ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25may1771

Nonequilibrium Thermodynamics and its Role in Biochemical Systems: A Review

Nawal Daamy Resen[1]; Hanaa K Sacheat[2]; Nahida A. Jinzeel[3]

[1,2,3] Department of Chemistry, College of Science, Mustansiriya University, Baghdad-Iraq

Publication Date: 2025/06/01

Abstract: Physical systems that are not in thermodynamic equilibrium but can be sufficiently described by variables that are an extension of the various elements required to explain the system in thermodynamic equilibrium are the subject of thermodynamics. Living systems, it is an open system that are governed by the rules of nonequilibrium thermodynamics. As a result, understanding biological systems from a non-equilibrium thermodynamic perspective is beneficial. We will quickly review the history and current state of nonequilibrium thermodynamics, particularly in biological systems, in this article. We begin by discussing how people first discovered the value of studying biological systems from a thermodynamic standpoint. The evolution of stochastic thermodynamics is then discussed, with a focus on three key concepts: Jarzynski equality, the Crooks fluctuation theorem, and the thermodynamic uncertain relation. We also provide an overview of the current theoretical model for stochastic thermodynamics in biological reaction networks, with a focus on thermodynamic principles and apparatus at nonequilibrium stable state. Finally, two applications and potential avenues for thermodynamic research in biological systems are examined.

How to Cite: Nawal Daamy Resen; Hanaa K Sacheat; Nahida A. Jinzeel (2025) Nonequilibrium Thermodynamics and its Role in Biochemical Systems: A Review. *International Journal of Innovative Science and Research Technology*, 10(5), 2782-2787. https://doi.org/10.38124/ijisrt/25may1771

I. INTRODUCTION

In his book, Erwin Schrödinger outlined the basic physical reasoning underlying cellular activity and asserted that the main factor separating a living cell from a "dead" organism is its ORDER. In a living cell, a variety of biochemical processes take place continuously, methodically, and indefinitely that would not take place in a nonliving organism. A system without living activity, such as a box of gas mixture, quickly enters an inactive, stable, dead thermodynamic equilibrium state when its intrinsic reactions are placed in a fixed environment. This is in contrast to a living system, which maintains an ordered and relatively steady state and never reaches equilibrium. The system's entropy reaches its maximum at this point, and all ordered intrinsic activities cease [1]. Therefore, as Schrödinger noted, living cells exchange materials and energy with the environment, obtain energy and essential nutrients for metabolic reactions, and expel waste and heat as a result of those processes. The system is kept at a low entropy condition by absorbing "negative entropy" from the surroundings, which eliminates the entropy formation from its basic biological activity. Other researchers discovered what is known as the "minimum entropy production principle" for systems that are close to equilibrium. According to this theory, the state with the lowest rate of entropy creation is the stable state (under a thermodynamic force) for sufficiently substantial equilibrium with a linear response to the force. However, certain complex nonequilibrium phenomena cannot be described by this method [2,3]. According to their famous dissipative structure theory [4], systems that are arbitrarily far from equilibrium achieve a nonlinear regime when they are performed in accordance with different thermodynamic factors, surpassing the linear domain that linear response theory represents. In this regime, which can display intricate and well-organized dynamics, the system can be maintained at a fairly constant state by generating entropy and wasting free energy.

II. THE EVOLUTION OF STOCHASTIC THERMODYNAMIC AND NONEQUILIBRIUM STATISTICAL PHYSICS

Advanced statistical mechanics is founded on stochastic theory, in which a stochastic process describes the dynamics of a system [5]. The dynamics of a system at equilibrium is simple variation near the equilibrium position. As previously said, physicists have known how to explain such fluctuation for a long time. . It was challenging for physicists to create universal principles that applied to systems that were endlessly distant from equilibrium, nevertheless, until recently. The so-called Jarzynski equality [6], a collection of fluctuation theorems [7], constrains the probability distribution of entropy production

