BIT Numer Math (2011) 51: 177–196
DOI 10.1007/s10543-011-0322-8

BIT

Hybrid simulation of autoregulation within transcription and translation

Desmond J. Higham · Somkid Intep · Xuerong Mao · Lukasz Szpruch

Received: 13 August 2010 / Accepted: 15 February 2011 / Published online: 3 March 2011

Abstract We analyse a simple gene regulatory system where a protein enhances its own rate of mRNA transcription. For the integer-valued, chemical master equation formulation of the first order reaction network, the first and second moments can be studied analytically. In particular, this allows us to characterise the noise strength in terms of the rate constants. Motivated by the need for efficient multi-scale simulation tools, we then consider a hybrid model where the protein is assumed to be abundant, so that its level may be described by a continuous-valued random variable. This leads to a stochastic differential equation driven by a state-dependent switch, and our aim is to study the extent to which this model can accurately approximate the underlying fully discrete system. We discuss some of the technical difficulties that can arise when such a hybrid system is analysed and simulated and show that the noise strength can be analysed by introducing a discrete-time Euler–Maruyama style approximation and using recent results concerning the convergence of numerical methods for hybrid systems. In this manner, numerical analysis techniques are employed to examine

Communicated by Per Lötstedt.

D.J. Higham was supported by Engineering and Physical Sciences Research Council grant EP/E049370/1. S. Intep was sponsored by Thailand's Commission on Higher Education.

D.J. Higham (✉) · X. Mao · L. Szpruch
Department of Mathematics and Statistics, University of Strathclyde, Glasgow G1 1XH, Scotland, UK
e-mail: djh@maths.strath.ac.uk

X. Mao
e-mail: x.mao@strath.ac.uk

L. Szpruch
e-mail: lukas.szpruch@strath.ac.uk

S. Intep
Department of Mathematics, Burapha University, Chonburi 20131, Thailand
e-mail: intep@buu.ac.th

properties of the continuous-time model by treating it as the limit of a discrete-time approximation.

Keywords Convergence · Diffusion · Euler–Maruyama · Multiscale · Noise strength · State dependent switch · Stochastic differential equation · Stopping time · Thermodynamic limit

Mathematics Subject Classification (2000) 65C20 · 92C42

1 Motivation

Gene regulation models, which deal with transcription, translation and many other events taking place inside the cell, are typically cast in terms of chemical reactions [15, 23, 24, 26]. The most appropriate setting is usually a discrete state space, continuous time Markov jump process, where integer valued random variables record the current population counts. This so-called *chemical master equation* regime can be treated by evolving the full set of probabilities over all possible states [3, 4, 11, 14, 21], or by computing individual trajectories through the state space [7, 8], but both approaches pose significant computational challenges for large or fast systems. For this reason, approximation techniques, either at the modelling or simulation level, are valuable [1, 5, 17, 27].

We consider here a setting where discrete and continuous valued stochastic processes are combined in order to provide a hybrid model of autoregulation. Although the underlying biological system is stripped down to its essential features, the resulting mathematical object—a nonlinear stochastic differential equation (SDE) driven by a state-dependent switch—offers a number of technical challenges for analysis and simulation that are representative of more complex modelling scenarios. By focusing on a simple system we are able to characterise important properties of the underlying fully discrete system and thereby quantify the effectiveness of this type of multiscale approximation.

In the next section, we describe the model and show how its first and second moments can be analysed in the fully discrete, chemical master equation, regime. In particular, this allows us to characterise the noise strength and make precise statements about how the variance and noise strength of mRNA and protein vary with the feedback level. Section 3 then looks at a hybrid, multiscale, approximation. First, we introduce stopping times in order to deal with issues of unboundedness and negativity. Then we show how the moments of this hybrid system can be analysed as the asymptotic limit from a discrete-time Euler–Maruyama style approximation. Overall, we are able to conclude that, up to a stopping time, the hybrid model recovers the exact noise strength of the underlying fully discrete system.

2 The full autoregulation model

We consider a gene regulation model where a protein enhances its own transcription rate. Figure 1 summarizes the scenario. Here, we assume that mRNA is produced at

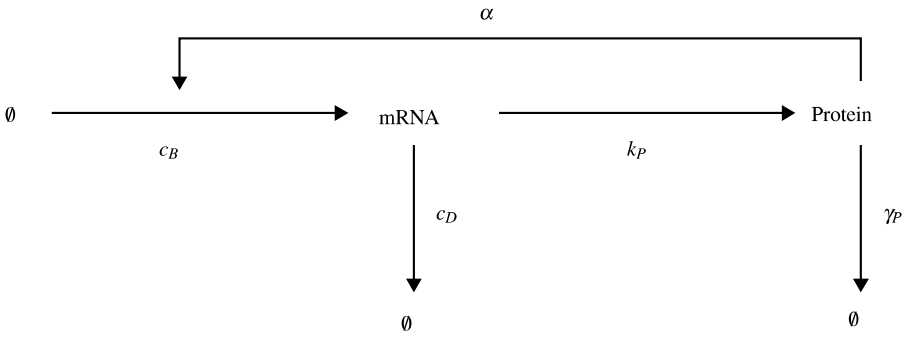

Fig. 1 Schematic representation of the autoregulatory system

some basal rate c_B and decays at rate c_D. A molecule of mRNA may then produce a molecule of protein at rate k_P, and protein decays at rate γ_P. These components agree precisely with the framework used in the influential work of Thattai and van Oudenaarden [26]. However, the figure also includes an autoregulatory feedback, where an increase in the protein level positively affects the rate of mRNA production, with associated rate constant α. This type of autoregulation is an important component of many regulatory systems in the cell [15, 19, 20].

2.1 Fully discrete model

The system in Fig. 1 may be interpreted as a set of reactions of the form

$$\emptyset \to M, \quad \text{with rate constant } c_B, \tag{2.1}$$

$$\emptyset \to M, \quad \text{with rate constant } c_B\alpha, \tag{2.2}$$

$$M \to \emptyset, \quad \text{with rate constant } c_D, \tag{2.3}$$

$$\emptyset \to P, \quad \text{with rate constant } k_P, \tag{2.4}$$

$$P \to \emptyset, \quad \text{with rate constant } \gamma_P. \tag{2.5}$$

More precisely, in standard stoichiometric notation [7, 8], we may introduce the state vector

$$X(t) := \begin{bmatrix} M(t) \\ P(t) \end{bmatrix},$$

stoichiometric vectors

$$\boldsymbol{\nu}_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, \quad \boldsymbol{\nu}_2 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, \quad \boldsymbol{\nu}_3 = \begin{bmatrix} -1 \\ 0 \end{bmatrix}, \quad \boldsymbol{\nu}_4 = \begin{bmatrix} 0 \\ 1 \end{bmatrix}, \quad \boldsymbol{\nu}_5 = \begin{bmatrix} 0 \\ -1 \end{bmatrix},$$

and corresponding propensity functions

$$a_1(X) = c_B,$$
$$a_2(X) = c_B\alpha X_2(t),$$

$$a_3(X) = c_D X_1(t),$$
$$a_4(X) = k_P X_1(t),$$
$$a_5(X) = \gamma_P X_2(t).$$

It is then clear that the reactions (2.1)–(2.5) fit into the framework of a *first-order reaction network*. Therefore, we may use a general result in [6] to obtain a closed linear system of ordinary differential equations (ODEs) that describe the evolution of the first and second moments and correlation. Letting

$$z(t) := \begin{bmatrix} \mathbb{E}[M(t)] \\ \mathbb{E}[P(t)] \\ \mathbb{E}[M(t)^2] \\ \mathbb{E}[P(t)^2] \\ \mathbb{E}[M(t)P(t)] \end{bmatrix}, \tag{2.6}$$

this leads to

$$\frac{dz(t)}{dt} = Nz(t) + b, \tag{2.7}$$

where

$$N = \begin{bmatrix} -c_D & c_B\alpha & 0 & 0 & 0 \\ k_P & -\gamma_P & 0 & 0 & 0 \\ 2c_B + c_D & c_B\alpha & -2c_D & 0 & 2c_B\alpha \\ k_P & \gamma_P & 0 & -2\gamma_P & 2k_P \\ 0 & c_B & k_P & c_B\alpha & -(c_D + \gamma_P) \end{bmatrix} \quad \text{and} \quad b = \begin{bmatrix} c_B \\ 0 \\ c_B \\ 0 \\ 0 \end{bmatrix}.$$

