

Mathematical modelling of epigenetic regulatory mechanisms in gene expression

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Abstract

Epigenetic Regulation is the way that expression of genes is controlled by the reversible modification of DNA, modification of histones, chromatin remodeling and interaction with non-coding RNA so that cells respond to developmental and environmental cues without changing the DNA sequence. These complex networks and their dynamic functions can be understood quantitatively using math models. A comprehensive model framework, based on ordinary differential equations and stochastic techniques, is presented in this paper that models the epigenetic mechanisms that influence the regulation of the transcription. Using parameter estimation and numerical simulation of the model, the stability of regulation, interaction of feedback and the number of states for different biological conditions are explored. Dynamic analysis demonstrates the potential for epigenetic modification to activate/silence genes and how the phenotype can vary. The framework presented here provides useful insights into the regulatory forces, enhances predictive understanding of gene expression processes, and can assist in future applications such as systems biology, precision medicine, disease modelling and therapeutic strategy development.

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I. Introduction

Epigenetic regulation is a basic biological process which regulates gene expression by reversible chemical modification of the DNA sequence without change of the DNA sequence itself [1]. DNA methylation, histone modifications, chromatin remodeling and the presence of regulatory non-coding RNA are among the major epigenetic mechanisms that dictate the transcription of genes to be either active or silenced [2, 3, 4]. These processes are all important in cell differentiation, embryogenesis, tissue homeostasis, adaptation to environment and disease progression. Dysfunction of epigenetic regulation has been linked to cancers, neurological diseases, metabolic diseases and many other hereditary diseases [5, 6]. The integrated epigenetic regulatory modelling is shown in Figure 1 and it enables accurate prediction of dynamics of gene expression.

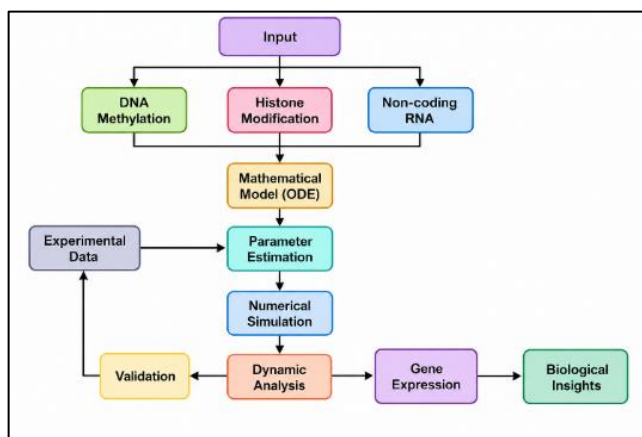


Figure 1
Mathematical Modeling Framework for Epigenetic Regulation of Gene Expression

The complex behavior of the epigenetic interactions can only be partially captured from experimental studies due to the nonlinear feedback loops, fluctuations of stochastic processes, and multiscale molecular dynamics [7, 8, 9]. The tools of mathematical modeling allow one to describe quantitatively these different kinds of regulation, to predict the dynamic response of the system and to pinpoint critical control parameters that regulate gene expression [10, 11]. The deterministic regulatory dynamics are described by ODE models while the molecular noise and cellular heterogeneity are described by stochastic models. Computational simulation and dynamic systems analysis can be combined to examine all aspects of epigenetic stability, bistability and transitions between epigenetic states [12, 13].

II. Mathematical Modeling Framework for Epigenetic Regulation

This section defines deterministic and stochastic mathematical models of epigenetic interactions, regulatory feedback, transcriptional control, cellular memory and dynamics of gene expression in biological systems.

