ Z_i &= \Sigma(y_i, \theta_i, q_i), \\ y_i &= \mathfrak{R}_i x_i, \quad t \geq 0, \quad i = 1, \dots, n, \end{aligned} \tag{16}$$

describes GRNs when changes in one or more genes happen slower than in the others. This property causes time lags in the system, which are incorporated through the auxiliary variables y_i and the nonlinear Volterra (i.e., depending on the prehistory) operators \mathfrak{R}_i [16,17]. If \mathfrak{R}_i is the identity operator, then $x_i = y_i$ and x_i becomes a non-delay variable.

As in [16,17], we assume \mathfrak{R}_i to be integral operators of the form

$$(\mathfrak{R}_i x_i)(t) = {}^0c_i x_i(t) + \int_{-\infty}^t K_i(t-s)x_i(s)ds, \quad t \geq 0, \quad i = 1, \dots, n,$$

where

$$K_i(u) = \sum_{v=1}^p {}^v c_i {}^v K_i(u), \quad {}^v K_i(u) = \frac{\alpha_i^v u^{v-1}}{(v-1)!} e^{-\alpha_i u}, \quad i = 1, \dots, n, \quad p = 1, \dots, n.$$

The coefficients ${}^v c_i$ are real non-negative numbers satisfying the normalization condition

$$\sum_{v=0}^p {}^v c_i = 1.$$

It is also assumed that $\alpha_i > 0$.

In order to study System (16), we remove the delays by applying the modified linear chain trick method, which was suggested in [16]. The main idea is to introduce the auxiliary variables

$${}^1 v_i = {}^0 c_i x_i + \sum_{v=1}^p {}^v c_i {}^v w_i \quad \text{and} \quad {}^v v_i = \sum_{j=1}^{p-v+1} {}^{j+v-1} c_i {}^j w_i,$$

where

$${}^v w_i(t) = \int_{-\infty}^t {}^v K_i(t-s)x_i(s)ds, \quad v = 1, \dots, p, \quad i = 1, \dots, n.$$

It is shown in [16] that System (16) is equivalent to the following non-delay system:

$$\begin{aligned} \dot{x}_i &= F_i(Z_1, \dots, Z_n) - G_i(Z_1, \dots, Z_n)x_i + \sigma_i(q_i)\dot{\mathcal{B}}_i, \\ {}^1 \dot{v}_i &= -\alpha_i {}^1 v_i + \alpha_i {}^2 v_i + \alpha_i x_i ({}^0 c_i + {}^1 c_i) \\ &\quad + {}^0 c_i (F_i(Z_1, \dots, Z_n) - G_i(Z_1, \dots, Z_n)x_i + \sigma_i(q_i)\dot{\mathcal{B}}_i), \\ {}^2 \dot{v}_i &= -\alpha_i {}^2 v_i + \alpha_i {}^3 v_i + \alpha_i x_i {}^2 c_i \\ &\quad \dots \\ {}^p \dot{v}_i &= -\alpha_i {}^p v_i + \alpha_i x_i {}^p c_i, \\ Z_i &= \Sigma(y_i, \theta_i, q_i), \quad y_i = {}^1 v_i, \quad i = 1, \dots, n. \end{aligned} \tag{17}$$

As in the non-delay case, the right-hand sides of (17) satisfy the linear growth and local Lipschitz conditions if $q_i > 0, i = 1, \dots, n$. By Theorem A1 from Appendix A, System (17) has a unique solution for an arbitrary initial condition, and this solution is defined for all $t \geq 0$.

If $q_i \rightarrow 0, i = 1, \dots, n$, then the smooth response functions $\Sigma(y_i, \theta_i, q_i)$ will be replaced by the Heaviside functions, and the system will split into a collection of linear nonhomogeneous systems defined in the disjoint continuity domains. This framework works perfectly if a particular trajectory travels through a discontinuity hyperplane, but fails in the case of sliding trajectories. The paper [17] offers a method, which is similar to the one used in the non-delay case and which explains how to calculate the sliding trajectories in the Heaviside limit. The stochastically perturbed genetic models with delay are studied in detail in the next section.

6. Analysis in the Delay Case

This analysis is very similar to that offered in Section 4. Therefore, we omit technical details concentrating on the overall description of the algorithm. Let us just recall that, as before, at most one variable may reach its threshold value at any time.