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25may1771

in nonequilibrium systems. recently found far off from equilibrium expression connects nonequilibrium work measurements to equilibrium free power discrepancies Crooks' fluctuation theory is the most well-known of them; even the thermodynamic uncertainty relation (TUR) that states that dissipation limits current fluctuation under steady settings arbitrarily far from equilibrium [8] is a groundbreaking finding. The relationship between energy changes and work output during a general isothermal process is established by Jarzynski equality. According to equilibrium statistical physics, a heat bath with temperature (T) corresponds to a single equilibrium state, whose probability of each microscopic state follows the Boltzmann distribution (pAs=Z1Aexp [HA(s)]), where β=(kBT)$^{-1}$, ZA=sexp [HA(s)] is the partition function, and HA(s) is the Hamiltonian for such microscopic state (s). FA=kBTlnZA's free energy is fixed. The Hamiltonian changes to HB when work is done to transform a macroscopic state A into a macroscopic state (B), such as pulling a spring or changing the structure of a protein complex. The work performed during this process must not be less than their free difference in energy F=FBFA in the thermodynamic limit, according to the second law. Thermodynamic limits, on the other hand, only apply in the context of an ensemble. The starting system state follow the Boltzmann distribution for every single act of this stochastic and is influenced by heat bath noise.

Consequently, the work being done in each particular realization W may vary, and the system may not always follow the exact same phase space trajectory during this process. In a prior study that included the second law, the average work can be finished (⟨W⟩≥ΔF). Jarzynski pointed out that we should consider the job allocation for each realization as well as the average work done, W. He also found the following equality:

$$e^{-\beta w} = e^{-\beta \Delta f}$$

The second law WF is simply indicated by the equation above, and Jensen's inequality makes it simple to confirm. According to research conducted in the 2000s, Jarzynski equality represents a substantial development in the second law [9]. Jarzynski equality, which is applicable to systems that are infinitely distant from equilibrium, shows for the first time in centuries how the second law governs thermodynamic activities in the form of equality rather than the earlier inequality formulation.

Crooks' fluctuation theorem [10] describes the relationship between a route's entropy production in phase space and its likelihood. If one pathway (ahead trajectory) generates a certain amount of entropy, the analogous reverse process (reverse trajectory) will naturally produce −ω entropy (absorb ω entropy). PR(−ω) represents the probability of a backward trajectory, while PF(ω) represents the chance of a forward trajectory. According to the second law, the process that reduces total entropy, or the thermodynamic limit PR(−ω)/PF(ω)→0, would never happen when ω >0. When stochasticity is not negligible, it can happen with a very small probability in small systems.

$$\frac{PR(-W)}{PF(W)} = e^{-w/KB}$$

This calculation shows that the opposite procedure would be more impossible the larger ω is. This is consistent with the second rule since it is a large quantity proportionate to the particle number. /kB is extremely large since the entropy produced for a "macroscopic" trajectory with a particle mass of about 1 mol is on the scale of ∼1molNAkB ∼ 1023kB. In this regard, e−ω/kB0 and the opposite process are very challenging. Processes that "appear to break" the second law would be more common in tiny systems since it is finite. The fluctuation brought on by stochasticity is where the term "fluctuation theorem" originates. The quantitative relationship between the associated entropy production and the fluctuation probability has been demonstrated by experiments [11,12,13].

Crooks' fluctuation theorem is a breakthrough in the second law, much like Jarzynski equality. It is possible to simplify Crooks' fluctuation theorem by considering Jarzynski equality:

$$[e^{-w/KB}] = 1$$

These are the most groundbreaking theories in the last 30 years. With these theoretical instruments, physicists may be able to investigate statistical physics laws far from equilibrium for the first time. They also show that only statistical rules in mesoscopic systems are fundamental, where the system is small enough for fluctuation to be noticeable but not so small that statistical physics fails.

