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Milan Češka · Nicola Paoletti (Eds.)

# Hybrid Systems Biology

6th International Workshop, HSB 2019  
Prague, Czech Republic, April 6–7, 2019  
Revised Selected Papers

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# Preface

This volume contains the papers presented at HSB 2019, the 6th International Workshop on Hybrid Systems Biology, held during April 6–7, 2019, at the Faculty of Mathematics and Physics, Charles University, Prague, Czech Republic. HSB 2019 was co-located with ETAPS 2019, the European Joint Conferences on Theory and Practice of Software, including five prime conferences and 17 satellite workshops.

HSB provides a unique forum for discussion on dynamical models in biology, with an emphasis on both hybrid systems (in the classic sense, i.e., mixed continuous/discrete/stochastic systems) and hybrid approaches that combine modelling, analysis, algorithmic and experimental techniques from different areas. HSB 2019 strengthened the focus on the design and analysis of artificial biochemical systems (e.g., engineered bacteria or molecular machines) and of medical cyber-physical systems. Hybrid systems and approaches are essential to the understanding of complex living systems, which are characterized by stochasticity and heterogeneous spatiotemporal scales. The complexity of such systems makes their formal analysis challenging, and even their simulations are often impractical, calling for appropriate model abstractions and scalable analysis methods. To overcome these challenges, HSB aims at bringing together researchers from different disciplines and at applying these methods to the study of structure, dynamics, and control mechanisms of living systems ranging from genetic regulatory networks to metabolic networks.

HSB 2019 offered a dense two-day program, including three invited talks, regular single-track sessions, and a poster session. Moreover, HSB 2019 had the honor of including a special session dedicated to the memory of Oded Maler, a very much missed member of HSB's Steering Committee and one of the founders of the workshop. The session celebrated his life and scientific contributions with three invited talks by some of his closest collaborators. All contributed talks were of high quality, and the participation was lively, interactive, and stimulating. The workshop hosted about 30 registered participants and registered a constant inflow of attendees from other co-located events at ETAPS 2019.

A highlight of HSB 2019 was the three invited talks and three talks dedicated to the memory of Oded Maler. The speakers were selected in view of the breadth and interdisciplinarity of the workshop: Marta Kwiatkowska (University of Oxford, UK, on formal methods for behavioral prediction), Michela Chiappalone (Istituto Italiano di Tecnologia, Italy, on closed-loop neuro-hybrid interfaces), Igor Schreiber (University of Chemistry and Technology of Prague, Czech Republic on stability analysis of reaction networks), Thao Dang (CNRS/VERIMAG, France, on research odyssey of Oded Maler), Alexandre Donzé (Decyphir SAS, France, on formal barbaric systems biology), and Eugene Asarin (IRIF, University Paris Diderot and CNRS, France, on timed patterns and their monitoring).

HSB 2019 had 40 Program Committee (PC) members who provided detailed reviews of the submitted contributions, out of which nine articles were accepted for

presentation during the single-track sessions and appear as full or short papers in these proceedings. To ensure the highest quality for this volume, five submissions underwent a second round of review or a shepherding process before inclusion in the proceedings. The proceedings also include three invited papers from our invited speakers.

As the program co-chairs, we are extremely grateful to the PC members and the external reviewers for their work and the valuable feedback they provided to the authors. We thank all the members of the HSB Steering Committee, for their advice on organizing and running the conference. Our special thanks go to David Šafránek for helping us with the organization and for securing our sponsors. We are pleased to acknowledge the financial support kindly received from the National Center for Systems Biology of the Czech Republic (C4SYS) and the Faculty of Information Technology, Brno University of Technology, Czech Republic. We acknowledge the support of the EasyChair conference system during the reviewing process and the production of these proceedings. We also thank Springer for publishing the HSB proceedings in its *Lecture Notes in Bioinformatics* series. Finally, we would like to thank all the participants of the conference. It was the quality of their presentations and their contribution to the discussions that made the meeting a scientific success.