2.2 Analytical results: feedback effect

In this subsection we consider how (2.7) depends on the feedback strength, α. Let $0 \le \alpha_1 < \alpha_2$, and let M_{α_i} and P_{α_i} denote the number of mRNA and protein molecules at time t with $\alpha = \alpha_i$. Define

$$y(t) := \begin{bmatrix} \mathbb{E}[M_{\alpha_2}(t)] - \mathbb{E}[M_{\alpha_1}(t)] \\ \mathbb{E}[P_{\alpha_2}(t)] - \mathbb{E}[P_{\alpha_1}(t)] \\ \mathbb{E}[M_{\alpha_2}(t)^2] - \mathbb{E}[M_{\alpha_1}(t)^2] \\ \mathbb{E}[P_{\alpha_2}(t)^2] - \mathbb{E}[M_{\alpha_1}(t)^2] \\ \mathbb{E}[M_{\alpha_2}(t)P_{\alpha_2}(t)] - \mathbb{E}[M_{\alpha_1}(t)P_{\alpha_1}(t)] \end{bmatrix}, \quad \text{with } y(0) = 0.$$

The first two components satisfy the uncoupled system

$$\frac{dy_1}{dt} = -c_D y_1 + \alpha_1 c_B y_2 + c_B(\alpha_2 - \alpha_1)\mathbb{E}[P_{\alpha_2}], \tag{2.8}$$
$$\frac{dy_2}{dt} = k_P y_1 - \gamma_P y_2. \tag{2.9}$$

We will show that both components remain nonnegative for all time. Suppose the solution is such that $y_1(t) = 0$ and $y_2(t) > 0$. Then from (2.8), we see that $y_1(t)$ has a

positive derivative, so the solution returns to the first quadrant. Similarly, if $y_2(t) = 0$ and $y_1(t) > 0$ then from (2.9) we see that the solution also returns to the first quadrant. Finally, if $y_1(t) = y_2(t) = 0$ both derivatives are nonnegative, so neither component can decrease.

The remaining components then satisfy

$$\frac{d}{dt}\begin{bmatrix} y_3 \\ y_4 \\ y_5 \end{bmatrix} = \begin{bmatrix} -2c_D & 0 & 2c_B\alpha_1 \\ 0 & -2\gamma_P & 2k_P \\ k_P & c_B\alpha_1 & -(c_D+\gamma_P) \end{bmatrix}\begin{bmatrix} y_3 \\ y_4 \\ y_5 \end{bmatrix} + h(t),$$

where

$$h(t) := \begin{bmatrix} (2c_B + c_D)y_1 + c_B\alpha_1 y_2 + c_B(\alpha_2 - \alpha_1)\mathbb{E}[P_{\alpha_2}] + 2c_B(\alpha_2 - \alpha_1)\mathbb{E}[M_{\alpha_2}P_{\alpha_2}] \\ k_P y_1 + \gamma_P y_2 \\ c_B y_2 + c_B(\alpha_2 - \alpha_1)\mathbb{E}[P_{\alpha_2}^2] \end{bmatrix}$$

is nonnegative. The arguments used above for $y_1(t)$ and $y_2(t)$ may now be applied to $y_3(t)$, $y_4(t)$ and $y_5(t)$ and we conclude that all solution components remain nonnegative.

In summary, we have shown that, for any choice of model parameters, increasing the protein feedback rate cannot decrease the first and second moments and correlation of mRNA and protein.

Now, let us consider differences in the variances of mRNA and protein between the feedback rates α_1 and α_2. We let

$$v := \begin{bmatrix} \mathsf{var}[M_{\alpha_2}] - \mathsf{var}[M_{\alpha_1}] \\ \mathsf{var}[P_{\alpha_2}] - \mathsf{var}[P_{\alpha_1}] \end{bmatrix},$$

where $\mathsf{var}[X]$ denotes the variance of X; that is,

$$\mathsf{var}[X] := \mathbb{E}[X^2] - (\mathbb{E}[X])^2.$$

We have

$$\begin{aligned} \frac{dv_1}{dt} &= \frac{d}{dt}\mathsf{var}[M_{\alpha_2}] - \frac{d}{dt}\mathsf{var}[M_{\alpha_1}] \\ &= \frac{d}{dt}\left(\mathbb{E}[M_{\alpha_2}^2] - (\mathbb{E}[M_{\alpha_2}])^2\right) - \frac{d}{dt}\left(\mathbb{E}[M_{\alpha_1}] - (\mathbb{E}[M_{\alpha_1}])^2\right) \\ &= c_D y_1 + c_B(\alpha_2\mathbb{E}[P_{\alpha_2}] - \alpha_1\mathbb{E}[P_{\alpha_1}]) - 2c_D v_1 \\ &\quad + 2c_B(\alpha_2\mathbb{E}[M_{\alpha_2}P_{\alpha_2}] - \alpha_1\mathbb{E}[M_{\alpha_1}P_{\alpha_1}]) \\ &\quad - 2c_B(\alpha_2\mathbb{E}[M_{\alpha_2}]\mathbb{E}[P_{\alpha_2}] - \alpha_1\mathbb{E}[M_{\alpha_1}]\mathbb{E}[P_{\alpha_1}]). \end{aligned}$$

So,

$$v_1 = e^{-2c_D t}\int_0^t h_4(s)e^{2c_D s}ds,$$

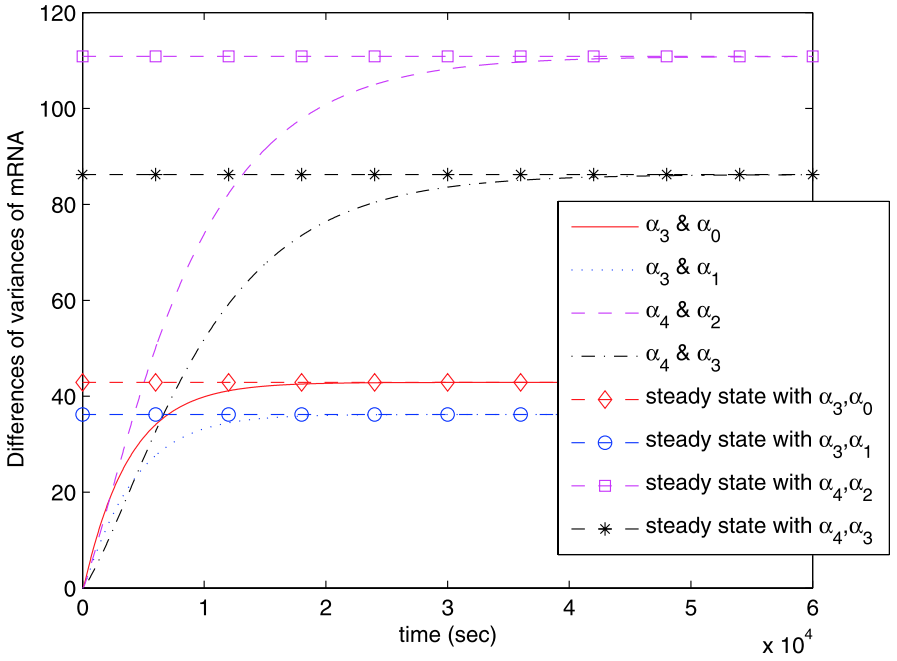

Fig. 2 (Color online) Differences of variances in mRNA for the feedback model, using feedback rates $\alpha_i = ic_D\gamma_P/5c_Bk_P$ for $i = 0, 1, 2, 3, 4$

where

$$h_4(t) := c_D y_1 + c_B(\alpha_2\mathbb{E}[P_{\alpha_2}] - \alpha_1\mathbb{E}[P_{\alpha_1}]) + 2c_B(\alpha_2\mathbb{E}[M_{\alpha_2}P_{\alpha_2}] - \alpha_1\mathbb{E}[M_{\alpha_1}P_{\alpha_1}])$$
$$- 2c_B(\alpha_2\mathbb{E}[M_{\alpha_2}]\mathbb{E}[P_{\alpha_2}] - \alpha_1\mathbb{E}[M_{\alpha_1}]\mathbb{E}[P_{\alpha_1}]).$$

Because h_4 contains both positive and negative terms we are not able to draw generic conclusions about the sign of v_1. Similar comments apply for v_2. Thus, we cannot show explicitly that for all sets of parameter values the mRNA and protein variances increase with the feedback rate. However, we did observe such monotonicity in the following simulations that use biologically realistic parameters. Figures 2 and 3 show differences in variances for mRNA and protein, respectively. Initial conditions and rate constants were set to $M(0) = 2$, $P(0) = 4$ and $c_B = 0.3$, $c_D = 0.012$, $k_P = 0.17$ from [24] and $\gamma_P = 0.0007$ from [2]. We set the feedback rates as $\alpha_i = ic_D\gamma_P/5c_Bk_P$ for $i = 0, 1, 2, 3, 4$. The horizontal lines are steady state values, as given in Sect. 2.3. We see that the variances increase monotonically in α.