Seifert and other researchers have applied these theories to the motion of single particles, along with the determination of certain other thermodynamic variables. In this scenario, they estimated the entropy production rate and established the associated fluctuation theorem [14]:

$$[e^{-\Delta \beta_{t\alpha}/KB}] = 1$$

where entropy production for a particle along a trajectory is Δstot. Crooks' fluctuation theorem is the same way. In the meantime, there are various other types of fluctuations theorems, which are listed in Seifert's paper [15].

Because of these advances, statistical physics may now be applied to a far wider spectrum of topics. Researchers may now discuss systems that are arbitrarily far from equilibrium, systems as small as a single particle with an external stochastic force, and systems that are not only at or close to equilibrium in terms of thermodynamics. This leads to the emergence of a new field called stochastic thermodynamics [15,14,16,17,18], which rapidly becomes a center for statistical physics research and related fields.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25may1771

Since the branch was established, one of the most important and influential theoretical findings in recent years has been the relationship between fluctuation and entropy production at nonequilibrium steady state, which is demonstrated by an inequality known as the "thermodynamic uncertainty relation" (TUR) [19,20,21,22]. The microstates of the system can generally produce a lot of cycles. In a nonequilibrium steady state, these cycles would have cyclic fluxes. There will be a relationship if the associated entropy rate of production on a cycle is represented by the symbol j and the stochastic net cyclical flux on that cycle is represented by the symbol e_p^8.

$$\frac{\sigma_j^2}{\langle j \rangle^2} \cdot e_p^s \geq 2k_B,$$

where σ2j is the variance of j and j is the average. Increasing the entropy generation rate e_p^8 may reduce the bottom bound of the relative fluctuation σ2j/j2 of the cyclic flux. This relation can also be expressed in integral form in a finite time interval τ: will hold:

$$\frac{\sigma_{j_\tau}^2}{\langle j_\tau \rangle^2} \cdot \Sigma_\tau \geq 2k_B,$$

Where ⟨jτ⟩=⟨j⟩×τ is the average number of times the cycles is completed in the time interval τ and Στ, and is the entropy generated in Thermodynamic uncertainty relations are what they're termed (TURs). TUR depicts the relationship between stochastic dynamic variables (fluctuations) and thermodynamic properties (entropy production rates). The noise of the dynamics can be decreased by raising the entropy production rate, and vice versa. It also demonstrates that reducing the variation and entropy production levels to infinitely tiny is unattainable. This relationship is gaining in popularity, and it is one of the most significant conceptual findings in this field in recent years.

III. INFORMATION PROCESSING THERMODYNAMICS IN LIVING SYSTEMS

Burning chemical fuels to perform different biological tasks is one way to maintain the steady state by dissipating free energy in realistic systems. Certain functions, such as the well-known molecular motor [23, 24, 25], which is crucial for bacterial motion and translocation inside cells, directly convert the chemical energy in the fuel into mechanical energy. Complex molecules, such as the DNA and protein complex, are synthesized during certain processes [26,27,28].

There is another large category of processes that are only involved in signal transduction, in addition to these activities where the energy is obviously used for physical or chemical goals. These functions are known as information processing functions. Allosteric transitions and signal molecule change (phosphorylation, methylation, ubiquitination, etc.) are important factors in the signal's frequent transduction through a series of routes and networks. For instance, a crucial phase in the chemotaxis network of E. coli is the methylation and demethylation of the chemoreceptor dimer [29]. Free energy is wasted when the information is digested because of the hydrolysis of energy molecules (GTP, ATP, etc.) that takes place during such altering processes.

The need for free energy dissipation during information processing is a natural topic from a physics standpoint. The clue comes from modern statistical physics' development of information theory, particularly a branch dubbed "information thermodynamics" [30,31,32] that investigates the thermodynamic cost of manipulating information or vice versa. As a result, it's intuitive to believe that free power dissipation is a required cost of processing information, or that it may be employed to improve processing accuracy.

