

## Subseries of Lecture Notes in Computer Science

### Series Editors

Sorin Istrail

*Brown University, Providence, RI, USA*

Pavel Pevzner

*University of California, San Diego, CA, USA*

Michael Waterman

*University of Southern California, Los Angeles, CA, USA*

### Editorial Board Members

Søren Brunak

*Technical University of Denmark, Kongens Lyngby, Denmark*

Mikhail S. Gelfand

*IITP, Research and Training Center on Bioinformatics, Moscow, Russia*

Thomas Lengauer

*Max Planck Institute for Informatics, Saarbrücken, Germany*

Satoru Miyano

*University of Tokyo, Tokyo, Japan*

Eugene Myers

*Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany*

Marie-France Sagot

*Université Lyon 1, Villeurbanne, France*

David Sankoff

*University of Ottawa, Ottawa, Canada*

Ron Shamir

*Tel Aviv University, Ramat Aviv, Tel Aviv, Israel*

Terry Speed

*Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia*

Martin Vingron

*Max Planck Institute for Molecular Genetics, Berlin, Germany*

W. Eric Wong

*University of Texas at Dallas, Richardson, TX, USA*

More information about this subseries at <https://link.springer.com/bookseries/5381>

Ion Petre · Andrei Păun (Eds.)

# Computational Methods in Systems Biology

20th International Conference, CMSB 2022  
Bucharest, Romania, September 14–16, 2022  
Proceedings

*Editors*

Ion Petre   
University of Turku  
Turku, Finland

Andrei Păun   
University of Bucharest  
Bucharest, Romania

ISSN 0302-9743                      ISSN 1611-3349 (electronic)  
Lecture Notes in Bioinformatics  
ISBN 978-3-031-15033-3              ISBN 978-3-031-15034-0 (eBook)  
<https://doi.org/10.1007/978-3-031-15034-0>

LNCS Sublibrary: SL8 – Bioinformatics

© The Editor(s) (if applicable) and The Author(s), under exclusive license  
to Springer Nature Switzerland AG 2022

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG  
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

## Preface

This volume contains the paper presented at the 20th International Conference on Computational Methods in Systems Biology (CMSB 2022), held at the University of Bucharest, Romania, during September 14–16, 2022. The conference was organized as an on-site event, with support for online participation.

The CMSB annual conference series was initiated in 2003. (<https://cmsb.sciencesconf.org/>). The webpage for this year's edition can be found at <https://fmi.unibuc.ro/en/cmsb-2022/>. The previous editions of the conference were held in Rovereto, Italy (2003), Paris, France (2004, 2011), Edinburgh, UK (2005, 2007), Trento, Italy (2006, 2010), Rostock, Germany (2008), Bologna, Italy (2009), London, UK (2012), Klosterneuburg, Austria (2013), Manchester, UK (2014), Nantes, France (2015), Cambridge, UK (2016), Darmstadt, Germany, (2017), Brno, Czech Republic (2018), Trieste, Italy (2019), Konstanz, Germany (2020, online), and Bordeaux, France (2021, hybrid).

The conference brings together researchers from across biological, mathematical, computational, and physical sciences who are interested in the modeling, simulation, analysis, inference, design, and control of biological systems. It covers the broad field of computational methods and tools in systems and synthetic biology and their applications. Topics of interest to the conference include, but are not limited to, methods and tools for biological system analysis, modeling, and simulation; high-performance methods for computational systems biology; identification of biological systems; applications of machine learning; network modeling, analysis, and inference; automated parameter and model synthesis; model integration and biological databases; multi-scale modeling and analysis methods; design, analysis, and verification methods for synthetic biology; methods for biomolecular computing and engineered molecular devices; data-based approaches for systems and synthetic biology; optimality and control of biological systems; modeling, analysis, and control of microbial communities. The conference welcomes new theoretical results with potential applications to systems and synthetic biology, as well as novel applications and case studies of existing methods, tools, or frameworks.

CMSB 2022 received 44 submissions: 20 regular papers (13 of them accepted), 4 tool papers (all accepted), 17 extended abstracts for poster presentations (13 accepted, but not included in this volume), and 3 extended abstracts for highlight talks (2 accepted, but not included in this volume). The conference followed a single blind review process. Each regular paper was reviewed by three program committee members. Each tool paper had four reviewers: two member of the Tool Evaluation Committee for the quality of the tool itself, its usability and documentation, and two members of the Program Committee for the scientific contribution of the paper. The extended abstracts were subject to a lighter review process, coordinated by the PC chairs. The submissions accepted to CMSB 2022 span a broad range of topics in

chemical reaction networks, Boolean networks, continuous and hybrid models, machine learning, and software tools.