The Fano factor, or more loosely *noise strength*, for a random variable X may be defined as

$$\mathrm{ns}[X] := \frac{\mathrm{var}[X]}{\mathbb{E}[X]}.$$

This quantity is commonly used to summarise the intrinsic level of fluctuation [26].

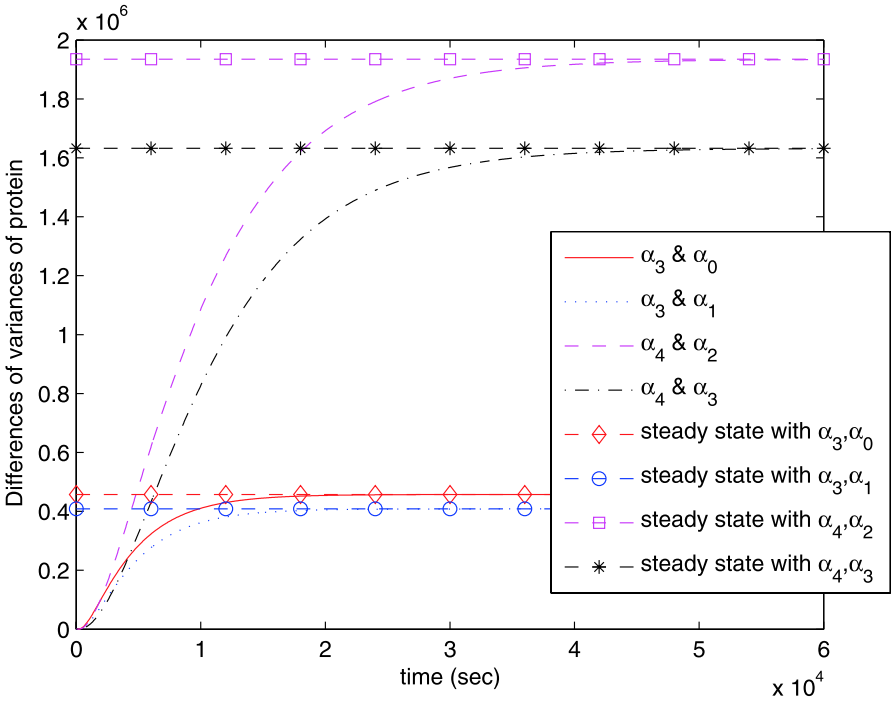

Fig. 3 (Color online) Differences of variances in protein for the feedback model, using feedback rates $\alpha_i = ic_D\gamma_P/5c_Bk_P$ for $i = 0, 1, 2, 3, 4$

Figures 4 and 5 show the differences in noise strengths for mRNA and protein, respectively, using the same feedback rates, initial conditions, and rate constants as in Fig. 2. We see that in these examples the noise strength increases with the feedback rate.

2.3 Feedback effect at steady state

It is straightforward to show that the ODE system (2.7) has a stable steady state if and only if $0 \le \alpha < \bar{\alpha} := c_D\gamma_P/c_Bk_P$. This has a natural interpretation—the feedback strength cannot be too great relative to the growth and decay constants governing the transcription and translation processes. For $0 \le \alpha < \bar{\alpha}$, the steady state moments have the form

$$\mathbb{E}[M^\star] = \frac{\gamma_P c_B}{c_D\gamma_P - k_P c_B\alpha},$$

$$\mathbb{E}[P^\star] = \frac{k_P c_B}{c_D\gamma_P - k_P c_B\alpha},$$

$$\mathbb{E}[(M^\star)^2] = \frac{c_Bc_D\gamma_P(c_D\gamma_P - k_Pc_B\alpha) + c_B^2\gamma_P(k_P\alpha^2c_B + c_D\gamma_P) + c_B\gamma_P^3(c_B + c_D)}{(c_D + \gamma_P)(c_D\gamma_P - k_Pc_B\alpha)^2},$$

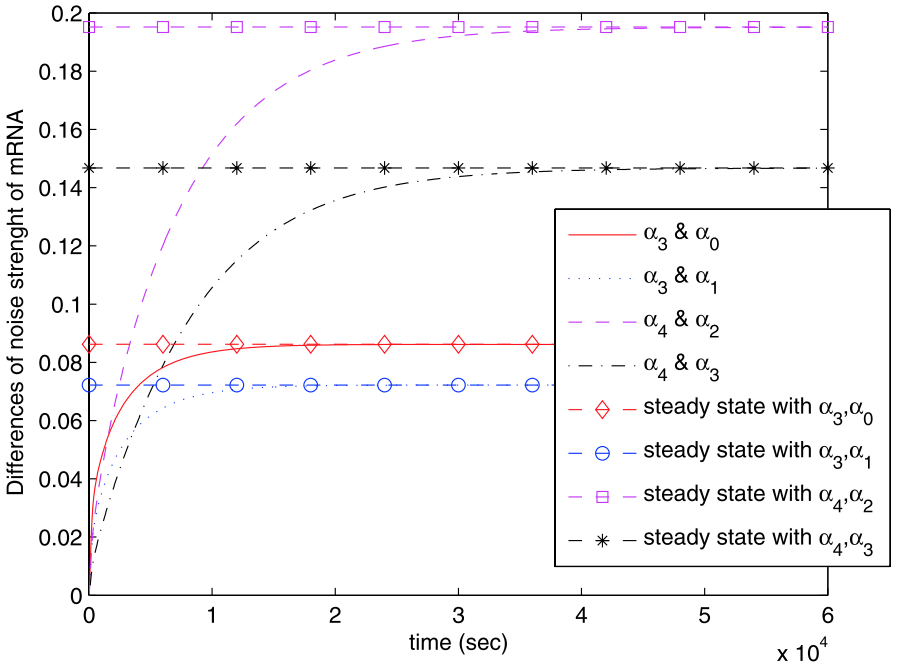

Fig. 4 (Color online) Differences of noise strengths in mRNA for the feedback model, using feedback rates $\alpha_i = ic_D\gamma_P/5c_Bk_P$ for $i = 0, 1, 2, 3, 4$

$$\mathbb{E}[(P^\star)^2] = \frac{c_Bk_P\gamma_P(c_D\gamma_P - k_Pc_B\alpha) + c_B^2k_P^2(c_D+\gamma_P) + c_Bc_Dk_P\gamma_P(c_D+k_P)}{(c_D+\gamma_P)(c_D\gamma_P - k_Pc_B\alpha)^2}.$$

Unlike in the general time-dependent case considered in Sect. 2.2, at steady state we are able to establish generic monotonicity of the variance and noise strength of mRNA and protein. For $0 \le \alpha_1 < \alpha_2 < \bar{\alpha}$, let $M^\star_{\alpha_i}$ and $P^\star_{\alpha_i}$ denote the number of mRNA and protein molecules at steady state with $\alpha = \alpha_i$. We find that

$$\begin{aligned}
&\mathrm{var}[M^\star_{\alpha_2}] - \mathrm{var}[M^\star_{\alpha_1}] \\
&\quad = \frac{c_B^2\gamma_Pk_Pc_D(\alpha_2-\alpha_1)}{(c_D\gamma_P - k_Pc_B\alpha_2)(c_D\gamma_P - k_Pc_B\alpha_1)(c_D+\gamma_P)} \\
&\qquad + \frac{c_B^2\gamma_P^2k_Pc_D(\alpha_2-\alpha_1)(\gamma_P+\alpha_2c_B)}{(c_D\gamma_P - k_Pc_B\alpha_1)(c_D+\gamma_P)(c_D\gamma_P - k_Pc_B\alpha_2)^2} \\
&\qquad + \frac{c_B^2\gamma_P^2k_Pc_D(\alpha_2-\alpha_1)(\gamma_P+\alpha_1c_B)}{(c_D\gamma_P - k_Pc_B\alpha_2)(c_D+\gamma_P)(c_D\gamma_P - k_Pc_B\alpha_1)^2}, \\
&\mathrm{var}[P^\star_{\alpha_2}] - \mathrm{var}[P^\star_{\alpha_1}] \\
&\quad = \frac{c_B^2k_P^2\gamma_P(\alpha_2-\alpha_1)}{(c_D\gamma_P - k_Pc_B\alpha_2)(c_D\gamma_P - k_Pc_B\alpha_1)(c_D+\gamma_P)}
\end{aligned}$$