Letting $q_i \rightarrow 0, i = 1, \dots, n$ and renumbering the variables we may always assume that the singular variable is ${}^1v_1 = y_1$. In the limit, we thus obtain that ${}^1v_1 = \theta_1$ and $Z_i(y_i) = 1$ or 0 for $i = 2, \dots, n$. The corresponding singular domain becomes in this case

$$\mathcal{SD}(\theta_1, B_R) = \{(x, v) : {}^1v_1 = \theta_1, Z_i(y_i) = B_i, i = 2, \dots, n\},$$

where $x = (x_1, \dots, x_n), v = (v_1, \dots, v_n)$ with $v_i = ({}^1v_i, \dots, {}^pv_i)$, and B_i is either 0 or 1 for all $i = 2, \dots, n$.

In addition, System (17) is assumed to be equipped with the initial conditions

$$x(0) = x^0, v(0) = v^0, (x^0, v^0) \in \mathcal{SD}(\theta_1, B_R), \tag{18}$$

where $x = (x_1, \dots, x_n), v = (v_1, \dots, v_n), v_i = ({}^1v_i, \dots, {}^pv_i), i = 1, \dots, n$.

Suppose that:

Hypothesis 3. ${}^0c_1 \neq 0$ and the functions F_1 and G_1 satisfy.

$$\begin{cases} -\alpha_1 \theta_1 + \alpha_1 {}^2v_1 + \alpha_1 x_1 ({}^0c_1 + {}^1c_1) + {}^0c_1 (F_1(1, B_R) - G_1(1, B_R)x_1) < 0 \\ -\alpha_1 \theta_1 + \alpha_1 {}^2v_1 + \alpha_1 x_1 ({}^0c_1 + {}^1c_1) + {}^0c_1 (F_1(0, B_R) - G_1(0, B_R)x_1) > 0. \end{cases} \tag{19}$$

As in Section 4, the variable ${}^1v_1 = y_1$ will be replaced by the corresponding response function Z_1 . Applying Itô's formula to the representation (2) yields

$$\begin{aligned} q_1 dZ_1 &= \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)} \left[-\alpha_1 \Sigma^{-1}(Z_1, \theta_1, q_1) + \alpha_1 {}^2v_1 + \alpha_1 x_1 ({}^0c_1 + {}^1c_1) + {}^0c_1 (F_1(Z_1, Z_R) - G_1(Z_1, Z_R)x_1) \right] dt \\ &\quad + \frac{Z_1(1 - Z_1)(1 - 2Z_1 - q_1)}{2q_1(\Sigma^{-1}(Z_1, \theta_1, q_1))^2} {}^0c_1^2 \sigma_1^2(q_1) dt + \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)} {}^0c_1 \sigma_1(q_1) d\mathcal{B}_1, \\ dx_i &= [F_i(Z_1, Z_R) - G_i(Z_1, Z_R)x_i] dt + \sigma_i(q_i) d\mathcal{B}_i, \\ d({}^1v_j) &= \left[-\alpha_j {}^1v_j + \alpha_j {}^2v_j + \alpha_j x_j ({}^0c_j + {}^1c_j) + {}^0c_j (F_j(Z_1, Z_R) - G_j(Z_1, Z_R)x_j) \right] dt + {}^0c_j \sigma_j(q_j) d\mathcal{B}_j, \\ d({}^2v_i) &= \left[-\alpha_i {}^2v_i + \alpha_i {}^3v_i + \alpha_i x_i {}^2c_i \right] dt, \\ d({}^3v_i) &= - \left[\alpha_i {}^3v_i + \alpha_i {}^4v_i + \alpha_i x_i {}^3c_i \right] dt, \\ &\dots \\ d({}^pv_i) &= - [\alpha_i {}^pv_i + \alpha_i x_i {}^pc_i] dt, \quad i = 1, \dots, n, \quad j = 2, \dots, n, \end{aligned} \tag{20}$$

and the initial conditions become

$$x(0) = x^0, Z(0) = 0.5, V(0) = V^0, \tag{21}$$

where $x = (x_1, \dots, x_n), V = (v_1^R, v_2, \dots, v_n), v_1^R = ({}^2v_1, {}^3v_1, \dots, {}^pv_1), v_j = ({}^1v_j, \dots, {}^pv_j), j = 2, \dots, n$.

Below we sketch the proof of the statement that the initial value problem (20)–(21) satisfy all the conditions of the stochastic Tikhonov theorem from Appendix B, provided that Hypotheses H2 and H3 are fulfilled.