IV. THE ACCURACY OF KINETIC PROOFREADING AND SPECIFICITY

The study on the accuracy of specificity and kinetic proofreading is among the first to apply nonequilibrium thermodynamic concepts to information processing in living systems. Hopfield's 1974 work [33], which has already become a common research paradigm in the field, may be connected to this study. Complex molecule production, like DNA replication, is the cause of this issue. As is well known, base paring is necessary for effective DNA replication. The "correct" base that should be coupled to a certain spot in the template DNA strand has a far higher affinity than the "wrong" base. The so-called specificity refers to the ability of a certain ligand to bind to a given substrate or receptor. Even so, there is a slight chance that a base pair will be chosen incorrectly. By examining the free energy difference between correct and incorrect base pairs, researchers calculated that the error rate during DNA replication is approximately 10^{-4},10^{-5} assuming the affinity difference is the only factor influencing specificity. The gene's relative invariance cannot be maintained at this mistake rate. However, in practical situations, the error rate for eukaryotes is only about 109 [33], which is much lower than what is estimated by affinity. Therefore, there must be another mechanism that decreases error, which has long been of interest to researchers.

Hopfield presented a kinetic proofreading model in this context [33]. Two ligands—one "correct" and one "wrong"—as well as one receptor are presumed to be present in this situation. When the two ligands are in equilibrium, their differing affinities result in a fundamental binding error rate, f0. An irreversible "proofreading reaction" that separates the ligand from the receptor and enables the receptor to select the ligand again might also be added to further reduce the error rate. In this case, the system loses equilibrium as a result of the "proofreading reaction" upsetting the delicate balance. The low mistake

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25may1771

rate during DNA replication can be explained by the possibility that the error rate could possibly be lowered to f20 in specific situations.

Due to the limitations of thermodynamic theory development at the time, Hopfield did not thoroughly examine the relationship between the error rate decrease and the system's displacement from equilibrium in his study. Qian addressed the same issue in further detail in a more recent paper published in 2006 [34]. Hong provided a more detailed description of Hopfield's model using nonequilibrium thermodynamics and cycle theories, as seen in Figure 1A. By hydrolyzing ATP, the complex RL—which is formed by ligand L and receptor R—can be activated to produce RL*. The free ligand L and receptor R are released when the RL separates upon activation. When [L] represents the ligand concentration, yields the rate product ratio.

$$\gamma = \frac{k_1^0 [L] k_2 k_3}{k_{-1} k_{-2} k_{-3}^0 [L]} = \frac{k_1 k_2 k_3}{k_{-1} k_{-2} k_{-3}},$$

$k1=k^0_1[L]$, and $k_{-3}=k^0_{-3}[L]$. It can be demonstrated that k_BTln is exactly the amount of energy needed to hydrolyze one ATP molecule, as was covered in the preceding section. When the ratio of ATP to ADP [T]/[D] is high enough, >1, ATP can effectively be hydrolyzed, which causes the system to lose equilibrium.

