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Stochastic simulation methods in the study of cell rhythm

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Abstract. Stochastic simulation methods play a crucial role in the study of cellular rhythms. Based on the characteristics of stochastic algorithms, we can more accurately capture the noise effects existing in biological systems and explore their impact on cell rhythms. The findings from stochastic simulation methods shed light on how cell rhythms operate at the molecular level, and this paper presents them inductively for different algorithm types, enabling a deeper understanding of their characteristics. Furthermore, based on the analysis of existing studies, this paper finds that a stochastic simulation approach that considers spatial heterogeneity and intercellular coupling helps reveal the design principles and functional characteristics of the cellular rhythmic system. However, existing stochastic methods also have limitations, including the arbitrariness of parameters and ignoring spatial features. This paper argues that future improvements should focus on integrating quantitative data, accounting for spatial effects, and increasing computational efficiency. These enhancements will contribute to a comprehensive understanding of the generation of cellular rhythms and their importance in biological processes.

Keywords: circadian rhythm, mathematical modeling, Gillespie algorithm, SDEs, stochastic simulation.

1. Introduction

The biological clock, also known as the circadian clock, is an adaptive mechanism that has evolved in organisms on Earth in response to the alternating cycles of day and night. Under constant external conditions, biological rhythms typically follow a 24-hour period and operate autonomously or with the ability to resist external disturbances [1, 2, 3]. The source of these rhythms lies in the gene regulatory feedback reactions, which occur in nearly every cell that comprises life.

To approach the real intracellular reactions, researchers have chosen to abstractly model specific pathways of the cell rhythm.

In the 1950s, computers began to be applied in scientific research [4]. However, due to hardware limitations at that time, verifying complex models still presented significant challenges. This is mainly because the hardware conditions at that time could not meet the needs of the experimenters for continuous simulation of the coupled ordinary differential equation model. To solve this contradiction, the researchers split the concurrent reactions that occur simultaneously in a short period into several sub-reactions that occur continuously and rapidly for simulation. The product of this attempt is the stochastic simulation method we will discuss.

Different stochastic simulation methods commonly used in the study of cell rhythms will be the focus of detailed discussion in this paper. Specifically, we will review the applications of the Gillespie

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algorithm (Stochastic Simulation Algorithm, SSA) and stochastic differential equation simulations (SDEs) in cell rhythm research over the past five years.

In the following sections, we will delve into an in-depth investigation of the Gillespie algorithm, focusing on its stochastic nature and its ability to accurately capture the dynamics of cell rhythms. Additionally, we will analyze the advantages and limitations of the Gillespie algorithm, including factors such as computational efficiency, accuracy, and applicability in different research contexts. Subsequently, we will shift our focus to the application of stochastic differential equation simulations in the study of cell rhythms. We will explore the mathematical foundations of stochastic differential equations, which allow the incorporation of stochastic factors into the models. We will also assess the effectiveness and advantages of SDE simulations in capturing the inherent randomness and dynamic characteristics of cell rhythms.

2. Gillespie algorithm in cellular rhythm research

As one of the most important stochastic simulation algorithms in history, the Gillespie algorithm has a simple core concept and provides reliable effectiveness for experimentalists. In cases where reaction networks are relatively simple, one can solve the governing equations analytically using computers. However, when the situation becomes more complex (e.g., with dozens of different reactions occurring simultaneously), brute force methods are impractical. In contrast, the Gillespie algorithm allows us to simulate the exact dynamics described by the continuous master equation. By discretizing the system through time-division-based stochastic simulation, a single simulation trajectory represents an exact sample of the probability mass function of the master equation solution.

