SysMod: the ISCB community for data-driven computational modelling and multi-scale analysis of biological systems

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Summary: Computational models of biological systems can exploit on a broad range of rapidly developing approaches, including novel experimental approaches, bioinformatics data analysis, emerging modelling paradigms, data standards, and algorithms. A discussion about the most recent advances among experts from various domains is crucial to foster data-driven computational modelling and its growing use in assessing and predicting the behaviour of biological systems. Intending to encourage the development of tools, approaches, and predictive models, and to deepen our understanding of biological systems, the Community of Special Interest (COSI) was launched in Computational Modelling of Biological Systems (SysMod) in 2016. SysMod's main activity is an annual meeting at the Intelligent Systems for Molecular Biology (ISMB) conference, which brings together computer scientists, biologists, mathematicians, engineers, computational and systems biologists. In the five years since its inception, SysMod has evolved into a dynamic and expanding community as the increasing number of contributions and participants illustrate. SysMod maintains several online resources to facilitate interaction among the community members, including an online forum, a calendar of relevant meetings, and a YouTube channel with talks and lectures of interest for the modelling community. Since more than half a decade, the growing interest in computational systems modelling and multi-scale data integration has continued to inspire and support the SysMod community. Its members get progressively more involved and actively contribute not only to the annual COSI meeting but also to several related community workshops and meetings, which focus on specific topics, including particular techniques for computational modelling or standardisation efforts.

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1. Introduction

Advances in experimental technologies, such as multi-omics, sequencing, and mass spectrometry, among others, have resulted in unprecedented amounts of highly heterogeneous data. Computational modelling and methods enable the integration of these data into systems models representing the underlying complexity, and, typically, networks of interconnected biological processes. Novel methods and the types of -omics data being integrated into these models (whether to calibrate, parameterise, or validate them) are vast. They may, for instance, include transcriptomics, proteomics, and metabolomics, at the bulk and single-cell levels. Simulations of these models, in turn, allow us to interrogate the models' dynamics, characterise their emergent properties, and predict new properties (e.g., drug targets, biomarkers).

Computational modelling also plays an essential role in precision medicine. In this field, dynamic models are, for instance, used to model an individual patient's disease trajectory, facilitating patient stratification and patient-specific predictions (e.g., of drug responses). Computational modelling continues to push the boundaries by expanding to whole-cell, multi-scale, and multicellular models, providing new opportunities to accelerate the advancements of fundamental and applied sciences, such as molecular biology, bioengineering, and medicine. Interdisciplinary collaborations among computational systems biologists, molecular biologists, biochemists, engineers, biotechnologists, computer scientists, and mathematicians will continue to be critical to leverage the potential of the field altogether.

In 2016, the SysMod Community of Special Interest (COSI) of the International Society for Computational Biology (ISCB) was established, to foster communication among systems biologists, computational biologists, and bioinformaticians. Figure 1 on the facing page depicts SysMod's activities, topic areas, and integration into an ecosystem within the ISCB by thematic COSIs with a focus on complementary, yet adjacent subjects. The thematically closely related COSIs include Network Biology (NetBio), Biological Data Visualisation (BioVis), and, since 2018, Machine Learning in Computational Systems Biology (MLCSB). SysMod envisions to provide an interdisciplinary forum

for the discussing latest developments towards predictive, knowledge-based computer models of biological systems and processes (such as dynamic or logical models of metabolism, signalling, and regulatory processes) as well as methods that advance our understanding in biological science, precision medicine, and synthetic biology. By fostering interdisciplinary collaborations and the application of approaches from different fields that combine modelling and data, SysMod enables an advance in technology, data analysis, and data sharing as an opportunity to use data for creating more accurate, detailed, and re-usable predictive models.

2. Resources

SysMod invites researchers to contribute, contact, and interact with others in a variety of ways beyond its annual meetings.

The following resources contain information about the most recent events relevant to the community:

➢ the SysMod Twitter account ▼ @cosi_sysmod,

➢ the SysMod ▶ YouTube channel,

➢ the mailing list sysmod@googlegroups.com, and

➢ the SysMod website ⌂ sysmod.info.