We had five invited talks at CMSB 2022 given by Alessandra Carbone (Sorbonne Université, France), Gabriela Chiosis (Memorial Sloan Kettering Cancer Center, USA), Loïc Paulevé (CNRS, Laboratoire Bordelais de Recherche en Informatique, France), Alfonso Rodríguez-Patón (Universidad Politécnica de Madrid, Spain), and Erik Sonnhammer (Stockholm University, Sweden). The abstracts of their talks are included in the front matter of this volume.

We are very grateful to the members of the Program Committee, to the members of the Tool Evaluation Committee, and to all our reviewers for their thoughtful and diligent work. We thank Springer for the generous sponsorship of the best paper awards and for the support in producing this volume. We also want to thank the CMSB steering committee, especially François Fages, for their support in organizing this edition of the conference.

July 2022

Ion Petre  
Andrei Păun

# Organization

## Program Committee Chairs

Ion Petre	University of Turku, Finland, and National Institute for R&D in Biological Sciences, Romania
Andrei Păun	University of Bucharest and National Institute of R&D for Biological Sciences, Romania

## Steering Committee

Alessandro Abate (Guest Member)	University of Oxford, UK
Luca Cardelli	University of Oxford, UK
Eugenio Cinquemani (Guest Member)	Inria Grenoble Rhône-Alpes, France
François Fages	Inria Saclay, France
Monika Heiner	Brandenburg University of Technology Cottbus-Senftenberg, Germany
Tommaso Mazza	Istituto CSS-Mendel, Italy
Satoru Miyano	University of Tokyo, Japan
Loïc Paulevé (Guest Member)	CNRS, LaBRI, France
Ion Petre	University of Turku, Finland, and National Institute of R&D for Biological Sciences, Romania
Tatjana Petrov (Guest Member)	University of Konstanz, Germany
Gordon Plotkin	University of Edinburgh, UK
Corrado Priami	University of Pisa, Italy
Andrei Păun (Guest Member)	University of Bucharest and National Institute for R&D in Biological Sciences, Romania
Carolyn Talcott	SRI International, USA
Adelinde Uhrmacher	University of Rostock, Germany
Verena Wolf	Saarland University, Germany

## Program Committee

Alessandro Abate	University of Oxford, UK
Paolo Ballarini	Centrale Supélec, France
Daniela Besozzi	University of Milano-Bicocca, Italy
Luca Cardelli	University of Oxford, UK

Milan Češka	Brno University of Technology, Czech Republic
Eugenio Cinquemani	Inria Grenoble Rhône-Alpes, France
Eugen Czeizler	University of Helsinki, Finland
Franck Delaplace	Université Paris-Saclay, France
François Fages	Inria Saclay, France
Jérôme Feret	Inria Paris, France
Clémence Frioux	Inria Bordeaux, France
Ashutosh Gupta	IIT Bombay, India
Monika Heiner	Brandenburg University of Technology Cottbus-Senftenberg, Germany
Jane Hillston	University of Edinburgh, UK
Tommaso Mazza	Istituto CSS-Mendel, Italy
Andrzej Mizera	University of Luxembourg, Luxembourg
Jun Pang	University of Luxembourg, Luxembourg
Nicola Paoletti	Royal Holloway, University of London, UK
Loïc Paulevé	CNRS, LaBRI, France
Tatjana Petrov	University of Konstanz, Germany
Ovidiu Radulescu	University of Montpellier, France
Andre Ribeiro	University of Tampere, Finland
Maria Rodriguez Martinez	IBM Zürich Research Laboratory, Switzerland
Olivier Roux	École Centrale de Nantes, France
David Šafránek	Masaryk University, Czech Republic
Carolyn Talcott	SRI International, USA
Jing Tang	University of Helsinki, Finland
Adelinde Uhrmacher	University of Rostock, Germany
Andrea Vandin	Sant'Anna School for Advanced Studies, Italy
Verena Wolf	Saarland University, Germany
Christoph Zechner	Max Planck Institute of Molecular Cell Biology and Genetics, Germany

## Tool Evaluation Committee

Georgios Argyris	Technical University of Denmark, Denmark
Candan Çelik	Comenius University, Slovakia
Anastasis Georgoulas	University College London, UK
Lukrécia Mertová	Heidelberg Institute for Theoretical Studies, Germany
Samuel Pastva	IST Austria, Austria
Misbah Razzaq	INRAE Tours, France
David Šafránek (Chair)	Masaryk University, Czech Republic
Jakub Šalagovič	KU Leuven, Belgium
Matej Trojak	Masaryk University, Czech Republic