We can represent the algorithm using the following figure 1:

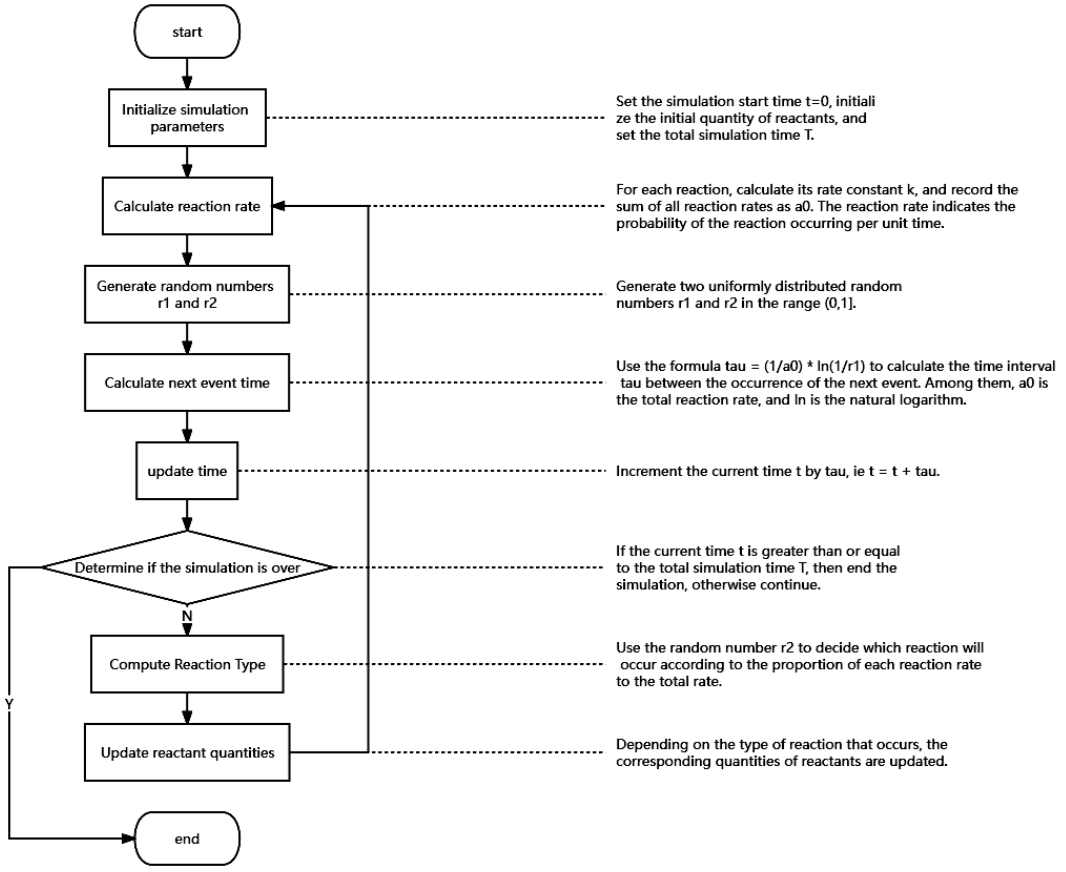

Figure 1. Gillespie algorithm flowchart.

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The discretization of the algorithm is based on individual reaction events rather than a given time step (modeling based on events rather than time). This means that any simulation trajectory faithfully follows the dynamics of the master equation. However, due to the stochastic nature of the algorithm's simulation trajectories, multiple iterations of the above steps are required to obtain the most representative reaction path.

Certainly, due to the different fundamental concepts of the algorithm, deterministic models dominated by the governing equations and stochastic models dominated by the Gillespie algorithm differ significantly in parameter selection as well. B. Xu, H.-W. Kang, and others compared and analyzed the resistance to noise of oscillatory patterns in deterministic and stochastic models based on the dynamics of the Cdc42 GTPase oscillation in yeast [5]. Through numerical simulations and analysis techniques, they observed significant differences between deterministic and stochastic models within the parameter range of interest.