3. Annual meetings

3.1. First annual meeting: Orlando, 2016

The first SysMod event was a one-day meeting on July 9, 2016, before the ISMB Conference in Orlando, Florida. The meeting featured a poster session, eight contributed talks, and three keynote presentations by (i) Vassily Hatzimanikatis, École Polytechnique Fédérale de Lausanne (EPFL), "Towards kinetic modelling of genome-scale metabolic networks without sacrificing stoichiometric, thermodynamic and physiological constraints" (Chakrabarti et al., 2013), (ii) Nathan Price, Institute for Systems Biology (ISB) and the University of Washington, "Metabolic analyses in microbes and humans" (Imam et al., 2015), and (iii) Ioannis Xenarios, Swiss Institute of Bioinformatics (SIB), "From biocuration to
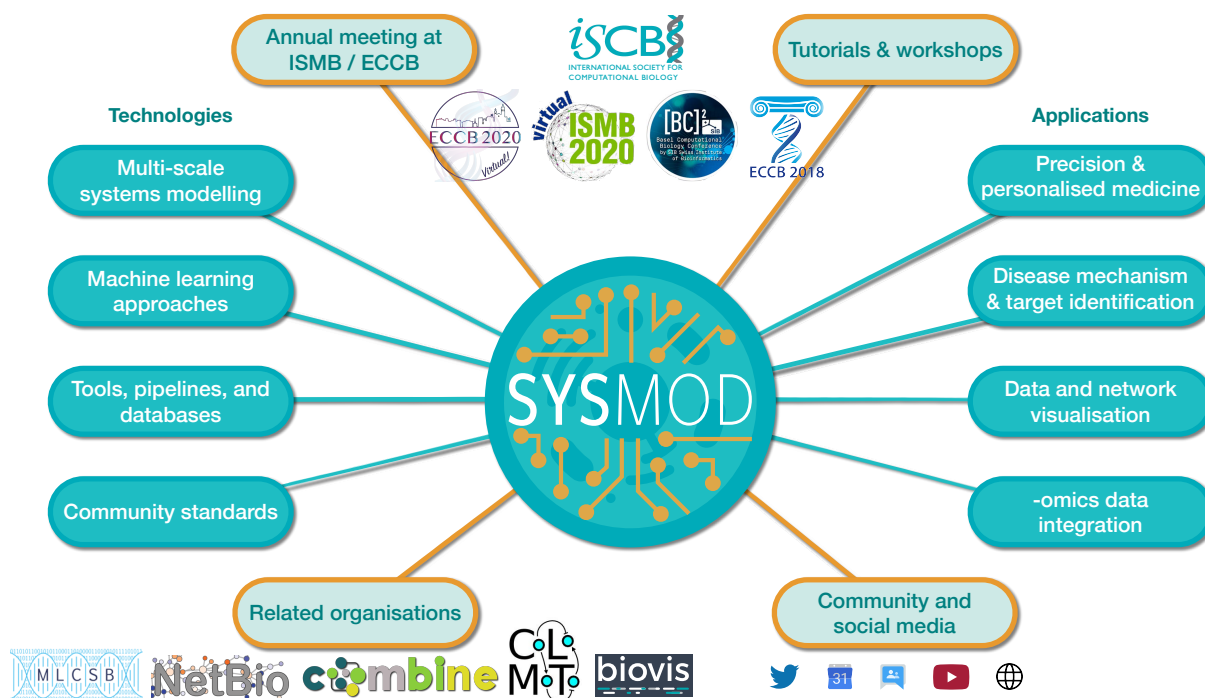
Figure 1 | Overview of the COSI SysMod. SysMod is an organisation within the International Society for Computational Biology (ISCB) that offers a variety of activities to its community, such as tutorials, workshops, and annual meetings as part of the conferences ISMB/ECCB. To this end, it provides various channels for communication, including popular social media platforms, and mailing lists. SysMod connects researchers from various fields whose expertise covers a plethora of topics on technologies and their applications. Many members of the SysMod community are active in related organisations, such as those shown to the bottom left.

model predictions and back." In a joint session with the NetBio COSI, four additional presentations followed the next day.