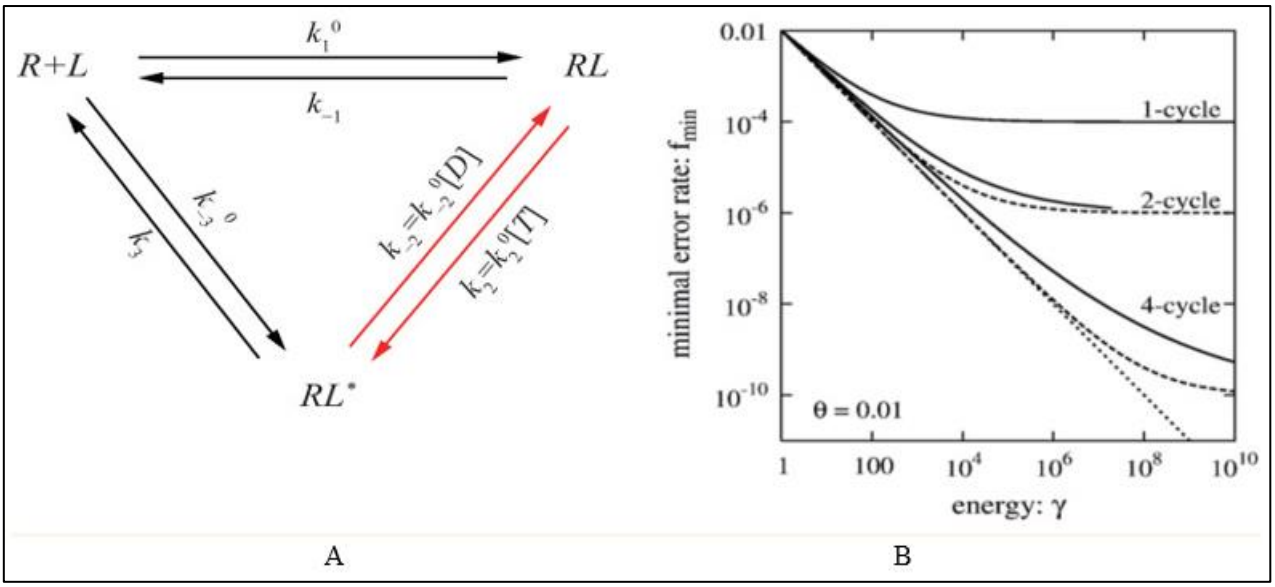

Fig 1: The Figure Illustrates the Thermodynamic Constraints on Specificity and Kinetic Regression.

The thermodynamic limitations on specificity and kinetic proofreading are taken from Ref [35]. (A) displays the reaction cycle between ligand L and receptor R. R and L could combine to form the complex RL, which could then be triggered to produce RL*. The receptor R and ligand L could be released when the active RL* splits. To show where the external energy is introduced, this reaction arrow is red. Alterations like phosphorylation are commonly used to activate RL, and phosphorylation is frequently coupled with ATP hydrolysis. T stands for ATP, D for ADP, and Pi is not displayed in the panel. (B) ATP hydrolysis energy restricts the specificity's accuracy.

Furthermore, suppose that the system has two ligands with the same concentration: L′ (the proper ligand) and L (the erroneous ligand). Even though their structures are similar and their k1, k2, k-2, and k-3 are the same, L′ has a far higher affinity than L. The dissociation rate is therefore less than L:

The attraction ratio for the two ligands in the active state can be used to determine the mistake rate.

$$f = \frac{[PL*]/([R][L])}{[RL]/([R][L]}$$

$$\frac{k'_{-1}}{k_{-1}} = \frac{k'_3}{k_3} \equiv \theta < 1.$$

It is demonstrable that f= at equilibrium. When the system is forced out of equilibrium, f>1, and it is possible for it to be less than. For a fixed, it can be calculated that the minimal error rate by adjusting other parameters is

$$f_{min}(\gamma) = \theta \left(\frac{1 + \sqrt{\gamma\theta}}{\sqrt{\gamma} + \sqrt{\theta}} \right)^2.$$

You can verify that f_{min} (γ) monotonically lowers with γ--∞ and that f_{min}-- θthe same as Hopfield's finding when.

V. CONCLUSION

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25may1771

The review concludes that physical systems that are not in thermodynamic equilibrium, but can be accurately described by variables that represent an extension of the various elements necessary to explain the system in thermodynamic equilibrium, are the subject of thermodynamics. Living systems are open systems governed by the rules of non-equilibrium thermodynamics. Consequently, understanding biological systems from a non-equilibrium thermodynamic perspective is useful. How people first discovered the value of studying biological systems from a thermodynamic perspective is discussed. The development of stochastic thermodynamics is discussed, focusing on three key concepts: Jarzynski's equality, Crookes' fluctuation theorem, and the uncertainty thermodynamic relationship. An overview of the current theoretical paradigm of stochastic thermodynamics in biological interaction networks is provided, with emphasis on the principles and apparatus of thermodynamics in non-equilibrium steady-state conditions. Finally, two potential applications and avenues of thermodynamic research in biological systems are examined.

