Dear Prof Krasimira Tsaneva-Atanasova,

We thank you for your interest and comments in our work and the opportunity to revise it. We would like to thank the anonymous reviewer for the careful reading of the second version of our manuscript.

The initial comments are in black and our response is in blue.

We thank you again for your consideration and hope that our manuscript is now acceptable for recommendation.

Yours sincerely,
On the behalf of authors,
Dr. Ramsès Djidjou-Demasse.

Reviewer:

In the formulation of the time dynamics in equations 2.1 and 2.2, the authors deviate from classical population genetics literature (cf. e.g. Wright, Genetics, 1931; Kimura "The Neutral Theory of Molecular Evolution", 1983). They do not cite any paper that would explain the reasoning behind these deviations, hence I consider it important that they are carefully explained and motivated.

The main deviations that I see are the following (where I am going to just focus on Eq. 2.1, since 2.2 is just a special case of 2.1):

(1) In the first term of Eq. 2.1, the authors multiply a mutation term, J(x-y), with a growth term, p(y). In the classical formulation, these are, however, two separate terms. The growth term describes the relative fitness of the genotype x (relative to the other genotypes in the population) and is proportional to p(x)*b(x). On the other hand, the (separate) mutation term is usually applied to the current subpopulation sizes, i.e. to b(x) and b(y).
Answer: In the model proposed here, mutations are assumed to be sufficiently frequent during replication (*i.e.*, new mutants occur during growth), and randomly displace strains into the phenotype space at each generation according to a mutation kernel. However, this constitutes a potential limitation in the model formulation. Indeed, in exponentially growing cells, mutations usually occur during replication (Loewe, "High Deleterious Genomic Mutation Rate in Stationary Phase of Escherichia Coli", 2003), but some studies indicate that mutations can be substantially higher in non-growing than growing cultures (Sniegowski, "Evolution: Bacterial Mutation in Stationary Phase. Current Biology", 2004). Thus, the occurrence of new mutants depends either on the abundance of parental cells or both the abundance and growth rate of the parental cells (zur Wiesch *et al.*, "Compensation of Fitness Costs and Reversibility of Antibiotic Resistance Mutations",2010). Therefore, another potential extension of the model would be to allow both processes for the occurrence of new mutants.
↪ *We agree that such precision is important within the context of the work proposed here. This has been added to the end of the page 14 of the manuscript.*

(2) This leads to the second point. While the given expression contains the incoming mutations from state y to state x, it appears to be missing a term for the outgoing mutations from x to y. This term should be proportional to -J(y-x)*b(x).
Answer: Here, we think that there is a bit of confusion with something similar to a 'diffusion process'. As stated previously, in the model proposed here, mutations randomly displace strains into the phenotype space at each generation according to a mutation kernel J. However, for a diffusion process, $J(x-y)$ is thought of as the probability distribution of jumping from the site y to site x such that, $\int J(x-y)b(t,y)dy$ is the incoming rate at site x from all other sites, and, $-\int J(x-y)b(t,x)dy = -b(t,x)\int J(x-y)dy$, is the outgoing rate from the site x.