3.2. Second annual meeting: Prague, 2017

The second annual SysMod meeting took place on July 22, 2017, during the European Conference on Computational Biology (ECCB)/ISMB in Prague, Czech Republic. A common theme spanning the three sessions was variability resulting from biological systems, experiments, and simulations. The talks were organised into three thematic sessions: (i) Accounting for uncertainty in modelling and simulation, (ii) Using modelling to understand gene regulation, signalling, and response to drugs, (iii) Genome-scale and multi-scale modelling. Two keynotes were delivered by (i) Rainer Breitling, University of Manchester, "Modelling in uncertain times," and (ii) Jana Wolf, Max Delbrück Center

for Molecular Medicine, "Computational modelling of promoter occupancies in MYC-dependent gene regulation" (Lorenzin et al., 2016). The 13 speakers discussed how to maximise the accuracy and usefulness of computational models, given existing challenges. In 2017, SysMod accepted, for the first time, four proceedings papers (Cinquemani et al., 2017; Damiani et al., 2017; Kazeroonian et al., 2017; Pischel et al., 2017) out of 37 initial submissions.

3.3. Third annual meeting: Chicago, 2018

The third annual SysMod meeting took place on July 7, 2018, during the ISMB in Chicago, Illinois, and featured three sessions: (i) "Detailed models of individual cellular processes," (ii) "Comprehensive models of cells and tissues," and (iii) "Models of human physiology and disease." Keynote presentations were delivered by (i) Andre Levchenko, Yale University, "Variability and phe-

notype selection in invasive cancer spread," (ii) Peter Sorger, Harvard Medical School, "Trials, biomarkers, and data science," and (iii) John Tyson, Virginia Tech, "The cell division cycle: a closed loop of switches embedded in switches" (Novak et al., 2018). The meeting also featured ten contributed talks, four lightning talks, and 33 posters. A recurrent theme was the need for multi-scale models to explain how to integrate emergent molecular behaviours and patterns into processes and data at multiple scales of biological organisation. Several presenters discussed how signal integration across different scales was critical to define the interactions among cellular processes, bacterial infection, and cancer spread. The meeting stimulated vibrant discussions on challenges in systems modelling, and the need for collaboration within the modelling community, in particular with regards to the development of comprehensive multi-scale models. This discussion called for further efforts to make modelling more modular, to improve the association of models with their underlying data and assumptions, and to verify models, thus rigorously improving accuracy.

3.4. Fourth annual meeting: Basel, 2019

The fourth annual SysMod meeting took place on July 22, 2019, during the ISMB in Basel, Switzerland, and comprised three sessions spanning human cells and disease modelling, systems biology of microorganisms, and current trends in the field. Each of the three sessions featured a keynote speaker: (i) Trey Ideker, University of California, San Diego, "Interpreting the cancer genome through physical and functional models of the cancer cell," (ii) Edda Klipp, Humboldt-Universität zu Berlin, Germany, "Systematic integration of models and data for yeast growth, division and stress response" (Münzner et al., 2019), and (iii) Jörg Stelling, ETH Zürich, Switzerland "Systems analysis of cell-to–cell variability" (Azizoglu and Stelling, 2019). The first session, "Systems biology of human cells and diseases," covered the following emerging themes: modelling approaches for personalised medicine, disease diagnosis and treatment, and approaches to investigate heterogeneity in healthy and diseased tissues, such as tumours or in immune responses. The second session, "Systems biology of microorganisms," was centred around the theme

of using -omics data for integrative modelling of processes that are strongly interlinked at the cellular level, but measured separately at the population and single-cell levels. Further topics included computational tools for the analysis of -omics data and to predict metabolic interactions within microbial communities. The final session concluded the meeting with presentations on "Current trends in systems biology." These presentations discussed various computational approaches to infer dynamical information such as protein-folding states, mutation pathways and rates from an ensemble of instantaneous data, i.e., one time-point data. Physical whole-cell models that can connect molecular structure with biological function were also discussed. Such models aim at predicting how changes at the molecular level propagate to alter function at the cellular level. Furthermore, these models can improve our understanding of how biological macromolecules behave inside cells while navigating a spectrum of specific and nonspecific interactions in the presence of a variety of electrolytes, osmolytes, and other small molecules. Further discussion included how modelling techniques, in combination with large-scale -omics data, facilitate the elucidation of biochemical regulation mechanisms.

