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

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Potential competing interests: No potential competing interests to declare.

While I am quite a fan of those bringing thermodynamic and information theories into Biological science, I think this paper misses the mark a bit.

As some have already commented, the authors do not present sufficient evidence to support their claim. There are also some biological errors. These include: “most mutations are deleterious”. No, I think most would say most are neutral - at least with regard to the functions of proteins. Mutations could lead to loss of fitness (Muller's Ratchet idea), however, that depends on compensatory mutations at other loci. That's not, necessarily epistasis, which relates to the effects of mutations acting in concert to produce similar outcomes.

The authors then state that there are few mutations in Lenski's cultures but significant upswings in fitness. As has been said by a previous reviewer, there is no reason to expect a relationship between the two in the manner described. Indeed, enhanced mutation rates would (most likely) reduce fitness. Instead the fitness increases because of fixation of those mutations that occur.

Then there is “conclusion 1 (genetic variation does NOT drive evolution)”, which is roundly rejected by a range of straightforward experiments. While, we could simply say that mutations work in concert with varying selection, for example, negating the role of genetic variation is simply untrue. Conclusion 3 also does not follow from conclusion 1, in the sense that there are more components or targets for selection than genes. There is also a wealth of epigenetic effects on fitness that follow from the environment in which the selection is occurring. Therefore, while (in some eyes) these “extend” the modern synthesis, they do not negate it. The extensive work of Kevin Laland (and others) is worth looking at, in that regard.

Finally, I was really hoping to see a novel argument or piece of evidence to support a discrete thermodynamic model for these observations. However, that is not presented, which is a shame. There is, I believe, much traction in the application of thermodynamics. While I remain to be convinced of some of this work, papers such as those of Vanchurin et al (PNAS, 2022) do underpin their models with a strong mathematical foundation. I would like to see the presented manuscript strengthened by the inclusion of a more precise critique of the modern synthesis; and with a proposal for how thermodynamics could replace this synthesis.