Skoltech
Skolkovo Institute of Science and Technology

Jury Member Report – Doctor of Philosophy thesis.

Name of Candidate: Alexander Martynov

PhD Program: Life Sciences

Title of Thesis: Using mathematical modeling to Understand prokaryotic adaptive Immunity

Supervisor: Prof. Konstantin Severinov

Co-Supervisor: Dr. Jaroslav Ispolatov

Chair of PhD defense Jury: Prof. Mikhail Gelfand ***Email**: m.gelfand@skoltech.ru*

Date of Thesis Defense: 23 October 2018

Name of the Reviewer:

I confirm the absence of any conflict of interest	**Signature:**  **Date: 09-09-2018**

Reviewer's Report
This is a strong thesis addressing an old problem of the interaction of CRISPR-Cas systems with plasmids and viruses, but at a non-standard angle. The author concentrates on functional aspects of this interaction, modeling kinetic behavior of the system as dependent on the number of spacers (in the case of viruses) and plasmids. The thesis consists of two main chapters largely formed by two research papers. As a result, each chapter has its own introduction; however, these introductions do not duplicate Chapter 1, but rather provide motivation for the performed study. At that, the review Chapter 1 is well-written and complete, providing a solid foundation for the reported research. Chapter 2 describes how the outcome of cell-virus (phage) interaction depends on the number of spacers in a cassette, virus mutation rate etc. The key observation is that efficiency of cassettes saturates as their size increases due to limited ability of the cell to produce Cas complexes. I have a couple of suggestions that could make the results even stronger. Firstly, it might be interesting to add an evolutionary process of spacer gain and, even more importantly, elimination. At that, it might be interesting to see whether the observed distribution of cassette sizes is consistent with the predictions of the author's mode, with a

simple model of spacer gain at one end and loss of spacers by recombination, or a mixed model. Secondly, the author considers an idealized situation of a single, non-changing cell attacked by same or different viruses. Adding a population aspect also might make the model closer to real life.

Chapter 3 describes an interesting phenomenon of stable plasmid maintenance in a subpopulation of cells observed in an experiment and modelled as a competition between CRISPR-Cas interference and plasmid replication. The results of the modeling describe the observed bimodality in the number of retained plasmids, and also demonstrate that while the plasmid survival is stochastic and depends on random events at the start of the infection, the number of surviving plasmids tends to a constant determined by the rates of the involved processes.

All these results are new and interesting, and results from a nice blend of experimental and modeling analyses. They are published in (or submitted to) reputable journals, and the author's contribution to these papers is crucial. Given that the author also has a number of good papers on unrelated topics and hence not listed in the thesis, the publications requirements of SkolTech are satisfied.

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*