様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

令和　５ 年　 ６ 月 １４ 日現在

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課題番号：１８Ｋ０３４７３

研究課題名（和文）Optimal information processing in biophysical networks

研究課題名（英文）Optimal information processing in biophysical networks

研究代表者
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交付決定額（研究期間全体）：（直接経費）　　3,400,000円

研究成果の概要（和文）：このプロジェクトの目的は、情報を複製する分子の最適な性能を特徴づけることである。生物学で最も重要な例は、DNAのコピーを担当する分子である。我々のプロジェクトは、これらの分子の物理的限界を、速度、精度、散逸の観点から明らかにした。また、分子の性能のばらつきを調べ、このばらつきを利用して分子の機能を理解する方法についても研究した。我々のプロジェクトは理論的なものであったが、実験グループと共同して予測の検証もした。特に、細菌のDNA複製時の速度変動と、生物学で多くの応用があるポリメラーゼ連鎖反応（PCR）を最適化する方法について研究した。

研究成果の学術的意義や社会的意義
From the scientific point of view, our project made significant steps to understand replication of information in biology in a quantitative way. Its application can have a deep societal relevance for understanding genetic diseases and for optimizing widely used techniques such as PCR.

研究成果の概要（英文）：The goal of this project was to characterize the optimal performance of molecules that replicate information. The most important examples in biology are the molecules responsible of copying DNA. Our project has clarified the physical limit of these molecules in terms of their speed, accuracy, and dissipation. We also studied the variability of their performance, and how one can use this variability to understand the functioning of these molecules. Our project was theoretical in nature but we also tested our predictions in collaboration with experimental groups. We studied, in particular, speed variability during bacterial DNA replication and how one can optimize the Polymerase Chain Reaction (PCR), a process that finds numerous applications in biology.

研究分野：Physics

キーワード：Information processing　Polymerization　Kinetic Proofreading　Speed-error tradeoff　Chemical networks　Information theory

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１．研究開始当初の背景 (background at the beginning of the research)

This KAKENHI project aimed at understanding the optimal way of processing biological information by small biophysical systems such as polymerases.

Previously to the beginning of the project, there has been a significant research activity in understanding the performance of information-processing molecular systems, such the proteins that are responsible of replicating DNA, using ideas from non-equilibrium thermodynamics, and in particular of stochastic thermodynamics. In this framework, these proteins are seen as thermodynamic machines that consume chemical energy to improve their speed and accuracy of the copies they produce.

The PI of this project has pioneered the use of non equilibrium thermodynamics to characterize these systems before the beginning of this project. Our main result has been the derivation of universal bounds linking the speed, accuracy, and dissipation of the copying process. These bounds are based on the second law of thermodynamics and are therefore valid independently of the system details.

The theoretical approaches proposed before the beginning of our project considered speed, accuracy, and dissipation as average, deterministic quantities. However, these observables might display significant fluctuations. Characterizing these fluctuations might shed light on the underlying dynamics of these machines.

Moreover, further studies by our group and others attempted at using the existing body of theory to characterize the performance of the actual proteins that replicate DNA. It turned out that these proteins appear to operate far from the theoretically derived physical limit. This discrepancy called for novel approaches to theoretically study the optimal performance of these machines.

２．研究の目的 (purpose of the research)

The purpose of this project has been to understand the performance of information-processing physical systems using ideas of non-equilibrium thermodynamics. In particular, we aimed at addressing the two following questions. Can we characterize the fluctuating behavior (in terms of speed, accuracy, and dissipation) of proteins replicating information? Can we understand the general tradeoffs between speed, accuracy, and dissipation?

To complement our theoretical work, we established collaborations with experimental groups to test the predictions of our theory.

３．研究の方法 (method of research)

Our project used an approach based on non-equilibrium statistical physics to understand the optimal operating regimes for replicating information encoded in DNA. We used a rather diverse range of techniques from this field to answer our research question.

In particular, for the project “Error-speed correlations in biopolymer synthesis” (see point 4.), we used techniques based on stochastic thermodynamics and large deviation theory.