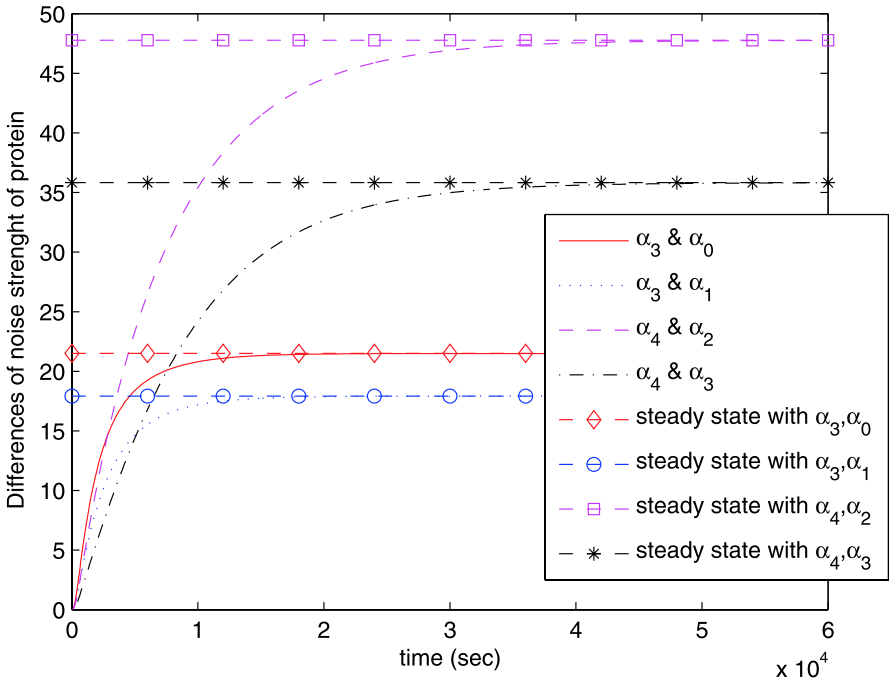

Fig. 5 (Color online) Differences of noise strengths in protein for the feedback model, using feedback rates $\alpha_i = ic_D\gamma_P/5c_Bk_P$ for $i = 0, 1, 2, 3, 4$

$$+\frac{c_B^2k_P^2\gamma_Pc_D(\alpha_2-\alpha_1)(c_D+k_P)(2c_D\gamma_P-k_Pc_B\alpha_1-k_Pc_B\alpha_2)}{(c_D+\gamma_P)(c_D\gamma_P-k_Pc_B\alpha_1)^2(c_D\gamma_P-k_Pc_B\alpha_2)^2},$$

and

$$\begin{aligned}&\mathrm{ns}[M^\star_{\alpha_2}]-\mathrm{ns}[M^\star_{\alpha_1}]\\&=\frac{c_Bk_P(\alpha_2-\alpha_1)(\alpha_1c_B(c_D\gamma_P-k_Pc_B\alpha_2)+\gamma_P^2c_D+\alpha_2c_Bc_D\gamma_P)}{(c_D+\gamma_P)(c_D\gamma_P-k_Pc_B\alpha_1)(c_D\gamma_P-k_Pc_B\alpha_2)},\\&\mathrm{ns}[P^s_{\alpha_2}]-\mathrm{ns}[P^s_{\alpha_1}]=\frac{\gamma_Pc_Bk_Pc_D(\alpha_2-\alpha_1)(c_D+k_P)}{(c_D+\gamma_P)(c_D\gamma_P-k_Pc_B\alpha_1)(c_D\gamma_P-k_Pc_B\alpha_2)}.\end{aligned}$$

Hence, both variances and noise strengths increase monotonically in α over the stable interval $[0, \tilde{\alpha})$.

We now turn our attention to a hybrid model.

3 Hybrid stochastic differential equation for autoregulation

Autoregulation effects are studied in a hybrid discrete-continuous setting in [19, 20]. These authors use deterministic *mass action* ODE kinetics to describe the

more abundant species, while treating the low copy number species discretely. However, it has been shown for simple non-feedback gene regulation models, such as those in [22], that this approach can systematically underestimate the variance, and hence the noise strength, whereas a suitable continuous-valued diffusion process does not have this drawback [12, 13, 16].

Under the assumption that the proteins are relatively abundant, we therefore study a hybrid model over some finite time interval $[0, T]$ that combines a discrete Markov jump process for mRNA with an SDE for protein. In this manner, the mRNA count acts as a state-dependent Markovian switch for the diffusing protein level. Our switching process, $\bar{M}(t)$, which represents the mRNA count, has the infinitesimal characterisation

$$\mathbb{P}(\bar{M}(t+\Delta t) = s-1 \mid \bar{M}(t) = s) = \Delta t c_D \bar{M}(t) + o(\Delta t), \tag{3.1}$$

$$\mathbb{P}(\bar{M}(t+\Delta t) = s+1 \mid \bar{M}(t) = s) = \Delta t c_B (1 + \alpha \bar{P}(t)) + o(\Delta t), \tag{3.2}$$

$$\mathbb{P}(\bar{M}(t+\Delta t) = s \mid \bar{M}(t) = s) = 1 - \Delta t (c_D \bar{M}(t) + c_B (1 + \alpha \bar{P}(t))) + o(\Delta t), \tag{3.3}$$

where the protein level, $\bar{P}(t)$, satisfies the SDE

$$d\bar{P}(t) = (k_P \bar{M}(t) - \gamma_P \bar{P}(t))dt + \sqrt{k_P \bar{M}(t)} dW_1 - \sqrt{\gamma_P \bar{P}(t)} dW_2. \tag{3.4}$$

Here $W_1(t)$ and $W_2(t)$ are independent scalar Brownian motions that arise from a *chemical Langevin* approximation to the fluctuations around the mean of certain Poisson processes appearing in the fully discrete system [9, 18]. The system (3.1)–(3.4) may be regarded as a *hybrid switching diffusion* [28], and we hope to show that this is a fruitful setting in which to study certain multiscale modelling and simulation techniques.

Following (2.6), we will let

$$Z(t) := \begin{bmatrix} \mathbb{E}[\bar{M}(t)] \\ \mathbb{E}[\bar{P}(t)] \\ \mathbb{E}[\bar{M}(t)^2] \\ \mathbb{E}[\bar{P}(t)^2] \\ \mathbb{E}[\bar{M}(t)\bar{P}(t)] \end{bmatrix}. \tag{3.5}$$

At this stage it is appropriate to mention two technical issues. First, it is known that the chemical Langevin approximation is, generally, not well defined for all time [25]. In the case of (3.4) this is intuitively clear: the first diffusion coefficient $\sqrt{k_P \bar{M}(t)}$ does not vanish when $\bar{P} = 0$, and yet if the protein level is then pushed into the negative region, the second diffusion coefficient $\sqrt{\gamma_P \bar{P}(t)}$ becomes undefined. A second issue is that the stochastic calculus results that we wish to use have, so far, only been established for the case where the drift and diffusion coefficients are uniformly bounded functions of the switching variable.

To deal with these issues, we introduce the stopping times

$$\tau_0 := \inf\{t \geq 0 : \bar{P}(t) < 0\},$$
$$\tau_k := \inf\{t \geq 0 : \bar{P}(t) > k \text{ or } \bar{M}(t) > k\}.$$

The first of these, τ_0, is introduced to deal with the negativity issue, and the second, τ_k, deals with unboundedness. With the notation $a \wedge b = \min(a, b)$, by [28, Theorem 2.1] there exists a unique solution $(\bar{M}(t), \bar{P}(t))$ for (3.1)–(3.4) on $[0, T \wedge \tau_k \wedge \tau_0]$, for any given (deterministic) initial data $\bar{P}(0) \in [0, k]$ and $\bar{M}(0) \in [0, k]$, $k > 1$.

We begin by bounding first and second moments. For any $t \in [0, T]$ we have

$$\mathbb{E}[\bar{M}(t \wedge \tau_k \wedge \tau_0)] = \mathbb{E}[\bar{M}(0)] - c_D \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} \bar{M}(s) ds + c_B \alpha \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} \bar{P}(s) ds + c_B \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} ds \tag{3.6}$$

and

$$\begin{aligned}
\mathbb{E}[\bar{M}(t \wedge \tau_k \wedge \tau_0)^2] &= \mathbb{E}[\bar{M}(0)^2] + (2c_B + c_D) \int_0^{t \wedge \tau_k \wedge \tau_0} \mathbb{E}[\bar{M}(s)] ds \\
&\quad + c_B \alpha \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} \bar{P}(s) ds - 2c_D \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} \bar{M}(s)^2 ds \\
&\quad + 2c_B \alpha \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} \bar{M}(s) \bar{P}(s) ds + c_B \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} ds \\
&\leq \mathbb{E}[\bar{M}(0)^2] + (2c_B + c_D) \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} \bar{M}(s) ds \\
&\quad + c_B \alpha \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} \bar{P}(s) ds - 2c_D \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} \bar{M}(s)^2 ds \\
&\quad + c_B \alpha \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} [\bar{M}(s)^2 + \bar{P}(s)^2] ds + c_B \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} ds.
\end{aligned}$$

From (3.4) we have

$$\mathbb{E}[\bar{P}(t \wedge \tau_k \wedge \tau_0)] = \mathbb{E}[\bar{P}(0)] + \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} (k_P \bar{M}(s) - \gamma_P \bar{P}(s)) ds. \tag{3.7}$$

By the Itô isometry and the Hölder inequality we then find the following upper bound for the second moment of the protein level

$$\begin{aligned}
\mathbb{E}[\bar{P}(t \wedge \tau_k \wedge \tau_0)^2] \leq 4 \Bigg(& 2T(k_P^2 + \gamma_P^2) \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} (\bar{M}(s)^2 + \bar{P}(s)^2) ds \\
& + (k_P + \gamma_P) \mathbb{E} \int_0^{t \wedge \tau_k \wedge \tau_0} (\bar{P}(s) + \bar{M}(s)) ds \Bigg).
\end{aligned}$$

This leads us to the following lemma.

