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Ion Petre · Andrei Păun (Eds.)

Computational Methods in Systems Biology

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

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Editors
Ion Petre
University of Turku
Turku, Finland

Andrei Păun
University of Bucharest
Bucharest, Romania

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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

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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

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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[1].

By leveraging the properties of MPBNs, we are developing BoNesis[2], 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.

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[1] https://github.com/bnediction/mpbn

[2] 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.

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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.

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