For project “Speed variations of bacterial replisomes” we used an age-structured population model for the density of incomplete genomes in a growing population, and managed to solve this model exactly in some simple cases. In more complex cases, we solved the model numerically using an analogy with stochastic resetting, which is another important tool in contemporary non-equilibrium physics.

Finally, for project “Pareto optimal front of kinetic proofreading” we employed

theoretical and numerical techniques of mathematical optimization theory.

4．研究成果 (research results)

In the following, we will briefly outlined the main research results of our KAKENHI project. The project has led to five publications in high-impact international journals, of which three (marked with *) were lead by our research unit and two were collaborations.

***Error-speed correlations in biopolymer synthesis (Chiuchiù, Tu, Pigolotti, Physical Review Letters, 2019).** In this paper, we extended the theory of error correction in biopolymers to account for random fluctuations. The project was led by Davide Chiuchiu, a previous postdoc in our unit and Co-PI in the project. We studied in particular how the error rate and the copy speed randomly fluctuate when copying a large but finite heteropolymer. Our main finding is that these fluctuations are not independent, i.e. error and speed have, in general, a finite covariance. This covariance can be seen as a ``natural'' tradeoff between error and speed, in the sense that it emerges without having to modify any external parameter. The sign of this covariance can be positive or negative depending on the error correction strategy implemented by the enzyme. This result leads to an experimental prediction, should it be possible in the future to measure the covariance of error and speed in replicating biopolymers.

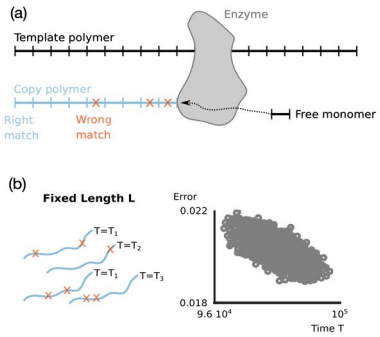

Figure 1: Error-speed correlations in biopolymer synthesis. (a) Scheme of a protein (enzyme) replicating information. (b) correlation between error and time necessary to copy a polymer

Physical Bioenergetics: Energy fluxes, budgets, and constraints in cells (Yang, …, Pigolotti, … , Foster, Proceedings of the National Academy of Sciences, 2021). This collaboration stemmed from a program at the Kavli Institute for Theoretical Physics at UCSB. The goal was to outline how ideas from thermodynamics and energetics can help us understanding biological processes. The PI's contribution to this perspective paper was to present the state of the art of energetics in the context of replication of information in cells.

***Speed variations of bacterial replisomes (Bhat, Hauf, Plessy, Yokobayashi, Pigolotti, Elife 2022).** Replisomes are large protein complexes responsible of copying DNA. We characterized the dynamics of these machines in living bacteria. To quantitatively infer the dynamics of bacterial replisomes, we derived an exact mathematical theory that predicts the density of DNA fragments in a deep sequencing experiment if the replisomes undergo a certain dynamics. Thanks to our theory, we can make statistical inference, i.e. predict the replisome dynamics from the measured DNA abundance distribution. Our main finding is that the speed of replisomes presents wave-like oscillations along the genome. It was previously observed that the bacterial mutation rate present a similar oscillatory pattern along the genome. Our result suggests a dynamical explanation according to which replisomes make more mistakes when their speed is higher.

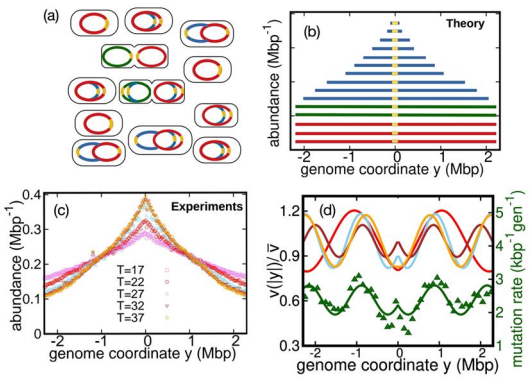

Figure 2: Speed variations of bacterial replisomes. (a) bacteria replicating their genome. (b) Prediction on the abundance of DNA fragments (c) Corresponding experimental measurement. (d) Speed variations of bacterial replisome and mutation rate.