June 2019

Milan Češka  
Nicola Paoletti

# Organization

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## **Invited Abstracts**

# Modelling and Personalisation Techniques for Behavioural Prediction and Emotion Recognition

Marta Kwiatkowska

Department of Computer Science, University of Oxford, UK

**Abstract.** The prevalence of wearable sensing devices and smartphones is resulting in a multitude of physiological data being collected, for example heart rate, gait and eye movement. Driven by applications in health and behavioural monitoring, as well as affective computing, there is a growing demand for computational models that are able to accurately predict multimodal features in a variety of contexts. While machine learning models excel at identifying features in physiological signals, they lack reliability guarantees and need to be adapted to the user. This talk will give an overview of modelling and personalisation techniques developed as part of the AffecTech project<sup>1</sup> and their applications in the context of biometric security and emotion recognition. Future challenges in this important field will also be discussed.

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<sup>1</sup> <http://www.cs.ox.ac.uk/projects/AFFECTech/index.html>.

# Timed Patterns: From Definition to Matching and Monitoring

## A Survey in Memoriam Oded Maler

Eugene Asarin

IRIF, Université de Paris and CNRS, Paris, France

**Abstract.** At timed level of abstraction, system behaviors are considered as sequences of discrete events (from a finite alphabet) and real-valued time lapses between them; or as discrete-valued signals over continuous time. Initiated by works of Alur & Dill and aiming modeling and verification of real-time sequences, this approach became quite popular and was successfully extended to other domains. As usual in verification, sets of timed behaviors were defined by (timed) automata, and by logical formulas.

In mid 90s, Oded Maler initiated a search for simpler, suitable for engineers, and still powerful formalism to describe sets of timed behaviors. After overcoming many technical obstacles, timed regular expressions were born, and their equivalence to timed automata proven. In follow-up works, alternative formalisms have been proposed by several researchers.

In 2010s, Oded Maler and his group came back to timed regular expressions, with a new optics of pattern-matching: given a (large) record of timed behavior of a system, and a timed regular expression describing patterns of interest (e.g. faulty sequences), detect all the occurrences of the pattern in the record. Most of this research is automata-free: pattern-matching algorithms work directly on timed behaviors. Efficient algorithms have been developed and implemented, allowing off-line and on-line pattern-matching, and using several formalisms for pattern specification, and applications to monitoring prospected.

In this talk I will present the timed view on system behaviors, and the two periods of timed regular expressions: theoretical study on expressiveness from 1990s and practice-oriented works on pattern-matching and monitoring from 2010s. No special knowledge is required from the audience. This will also be a memorial talk, on Oded's philosophical, creative and personal style of choosing research topics, leading research, and supervising students and co-workers.

# From Sensitive to Formal Barbaric Systems Biology

Alexandre Donzé

Decyphir SAS, France

**Abstract.** Oded Maler often characterized as “barbaric” some of his approaches to solving complex problems. By this, he meant the modern meaning, i.e., “unsophisticated”, for example when he suggested to compute bunch of simulations to approximate reachable sets of dynamical systems - at a time when the trend was to fill pages of fancy theorems in advanced computational geometry or functional analysis. However, it is fair to say that he was in effect a true Barbarian but in the antique sense: Ancient Greeks called “Barbarians” those who were not Greek themselves. As a matter of fact, Oded as a scientist knew no boundaries: he wandered freely between theoretical computer science and applied mathematics, control theory, logics, Physics and Biology, etc. Always with humility, humor, and avid curiosity about local customs and knowledge he would bring in his own extended scientific baggage with genuine intention and efforts to mix in and contribute to the fields he was exploring.

Systems Biology was a natural target of these explorations. There he found problems related to hybrid dynamical systems, another cross-field he contributed to pioneer. Together with various collaborators including biologists, both from wet labs and theoreticians, and myself, we experimented with and improved techniques such as systematic simulation [1, 3] and the monitoring of signal temporal logic [2, 4, 5], an extension of a logic used in program verification adapted to continuous and real-world processes, to help in particular with the difficult problem of parameter uncertainty in the modeling of living systems. I will try to recount some results we obtained and the avenues of research that this work from Oded’s legacy helped create and remain open today.

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