Lemma 3.1 *There exists a positive constant $K = K(T)$ such that*

$$\mathbb{E}[\bar{P}(T \wedge \tau_0)] + \mathbb{E}[\bar{M}(T \wedge \tau_0)] \leq K \quad \text{and} \quad \mathbb{E}[\bar{P}(T \wedge \tau_0)^2] + \mathbb{E}[\bar{M}(T \wedge \tau_0)^2] \leq K. \tag{3.8}$$

Proof By (3.6) and (3.7)

$$\begin{aligned}
&\mathbb{E}[\bar{M}(T \wedge \tau_k \wedge \tau_0)] + \mathbb{E}[\bar{P}(T \wedge \tau_k \wedge \tau_0)] \\
&\quad \leq \mathbb{E}[\bar{M}(0)] + \mathbb{E}[\bar{P}(0)] + T c_B \\
&\qquad + \mathbb{E} \int_0^{T \wedge \tau_k \wedge \tau_0} ((k_P - c_D)\bar{M}(s) + (\alpha c_B - \gamma_P)\bar{P}(s))ds \\
&\quad \leq \mathbb{E}[\bar{M}(0)] + \mathbb{E}[\bar{P}(0)] + T c_B \\
&\qquad + \int_0^T (k_p + c_D)\mathbb{E}[\bar{M}(s)]\mathbf{1}_{\{s < \tau_k \wedge \tau_0\}} + (\alpha c_B + \gamma_P)\mathbb{E}[\bar{P}(s)]\mathbf{1}_{\{s < \tau_k \wedge \tau_0\}} ds \\
&\quad \leq \mathbb{E}[\bar{M}(0)] + \mathbb{E}[\bar{P}(0)] + T c_B \\
&\qquad + C \int_0^T \Big(\mathbb{E}[\bar{M}(s \wedge \tau_k \wedge \tau_0)] + \mathbb{E}[\bar{P}(s \wedge \tau_k \wedge \tau_0)] \Big) ds,
\end{aligned}$$

where $C = \max\{k_p + c_D, \alpha c_B + \gamma_P\}$. By Gronwall's inequality we then have

$$\mathbb{E}[\bar{M}(T \wedge \tau_k \wedge \tau_0)] + \mathbb{E}[\bar{P}(T \wedge \tau_k \wedge \tau_0)] \leq (\mathbb{E}[\bar{M}(0)] + \mathbb{E}[\bar{P}(0)] + T c_B) \exp(CT).$$

Fatou's lemma completes the proof for the first moments. The inequality involving second moments can be proved analogously. □

It is also useful to observe that

$$\begin{aligned}
&\mathbb{E}[\bar{P}(T \wedge \tau_0 \wedge \tau_k)^2] + \mathbb{E}[\bar{M}(T \wedge \tau_0 \wedge \tau_k)^2] \\
&\quad \geq \mathbb{E}[\mathbf{1}_{\tau_k < T \wedge \tau_0} \bar{P}(\tau_k)^2] + \mathbb{E}[\mathbf{1}_{\tau_k < T \wedge \tau_0} \bar{M}(\tau_k)^2] \\
&\quad \geq \mathbb{E}[\mathbf{1}_{\tau_k < T \wedge \tau_0} 2k^2].
\end{aligned}$$

Hence

$$\lim_{k \to \infty} \mathbb{P}(\tau_k < T \wedge \tau_0) = 0.$$

Loosely, the probability is small that the process will explode either in finite time or before hitting zero.

3.1 Moments for hybrid approximation

First and second moments for the fully discrete model were characterised in Sect. 2.1 Based on insights from simpler cases [12, 13] we aim to test whether the hybrid

model reproduces these moments. We would like to emphasize that the presence of a state-dependent switch greatly complicates the SDE analysis, and standard tools from stochastic calculus may not apply. In particular, direct application of a generalisation of the Itô Lemma is not straightforward. Our approach is to introduce a discrete approximation to the hybrid SDE that, as well as providing a practical means to simulate the model, also allows us to study the moments of the underlying continuous time process, via finite-time convergence theory from [28].

We therefore consider an Euler–Maruyama type approximation to the hybrid SDE (3.1)–(3.4). Let $\bar{M}_n$ and $\bar{P}_n$ denote our discrete time approximations at $t = n\Delta t$. Then $\bar{M}_n$ may be defined through

$$\begin{aligned}
\mathbb{P}(\bar{M}_{n+1} - \bar{M}_n = -1 \mid \bar{M}_n, \bar{P}_n) &= \Delta t c_D \bar{M}_n + o(\Delta t),\\
\mathbb{P}(\bar{M}_{n+1} - \bar{M}_n = 1 \mid \bar{M}_n, \bar{P}_n) &= \Delta t c_B (1 + \alpha \bar{P}_n) + o(\Delta t),\\
\mathbb{P}(\bar{M}_{n+1} - \bar{M}_n = 0 \mid \bar{M}_n, \bar{P}_n) &= 1 - \Delta t (c_D \bar{M}_n + c_B (1 + \alpha \bar{P}_n)) + o(\Delta t),
\end{aligned}$$

where we assume that the $o(\Delta t)$ terms are uniform in $\bar{P}_n$, and the protein level is given by the Euler–Maruyama approximation

$$\bar{P}_{n+1} = \bar{P}_n + \Delta t (k_P \bar{M}_n - \gamma_P \bar{P}_n) + \sqrt{k_P \bar{M}_n} \Delta W_1^n - \sqrt{\gamma_P \bar{P}_n} \Delta W_2^n. \tag{3.9}$$

In the same way as before we define stopping times

$$\lambda_k = \inf\{n \geq 0 : \bar{P}_n > k \text{ or } \bar{M}_n > k\} \quad \text{and} \quad \lambda_0 = \inf\{n \geq 0 : \bar{P}_n < 0\}.$$

Let

$$Z_{n\wedge\lambda_0} = \begin{bmatrix} \mathbb{E}[\bar{M}_{n\wedge\lambda_0}] \\ \mathbb{E}[\bar{P}_{n\wedge\lambda_0}] \\ \mathbb{E}[\bar{M}^2_{n\wedge\lambda_0}] \\ \mathbb{E}[\bar{P}^2_{n\wedge\lambda_0}] \\ \mathbb{E}[\bar{M}_{n\wedge\lambda_0}\bar{P}_{n\wedge\lambda_0}] \end{bmatrix}.$$

To simplify notation we will calculate these moments under the assumption that $n < \lambda_k \wedge \lambda_0$. Our aim is to produce discrete analogues of the relations derived for the continuous-time model. We have

$$\begin{aligned}
\mathbb{E}[\bar{M}_{n+1}] &= \mathbb{E}[\bar{M}_{n+1} - \bar{M}_n] + \mathbb{E}[\bar{M}_n]\\
&= \mathbb{E}[\mathbb{E}[\bar{M}_{n+1} - \bar{M}_n | \bar{M}_n, \bar{P}_n]] + \mathbb{E}[\bar{M}_n]\\
&= \mathbb{E}[-\mathbb{P}(\bar{M}_{n+1} - \bar{M}_n = -1 | \bar{M}_n, \bar{P}_n) + \mathbb{P}(\bar{M}_{n+1} - \bar{M}_n = 1 | \bar{M}_n, \bar{P}_n)]\\
&\quad + \mathbb{E}[\bar{M}_n]\\
&= \mathbb{E}[-\Delta t c_D \bar{M}_n + \Delta t c_B (1 + \alpha \bar{P}_n)] + \mathbb{E}[\bar{M}_n] + o(\Delta t)\\
&= -\Delta t c_D \mathbb{E}[\bar{M}_n] + \Delta t c_B (1 + \alpha \mathbb{E}[\bar{P}_n]) + \mathbb{E}[\bar{M}_n] + o(\Delta t).
\end{aligned}$$