It is worth noting that deterministic models converge to stable limit cycles, while stochastic simulations indicate the existence of noise-induced limit cycles and quasi-cycles. Near the bifurcation point of an infinite period, the deterministic model exhibits sustained oscillations, while the stochastic trajectories initially exhibit oscillatory patterns but tend to approach deterministic steady states. Furthermore, within the low copy number regime, the stochastic model exhibits a transition from oscillatory to stable behavior. In summary, the research by Xu, Kang, and Jilkine reveals the role of stochasticity in Cdc42 oscillations in yeast. Their study demonstrates that through the Gillespie algorithm and its stochastic modeling capabilities, valuable insights into the complex dynamics of cell oscillations can be obtained. Understanding the interplay between determinism and stochasticity is crucial for unraveling the biological oscillatory mechanisms and their functional significance.

R. Zhang, D. Gonze, and others explored the behavior of plant cell circadian rhythms using the Gillespie algorithm embedded in xpp-auto to simulate various aspects [6, 7]. They investigated the effects of molecular noise, light-dark cycles, multiple light inputs, intercellular coupling, and mutations on the variability of rhythm period, phase, and amplitude. Additionally, they utilized discrete simulation methods to capture the stochastic nature of biochemical reactions and studied the robustness of plant circadian rhythms under different conditions. The study observed that light-dark synchrony enhances the robustness of circadian rhythms compared to constant conditions (DD or LL). Multiple light inputs and intercellular coupling improve the robustness of rhythms to noise. Noise leads to phase diffusion, resulting in cells gradually becoming desynchronized under constant conditions.

The Gillespie algorithm provides essential tools for Zhang et al.'s investigation of plant circadian rhythms. By explicitly considering the stochastic nature of biochemical reactions, the algorithm captures the influence of molecular noise on circadian rhythm dynamics. The simulation results demonstrate that discretization provides a more comprehensive understanding of oscillatory behavior, revealing the behavior of mutants and the role of intercellular coupling. It enables researchers to explore different parameters and conditions to gain insights into the robustness and precision of plant circadian rhythms.

3. SDEs in cellular rhythm research

Stochastic Differential Equations (SDEs) are mathematical tools used to describe dynamic systems with inherent randomness. By introducing stochastic terms, SDEs offer a flexible approach to modeling uncertainties and noise in the system. These stochastic terms appear as stochastic differentials in the equations, working alongside deterministic differentials to describe the system's variations [8].

SDEs possess the following characteristics: Firstly, they provide a more accurate representation of complex phenomena in the real world and offer a detailed description of system dynamics. Secondly, the evolution of SDEs has a probabilistic nature, where the same initial conditions can lead to different trajectories. Additionally, SDEs are typically simulated and solved using methods such as Itô calculus, which offers mature analytical techniques. Overall, SDEs provide researchers with a powerful tool for understanding and analyzing dynamic systems with inherent randomness.

S. Miura and T. Shimokawa investigated a cell rhythm model in fruit flies and compared the dynamic outcomes of the Stochastic Simulation Algorithm (SSA) with those of the Chemical Langevin Equation

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(a type of SDE) [9]. They evaluated the system behavior using the oscillation period of the circadian rhythm and the decay time constant of the ensemble-averaged waveform as quantitative metrics. The results showed that the oscillation period of the circadian rhythm was similar in both the deterministic model and the two stochastic methods, regardless of the system size. However, some differences were observed in the decay time constant of the ensemble-averaged waveform, which reflects the oscillation coherence in the presence of noise. Particularly for small system sizes, the Chemical Langevin Equation demonstrated a more significant impact of molecular noise compared to the direct method. The study also indicated that the Chemical Langevin Equation is more suitable for simulating systems with characteristics similar to real biological systems, such as small volume and low molecule numbers in single-cell systems.

As a commonly used type of SDE, the Langevin equation provides a systematic quantification approach for incorporating stochastic effects into mathematical models. By introducing noise intensity as a function of state and time, the Chemical Langevin Equation accurately describes biochemical reactions with low molecular counts. It contributes to a better understanding of the influence of randomness on circadian rhythm generation and provides insights into system behavior in the presence of molecular noise.

In summary, SDEs, including the Chemical Langevin Equation, are powerful tools for studying dynamic systems with inherent randomness. They can capture the probabilistic nature of system dynamics and provide a more accurate representation of real-world phenomena offers valuable insights. These insights have enhanced the understanding of the impact of stochasticity on circadian rhythm generation and provide a comprehensive view of system behavior in the presence of molecular noise.