REFERENCES

[1]. Schrödinger, E. What Is Life? The Physical Aspect of the Living Cell; Cambridge University Press: Cambridge, UK, 1944.

[2]. Prigogine, I. Etude Thermodynamique des Phénomènes Irréversibles; Desoer: Liège, Belgium, 1947.

[3]. Jaynes, E.T. The minimum entropy production principle. Annu. Rev. Phys. Chem. 1980, 31, 579–601.

[4]. Nicolis, G.; Prigogine, I. Self-Organization in Nonequilibrium Systems: From Dissipative Structures to Order through Fluctuations; Wiley: New York, NY, USA, 1977.

[5]. Sekimoto, K. Stochastic Energetics; Springer: Berlin/Heidelberg, Germany, 2010; Volume 799.

[6]. Jarzynski, C. Equilibrium free-energy differences from nonequilibrium measurements: A master-equation approach. Phys. Rev. E 1997, 56, 5018.

[7]. Crooks, G.E. Entropy production fluctuation theorem and the nonequilibrium work relation for free energy differences. Phys. Rev. E 1999, 60, 2721.

[8]. Horowitz, J.M.; Gingrich, T.R. Thermodynamic uncertainty relations constrain non-equilibrium fluctuations. Nat. Phys. 2020, 16, 15–20.

[9]. Mossa, A.; de Lorenzo, S.; Huguet, J.M.; Ritort, F. Measurement of work in single-molecule pulling experiments. J. Chem. Phys. 2009, 130, 234116.

[10]. Crooks, G.E. Entropy production fluctuation theorem and the nonequilibrium work relation for free energy differences. Phys. Rev. E 1999, 60, 2721. [Google Scholar] [CrossRef].

[11]. Collin, D.; Ritort, F.; Jarzynski, C.; Smith, S.B.; Tinoco, I.; Bustamante, C. Verification of the Crooks fluctuation theorem and recovery of RNA folding free energies. Nature 2005, 437, 231–234. [Google Scholar] [CrossRef] [PubMed].

[12]. Schuler, S.; Speck, T.; Tietz, C.; Wrachtrup, J.; Seifert, U. Experimental test of the fluctuation theorem for a driven two-level system with time-dependent rates. Phys. Rev. Lett. 2005, 94, 180602. [Google Scholar] [CrossRef].

[13]. Wang, G.; Reid, J.; Carberry, D.; Williams, D.; Sevick, E.M.; Evans, D.J. Experimental study of the fluctuation theorem in a nonequilibrium steady state. Phys. Rev. E 2005, 71, 046142. [Google Scholar] [CrossRef].

[14]. Seifert, U. Entropy production along a stochastic trajectory and an integral fluctuation theorem. Phys. Rev. Lett. 2005, 95, 040602. [Google Scholar] [CrossRef].

[15]. Seifert, U. Stochastic thermodynamics, fluctuation theorems and molecular machines. Rep. Prog. Phys. 2012, 75, 126001. [Google Scholar] [CrossRef].

[16]. Seifert, U. Stochastic thermodynamics: Principles and perspectives. Eur. Phys. J. B 2008, 64, 423–431. [Google Scholar] [CrossRef.

[17]. Qian, H. Phosphorylation energy hypothesis: Open chemical systems and their biological functions. Annu. Rev. Phys. Chem. 2007, 58, 113–142. [Google Scholar] [CrossRef].

[18]. Gong, Z.; Quan, H.T. Jarzynski equality, Crooks fluctuation theorem, and the fluctuation theorems of heat for arbitrary initial states. Phys. Rev. E 2015, 92, 012131. [Google Scholar] [CrossRef] [PubMed].

[19]. Barato, A.C.; Seifert, U. Thermodynamic uncertainty relation for biomolecular processes. Phys. Rev. Lett. 2015, 114, 158101. [Google Scholar] [CrossRef].