This implies that

$$\frac{\mathbb{E}[\bar{M}_{n+1}] - \mathbb{E}[\bar{M}_n]}{\Delta t} = -c_D \mathbb{E}[\bar{M}_n] + c_B \alpha \mathbb{E}[\bar{P}_n] + c_B + o(1). \tag{3.10}$$

In a similar way, we can show that

$$\frac{\mathbb{E}[\bar{M}_{n+1}^2] - \mathbb{E}[\bar{M}_n^2]}{\Delta t} = (2c_B + c_D)\mathbb{E}[\bar{M}_n] + c_B\alpha\mathbb{E}[\bar{P}_n] - 2c_D\mathbb{E}[\bar{M}_n^2] + 2c_B\alpha\mathbb{E}[\bar{M}_n\bar{P}_n] + c_B + o(1), \tag{3.11}$$

$$\frac{\mathbb{E}[\bar{P}_{n+1}] - \mathbb{E}[\bar{P}_n]}{\Delta t} = k_P\mathbb{E}[\bar{M}_n] - \gamma_P\mathbb{E}[\bar{P}_n], \tag{3.12}$$

$$\frac{\mathbb{E}[\bar{P}_{n+1}^2] - \mathbb{E}[\bar{P}_n^2]}{\Delta t} = k_P\mathbb{E}[\bar{M}_n] + \gamma_P\mathbb{E}[\bar{P}_n] - 2\gamma_P\mathbb{E}[\bar{P}_n^2] + 2k_P\mathbb{E}[\bar{M}_n\bar{P}_n] + \Delta t\mathbb{E}[(k_P\bar{M}_n - \gamma_P\bar{P}_n)^2], \tag{3.13}$$

$$\frac{\mathbb{E}[\bar{M}_{n+1}\bar{P}_{n+1}] - \mathbb{E}[\bar{M}_n\bar{P}_n]}{\Delta t} = k_p\mathbb{E}[\bar{M}_n^2] - (\gamma_p + c_D)\mathbb{E}[\bar{M}_n\bar{P}_n] + c_B(\mathbb{E}[\bar{P}_n] + \alpha\mathbb{E}[\bar{P}_n^2]) + \mathbb{E}[\Delta t(k_p\bar{M}_n - \gamma_p\bar{P}_n)(c_B(1+\alpha\bar{P}_n) - c_D\bar{M}_n)]. \tag{3.14}$$

We give more details in the Appendix and also show that first and second moments are appropriately bounded.

3.2 Agreement of the moments

The results in Sect. 3.1 essentially show that the moments of the discrete time, Euler–Maruyama approximation correspond closely to an Euler approximation of the ODE (2.7) that governs the evolution of the exact moments for the fully discrete model. Because the Euler approximation is convergent over finite time intervals, the triangle inequality then allows us to conclude that the moments of the hybrid SDE (3.1)–(3.4) exactly match those of the fully discrete model.

To formalize this argument, we first define the stopping time

$$\theta_0 = \tau_0 \wedge \lambda_0.$$

Theorem 3.1 *The first and second moments and correlations for the fully discrete and hybrid diffusion models agree, in the sense that* $z(t) = Z(t)$ *for* $t \in [0, T \wedge \theta_0]$.

Proof Letting $t = (n+1)\Delta t$ denote a general mesh point, the triangle inequality gives

$$|z(t) - Z(t)| \le |z(t) - Z_{n+1}| + |Z_{n+1} - Z(t)|, \tag{3.15}$$

where $|\cdot|$ denotes the Euclidean norm.

Now an Euler scheme for (2.7) has the form

$$\hat{Z}_{n+1} = \hat{Z}_n + N\hat{Z}_n\Delta t + b\Delta t, \tag{3.16}$$

and classical numerical ODE theory [10] gives

$$|z(t) - \hat{Z}_{n+1}| = O(\Delta t).$$

It follows from (3.10)–(3.14) that

$$Z_{n+1} = Z_n + NZ_n\Delta t + b\Delta t + CZ_n\Delta t^2 + o(\Delta t), \tag{3.17}$$

where the matrix C has the form

$$C = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & k_P^2 & \gamma_P^2 & -2k_P\gamma_P \\ k_P c_B & -\gamma_P c_B & -k_P c_D & -\gamma_P c_B \alpha & k_P c_B \alpha + \gamma_P c_D \end{bmatrix}.$$

Using the discrete Gronwall inequality with (3.16) and (3.17) gives

$$|\hat{Z}_{n+1} - Z_{n+1}| = o(1).$$

Therefore

$$|z(t) - Z_{n+1}| \le |z(t) - \hat{Z}_{n+1}| + |\hat{Z}_{n+1} - Z_{n+1}| = o(1).$$

Hence, from (3.15) it remains to show that

$$\lim_{\Delta t \to 0} |Z_{n+1} - Z(t)| = 0 \quad \text{for all } t \in [0, T \wedge \theta_0].$$

Defining the stopping time

$$\chi_k = \lambda_k \wedge \tau_k,$$

we first observe that

$$|Z_{n+1} - Z(t)| \le |Z_{n+1} - Z_{n+1\wedge\chi_k}| + |Z_{n+1\wedge\chi_k} - Z(t \wedge \chi_k)| + |Z(t \wedge \chi_k) - Z(t)|.$$

Now by [28, Theorem 5.13] we have

$$\lim_{\Delta t \to 0} |Z_{n+1\wedge\chi_k} - Z(t \wedge \chi_k)| = O(\Delta t).$$

From Appendix and Lemma 3.1 we know that there exists a constant K such that

$$Z_{n+1} + Z(t) \le K.$$

Therefore

$$\lim_{k \to \infty} |Z_{n+1} - Z_{n+1\wedge\chi_k}| + |Z(t \wedge \chi_k) - Z(t)| = 0,$$

which completes the proof of the theorem. □

4 Discussion

The main goal of this work is to show how certain analytical difficulties can be overcome in order to conclude that hybrid diffusions, and their discrete approximations, form a useful framework in which to study certain types of multiscale model. We studied an autoregulation model that has clear-cut biological properties. For the discrete-space, master equation formulation, we analysed the first and second moments directly and showed that interesting, and perhaps counterintuitive, effects arise: although the first and second moments of mRNA and protein, and the correlation between them, are always monotonically increasing functions of the feedback strength, the same is not true in general of the variances and the noise strengths at any particular point in time. However, if we look at their steady state values, we find that the variances and the noise strengths are monotonic, up to the stability threshold. This gives a useful set of behaviours to study for the hybrid model. Overall, by carefully analysing a discrete version of the model, we were able to show that the hybrid model recovers these important properties.

This work represents a proof-of-principle, where we focused on a linear reaction network with a linear autoregulatory effect. Our aims were to point out technical issues that arise even in this biologically simple case, and to show how they can be overcome to derive results about the quality of the diffusion approximation. The linearity allowed us (a) to obtain explicit characterizations of the moments in the underlying discrete-space model and (b) to analyze a corresponding hybrid switching SDE model using recent results from stochastic numerics. It would, of course, be of great interest, but also extremely challenging, to extend these results to more general scenarios. Within the autoregulation setting, it would be natural to study non-linear switching rates—for example the feedback rate could take the form of a hill-type function. In this case the underlying fully discrete model is less amenable to analysis since it is no longer a first order network, and it is highly relevant to study the accuracy of the hybrid diffusion (which is cheaper to simulate). Similarly, we could look at simulating autoregulation in a reaction network that was not of first order. Some computational tests in [13] for a simple second order regulation network, with no feedback, indicated that a suitable diffusion approximation can give good results. More generally, although the issue of negative solutions was dealt with here through the use of stopping times, it would be more satisfying to have a generic, modelling-based, procedure for building non-negativity into the diffusion process.

Appendix: Analysis of moments in hybrid model

In this appendix we establish the moment relations (3.11)–(3.14) and confirm that the first and second moments of the mRNA and protein level in the discrete time, Euler–Maruyama approximation in Sect. 3.1 are bounded.

Introducing conditional expectations, we have

$$\begin{aligned}\mathbb{E}[\bar{M}_{n+1}^2] &= \mathbb{E}[(\bar{M}_{n+1} - \bar{M}_n + \bar{M}_n)^2] \\ &= \mathbb{E}[(\bar{M}_{n+1} - \bar{M}_n)^2 + 2\bar{M}_n(\bar{M}_{n+1} - \bar{M}_n) + \bar{M}_n^2]\end{aligned}$$

$$
\begin{aligned}
&= \mathbb{E}[\mathbb{E}[(\bar{M}_{n+1} - \bar{M}_n)^2 | \bar{M}_n, \bar{P}_n]] \\
&\quad + \mathbb{E}[\mathbb{E}[2\bar{M}_n(\bar{M}_{n+1} - \bar{M}_n) | \bar{M}_n, \bar{P}_n]] + \mathbb{E}[\bar{M}_n^2] \\
&= \mathbb{E}[\Delta t(c_D \bar{M}_n + c_B(1 + \alpha \bar{P}_n)) + o(\Delta t)] \\
&\quad + 2\mathbb{E}[\Delta t(-c_D \bar{M}_n^2 + c_B(\bar{M}_n + \alpha \bar{M}_n \bar{P}_n))] + \mathbb{E}[\bar{M}_n^2].
\end{aligned}
$$

The relation (3.11) follows immediately.

