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Skolkovo Institute of Science and Technology

Jury Member Report – Doctor of Philosophy thesis.

Name of Candidate: Anastasiia Stoliarova

PhD Program: Life Sciences

Title of Thesis: Genomic patterns of epistasis at macro- and microevolutionary scales

Supervisor: Professor Georgii Bazykin

Name of the Reviewer: Mikhail Gelfand

I confirm the absence of any conflict of interest	**Date:** 01-11-2021 

Reviewer's Report
This is an important study of an important, but until recently little studied phenomenon – epistasis. Relying on unique objects and datasets, the candidate has demonstrated the presence of positive epistasis in genes of fungus *Schisophillum commune* (the most polymorphic known species), based on several linked, distinct observations: short-range linkage disequilibrium, attraction of rare alleles, shared pairs of polymorphisms in different populations, and correlations in pairs of interacting amino acids. An important theoretical conclusion is that epistasis maintains beneficial, co-adapted combinations of alleles: something that people long expected, but never demonstrated on a large scale. Then the author identified bursts of mutations in amphipods, for which the most natural explanation is correlated positive selection. Finally, the author has demonstrated that amino acids originating at neutral sites then co-evolve epistatically with other sites, further increasing fitness, whereas amino acids originating at negatively selected sites decrease in fitness with time, likely due to environmental factors changing the fitness landscape. All these findings are of major importance, and I predict that eventually they will be included in textbooks on molecular evolution. These results are presented in three chapters, each with its own introduction (review) and discussion; the chapters correspond to the

published (and submitted?) papers. Combined with a detailed literature review (that is well-written and deserves to be published separately) and general conclusions, this makes the text easy to read. In addition to standard methods, the author has developed original techniques; overall the methodical level of the study is very high.

The conclusions are adequate and well-formulated.

The candidate is the first author in two papers (Nature Communications, IF=14.9, and Royal Society Open Science, IF=2.9); hence her major personal contribution to the described results is obvious. The results have been presented at several high-level international conferences (in particular: MCCMB 2021 and 2019, oral; SMBE 2019, 2018, 2017, posters). Hence all formal Skoltech requirements have been met.

Technical comments to the previous versions of the thesis have been addressed adequately.

Provisional Recommendation

☒ *I recommend that the candidate should defend the thesis by means of a formal thesis defense*

☐ ~~*I recommend that the candidate should defend the thesis by means of a formal thesis defense only after appropriate changes would be introduced in candidate's thesis according to the recommendations of the present report*~~

☐ ~~*The thesis is not acceptable and I recommend that the candidate be exempt from the formal thesis defense*~~