

Stochastic differential equations in modeling gene regulatory networks

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Abstract

Genetic regulatory networks, or GRNs, are made up of genes, proteins, and regulatory factors that control how cells work. Most of the time, traditional fixed models cannot explain how gene expression is naturally random because of changes in molecules and noise in the surroundings. Stochastic differential equations (SDEs) are a strong way to model this kind of variation, which lets us give more accurate descriptions of network stability, regulatory delays, and transcriptional bursts. SDE-based methods help us understand genetic diversity, stability, and cellular decision-making better by adding noise to dynamic models.

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1. Introduction

Gene regulatory networks (GRNs) are what make cells work. They control gene expression by coordinating how DNA, RNA, proteins, and signaling molecules interact with each other [1, 2]. These networks manage important biological processes like how cells differentiate, grow, and change in response to environmental cues. Modelling GRNs is an important part of systems biology because it lets us guess how cells will behave and figure out what causes normal and abnormal states [3, 4, 5]. In the past, GRNs were shown using fixed models, mostly ordinary differential equations (ODEs), which show how chemical concentrations change over time assuming that dynamics are continuous and predictable [6]. ODE-based models work well for big groups of molecules, but

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they don't always take into account how gene expression is discrete and random at the single-cell level. There is stochasticity because of chance chemical interactions and outside forces like changing cellular surroundings [7, 8].

2. Mathematical Foundations of Stochastic Differential Equations (SDEs)

2.1. Comparison with ordinary differential equations (ODEs)

Ordinary differential equations describe the fixed paths of system variables, given that the dynamics are smooth and predictable. SDEs, on the other hand, include stochastic noise and pick up on the random changes that happen when molecules interact [9, 10]. An ODE shows how a state variable changes over time based on function derivatives.

$$\frac{dx(t)}{dt} = f(x(t), t), \quad x(0) = x_0 \quad (1)$$

If $f(x, t)$ is Lipschitz continuous in x and measurable in t , then a unique solution exists.

SDEs are more general than ODEs because they include random driving terms from stochastic processes.

$$dX_t = f(X_t, t)dt + g(X_t, t)dW_t \quad (2)$$

A Wiener process models Brownian motion with time-varying, Gaussian-distributed steps that are separate from each other.

$$W_t \sim N(0, t), \quad W(t+s) - W(t) \sim N(0, s) \quad (3)$$

Stochastic increments have no mean and a variance that is equal to the amount of time that has passed. This makes sure that the data is random:

$$E[dW_t] = 0, \quad E[(dW_t)^2] = dt \quad (4)$$

The stochastic system becomes simpler to standard deterministic differential equations when the diffusion term is taken out:

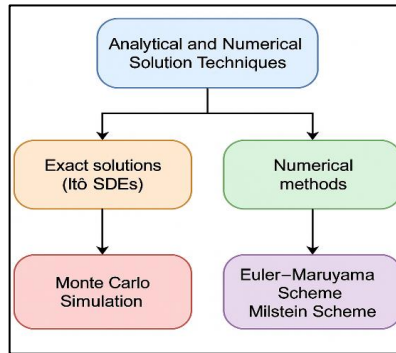
$$\text{If } g(X_t, t) = 0, \text{ then SDE reduces to ODE.}$$

Adding dW_t introduces randomness into trajectories $\rightarrow$ stochastic paths. The Itô integral formalises random accumulation using Riemann sums with Wiener steps.

$$\int_0^t g(X_s, s)dW_s = \lim(n \rightarrow \infty) \frac{\sum g(X_{tk}, tk)}{(W_{tk+1} - W_{tk})} \quad (5)$$

2.2. Analytical and numerical solution techniques

Analytical answers to SDEs are not common and usually only come from simple models. Figure 1 illustrate numerical methods like the Euler–Maruyama and Milstein schemes get close to paths, which lets us simulate random gene dynamics where it's not possible to find closed-form solutions mathematically [11, 12].

**Figure 1****Architecture of Analytical and Numerical Solution Techniques for SDEs**

For the SDE with the right growth/regularity and no border flux, the density (x, t) of Mt meets the Fokker–Planck PDE.

$$dX_t = f(X_t, t)dt + g(X_t, t)dW_t \quad (6)$$

This stochastic differential equation models dynamics with deterministic drift f and random diffusion $g dW_t$.

$$d\varphi(X_t) = \varphi'(X_t)dX_t + \left(\frac{1}{2}\right)\varphi''(X_t)g^2(X_t, t)dt \quad (7)$$

Applying Itô's Lemma gives differential for test function φ , including drift and diffusion contributions.