Next, consider the first and second moments of the protein level. Taking expectation in (3.9) gives the first moment relation (3.12). Squaring of (3.9) gives

$$
\begin{aligned}
\bar{P}_{n+1}^2 = \bar{P}_n^2 &+ 2\bar{P}_n\Big[\Delta t(k_P \bar{M}_n - \gamma_P \bar{P}_n) + \sqrt{k_P \bar{M}_n}\Delta W_1^n + \sqrt{\gamma_P \bar{P}_n}\Delta W_2^n\Big] \\
&+ (\Delta t(k_P \bar{M}_n - \gamma_P \bar{P}_n))^2 + k_P \bar{M}_n(\Delta W_1^n)^2 + \gamma_P \bar{P}_n(\Delta W_2^n)^2 \\
&+ 2\sqrt{k_P \bar{M}_n}\Delta W_1^n \sqrt{\gamma_P \bar{P}_n}\Delta W_2^n \\
&+ 2\Delta t(k_P \bar{M}_n - \gamma_P \bar{P}_n)\Big(\sqrt{k_P \bar{M}_n}\Delta W_1^n + \sqrt{\gamma_P \bar{P}_n}\Delta W_2^n\Big).
\end{aligned}
$$

Noting that W_1^n and W_2^n are independent, we find that

$$
\begin{aligned}
\mathbb{E}[\bar{P}_{n+1}^2] = \mathbb{E}[\bar{P}_n^2] &+ 2\Delta t[(k_P \mathbb{E}[\bar{M}_n \bar{P}_n] - \gamma_P \mathbb{E}[\bar{P}_n^2])] \\
&+ \Delta t^2 \mathbb{E}[(k_P \bar{M}_n - \gamma_P \bar{P}_n)^2] + \Delta t k_P \mathbb{E}[\bar{M}_n] + \Delta t \gamma_P \mathbb{E}[\bar{P}_n].
\end{aligned}
$$

This gives (3.13).

Now, consider the correlation. By the law of total probability

$$
\begin{aligned}
\mathbb{E}[\bar{M}_{n+1}\bar{P}_{n+1}] &= \mathbb{E}[\mathbb{E}[(\bar{M}_{n+1} - \bar{M}_n + \bar{M}_n)\bar{P}_{n+1} \mid \bar{M}_n \bar{P}_n]] \\
&= \mathbb{E}[\mathbb{E}[\bar{M}_n \bar{P}_{n+1} \mid \bar{M}_n \bar{P}_n]] \\
&\quad + \mathbb{E}[\mathbb{E}[\bar{P}_{n+1} \mid \bar{M}_n \bar{P}_n]\mathbb{P}(\bar{M}_{n+1} - \bar{M}_n = 1 \mid \bar{M}_n, \bar{P}_n)] \\
&\quad - \mathbb{E}[\mathbb{E}[\bar{P}_{n+1} \mid \bar{M}_n \bar{P}_n]\mathbb{P}(\bar{M}_{n+1} - \bar{M}_n = -1 \mid \bar{M}_n, \bar{P}_n)] \\
&= \mathbb{E}[\mathbb{E}[\bar{M}_n(\bar{P}_n + \Delta t(k_p \bar{M}_n - \gamma_p \bar{P}_n)) \mid \bar{M}_n \bar{P}_n]] \\
&\quad + \mathbb{E}[\mathbb{E}[\bar{P}_n + \Delta t(k_p \bar{M}_n - \gamma_p \bar{P}_n) \mid \bar{M}_n \bar{P}_n]\Delta t(c_B(1 + \alpha \bar{P}_n) \\
&\quad - c_D \bar{M}_n)] \\
&= \mathbb{E}[\bar{M}_n \bar{P}_n + \Delta t(k_p \bar{M}_n^2 - \gamma_p \bar{M}_n \bar{P}_n)] \\
&\quad + \mathbb{E}[(\bar{P}_n + \Delta t(k_p \bar{M}_n - \gamma_p \bar{P}_n))(\Delta t(c_B(1 + \alpha \bar{P}_n) - c_D \bar{M}_n))] \\
&= \mathbb{E}[\bar{M}_n \bar{P}_n] + \Delta t(k_p \mathbb{E}[\bar{M}_n^2] - \gamma_p \mathbb{E}[\bar{M}_n \bar{P}_n]) \\
&\quad + \mathbb{E}[\bar{P}_n \Delta t(c_B(1 + \alpha \bar{P}_n) - c_D \bar{M}_n)] \\
&\quad + \mathbb{E}[\Delta t^2(k_p \bar{M}_n - \gamma_p \bar{P}_n)(c_B(1 + \alpha \bar{P}_n) - c_D \bar{M}_n)] \\
&= \mathbb{E}[\bar{M}_n \bar{P}_n] + \Delta t(k_p \mathbb{E}[\bar{M}_n^2] - \gamma_p \mathbb{E}[\bar{M}_n \bar{P}_n])
\end{aligned}
$$

$$+\Delta t(c_B(\mathbb{E}[\bar{P}_n]+\alpha\mathbb{E}[\bar{P}_n^2])-c_D\mathbb{E}[\bar{P}_n\bar{M}_n])$$
$$+\mathbb{E}[\Delta t^2(k_p\bar{M}_n-\gamma_p\bar{P}_n)(c_B(1+\alpha\bar{P}_n)-c_D\bar{M}_n)],$$

giving (3.14).

The next two lemmas concern moment boundedness.

Lemma A.1 *Let $N>0$ be any positive integer. Then there exists a positive constant $C=C(T)>0$ such that*

$$|\mathbb{E}[\bar{M}_{N\wedge\lambda_0}]|+|\mathbb{E}[\bar{P}_{N\wedge\lambda_0}]|\le C.$$

Proof From (3.10) and (3.12)

$$|\mathbb{E}[\bar{M}_{n+1}]|\le|\mathbb{E}[\bar{M}_n]|+|c_D\mathbb{E}[\bar{M}_n]\Delta t|+|c_B\alpha\mathbb{E}[\bar{P}_n]\Delta t|+c_B\Delta t+o(\Delta t)$$

and

$$|\mathbb{E}[\bar{P}_{n+1}]|\le|\mathbb{E}[\bar{P}_n]|+|k_P\mathbb{E}[\bar{M}_n]\Delta t|+|\gamma_P\mathbb{E}[\bar{P}_n]\Delta t|.$$

Therefore

$$\begin{aligned}|\mathbb{E}[\bar{M}_{n+1}]|+|\mathbb{E}[\bar{P}_{n+1}]|\le{}&|\mathbb{E}[\bar{M}_n]|+|\mathbb{E}[\bar{P}_n]|\\&+((k_P+c_D)|\mathbb{E}[\bar{M}_n]|+(c_B\alpha+\gamma_P)|\mathbb{E}[\bar{P}_n]|)\Delta t\\&+c_B\Delta t+o(\Delta t).\end{aligned}$$

Summing up from $n=0$ to $N\wedge\lambda_k\wedge\lambda_0-1$ we find that

$$\begin{aligned}&|\mathbb{E}[\bar{M}_{N\wedge\lambda_k\wedge\lambda_0}]|+|\mathbb{E}[\bar{P}_{N\wedge l_k\wedge\lambda_0}]|\\&\quad\le|\mathbb{E}[\bar{M}_0]|+|\mathbb{E}[\bar{P}_0]|\\&\qquad+\sum_{n=0}^{N-1}((k_P+c_D)|\mathbb{E}[\bar{M}_{n\wedge\lambda_k\wedge\lambda_0}]|+(c_B\alpha+\gamma_P)|\mathbb{E}[\bar{P}_{n\wedge\lambda_k\wedge\lambda_0}]|)\Delta t\\&\qquad+\sum_{n=0}^{N\wedge\lambda_k\wedge\lambda_0-1}(c_B\Delta t+o(\Delta t)).\end{aligned}$$