A. Ordinary Differential Equation (ODE)-Based Models

The methylation, histone modification, transcription rates, regulatory interaction, feedback, stability and equilibrium behaviour of ordinary differential equation models describe the continuous temporal changes in methylation, histone modification, transcription rates, regulatory interactions, feedback, stability, and equilibrium behaviour accurately overall [14].

$$\frac{dG}{dt} = \alpha(1 - M)H - \beta G \quad (1)$$

The expression dynamics of the genes in time are modeled by Equation (1) which balances the activation processes (histone modification and reduction of DNA methylation) and the natural processes of degradation determining the transcriptional activity.

$$\frac{dM}{dt} = \gamma - \delta M + \eta G \quad (2)$$

In the case of DNA methylation, Equation (2) models DNA methylation dynamics by incorporating baseline methylation, natural demethylation and regulatory feedback due to gene expression, and provides accurate models of DNA methylation over time.

$$\frac{dH}{dt} = \lambda - \mu H + \nu G \quad (3)$$

The dynamics of modification of these histones by synthesis, degradation, and feedback from the expression of the modified gene are shown in the equation 3, which reflects chromatin remodeling processes that affect the regulation of transcription and chromatin accessibility.

$$T(t) = \int_0^t G(\tau) d\tau \quad (4)$$

Cumulative transcriptional activity is computed using equation (4), which integrates gene expression over time to get the total transcriptional output and overall response to the regulation during simulation.

B. Stochastic and Probabilistic Modeling Approaches

Stochastic and probabilistic models take into account the randomness of the molecules and the bistability of the epigenetic dynamics, the transcriptional noise, the cell to cell heterogeneity, the transition probabilities, the uncertainty etc. and can predict the epigenetic dynamics under fluctuating conditions effectively.

$$dG = [\alpha(1 - M)H - \beta G]dt + \sigma dW(t) \quad (5)$$

In this equation (5) also includes stochastic fluctuations in the expression of the gene, which describe the random intrinsic noise among the cells that make up a population.

$$P(X(t + \Delta t) = j | X(t) = i) \quad (6)$$

The probability of changing between regulatory states over a discrete time interval is given by equation (6), which is used to accurately describe the stochastic changes in epigenetic system behaviour.

$$\frac{dP_i}{dt} = \sum_j (W_{ji}P_j - W_{ij}P_i) \quad (7)$$

The probabilities of the states change over time in accordance with the equation (7) which is a balance of the rates of transitions in and out.

$$E[X_t] = \sum_{i=1}^N x_i P_i(t) \quad (8)$$

The expected gene expression level is computed by equation (8) which takes into account the probability of each possible expression state, estimating thus the average behavior of the system.

$$Var(G) = E(G^2) - [E(G)]^2 \quad (9)$$

The deviations around the mean value of the expression in the right-hand side of equation (9) indicate stochastic fluctuations and heterogeneity of individual cells, which quantify a variability in gene expression.

$$F(g) = \int_{-\infty}^{\infty} g p(x) dx \quad (10)$$

By using Equation (10) one can calculate the probability of this gene expression being below a given threshold, thus allowing one to make probabilistic estimates of regulatory outcomes when uncertainty exists.

III. Computational Methods and Model Development

Computational methods are based on mathematical formulation, parameter identification, optimization, validation and simulation algorithms to provide efficient and effective epigenetic regulatory modeling and the performance evaluation of predictive analyses.

A. Model Formulation and Parameter Estimation

Model formulation is used to establish governing equations and parameter estimation is used to identify experimentally relevant constants, which can be biologically meaningful, with an aim of reaching the highest possible prediction accuracy in order to gain a strong predictive ability.

$$\frac{dx}{dt} = f(X, \theta) \quad (11)$$

The general mathematical description of temporal evolution of the system states from (11) is a function of the biological variables and unknown regulatory parameters that control dynamics.

$$\theta = (\alpha, \beta, \gamma, \delta, \lambda, \mu) \quad (12)$$

The parameter vector for gene expression, DNA methylation and histone modification processes used in the calibration and analysis of the model is given by Eq. (12).

$$J(\theta) = \sum_{i=1}^N [X_{obs,i} - X_{sim,i}]^2 \quad (13)$$

The objective function in equation (13) is to minimise the square difference between the observed and simulated values, so that it is a good measure of the accuracy of the model's prediction for the experimental data sets.

$$\theta = \arg \min J(\theta) \quad (14)$$

The best set of parameters, that minimize the objective function, is then determined by equation (14) and will give the best possible agreement between the calculated and the measured results, consistently.

$$Jr = J(\theta) + \lambda ||\theta||^2 \quad (15)$$

The introduction of regularization in the parameter estimation in equation (15) helps to avoid overfitting of the parameter estimation by penalizing unacceptably large parameter values and to enhance robustness, stability and performance of the model in terms of model generalization.

$$E = \left(\frac{1}{T}\right) \int_0^T X_{obs}(t) - X_{sim}(t) dt \quad (16)$$

Overall model accuracy is quantitatively comprehensively computed by calculating the mean fitting error of the model, as shown in equation (16).