Verification of B1.

The proof of the fact that the right-hand side of (20) is continuous in $(Z_1, q_i, x_i, {}^pv_i)$ and satisfies the linear growth and locally Lipschitz conditions in $(x_i, {}^pv_i)$ is similar to the non-delay case.

Verification of B2.

By the assumptions, the diffusion coefficient $\sigma_1(q_1)$ goes to 0 as $q_1 \rightarrow 0$. In the limit, the right-hand side of the first equation in (20) becomes

$$\frac{Z_1(1 - Z_1)}{\theta_1} [-\alpha_1\theta_1 + \alpha_1^2v_1 + \alpha_1x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(Z_1, B_R) - G_1(Z_1, B_R)x_1)].$$

By H3, this equation has the isolated solution $\hat{Z}_1 = \hat{Z}_1(x_1, {}^2v_1) \in (0, 1)$ satisfying B2.

Verification of B3.

The boundary layer equation is given by

$$\frac{dZ_1}{d\tau} = \frac{Z_1(1 - Z_1)}{\theta_1} [-\alpha_1\theta_1 + \alpha_1^2v_1 + \alpha_1x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(Z_1, B_R) - G_1(Z_1, B_R)x_1)].$$

The Lyapunov stability of the stationary solution \hat{Z}_1 of this equation follows from the linearity of the function in the square brackets and condition (19).

Verification of B4.

For $t = 0$ and $q_i = 0$ ($i = 1, \dots, n$) we have $(x^0(\bar{0}), v^0(\bar{0})) \in \mathcal{SD}(\theta_1, B_R)$. Therefore, $(x_1^0(\bar{0}), {}^2v_1^0(\bar{0})) \in M$, where $M \subset \mathbf{R}^2$ is the set of all solutions $(x_1, {}^2v_1)$ of System (19). Solving the equation $-\alpha_1\theta_1 + \alpha_1^2v_1 + \alpha_1x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(\hat{Z}_1, B_R) - G_1(\hat{Z}_1, B_R)x_1) = 0$, it is easy to see that Z_1 belongs to the domain of attraction as soon as $(x^0(\bar{0}), v^0(\bar{0})) \in \mathcal{SD}(\theta_1, B_R)$.

Verification of B5.

Condition B5 coincides with Hypothesis H2.

Thus, we have proven

Theorem 2. Under Hypotheses H2 and H3

$$\begin{aligned} P\text{-}\lim_{\bar{q} \rightarrow \bar{0}} \sup_{0 \leq t \leq T} |x(t, \bar{q}) - x(t, \bar{0})| &\rightarrow 0, \\ P\text{-}\lim_{\bar{q} \rightarrow \bar{0}} \sup_{0 \leq t \leq T} |v(t, \bar{q}) - v(t, \bar{0})| &\rightarrow 0, \\ P\text{-}\lim_{\bar{q} \rightarrow \bar{0}} \sup_{\delta \leq t \leq T} |Z_1(y_1, \theta_1, q_1) - \hat{Z}| &\rightarrow 0 \end{aligned}$$

for each $\delta, 0 < \delta < T$. Here $\bar{q} = (q_1, \dots, q_n)$, $(x(t, \bar{q})$ and $v(t, \bar{q}))$ is the solution of the initial value problem (17), (18), while $(x(t, \bar{0}), v(t, \bar{0}))$ is the solution of the system

$$\begin{aligned} x_1 &= \theta_1, \\ \dot{x}_i &= F_i(\hat{Z}_1, B_R) - G_i(\hat{Z}_1, B_R)x_i \quad (i \geq 2), \\ {}^1\dot{v}_j &= -\alpha_j^1v_j + \alpha_j^2v_j + \alpha_jx_j({}^0c_j + {}^1c_j) + {}^0c_j(F_j(\hat{Z}_1, B_R) - G_j(\hat{Z}_1, B_R)x_j), \\ {}^2\dot{v}_i &= -\alpha_i^2v_i + \alpha_i^3v_i + \alpha_ix_i^2c_i, \\ {}^3\dot{v}_i &= -\alpha_i^3v_i + \alpha_i^4v_i + \alpha_ix_i^3c_i, \\ &\dots \\ {}^pv_i &= -\alpha_i^pv_i + \alpha_ix_i^pc_i, \quad i = 1, \dots, n, \quad j = 2, \dots, n, \end{aligned}$$

equipped with the initial conditions (18).

