Review of: "The evolution of E. coli is NOT driven by genetic variance but by thermodynamics."

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Thermodynamic laws play a fundamental role in shaping the evolution of natural systems, spanning the realms of chemistry, physics, and biology. Within the intricate tapestry of life, the evolution of organisms is no exception to these thermodynamic principles. While genetic mutations and variations are often viewed as the mechanisms steering evolution, it is essential to recognize that they are not detached from the realm of thermodynamics. **My perspective is that genetic variance and thermodynamics are not mutually exclusive; instead, they are intricately connected. Genetic variance could be a consequence of thermodynamics, and stable gene mutations at quasi-steady states, or equilibrium, might serve as alternative indicators or measures of thermodynamic properties within specific systems.**

Consider the fascinating example of antibiotic resistance in bacterial populations. Over prolonged exposure to antibiotics, certain bacterial cells accumulate mutations that confer resistance. On a molecular scale, these mutations can alter the drug target, reducing its binding affinity to the drug. When we scrutinize this system—comprising only the drug and the protein—in isolation, we observe that a diminished binding affinity leads to a higher Gibbs free energy change (ΔG) during the binding process, indicating a less energetically favorable interaction. When we extend our viewpoint to encompass resistant bacteria and their environment as a closed system, inefficient drug binding allows these bacteria to thrive until they deplete all available nutrients, releasing heat, $CO2$, and other waste products, thus increasing the entropy of the system. Both scenarios align harmoniously with the principles of thermodynamics. **Evolution selects for particular genetic variants that ultimately increase the system's entropy, establishing that genetic variations serve as pathways to reach equilibrium.**

Similarly, when bacteria grow in an environment with limited essential nutrients, evolution tends to favor mutants with a higher affinity for these nutrients. As a result, bacteria grow more rapidly, pushing the system (comprising the bacteria and the environment) toward equilibrium at an accelerated rate. Evolution follows thermodynamics.

In this context, genetic variants can be viewed as outcomes by thermodynamics. Genetic mutations represent the pathways toward reaching the equilibrium of the system. We can assert that **thermodynamics selects for genetic variants that minimize free energy and increase entropy within the system, which encompasses the organism and its environment.** Genetic variation does not oppose thermodynamics; instead, it is driven by it. Hence, we can posit that evolution itself is propelled by the underlying thermodynamic processes.

Another illustrative example comes from antibiotic evolution experiments, demonstrating that Darwinian evolution often follows a limited number of mutational paths to produce fitter proteins, even when numerous combinations are theoretically possible (Weinreich et al., 2006). While it might seem that a specific mutations directs the evolutionary path, it is essential to recognize that these sequences and orders are not obituary but constrained and driven by thermodynamics. The observed evolutionary path is a consequence of the underlying thermodynamic principles.

The evolution of SARS-CoV-2, the virus responsible for the COVID-19 pandemic, similarly adheres to thermodynamic principles. Throughout its evolutionary journey, multiple variants emerged, each vying for dominance. Over time, variants with higher transmissibility and lower pathogenicity, exemplified by the Omicron variants, prevailed. Here, Gibbs energy plays a pivotal role, orchestrating the biosynthesis of proteins and genomic RNA and guiding virus assembly. Analyzing the stoichiometry and thermodynamic properties of virion synthesis unveils a trend: the standard Gibbs energy of biosynthesis in SARS-CoV-2 variants steadily decreases during evolution (Popovic, 2022). In this intricate dance of viral evolution, it seems that the second law of Thermodynamics, with its mandate to minimize free energy by any means possible, takes the lead. Notably, variants with less negative Gibbs energy, such as Omicron BA.2.75, exhibit heightened infectivity and reduced pathogenicity compared to their predecessors, underscoring the profound thermodynamic influence on the virus's evolutionary trajectory.

In conclusion, **thermodynamics underpins and guides evolutionary processes, influencing genetic variations and shaping the trajectories of biological systems across different scales, from antibiotic-resistant bacteria to the evolution of viruses like SARS-CoV-2.** Genetic mutations and variations are not antithetical to thermodynamics but serve as pathways to equilibrium and manifestations of thermodynamic principles. This perspective highlights the profound interplay between thermodynamics and genetics in the fascinating realm of biological evolution.

References

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