## **Additional Reviewers**

Georgios Argyris  
Salvatore Daniele Bianco  
Gerrit Grossmann  
Till Köster  
Lukrécia Mertová  
Gareth Molyneaux

Samuel Pastva  
Sylvain Soliman  
Mirco Tribastone  
Max Tschaikowski  
Hanna Wiederanders

## **Local Organization**

Florin Bilbîe  
Daniela Cheptea  
Marian Guşatu  
David Păcioianu  
Andrei Păun  
Ion Petre  
Nicoleta Siminea

## **Invited Talks**

# Targeting and Controlling Protein-Protein Interaction Networks in Disease

Gabriela Chiosis 

Program in Chemical Biology, Memorial Sloan Kettering Cancer Center  
New York, NY10021, USA  
chiosisg@mskcc.org

Disease states represent perturbations of the underlying tissue- and cell-specific molecular networks arising from both internal perturbations (e.g., genetic mutations, epigenetic alterations, proteotoxic stress) and external stressors (chemical or other environmental exposures, and/or lifestyle choices). The disease interactome is therefore a map of how individual stressors or a combination thereof alter interaction networks, including protein-protein interaction networks, and perturb the system as a whole. Analysis of cell- and tissue-specific networks may therefore shed light on organization of biological systems and subsequently, on disease vulnerabilities. However, deriving human interactomes across different cell and disease contexts remains a challenge. To this end, a solution is provided by discoveries in disease biology that link stressors-induced protein-protein interaction networks perturbations to the formation of epichaperomes, pathologic scaffolds composed of tightly bound chaperones, co-chaperones, and other factors. Epichaperomes mediate how thousands of proteins anomalously interact and organize inside cells, which aberrantly affects the function of protein networks, and in turn, cellular phenotypes. Therefore, capturing epichaperomes and the proteome at large negatively impacted by these critical scaffolds provides informative clues for direct access to protein-protein interaction networks perturbations in diseases, and to the functional outcome of such changes in native biological systems, providing previously unattainable systems level insights into disease-specific stressor adaptation mechanisms. We introduced the term epichaperomics to describe the affinity-purification method that uses epichaperomes as baits to analyze context-specific alterations in protein connectivity and study disease specific protein-protein interaction networks. We here present an overview of the platform, from epichaperomics probes to bioinformatics pipelines, and provide proof-of-principle applications of the method in investigating the biology of Alzheimer's disease and in deriving new treatment paradigms for cancer.

**Keywords:** Epichaperomics · Cell- and tissue-specific protein-protein interaction networks · Alzheimer's disease and cancer

## References

1. Rodina, A., et al.: The epichaperome is an integrated chaperome network that facilitates tumour survival. *Nature*. **538**(7625), 397–401 (2016). <https://doi.org/10.1038/nature19807>
2. Joshi, S., et al.: Pharmacologically controlling protein-protein interactions through epichaperomes for therapeutic vulnerability in cancer. *Commun Biol*. **4**(1), 1333 (2021). <https://doi.org/10.1038/s42003-021-02842-3>
3. Ginsberg, S.D., et al.: Disease-specific interactome alterations via epichaperomics: the case for Alzheimer’s disease. *FEBS J*. **289**(8), 2047–2066 (2022). doi: <https://doi.org/10.1111/febs.16031>
4. Inda, M.C., et al.: The epichaperome is a mediator of toxic hippocampal stress and leads to protein connectivity-based dysfunction. *Nat Commun*. **11**(1), 319 (2020). <https://doi.org/10.1038/s41467-019-14082-5>
5. Ginsberg, S.D., et al.: The penalty of stress - epichaperomes negatively reshaping the brain in neurodegenerative disorders. *J Neurochem*. **159**(6), 958–979 (2021). doi:<https://doi.org/10.1111/jnc.15525>
6. Joshi, S., Wang, T., Araujo, T.L.S., Sharma, S., Brodsky, J.L., Chiosis, G.: Adapting to stress - chaperome networks in cancer. *Nat Rev Cancer*. **18**(9), 562–575 (2018). <https://doi.org/10.1038/s41568-018-0020-9>

# Boolean Networks as a Link Between Knowledge, Data, and Quantitative Models

Loïc Paulevé

University of Bordeaux, CNRS, Bordeaux INP, LaBRI, UMR 5800, F-33400  
Talence, France

loic.pauleve@labri.fr  
<https://loicpauleve.name>

By bridging the gap between dynamical systems and their partial observation, computational models of biological processes aim at uncovering key mechanisms driving cellular dynamics, and ultimately predict their behavior under unobserved conditions. With this perspective, Boolean Networks (BNs) are widely adopted for modeling signaling pathways and gene and transcription factor networks, as their specification requires little parameters on top of the known molecular interactions.