7. Discussion

Exploiting the theory of stochastic differential equations and the stochastic version of the Tikhonov singular perturbation analysis we proved that sliding trajectories in a vicinity of the threshold hyperplanes of a gene regulatory network, with or without delays, are preserved under small random perturbations, provided that asymptotics of the diffusion coefficients governing the stochastic perturbations of the actively regulated variables is

carefully chosen. On the other hand, our findings confirm that stochastic effects become less visible if the gene activation times are relatively small.

Potential practical implications of the study may include novel genetic engineering strategies to be used in synthetic biology, gene therapy, or drug development.

8. Conclusions and Outlook

The main results of the paper can be summarized as follows:

- (1) A novel stochastic version of the extended Glass–Kaufmann model is suggested and justified.
- (2) A framework to analyze and control rapidly changing dynamics in a vicinity of the system's thresholds is elaborated; mathematically, it is based on the uniform version of the stochastic Tikhonov theorem in singular perturbation analysis.
- (3) The model justifies simplified computational schemes, where stochastic perturbations are completely removed and all steep nonlinearities are replaced by the shifted Heaviside functions.
- (4) This model also explains the experimental fact that stochastic effects level gradually out if the gene activation times become much smaller than the time of interaction of genes.

The justification of these results assumes that only one gene concentration may approach its threshold value at a time. This assumption was purely technical, and in the future we, therefore, intend to develop the suggested technique to cover the general situation when different types of genes are activated simultaneously, as it is already done for deterministic GRNs [3,19]. This may require an extension of the stochastic singular perturbation theory offered in [18].

The study findings can be important for other computational models in the system biology in several ways, as they explain how one can reduce the level of complexity of a model without losing essential information about the system.

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Abbreviations

The following abbreviations are used in this manuscript:

GRN Gene Regulatory Network

Appendix A. Some Basic Definitions and Results from the Theory of Stochastic Differential Equations

This part is mostly borrowed from the monograph [20].

Let (Ω, \mathcal{F}, P) be a probability space with the standard m -dimensional Brownian motion $B = B(t, \omega)$ ($t \geq 0$) defined on it. Let \mathcal{F}_t be the σ -algebra generated by the random variables

$\mathcal{B}(s, \cdot), s \leq t$. In other words, \mathcal{F}_t is the smallest σ -subalgebra of \mathcal{F} containing all sets of the form

$$\{\omega : \mathcal{B}(t_1, \omega) \in F_1, \dots, \mathcal{B}(t_k, \omega) \in F_k\},$$

where $t_j \leq t$ and $F_j \subset \mathbf{R}^m$ are arbitrary Borel sets, $j \leq k, k \geq 1$.

A measurable process $g(t, \omega) : [0, \infty) \times \Omega \rightarrow \mathbf{R}^n$ is called \mathcal{F}_t -adapted if for each $t \geq 0$ the function $\omega \rightarrow g(t, \omega)$ is \mathcal{F}_t -measurable.

Adapted stochastic processes that almost surely satisfy $\int_S^T |f(t, \omega)|^2 dt < \infty$ can be integrated with respect to the Brownian motion. The corresponding Itô integral

$$I_f(\omega) = \int_S^T f(t, \omega) d\mathcal{B}(t, \omega)$$

possesses standard integration properties [20].

The n -dimensional stochastic differential equation of Itô-type

$$dx(t) = f(x(t), t)dt + g(x(t), t)d\mathcal{B}(t) \quad (0 \leq t \leq T) \tag{A1}$$

can then be interpreted as the following stochastic integral equation:

$$x(t) = x(0) + \int_0^t f(x(s), s)ds + \int_0^t g(x(s), s)d\mathcal{B}(s) \quad (0 \leq t \leq T). \tag{A2}$$

A solution of Equation (A1) is an \mathbf{R}^n -valued, (\mathcal{F}_t) -adapted stochastic process $\{x(t)\}_{0 \leq t \leq T}$ that has continuous trajectories and satisfy (A2) with probability 1.