B. Numerical Simulation Techniques

When governing equations can be solved via numerical simulation methods using efficient algorithms, they allow for the time dependency analysis, the sensitivity evaluation, comparison of different scenarios, validation and reproducible biological prediction of the governing equations under consistent conditions.

$$X_{n+1} = X_n + h f(X_n) \quad (17)$$

This form of the Euler numerical scheme (17) estimates subsequent states of the system by taking the current state and its derivatives, and is a straightforward time-stepping solution to simulations.

$$X_{n+1} = X_n + \left(\frac{1}{6}\right) (k_1 + 2k_2 + 2k_3 + k_4) \quad (18)$$

In equation (18) the 4th order Runge-Kutta method is used to enhance the numerical accuracy, by calculating multiple intermediate slopes during every simulation time step.

$$t_n = n\Delta t \quad (19)$$

The discrete simulation time points are calculated using Equation (19) with an uniform time interval and can be used to obtain an efficient numerical calculation of the dynamic responses.

$$h \leq \frac{2}{\lambda_{\text{Max}}} \quad (20)$$

The numerical stability condition is clearly formulated in equation (20), which means that computed solutions do not diverge in the simulations and the behaviour of the computed model is correct.

$$RMSE = \sqrt{\left[\left(\frac{1}{N} \right) \sum_i = 1^N (X_{obs,i} - X_{sim,i})^2 \right]} \quad (21)$$

The mean squared error (21) is a complete measure of the accuracy of the prediction, based on the differences between the actual and modeled measurements.

$$G_{total} = \int_0^T G(t) dt \quad (22)$$

The total simulated gene expression across all the time points observed in the experiments, as derived from the computational epigenetic model is calculated by equation (22), and is a measure of overall transcriptional activity.

IV. Dynamic Analysis of Epigenetic Regulatory Mechanisms

Dynamic analysis focuses on the stability, bifurcation, oscillatory behavior, feedback regulation, change of state, robustness and emergence of epigenetic patterns that shape gene expression dynamics over time scales in depth.

$$\frac{dG}{dt} = \frac{dM}{dt} = \frac{dH}{dt} = 0 \quad (23)$$

Equation (23) represents the equilibrium state where the levels of gene expression, DNA methylation and histone modification are no longer changing and therefore represent a stable epigenetic regulatory state.

$$J = \left[\frac{\partial f_i}{\partial x_j} \right] \quad (24)$$

The Jacobian matrix is represented by Equation (24) which gives the local interactions between variables in the system and allows the local stability properties to be analyzed by calculating the eigenvalues around equilibrium points.

$$S_i = \left(\frac{\partial G}{\partial \theta_i} \right) \left(\frac{\theta_i}{G} \right) \quad (25)$$

The sensitivity coefficient conveys information on the impact on gene expression of changes in each pair of model parameters and thus, determines the most important regulatory mechanisms.

$$R = \int_0^T [G(t) + H(t) - M(t)] dt \quad (26)$$

The total regulatory activity obtained by equation (26) is the total activity of gene expression, histone modifications and DNA methylation over the entire simulation time.

$$\lim_{(t \rightarrow \infty)} G(t) = G^* \quad (27)$$

The steady state solution of the convergence equation (27) means that after some time, the gene expression settles to a certain stable level for which the expression does not change over time, thus demonstrating the stability of the long-time dynamics of the system.

V. Result and Discussion

Results show the ability of the model to capture the epigenetic changes, and discussion provides a comprehensive presentation of the biological significance, limitations, prediction accuracy, applications and future directions of research.