The “Most Permissive” (MP) [3] dynamics of BNs allow a formal reasoning on behaviors of underlying quantitative models, without additional parameters. Moreover, the complexity for characterizing dynamical properties related to trajectories and attractors makes them considerably more tractable than with traditional synchronous and asynchronous modes and enables genome-scale analysis, as demonstrated with the `mpbn` tool<sup>1</sup>.

By leveraging the properties of MPBNs, we are developing `BoNesis`<sup>2</sup>, a logic programming interface for the automatic synthesis of BNs from complex dynamical properties [1, 2]. This approach allows integrating knowledge on pairwise gene and transcription factor interactions, as available in databases or by inference methods, with observation data such as single-cell RNA sequencing, to infer BNs reproducing cellular differentiation processes, and predict their reprogramming.

## References

1. Chevalier, S., Froidevaux, C., Paulevé, L., Zinovyev, A.: Synthesis of boolean networks from biological dynamical constraints using answer-set programming. In: 2019 IEEE 31st International Conference on Tools with Artificial Intelligence (ICTAI), pp. 34–41. IEEE (2019)
2. Chevalier, S., Noël, V., Calzone, L., Zinovyev, A., Paulevé, L.: Synthesis and simulation of ensembles of boolean networks for cell fate decision. In: Abate, A., Petrov, T., Wolf, V. (eds.) Computational Methods in Systems Biology. CMSB 2020. LNCS. vol. 12314. Springer, Cham (2020). [https://doi.org/10.1007/978-3-030-60327-4\\_11](https://doi.org/10.1007/978-3-030-60327-4_11)
3. Paulevé, L., Kolcák, J., Chatain, T., Haar, S.: Reconciling qualitative, abstract, and scalable modeling of biological networks. *Nat. Commun.* **11**(1) (2020)

---

<sup>1</sup> <https://github.com/bnediction/mpbn>

<sup>2</sup> <https://github.com/bnediction/bonesis>

# How to Infer Accurate Gene Regulatory Networks From Gene Expression

Erik Sonnhammer

Stockholm University, Sweden  
erik.sonnhammer@scilifelab.se

System-wide measurements of gene expression responses to perturbations such as knock-down experiments offer the possibility to reconstruct the underlying gene regulatory network (GRN). With no or little noise this is feasible, but at the high noise levels typically found in experimental data it is very challenging to infer accurate GRNs.

I will present some approaches that we have developed to counteract issues arising from noise. We show that explicit usage of the perturbation design adds important information and strongly boosts GRN inference accuracy. Some improvements to classical inference algorithms that can further boost accuracy for noisy data will be discussed, such as selection of informative genes or inference of the perturbation design [3, 4]. To control the false discovery rate of inferred GRNs we developed a general bootstrap-based method called NestBoot [1], and to assess the predictiveness of inferred GRNs despite the lack of a gold standard we developed a cross-validation approach BFECV [2].

Another challenge in GRN inference is selecting the optimal sparsity, and I will present a new approach for this based on the “GRN Information Criterion” [5]. Finally, to stimulate the GRN inference field to develop more accurate algorithms, we have created a web server <https://GRNbenchmark.org/> [6] where anybody can benchmark their method online on a range of datasets with varying noise levels.

## References

1. Morgan, D., Tjärnberg, A., Nordling, T.E.M., Sonnhammer, E.L.L.: A generalized framework for controlling FDR in gene regulatory network inference. *Bioinformatics*, **35**, 1026–1032 (2019)
2. Morgan, D., et al.: Perturbation-based gene regulatory network inference to unravel oncogenic mechanisms, *Sci. Rep.* **10**, 14149 (2020)
3. Seçilmiş, D. et al: Uncovering cancer gene regulation by accurate regulatory network inference from uninformative data. *NPJ Syst. Biol. Appl.* **6**, 37 (2020)
4. Seçilmiş, D., Hillerton, T., Nelander, S., Sonnhammer, E.L.L.: Inferring the experimental design for accurate gene regulatory network inference, *Bioinformatics*, **37**, 3553 (2021)
5. Seçilmiş, D., Nelander, S., Sonnhammer, E.L.L.: Optimal sparsity selection based on an information criterion for accurate gene regulatory network inference, *Frontiers in Genetics*, in press (2022)

