Annex No. 11 to the MU Directive on Habilitation Procedures and Professor Appointment Procedures

Habilitation Thesis Reviewer's Report

Masaryk University	
Faculty	Faculty of Informatics
Procedure field	Informatics
Applicant	RNDr. David Šafránek, Ph.D.
Applicant's home unit, institution	Faculty informatics, Masaryk University
Habilitation thesis	Formal Methods for Analysis of Biological Systems under Parameter Uncertainty
Reviewer	Prof. Ion Petre
Reviewer's home unit, institution	University of Turku, Finland

Dr. Safranek's broad area of research is computational systems biology, in particular foundational approaches for systems analysis. The topics he focused on in the last few years are around developing efficient methods for automatic analysis of models of biochemical systems under parameter uncertainty. This line of research is well motivated by the drive towards compiling large, detailed models of biochemical systems, while many of the parameters of such models cannot be experimentally measured.

Three problems are addressed in Dr. Safranek's habilitation thesis: parameter synthesis, parameter exploration, and robustness analysis. The parameter synthesis problem is, on a high-level presentation, about identifying the parameter values of a model that make the model satisfy a given temporal-logical property. The problem is relevant because it identifies the possible quantitative settings of a model that ensure its fit to experimental observations. The parameter exploration problem reformulates the question in the stochastic framework, asking that the model satisfies the temporal-logical property with a probability larger than a preset threshold. Even though related, the two questions deal with quite different mathematical frameworks (deterministic vs. stochastic modeling) and are given very different algorithmic solutions. The robustness analysis problem is investigating the stability of a temporal-logical property when the parameters of a model are being modified. The problem is discussed in the thesis both in the deterministic, as well as in the stochastic framework.

Dr. Safranek's background is in formal methods, especially on model checking. This forms the foundation on which he builds his approach to computational systems biology. His work is based on formulating a biochemical model as a deterministic or as a stochastic model, based on different forms of differential equations models or of Markov chains models. The questions he is asking are formulated in different forms of temporal logic, well adapted to the formalism of the model. The methods he develops to answer these questions are based on a broad spectrum of techniques based on automata theory, model checking, temporal logic, stochastic sampling, quantitative simulations, software prototyping. This versatility of methods is perhaps the strongest and most impressive aspect of Dr. Safranek's work. It is also the main vehicle that allows him to address a broad spectrum of questions and to successfully answer them with suitable computational methods, appropriately adapted to the nature of the problem. Even more, he is also able to convincingly demonstrate the applicability of his methods to a diversity of realistic biochemical models. This is in itself a challenge because it includes the separate problems of translating biological questions to computational challenges, and to interpret computational solutions in terms of biological properties. Dr. Safranek succeeds in this part of his work as well in a diversity of case studies, including a biodegradation process in bacteria, a regulation mechanism of the cell cycle, a signalling pathway, and a population model.

Dr. Safranek's work is solid, mathematically sound, computationally skilful, and with a focus on the significance of the solutions for the practice of modern systems biology. His work has been very well received, with his articles having been published in highly esteemed forums such as *Computational Methods in Systems Biology*, *Formal Methods*, and *Transactions on Computational Biology and Bioinformatics*. His work has received an impressive number of citations, some of them so-called essential citations, in contexts where Dr. Safranek's methods are presented as core contributions to a particular topic of research. His habilitation thesis is very well written, with the content spanning from the foundational techniques of his field, to the algorithmic details of his methods, to the demonstration of their efficiency in an array of case studies.

Dr. Safranek is by now a mature researcher, with a solid and well-articulated research agenda, very successful in his results, and an important contributor to the international computational systems biology community. He collaborates with many of the key researchers of his field, another testimony of his work being appreciated in his community. Also from the teaching and supervision perspective he is very successful, having designed and lectured many courses, some of them based in part on his own research, and having successfully supervised students on all levels. Dr. Safranek is an excellent example of the multi-disciplinary scientists that are needed in modern science and that are highly sought after at many universities worldwide.

The Habilitation degree is an important step in Dr. Safranek's career that comes in recognition of his successful work so far, and that will allow him to develop his career further. I have no hesitation in strongly recommending to the Faculty of Informatics of Masaryk University to award him the degree.

Reviewer's questions for the habilitation thesis defence (number of questions up to the reviewer)

1. The applicability domain of the methods developed in your thesis is systems biology, a field driven by building as large as possible models. On the other hand, many of the model checking solutions currently developed do not scale well, suffering by different form of combinatorial explosions. Can you describe the "sweet spot" of the (size of, type of) systems models where model checking can be most efficient.
2. Can machine learning play a role in the formal methods approach to systems biology?
3. Stochastic models offer in many cases a more detailed view of a systems behaviour, but the deterministic methods are often more efficient and scale better. Can you

discuss how modelers should choose one approach over the other and whether the two can be combined in analysing the same model.

Conclusion

The habilitation thesis entitled "*Formal Methods for Analysis of Biological Systems under Parameter Uncertainty*" by David Šafránek ***fulfils*** requirements expected of a habilitation thesis in the field of Informatics.

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In Turku, Finland on May 26, 2019

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