MASARYKOVA UNIVERZITA

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. Luca Cardelli
Reviewer's home unit, institution	University of Oxford, United Kingdom

[Review text] See attached report.

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

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Conclusion

The habilitation thesis entitled "*Formal Methods for Analysis of Biological Systems under Parameter Uncertainty*" by David Šafránek ***fulfils*** – ***does not fulfil*** requirements expected of a habilitation thesis in the field of Informatics.

In Oxford on May 7, 2019

[redacted]

Dr. Luca Cardelli FRS
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08 May 2019

Masaryk University
Faculty of Informatics

This is a review of David Šafránek's habilitation thesis "*Formal Methods for Analysis of Biological Systems under Parameter Uncertainty*".

I am a Royal Society Research Professor at the University of Oxford, since 2014. Between 1997 and 2018 I was a Principal Researcher at Microsoft Research Cambridge; I helped start that research lab and I was head of the Programming Principle and Tools and Security groups (~20 people) from 2000 to 2012. I am a Fellow of the Royal Society, a Fellow of the Association for Computer Machinery, and an Elected Member of the Academia Europaea. My main activities have been in the foundations of programming languages, in the theory of concurrency, and more recently in programmable biology and nanotechnology. I am knowledgeable of the core issues tackled in this thesis.

The techniques developed in this thesis are directed largely at biology, but they constitute general methods in computer science that are formulated on mathematical models and can be applied to a broad set of problem domains. They are part of a trend towards quantitative analysis that bridges the traditional analysis of discrete systems at the root of computing, to the analysis of continuous dynamical systems typical of the physical and biological sciences. Rather than a sign that computer science is becoming more applied, this is as an indication that it is becoming broader and that it will have an even bigger impact than the one it is now enjoying in technology. Concepts that arose strictly within computer science for application to discrete systems (in this case, formal verification techniques) can now be applied to quantitative dynamical systems, providing new original insights and methodologies in areas that are in themselves already mathematically very mature. It is in this context that I see this work as particularly significant, and well fitting within the core of our discipline and its future evolution.

The recent growth in synthetic biology, in particular, has meant that analysis techniques of every kind need to be scaled up to deal with increasingly complex models and increasingly large collections of experimental data, while large uncertainty remains about fundamental aspects of the systems being studied. We need a delicate balance of deductive power (analytical techniques) and inductive power (inference techniques), which is the main dichotomy addressed in the thesis. Moreover, all that must be coupled with enough computational efficiency to obtain useful results on practical problems.

The thesis gives an in-depth overview of concepts and techniques that arise in that problem domain. It has the quality of a textbook, in being well organized, mathematically precise, and comprehensive about the foundations of the subject, while at the same time presenting the

author's original contributions. In addition to the introductory chapters about foundations and related work, it is a considerable rewrite and reintegration of the original published results.

The core problem is to check whether (or how much) a partially known system satisfies a desirable or undesirable property. The techniques focus on modelchecking and temporal logic, which are extended from their traditional roots in discrete systems to cover continuous and stochastic state spaces, continuously-varying signals, and real-time and probabilistic properties. The problems being tackled by these techniques consist of parameter synthesis (finding the set of parameters satisfying a property), parameter exploration (finding the probability with which a set of parameters satisfies a property), and robustness analysis (finding the size of the parameter set that satisfies a property). Each of these problems if framed as a mathematical problem, preexisting solutions are described and evaluated, and new solutions are proposed. Finally, case studies are presented where the techniques have been used.

With respect to other methods of systems analysis in the biological and physical sciences, the main distinguishing characteristic is the use of temporal logics to both formally frame the properties of a system, and to drive the development of automated techniques to verify those properties. The often technically deep and highly optimized techniques developed to answer the three main questions previously mentioned, then become easily accessible by being expressed as logical properties in a query language. The recursive nature of those query languages also means that the complexity of the questions to be asked is not fixed to predefined properties, and can scale up naturally to intricate questions a domain expert may wish to ask. New temporal logics have been developed to enable the formulation of questions that are relevant to continuous and probabilistic domains, and questions that a biologist may want to ask about properties of a biological system.

In conclusion, I am happy to confirm that the thesis entitled "Formal Methods for Analysis of Biological Systems under Parameter Uncertainty" fulfils the requirements expected of a habilitation thesis in the field of Informatics.

Sincerely,