4. Conclusion

Stochastic simulation methods have played a crucial role in advancing our understanding of cell rhythm dynamics. In this paper, we have explored the application of stochastic simulation methods in cell rhythm research and discussed their limitations and potential future improvements.

Stochastic simulation methods, such as the Gillespie algorithm and the Chemical Langevin Equation, enable researchers to capture the influence of molecular noise on cell rhythm generation. These methods provide valuable insights into the stochastic effects on the behavior of biological systems with low molecule numbers. By incorporating noise intensity as a function of state and time, the Chemical Langevin Equation offers a more accurate representation of intracellular biochemical reactions.

One key advantage of stochastic simulation methods is their ability to model complex biological systems with spatial and temporal heterogeneity. These methods have been applied to investigate the dynamics of circadian rhythms, where the interplay between cellular circuits, synchronization, and robustness to noise is crucial. By incorporating spatial features and intercellular coupling mechanisms, stochastic simulation methods help uncover the design principles and functional characteristics of circadian rhythms.

However, we must acknowledge the limitations of current stochastic simulation methods. One common criticism is the arbitrariness of the choice of equations and parameter values. While these models provide qualitative insights into cell rhythm dynamics, they lack quantitative data such as precise parameter values and absolute concentrations. Furthermore, most models neglect spatial aspects and assume molecular-free diffusion within cells, which may not accurately represent the crowding and high-order nature of cellular processes.

To address these limitations, future improvements in stochastic simulation methods can focus on several aspects. Firstly, efforts should be made to incorporate more quantitative data, such as accurate parameter values, into the models. This will enable more precise quantitative predictions and facilitate the comparison of simulation results with experimental measurements. Secondly, incorporating spatial features and diffusion processes into stochastic simulations will provide a more realistic representation of cellular systems. This requires considering factors such as spatial organization, local interactions, and diffusion rates within cells. Lastly, further advancements in the analysis of large-scale stochastic state

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spaces and the development of efficient computational algorithms will allow us to explore larger and more complex biological systems.

In conclusion, stochastic simulation methods play a significant role in advancing our understanding of cell rhythm dynamics. While current methods have limitations, ongoing improvements in integrating quantitative data, spatial features, and efficient computational algorithms offer promising directions for future stochastic simulation methods. These advancements will contribute to a more comprehensive understanding of cell rhythm generation and its significance in biological processes.

References

[1] Dunlap J.C., Loros J.J., Decoursey P.J., (2004). Chronobiology: Biological Timekeeping, Sinauer Associates Inc., Sunderland.

[2] Edmunds L.N. (1987). Cellular and Molecular Bases of Biological Clocks: Models and Mechanisms for Circadian Timekeeping, Springer, New York.

[3] Mairan J. J., (1729). Botanical observation, History of the Royal Academy of Science, 35-36 (in French)

[4] Ceruzzi, P. E. (2003). A History of Modern Computing (pp. 30-32). MIT Press.

[5] Xu, B., Kang, H.-W., & Jilkine, A. (2019). Comparison of Deterministic and Stochastic Regime in a Model for Cdc42 Oscillations in Fission Yeast. Bulletin of Mathematical Biology, 81(5), 1268-1302.

[6] Ermentrout, B., & Mahajan, A. (2003). Simulating, analyzing, and animating dynamical systems: a guide to XPPAUT for researchers and students. Appl. Mech. Rev., 56(4), B53-B53.

[7] Zhang, R., & Gonze, D. (2021). Stochastic simulation of a model for circadian rhythms in plants. Journal of theoretical biology, 527, 110790.

[8] Oksendal, B. (2013). Stochastic differential equations: an introduction with applications. Springer Science & Business Media.

[9] Miura, S., Shimokawa, T., & Nomura, T. (2008). Stochastic simulations on a model of circadian rhythm generation. BioSystems, 93(1-2), 133-140.