Using the fact that

$$\sum_{n=0}^{N-1}(c_B\Delta t+o(\Delta t))\le(1+c_B)T,$$

we obtain

$$\begin{aligned}&|\mathbb{E}[\bar{M}_{N\wedge\lambda_k\wedge\lambda_0}]|+|\mathbb{E}[\bar{P}_{N\wedge\lambda_k\wedge\lambda_0}]|\\&\quad\le|\mathbb{E}[\bar{M}_0]|+|\mathbb{E}[\bar{P}_0]+(1+c_B)T|\end{aligned}$$

$$+ K \sum_{n=1}^{N} \Big(|\mathbb{E}[\bar{M}_{n\wedge\lambda_k\wedge\lambda_0}]| + |\mathbb{E}[\bar{P}_{n\wedge\lambda_k(n)\wedge\lambda_0}]| \Big) \Delta t,$$

where $K = \max\{c_B\alpha + \gamma_P, k_P + c_D\}$. The discrete Gronwall inequality and Fatou's lemma then yield

$$|\mathbb{E}[\bar{M}_{N\wedge\lambda_0}]| + |\mathbb{E}[\bar{P}_{N\wedge\lambda_0}]| \le \big(|\mathbb{E}[\bar{M}_0]| + |\mathbb{E}[\bar{P}_0]| + (1 + c_B)T\big) \exp(KT). \quad \square$$

Lemma A.2 *Let $N > 0$ be any positive integer. Then there exists a positive constant $C = C(T)$ such that*

$$\mathbb{E}|\bar{M}_{N\wedge\lambda_0}|^2 + \mathbb{E}|\bar{P}_{N\wedge\lambda_0}|^2 \le C.$$

Proof By (3.11) and (3.13) we have

$$\begin{aligned}
\mathbb{E}[\bar{M}_{n+1}^2] + E[\bar{P}_{n+1}^2] = {} & \mathbb{E}[\bar{M}_n^2] + E[\bar{P}_n^2] \\
& + ((2c_B + c_D + k_P)\mathbb{E}[\bar{M}_n] + (c_B\alpha + \gamma_P)\mathbb{E}[\bar{P}_n])\Delta t \\
& - 2c_D\mathbb{E}[\bar{M}_n^2]\Delta t - 2\gamma_P\mathbb{E}[\bar{P}_n^2]\Delta t \\
& + (2c_B\alpha + 2k_P)\mathbb{E}[\bar{M}_n\bar{P}_n]\Delta t \\
& + c_B\Delta t + o(\Delta t) \\
& + \Delta t^2\mathbb{E}[(k_P\bar{M}_n - \gamma_P\bar{P}_n)^2].
\end{aligned}$$

By Young's Inequality

$$\begin{aligned}
\mathbb{E}[\bar{M}_{n+1}^2] + E[\bar{P}_{n+1}^2] \le {} & \mathbb{E}[\bar{M}_n^2] + E[\bar{P}_n^2] \\
& + ((2c_B + c_D + k_P)\mathbb{E}[\bar{M}_n] + (c_B\alpha + \gamma_P)\mathbb{E}[\bar{P}_n])\Delta t \\
& + (2k_P^2\Delta t - 2c_D + c_B\alpha + k_P)\mathbb{E}[\bar{M}_n^2]\Delta t \\
& + (2\gamma_P^2\Delta t - 2\gamma_P + c_B\alpha + k_P)\mathbb{E}[\bar{P}_n^2]\Delta t \\
& + c_B\Delta t + o(\Delta t).
\end{aligned}$$

By Lemma A.1 there exists a constant $C > 0$ such that

$$\begin{aligned}
\mathbb{E}[\bar{M}_{n+1}^2] + E[\bar{P}_{n+1}^2] \le {} & \mathbb{E}[\bar{M}_n^2] + E[\bar{P}_n^2] + C\Delta t \\
& + K[\mathbb{E}[\bar{M}_n^2] + \mathbb{E}[\bar{P}_n^2]]\Delta t + c_B\Delta t + o(\Delta t),
\end{aligned}$$

where $K = \max\{|c_B\alpha + k_P + 2k_P^2\Delta t - 2c_D|, |c_B\alpha + k_P + 2\gamma_P^2\Delta t - 2\gamma_P|\}$. Now the proof can be completed in an analogous way to that of Lemma A.1. $\square$

References

1. Ball, K., Kurtz, T.G., Popovic, L., Rempala, G.: Asymptotic analysis of multiscale approximations to reaction networks. Ann. Appl. Probab. **16**, 1925–1961 (2006)

2. Bundschuh, R., Hayot, F., Jayaprakash, C.: The role of dimerization in noise reduction of simple genetic networks. J. Theor. Biol. **220**, 261–269 (2003)
3. Deuflhard, P., Huisinga, W., Jahnke, T., Wulkow, M.: Adaptive discrete Galerkin methods applied to the chemical master equation. SIAM J. Sci. Comput. **30**, 2990–3011 (2008)
4. Engblom, S.: Spectral approximation of solutions to the chemical master equation. J. Comput. Appl. Math. **229**, 208–221 (2009). doi:10.1016/j.cam.2008.10.029. http://portal.acm.org/citation.cfm?id=1534933.1535047
5. Ethier, S.N., Kurtz, T.G.: Markov Processes: Characterization and Convergence. Wiley, New York (1986)
6. Gadgil, C., Lee, C.H., Othmer, H.G.: A stochastic analysis of first-order reaction networks. Bull. Math. Biol. **67**, 901–946 (2005)
7. Gillespie, D.T.: A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. J. Comput. Phys. **22**, 403–434 (1976)
8. Gillespie, D.T.: Exact stochastic simulation of coupled chemical reactions. J. Phys. Chem. **81**, 2340–2361 (1977)
9. Gillespie, D.T.: The chemical Langevin equation. J. Chem. Phys. **113**, 297–306 (2000)
10. Hairer, E., Nørsett, S., Wanner, G.: Solving Ordinary Differential Equations I: Nonstiff Problems. Springer, Berlin (1993)
11. Hellander, A., Lötstedt, P.: Hybrid method for the chemical master equation. J. Comput. Phys. **227**, 100–122 (2007)
12. Intep, S., Higham, D.J.: Zero, one and two-switch models of gene regulation. Discrete Contin. Dyn. Syst. Ser. B **14**, 495–513 (2010)
13. Intep, S., Higham, D.J., Mao, X.: Switching and diffusion models for gene regulation networks. Multiscale Model. Simul. **8**, 30–45 (2009)
14. Jahnke, T.: An adaptive wavelet method for the chemical master equation. SIAM J. Sci. Comput. **31**, 4373–4394 (2010)
15. Kepler, T., Elston, T.: Stochasticity in transcriptional regulation: origins, consequences, and mathematical representations. Biophys. J. **81**(6), 3116–3136 (2001)
16. Khanin, R., Higham, D.J.: Chemical master equation and Langevin regimes for a gene transcription model. Theor. Comput. Sci. **408**(1), 31–40 (2008)
17. Kurtz, T.G.: Strong approximation theorems for density dependent Markov chains. Stoch. Process. Appl. **6**(3), 223–240 (1978). doi:10.1016/0304-4149(78)90020-0. http://www.sciencedirect.com/science/article/B6V1B-45FCSKW-46/2/7684142af0702406b0f7f7b824911b26
18. Kurtz, T.G.: Approximation of Population Processes. SIAM, Philadelphia (1981)
19. Lipniacki, T., Paszek, P., Brasier, A., Luxon, B., Kimmel, M.: Stochastic regulation in early immune response. Biophys. J. **90**(3), 725–742 (2006)
20. Lipniacki, T., Paszek, P., Marciniak-Czochra, A., Brasier, A.R., Kimmel, M.: Transcriptional stochasticity in gene expression. J. Theor. Biol. **238**(2), 348–367 (2006)
21. MacNamara, S., Burrage, K., Sidje, R.B.: Multiscale modeling of chemical kinetics via the master equation. Multiscale Model. Simul. **6**, 1146–1168 (2008)
22. Paszek, P.: Modeling stochasticity in gene regulation: characterization in the terms of the underlying distribution function. Bull. Math. Biol. **69**, 1567–1601 (2007)
23. Paulsson, J.: Models of stochastic gene expression. Phys. Life Rev. **2**, 157–175 (2005)
24. Swain, P.S., Elowitz, M., Siggia, E.D.: Intrinsic and extrinsic contributions to stochasticity in gene expression. Proc. Natl. Acad. Sci. USA **99**(20), 12795–12800 (2002)
25. Szpruch, L., Higham, D.: Comparing hitting time behavior of Markov jump processes and their diffusion approximations. Multiscale Model. Simul. **8**, 605 (2010)
26. Thattai, M., van Oudenaarden, A.: Intrinsic noise in gene regulatory networks. Proc. Natl. Acad. Sci. USA **98**(15), 8614–8619 (2001)
27. Wilkinson, D.J.: Stochastic Modelling for Systems Biology. Chapman & Hall/CRC Press, London/Boca Raton (2006)
28. Yin, G., Zhu, C.: Hybrid Switching Diffusions: Properties and Applications. Springer, Berlin (2009)