$$\frac{d}{dt}E[\varphi(X_t)] = E\left[\varphi'(X_t)f(X_t, t) + \left(\frac{1}{2}\right)\varphi''(X_t)g^2(X_t, t)\right] \quad (8)$$

Taking expectations eliminates stochastic integral term, leaving deterministic expression for time evolution of expectations.

$$E[\varphi(X_t)] = \int \varphi(x)p(x, t)dx \quad (9)$$

Expectation written as integral over density $p(x, t)$, linking probabilistic description with analytic PDE.

$$\frac{d}{dt} \int \varphi(x)p(x, t)dx = \int \varphi(x)L * p(x, t)dx \quad (10)$$

Integration by parts shifts derivatives onto coefficients, revealing adjoint operator structure involving f and g .

$$\frac{\partial p(x, t)}{\partial t} = -\frac{\partial}{\partial x}(f(x, t)p(x, t)) + \frac{\left(\frac{1}{2}\right)\partial^2}{\partial x^2(g^2(x, t)p(x, t))} \quad (11)$$

Since equality holds for all smooth φ , density satisfies derived Fokker–Planck partial differential equation.

$$p(x, 0) = \delta(x - x_0), \quad p(x, t) \geq 0, \quad \int p(x, t)dx = 1$$

Initial and boundary conditions ensure unique solution: normalization, positivity, and vanishing boundary probability flux.

3. Modeling Gene Regulatory Networks (GRNs)

3.1. Structure and dynamics of GRNs

GRNs are made up of nodes that represent genes and proteins and are linked by regulatory interactions. Their movements include feedback loops, activation, and repression, and they control how genes are expressed, how cells respond, and how new traits appear in biological systems.

Node Definition:

$$\text{Let } G = \{g1, g2, \dots, gn\} \text{ represent genes}$$

Regulatory Function:

$$Ri = f(gj, pk, \dots)$$

Interaction Graph:

$$GRN = (V, E), \quad V = \frac{\text{genes}}{\text{proteins}}$$

State Vector:

$$X(t) = [x1(t), x2(t), \dots, xn(t)]^T, xi(t)$$

Deterministic Law:

$$\frac{dxi}{dt} = Fi(X(t)), \quad i = 1, \dots, n \quad (12)$$

Boolean Approximation:

$$xi(t + 1) = H(\sum wjk xj(t) - \theta i) \quad (13)$$

Dynamical System Property:

Existence of fixed points:

$$X * s. t. Fi(X *) = 0 \quad (14)$$

Linearization:

$$X(t + \Delta t) \approx X * + J(X *)(X(t) - X *) \quad (15)$$

3.2. Deterministic ODE-based GRN models

GRNs are described by ODE-based models that use continuous equations to show the average amounts of molecules over time. They help us understand stability, cycles, and feedback processes, but they don't explain how random changes in gene expression events can happen.

Transcription Dynamics:

$$\frac{dx}{dt} = \alpha - \beta x, \quad \alpha = \text{synthesis}, \beta = \text{degradation}.$$

Protein Dynamics:

$$\frac{dy}{dt} = \gamma x - \delta y \quad (16)$$

Hill Function Definition:

$$f(x) = Vmax \frac{x^n}{(Kn + x^n)} \quad (17)$$

Step 4: Repression Function:

$$f(x) = \frac{v_{max}}{\left(1 + \left(\frac{x}{K}\right)^n\right)} \quad (18)$$

Step 5: Two-Gene Toggle Switch:

$$\frac{dx}{dt} = \frac{\alpha_1}{(1+y^n)} - \beta_1 x \quad (19)$$

Step 6: Two-Gene Toggle Switch (cont):

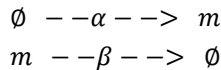
$$\frac{dy}{dt} = \frac{\alpha_2}{(1+x^m)} - \beta_2 y \quad (20)$$

3.3. Role of stochasticity in gene expression

Gene expression changes because of random chemical events, which is called stochasticity.

Theorem 1 (Intrinsic noise: $\Rightarrow$ Poisson fluctuations)

Model:



Let $P_{n(t)} = \Pr\{m(t) = n\}$. The Chemical Master Equation (CME) is:

$$\frac{dP_n}{dt} = \alpha P_{\{n-1\}} + \beta(n+1)P_{\{n+1\}} - (\alpha + \beta n)P_n, n \geq 0, P_{\{-1\}} = 0$$

Stationary solution:

At steady state,

$$\alpha P_{\{n-1\}}^* + \beta(n+1)P_{\{n+1\}}^* = (\alpha + \beta n)P_n^* \quad (21)$$

A sufficient detailed balance relation:

$$\alpha P_n^* = \beta(n+1)P_{\{n+1\}}^* \Rightarrow P_{\{n+1\}}^* = \left(\frac{\alpha}{\beta(n+1)}\right) P_n^* \quad (22)$$

Iterating gives:

$$P_n^* = \left(\frac{\left(\frac{\alpha}{\beta}\right)^n}{P_0} n!\right) \quad (23)$$

Theorem 2 (Extrinsic noise inflates fluctuations: Poisson mixtures are over dispersed)

Model:

Let production rate be random A (extrinsic variability), constant per cell.