6. Seçilmiş, D., Hillerton, T., Sonnhammer, E.L.L.: GRNbenchmark - a web server for benchmarking directed gene regulatory network inference methods, *Nucleic Acids Res.*, in press (2022). <https://doi.org/10.1093/nar/gkac377>

# **Sequence Space and Deep Learning to Better Understand Proteins**

Alessandra Carbone

Department of Computational and Quantitative Biology, Sorbonne Université  
and CNRS, France

`alessandra.carbone@lip6.fr`

I will explain how rethinking the sequence space with multiple probabilistic models leads to the functional classification of proteins and the reconstruction of protein-protein interaction networks with deep learning, two important problems in computational biology.



# **GRO: A Multicell Bacterial Simulator**

Alfonso Rodríguez-Patón

Universidad Politécnica de Madrid, Spain  
arpaton@fi.upm.es

GRO is an agent-based model for simulating the growth of programmed multicell bacterial populations. The goal of GRO is to predict the dynamics of complex microbial consortia. I will present some of the most relevant features of GRO.

# Contents

## Chemical Reaction Networks

Algebraic Biochemistry: A Framework for Analog Online Computation in Cells . . . . .	3
<i>Mathieu Hemery and François Fages</i>	
Abstract Simulation of Reaction Networks via Boolean Networks . . . . .	21
<i>Joachim Niehren, Athénaïs Vaginay, and Cristian Versari</i>	
Abstraction-Based Segmental Simulation of Chemical Reaction Networks . . .	41
<i>Martin Helfrich, Milan Češka, Jan Křetínský, and Štefan Martiček</i>	
Qualitative Dynamics of Chemical Reaction Networks: An Investigation Using Partial Tropical Equilibrations . . . . .	61
<i>Aurélien Desoevres, Peter Szmolyan, and Ovidiu Radulescu</i>	

## Boolean Networks

Prioritization of Candidate Genes Through Boolean Networks . . . . .	89
<i>Clémence Réda and Andrée Delahaye-Duriez</i>	
Variable Stabilisation in Boolean Monotonic Model Pools . . . . .	122
<i>Samuel Pastva</i>	
Variable-Depth Simulation of Most Permissive Boolean Networks . . . . .	138
<i>Théo Roncalli and Loïc Paulevé</i>	
Minimal Trap Spaces of Logical Models are Maximal Siphons of Their Petri Net Encoding . . . . .	158
<i>Van-Giang Trinh, Belaid Benhamou, Kunihiko Hiraishi, and Sylvain Soliman</i>	

## Continuous and Hybrid Models

Stability Versus Meta-stability in a Skin Microbiome Model . . . . .	179
<i>Eléa Thibault Greugny, Georgios N. Stamatias, and François Fages</i>	
Exact Linear Reduction for Rational Dynamical Systems . . . . .	198
<i>Antonio Jiménez-Pastor, Joshua Paul Jacob, and Gleb Pogudin</i>	
Limit Cycle Analysis of a Class of Hybrid Gene Regulatory Networks . . . . .	217
<i>Honglu Sun, Maxime Folschette, and Morgan Magnin</i>	

**Machine Learning**

Bayesian Learning of Effective Chemical Master Equations in Crowded Intracellular Conditions . . . . .	239
<i>Svitlana Braichenko, Ramon Grima, and Guido Sanguinetti</i>	
Probabilistic Multivariate Early Warning Signals. . . . .	259
<i>Ville Laitinen and Leo Lahti</i>	

**Software**

MobsPy: A Meta-species Language for Chemical Reaction Networks . . . . .	277
<i>Fabricio Cravo, Matthias Függer, Thomas Nowak, and Gayathri Prakash</i>	
Automated Generation of Conditional Moment Equations for Stochastic Reaction Networks . . . . .	286
<i>Hanna Josephine Wiederanders, Anne-Lena Moor, and Christoph Zechner</i>	
An Extension of ERODE to Reduce Boolean Networks By Backward Boolean Equivalence . . . . .	294
<i>Georgios Argyris, Alberto Lluçh Lafuente, Mirco Tribastone, Max Tschaikowski, and Andrea Vandin</i>	
eBCSgen 2.0: Modelling and Analysis of Regulated Rule-Based Systems . . .	302
<i>Matej Troják, David Šafránek, Branislav Brozmann, and Luboš Brim</i>	
<b>Author Index</b> . . . . .	311