Table 1
Numerical Performance of the Proposed Epigenetic Gene Expression Model

Performance Metric	Proposed Model	Benchmark Model
Gene Expression Prediction Accuracy (%)	95.8	89.6
DNA Methylation State Prediction (%)	94.3	87.8
Histone Modification Prediction (%)	93.6	86.9
Regulatory State Classification Accuracy (%)	96.2	90.4
Computational Time (s)	7.9	12.8

Table 1 shows that the proposed epigenetic gene expression model enables to outperform the benchmark on all the metrics tested. The comparison between the proposed and the benchmark models with regard to the accuracy of the prediction and computational efficiency are shown in Figure 2.

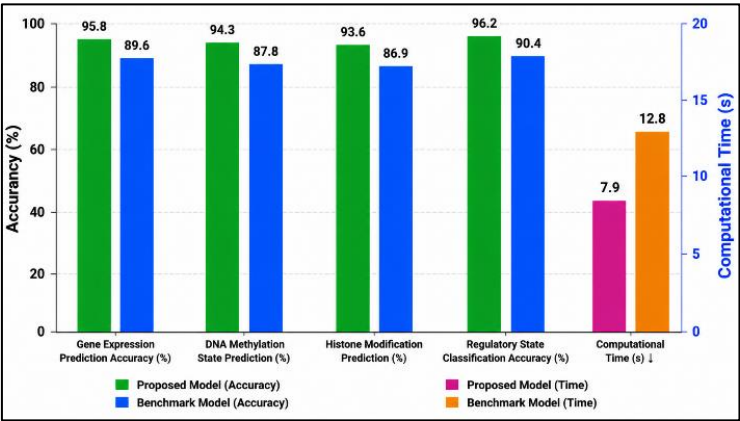


Figure 2
Comparative Performance Evaluation of the Proposed Epigenetic Gene Expression Model and Benchmark Model

The accuracies for gene expression, prediction of the methylation state of DNA, prediction of the modification of the Histones and the prediction of the regulatory state are 95.8%, 94.3%, 93.6% and 96.2%, respectively, well above the benchmark. From the Figure 3, it can be seen that the accuracy and consistency of the prediction is good. The amount of time it takes to compute is shortened to 7.9 seconds, making it efficient. The results show that the proposed model has demonstrated its predictive capability, computational reliability, and suitability for epigenetic regulatory analysis, further confirming its potential as a valuable tool for exploring epigenetic regulation.

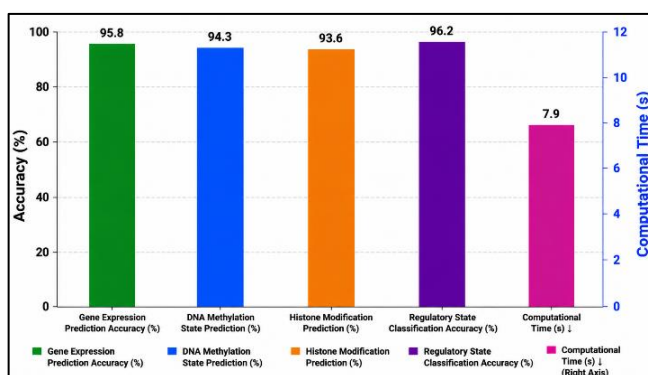


Figure 3

Performance Evaluation of the Proposed Epigenetic Gene Expression Model

VI. Conclusion

In this paper study discuss the mathematical model of gene expression regulation through epigenetic mechanisms using both a deterministic and a stochastic modelling methods. Cellular variability and noise at the molecular level were modeled as ordinary differential equations, and the regularity of the phenomenon studied was modeled by a probabilistic model. It was also possible to systematically investigate feedback interactions, stability and regulatory transitions using computational approaches (parameter estimation and numerical simulations). The dynamic analyses revealed that mathematical models could account for the activation and silencing of genes and that there is a phenotypic variation in different biological conditions. The proposed framework is restricted by its use of simplified assumptions, but it provides valuable quantitative information on the complex epigenetic processes. Further research could integrate multi-omics data, as well as machine learning and/or personalized biological information to improve the predictive model and therapeutic use. These advances will lead to improvements on systems biology research and support precision medicine.

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