Error-suppression mechanism of PCR by blocker strands (Aoyanagi, Pigolotti, Ono, Toyabe, Biophysical Journal 2023). The Polymerase Chain Reaction (PCR) is one of the most used technique in molecular biology. In this collaborative work, we attempted at using our theory on the optimal performance of proteins replicating information to optimize the performance of PCR. We found a novel regime of operation, where PCR can efficiently operate for a broad range of annealing temperatures.

***Pareto optimal front of kinetic proofreading** (Chiuchiù, **Mondal, Pigolotti, New Journal of Physics 2023).** In this work, we developed a computational method to characterize the optimal speed, error, dissipation of a chemical reaction characterizing a protein copying DNA. Our method revealed that the set of optimal solutions depend on the complexity of the underlying biochemical network. In particular, more complex networks lead to an increase of the performance in terms of speed, accuracy, and dissipation. We also characterized the scaling of these observables along the set of the optimal solutions.

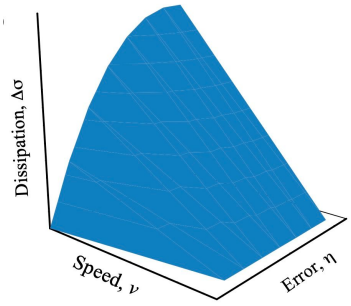

Figure 3: Pareto optimal front between Speed, Error, and Dissipation in kinetic proofreading.

５．主な発表論文等

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１．著者名 X. Yang, M. Heinemann, J. Howard, G. Huber, S. Iyer-Biswas, G. Le Treut, M. Lynch, K. L. Montooth, D. J. Needleman, S. Pigolotti, J. Rodenfels, P. Ronceray, S. Shankar, I. Tavassoly, S. Thutupalli, D. V. Titov, J. Wang, and P. J. Foster	４．巻 118 (26)
２．論文標題 Physical bioenergetics: Energy fluxes, budgets, and constraints in cells	５．発行年 2021年
３．雑誌名 Proc. Natl. Acad. Sci.	６．最初と最後の頁 e2026786118
掲載論文のDOI（デジタルオブジェクト識別子） 10.1073/pnas.2026786118	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 D. Chiuchiu, Y. Tu, S. Pigolotti	４．巻 123
２．論文標題 Error-speed correlations in biopolymer synthesis	５．発行年 2019年
３．雑誌名 Phys. Rev. Lett.	６．最初と最後の頁 38101
掲載論文のDOI（デジタルオブジェクト識別子） 10.1103/PhysRevLett.123.038101	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 D. Chiuchiu, J. Ferrare, S. Pigolotti	４．巻 100
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３．雑誌名 Phys. Rev.	６．最初と最後の頁 62502
掲載論文のDOI（デジタルオブジェクト識別子） 10.1103/PhysRevE.100.062502	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

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2．論文標題 Error-suppression mechanism of PCR by blocker strands	5．発行年 2023年
3．雑誌名 Biophysical Journal	6．最初と最後の頁 1334-1341
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.bpj.2023.02.028	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 －

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1．発表者名 Shrabani Mondal
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3．学会等名 APS March Meeting（国際学会）
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1．発表者名 Simone Pigolotti
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１．発表者名
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１．発表者名
Simone Pigolotti

２．発表標題
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４．発表年
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１．発表者名 Simone Pigolotti
２．発表標題 Speed variations of bacterial replisomes
３．学会等名 PS March Meeting 2023（国際学会）
４．発表年 2023年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考
研究分担者	ＣＨＩＵＣＨＩＵ　Ｄａｖｉｄｅ (CHIUCHIU Davide) (40817491)	沖縄科学技術大学院大学・生物複雑性ユニット・研究員 (38005)	

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関