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Extrinsic fluctuations in the p53 cycle

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Manuel Eduardo Hernández-García,[1,a)] Mariana Gómez-Schiavon,[2,3,b)] and Jorge Velázquez-Castro[1,c)]

AFFILIATIONS

[1] Facultad de Ciencias Físico Matemáticas, Benemérita Universidad Autónoma de Puebla, Heroica Puebla de Zaragoza 72570, Mexico

[2] Laboratorio Internacional de Investigacion sobre el Genoma Humano, Universidad Nacional Autónoma de México, Santiago de Querétaro 76230, Mexico

[3] Millennium Science Initiative Program, Millennium Institute for Integrative Biology (iBio), Chilean National Agency for Research and Development, Santiago 8331150, Chile

[a)] manuel.hernandezgarcia@viep.com.mx
[b)] mgschiavon@liigh.unam.mx
[c)] **Author to whom correspondence should be addressed:** jorge.velazquezcastro@correo.buap.mx

ABSTRACT

Fluctuations are inherent to biological systems, arising from the stochastic nature of molecular interactions, and influence various aspects of system behavior, stability, and robustness. These fluctuations can be categorized as intrinsic, stemming from the system's inherent structure and dynamics, and extrinsic, arising from external factors, such as temperature variations. Understanding the interplay between these fluctuations is crucial for obtaining a comprehensive understanding of biological phenomena. However, studying these effects poses significant computational challenges. In this study, we used an underexplored methodology to analyze the effect of extrinsic fluctuations in stochastic systems using ordinary differential equations instead of solving the master equation with stochastic parameters. By incorporating temperature fluctuations into reaction rates, we explored the impact of extrinsic factors on system dynamics. We constructed a master equation and calculated the equations for the dynamics of the first two moments, offering computational efficiency compared with directly solving the chemical master equation. We applied this approach to analyze a biological oscillator, focusing on the p53 model and its response to temperature-induced extrinsic fluctuations. Our findings underscore the impact of extrinsic fluctuations on the nature of oscillations in biological systems, with alterations in oscillatory behavior depending on the characteristics of extrinsic fluctuations. We observed an increased oscillation amplitude and frequency of the p53 concentration cycle. This study provides valuable insights into the effects of extrinsic fluctuations on biological oscillations and highlights the importance of considering them in more complex systems to prevent unwanted scenarios related to health issues.

I. INTRODUCTION

Fluctuations are inherent to biological systems, arising from the stochastic nature of molecular interactions, and influence various aspects of system behavior, stability, and robustness. The fluctuations play an even more pivotal role, necessitating thorough consideration in comprehensive analyses.[1–4] These fluctuations can be broadly categorized as intrinsic and extrinsic, with each contributing distinctively to system dynamics.

Intrinsic fluctuations stem from the inherent structure and dynamics of the system, reflecting the probabilistic nature of molecular interactions within biological networks.[5–8] These fluctuations manifest as variabilities in molecular concentrations influencing the emergence of spontaneous oscillations, bistability, and other behaviors observed in biological systems.[1–4]

In contrast, extrinsic fluctuations arise from external factors, such as variations in temperature, pH, nutrient availability, and variations in the concentrations of other chemical species, which can significantly affect system dynamics.[9] Although intrinsic fluctuations have received considerable attention in previous research, the importance of extrinsic fluctuations has garnered increasing recognition. Understanding the interplay between intrinsic and extrinsic fluctuations is crucial for obtaining a comprehensive understanding of biological phenomena because both types of fluctuations can coalesce to shape system behavior in experimental setups and natural environments.[10] It is worth pointing out that properties of