Then $\lambda = A/\beta$, and conditional distribution: $m | \lambda \sim \text{Poisson}(\lambda)$.

Law of total variance:

$$\begin{aligned} E[m] &= E[E[m | \lambda]] = E[\lambda]. \\ \text{Var}(m) &= E[\text{Var}(m | \lambda)] + \text{Var}(E[m | \lambda]) \\ &= E[\lambda] + \text{Var}(\lambda). \end{aligned}$$

4. Result Discussion

It is important to include randomness in biological systems, as shown by the comparison of model fit and predictive performance between deterministic ODE and stochastic differential equation (SDE) methods. With RMSE values of 24.6 for mRNA and 38.1 for protein and a negative log-likelihood (NLL) of 2.91, the deterministic ODE model makes more mistakes. It models how the system works in a general way, but it's not flexible enough to model changes that happen often in gene expression. Its poor predictive accuracy (R^2 of 71.2%) shows that it has this problem.

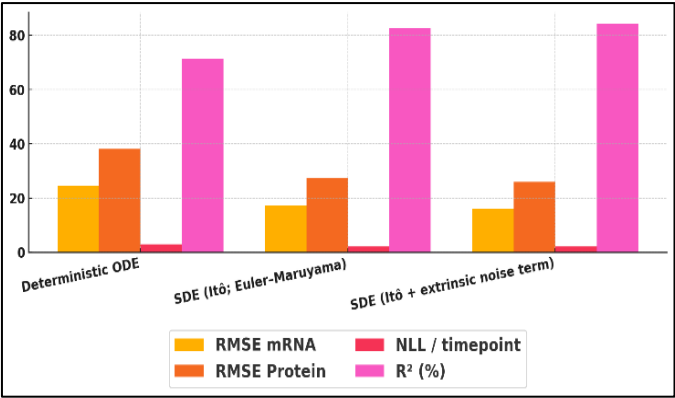


Figure 2
Model Performance Metrics Comparison

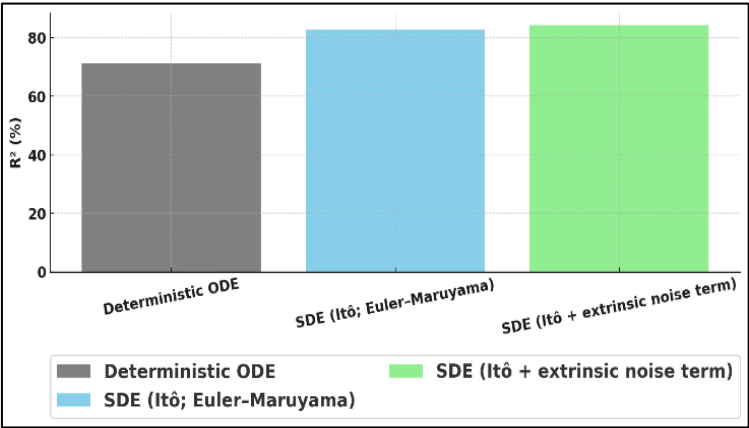


Figure 3
R² Performance Breakdown by Model

However, the SDE model does a much better job by adding random factors. It lowers the RMSE to 17.3 for mRNA and 27.5 for protein, and it also

lowers the NLL to 2.21. This leads to a higher R^2 of 82.8%, which means that the predictions are more in line with the actual data. In addition, the performance is at its best when outside noise is added to the Itô SDE system. The RMSE values go down even more, to 16.1 and 25.9. The NLL number goes up to 2.09, and R^2 goes up to 84.3%. This shows that modelling both internal and extrinsic noise gives a more accurate picture of biological variation. Figure 2 shows even better results when extraneous noise is added. This shows how important stochasticity is for making gene regulatory network models more accurate at making predictions. Figure 3 shows improved R^2 across stochastic models.

5. Conclusion

Stochastic differential equations are a strong way to model the internal and external noise that causes gene control networks to change. In contrast to fixed models, SDEs accurately show the popping, switching, and random processes that create genetic variation. Their skill at balancing noise with regulatory stability helps us learn more about how cells decide what to do, how strong they are, and how flexible they are. SDE-based methods improve systems biology by combining theoretical knowledge with numerical modeling. They make predictions more accurate and give us a better understanding of how complex DNA control processes work.

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