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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: Prof. Jaroslav Ispolatov

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

Date of Thesis Defense: 25 October 2018

Name of the Reviewer: Prof. Andrey Mironov

I confirm the absence of any conflict of interest (Alternatively, Reviewer can formulate a possible conflict)	**Signature:**  **Date: 08-10-2018**

The purpose of this report is to obtain an independent review from the members of PhD defense Jury before the thesis defense. The members of PhD defense Jury are asked to submit signed copy of the report at least 30 days prior the thesis defense. The Reviewers are asked to bring a copy of the completed report to the thesis defense and to discuss the contents of each report with each other before the thesis defense.

If the reviewers have any queries about the thesis which they wish to raise in advance, please contact the Chair of the Jury.

Reviewer's Report

Reviewers report should contain the following items:

- Brief evaluation of the thesis quality and overall structure of the dissertation.
- The relevance of the topic of dissertation work to its actual content
- The relevance of the methods used in the dissertation
- The scientific significance of the results obtained and their compliance with the international level and current state of the art
- The relevance of the obtained results to applications (if applicable)
- The quality of publications

The summary of issues to be addressed before/during the thesis defense

- Brief evaluation of the thesis quality and overall structure of the dissertation.

The presented thesis focused on the mathematical modeling of CRISP-CAS bacterial immune system. The thesis has typical structure and contains all necessary parts: Abstract, Literature review, Introduction, Results (chapters 3,4), Discussions and Conclusion and Literature. Every results chapter contains short introduction, main part and discussion. The literature review describes in detail the CRISP-CAS system and the mechanism of its operation. A separate part of the review is devoted to the mathematical models of the CRISP-CAS system. This part of the review is directly related to the topic of work, but it is written in a very concise form. I would like this part of the review to be more detailed. The thesis is well written and structured. It contains sufficient equations and appropriate figures.

- The relevance of the topic of dissertation work to its actual content

The title of the thesis fully reflects its content. The thesis considers two related tasks of the CRISP-CAS system mathematical modeling.
Chapter 3 is devoted to building a model of interaction of a CRISP-CAS system with a virus. Investigated the interaction of the cassette with the virus. The question of the optimal number of spacers in the cassette is considered. Surprisingly, there is an optimal number of spacers. Under reasonable assumptions, it turns out to be about 7. The question of the role of mutations in the cassette and in the virus was also considered.

Chapter 4 describes the interaction of the CRISP-CAS system with plasmids. The application of modeling to the analysis of experimental results is considered. The effect of plasmid replication on cell survival was studied. In addition, the kinetics of plasmid copy number under the action of the CRISP-CAS system and restricting conditions were studied.

- The relevance of the methods used in the dissertation

The work looks quite modern and is devoted to the actual problem of the role of the CRISP-CAS system in interaction with alien genomes. The author used fairly simple, but effective methods of mathematical modeling. Almost all the results were obtained analytically, but not by computer simulations, which gives the results a special value. Some of the methods are based on the analysis of simple differential equations. However, one should keep in mind that the typical number of interacting objects is not large, so the results of the analysis give an idea of the mean values over the ensemble, while with a small number of objects, large fluctuations are inevitable. Nevertheless, the main result – finding of optimal number of spacers – seems to be well proved. Using the stochastic modeling in chapter 4 is more relevant.

- The scientific significance of the results obtained and their compliance with the international level and current state of the art

The author find some new interesting properties of CRISP-CAS system. In particular he find optimal number of spacers. The result of the bimodal distribution of the cellular population with one subpopulation losing all plasmids while the other maintaining them seems important.

- The relevance of the obtained results to applications (if applicable)
- The quality of publications

Unfortunately, only one article has been published for the work (as indicated in the thesis), but the author of the theses is the first author of this article. The article is published in PLoS Comput Biol – good journal with the impact factor about 4.

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*