A measurable function $h : E_1 \times [0, T] \rightarrow E_2$ (E_1 and E_2 are finite dimensional spaces) satisfies the linear growth and the local Lipschitz condition on $[0, T]$, respectively, if

- There is a constant L , such that

$$|h(x, t)| \leq L(1 + |x|) \quad \forall t \in [0, T], \quad x \in E_1,$$

- For any $N > 0$, there is a constant L_N such that

$$|h(x_1, t) - h(x_2, t)| \leq L_N|x_1 - x_2| \quad \forall t \in [0, T], \quad x_i \in E_1, \quad |x_i| \leq N.$$

Theorem A1 (see e.g., [22] (p. 135)). Assume that the functions $f(x, t), g(x, t)$ satisfy the linear growth and local Lipschitz condition on $[0, T]$. Then for any $x_0 \in \mathbf{R}^n$ there exists a unique solution $x(t)$ of (A1) defined on $[0, T]$ and satisfying the initial condition $x(0) = x_0$.

We also need

Definition A1. Let X and $X_k, k \geq 1$, be \mathbf{R}^n -valued random variables.

If for every $\epsilon > 0, P\{\omega : |X_k(\omega) - X(\omega)| > \epsilon\} \rightarrow 0$ as $k \rightarrow \infty$, then X_k is said to converge to X in probability:

$$P\text{-}\lim_{k \rightarrow \infty} X_k = X.$$

Appendix B. A Useful Result from the Stochastic Theory of Singular Perturbations

Consider the initial value problem

$$\begin{aligned} cdx(t, q) &= a(q, x(t, q), y(t, q))dt + b(q, x(t, q), y(t, q))d\mathcal{B}^x(t), & x(0) &= x_0, \\ qdy(t, q) &= A(q, x(t, q), y(t, q))dt + B(q, x(t, q), y(t, q))d\mathcal{B}^y(t), & y(0) &= y_0, \end{aligned} \tag{A3}$$

on $\mathbf{R}^k \times \mathbf{R}^n$, where $\mathcal{B}^x(t), \mathcal{B}^y(t)$ are independent Brownian motions,

$$B(q, x(t, q), y(t, q)) = \sigma(q)B_0(q, x(t, q), y(t, q)) \quad (t \in [0, T]),$$

$q > 0$ is a real parameter and x_0 and y_0 are constant vectors from \mathbf{R}^k and \mathbf{R}^n , respectively.

The theorem formulated below is based on the following conditions [18]:

B1. Condition ensuring existence and uniqueness of solutions.

The functions a, A, b and B_0 in (B1) are continuous in the variables (q, x, y) and satisfy the linear growth and local Lipschitz conditions in (x, y) .

B2. Isolated root condition.

There is a function $\varphi : \mathbf{R}^k \rightarrow \mathbf{R}^n$ satisfying the linear growth and local Lipschitz conditions in x such that

$$A(0, x, \varphi(x)) = 0 \quad \forall x \in \mathbf{R}^k.$$

B3. Lyapunov stability condition for the boundary layer equation.

The derivative A_y exists, it is a continuous function in the variables (q, x, y) , and for any $N > 0$ there exists a constant $k_N > 0$ such that for every $x \in \mathbf{R}^k$ with $|x| \leq N$

$$u^T A_y(0, x, \varphi(x))u \leq -k_N |u|^2 \quad \forall u \in \mathbf{R}^n.$$

B4. The domain of attraction condition.

The solution of the problem

$$\frac{d\tilde{y}}{d\tau} = A(0, x_0, \tilde{y}(\tau)), \quad \tilde{y}(0) = y_0,$$

tends to $\varphi(x_0)$ as $\tau \rightarrow \infty$: $\lim_{\tau \rightarrow \infty} \tilde{y}(\tau) = \varphi(x_0)$, where τ is the scaled time variable.

Condition B4 says that the initial value y_0 belongs to the domain of attraction of the stationary solution $\varphi(x_0)$.

B5. Condition on asymptotics of the diffusion coefficient.

The coefficient $\sigma(q)$ obeys

$$\sigma(q) = o\left(\sqrt{\left|\frac{q}{\ln q}\right|}\right) \quad \text{as } q \rightarrow 0.$$

Theorem A2 (see [18]). *Under Conditions B1–B5, the solutions of System (B1) satisfy*

$$P\text{-}\lim_{q \rightarrow 0} \sup_{t \in [0, T]} |x(t, q) - x(t, 0)| = 0,$$

$$P\text{-}\lim_{q \rightarrow 0} \sup_{t \in [\delta, T]} |y(t, q) - y(t, 0)| = 0$$

for each $\delta, 0 < \delta \leq T$.

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