[20]. Polettini, M.; Lazarescu, A.; Esposito, M. Tightening the uncertainty principle for stochastic currents. Phys. Rev. E 2016, 94, 052104. [Google Scholar] [CrossRef].

[21]. Pietzonka, P.; Ritort, F.; Seifert, U. Finite-time generalization of the thermodynamic uncertainty relation. Phys. Rev. E 2017, 96, 012101. [Google Scholar] [CrossRef].

[22]. Horowitz, J.M.; Gingrich, T.R. Thermodynamic uncertainty relations constrain non-equilibrium fluctuations. Nat. Phys. 2020, 16, 15–20. [Google Scholar] [CrossRef].

[23]. Jülicher, F.; Ajdari, A.; Prost, J. Modeling molecular motors. Rev. Mod. Phys. 1997, 69, 1269. [Google Scholar] [CrossRef].

[24]. Mandadapu, K.K.; Nirody, J.A.; Berry, R.M.; Oster, G. Mechanics of torque generation in the bacterial flagellar motor. Proc. Natl. Acad. Sci. USA 2015, 112, E4381–E4389. [Google Scholar] [CrossRef].

[25]. Tu, Y.; Cao, Y. Design principles and optimal performance for molecular motors under realistic constraints. Phys. Rev. E 2018, 97, 022403. [Google Scholar] [CrossRef].

[26]. Mast, C.B.; Schink, S.; Gerland, U.; Braun, D. Escalation of polymerization in a thermal gradient. Proc. Natl. Acad. Sci. USA 2013, 110, 8030–8035. [Google Scholar] [CrossRef] [PubMed].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25may1771

[27]. Banerjee, K.; Kolomeisky, A.B.; Igoshin, O.A. Elucidating interplay of speed and accuracy in biological error correction. Proc. Natl. Acad. Sci. USA 2017, 114, 5183–5188. [Google Scholar] [CrossRef].
[28]. Chiuchiú, D.; Tu, Y.; Pigolotti, S. Error-speed correlations in biopolymer synthesis. Phys. Rev. Lett. 2019, 123, 038101. [Google Scholar] [CrossRef] [PubMed].
[29]. Lan, G.; Sartori, P.; Neumann, S.; Sourjik, V.; Tu, Y. The energy–speed–accuracy trade-off in sensory adaptation. Nat. Phys. 2012, 8, 422–428. [Google Scholar] [CrossRef].
[30]. Sagawa, T.; Ueda, M. Second law of thermodynamics with discrete quantum feedback control. Phys. Rev. Lett. 2008, 100, 080403. [Google Scholar] [CrossRef].
[31]. Sagawa, T.; Ueda, M. Generalized Jarzynski equality under nonequilibrium feedback control. Phys. Rev. Lett. 2010, 104, 090602. [Google Scholar] [CrossRef].
[32]. Deffner, S.; Jarzynski, C. Information processing and the second law of thermodynamics: An inclusive, Hamiltonian approach. Phys. Rev. X 2013, 3, 041003. [Google Scholar] [CrossRef].
[33]. Hopfield J.J. Kinetic proofreading: A new mechanism for reducing errors in biosynthetic processes requiring high specificity. Proc. Natl. Acad. Sci. USA. 1974;71:4135–4139. doi: 10.1073/pnas.71.10.4135. [PMC free article] [PubMed] [CrossRef] [Google Scholar].
[34]. Qian H. Reducing intrinsic biochemical noise in cells and its thermodynamic limit. J. Mol. Biol. 2006;362:387–392. doi: 10.1016/j.jmb.2006.07.068. [PubMed] [CrossRef] [Google Scholar]
[35]. Lan G., Sartori P., Neumann S., Sourjik V., Tu Y. The energy–speed–accuracy trade-off in sensory adaptation. Nat. Phys. 2012;8:422–428. doi: 10.1038/nphys2276. [PMC free article] [PubMed] [CrossRef] [Google Scholar]