3.5. Fifth annual meeting: "Virtual," 2020

Due to the COVID-19 pandemic, the fifth annual SysMod meeting was held on July 13 to 14, 2020 as a virtual conference. The meeting featured three keynote speakers: (i) Paul François, McGill University, delivered the first keynote presentation, titled "Robotic mapping and generative modelling of cytokine responses." In this talk, he described an evolutionary algorithm to identify features of antigenicity using high-throughput temporal cytokine profiling. (ii) Douglas Lauffenburger, Massachusetts Institute of Technology as the second keynote speaker, presented "Cross-species translation of biological information via computational systems modelling frameworks" (Brubaker et al., 2019), in which he outlined a systems biology- and machine learning approach to translate genetic and phenotypic information from animal models to humans for pre-clinical to clinical stages. (iii) Carolyn Cho, Merck, Inc., gave the third keynote presentation on the topic "Quantitative and Systems Pharmacology (QSP) and Model-Informed Drug

Development (MIDD) of a 'Smart' Insulin," which can evaluate therapeutic modulation of its target and assist human dose prediction as well as the determination of its efficacy (Visser et al., 2020).

The first virtual SysMod meeting in 2020 discussed various modelling techniques, including flux balance analysis, machine learning, logical and kinetic modelling, combined with their application to a multitude of biological systems. The contributed presentations focused on constraint-based modelling of metabolic networks, organism-level modelling, novel methods for network modelling, and modelling of cell populations. In the first session, metabolic models were developed to rationalise strategies for (i) the optimisation of energy use, such as to identify alternative sources of reactive oxygen species, (ii) to optimise proteomic allocation, integrate different sources of information, and (iii) to identify a reduced genome for functional optimisation (Széliová et al., 2020). The second session on organism-level models included presentations on (i) a scalable model for prokaryote and human cells using a modular pipeline, (ii) a cross-inhibited Turing reaction-diffusion system to model the regeneration and homeostasis in planaria (Herath and Lobo, 2020), and (iii) the first mathematical model of cell cycle control in budding yeast that can exhibit sustained, autonomous oscillations through previously unknown network designs (Mondeel et al., 2020). These talks described the role of modelling in revealing underlying mechanistic insights by predicting novel molecular regulations.

Further presentations described how to infer missing information on kinase-substrate interactions using an electric circuit-based model for network propagation, and how loopy belief propagation with node belief updates can be used to investigate gene probability of being in specific states (Kotiang and Eslami, 2020). In the final session, studies using mixed cell populations in tissue and Peripheral Blood Mononuclear Cells (PBMCs) were presented. Single-cell RNA sequencing data of PBMCs was analysed using pathway activities measured by Boolean Omics Network Invariant-Time Analysis (BONITA, Palli et al., 2019). Also sorting, intercalation, and involution of tissue behaviours due to regulated cell adhesion were investigated using partial differential equations (Ko and Lobo, 2019). During the second day, a stochastic spatio-temporal model of DNA replication

that incorporates experimental genome structural data and protein mobility dynamics and probabilistic activation firing was presented (Windhager et al., 2019). The final talk presented a metric to exploit concepts of reliability engineering, elementary flux modes and minimal cut sets to calculate the robustness of *E. coli*, *Shigella*, *Salmonella*, and fungal genome-scale metabolic models (Libiseller-Egger et al., 2020). In this context, the amino acid metabolism was stated to be more fragile than the central carbon metabolism. Throughout the virtual SysMod meeting, PhD students and postdocs lively discussed efforts to integrate further -omics data aiming to improve mechanistic understanding of biological processes.

4. Highlights and outcomes

The various SysMod meetings had a substantial impact and the community and met with great interest (fig. 2 on the next page). The formats of scientific contributions varied between the years (fig. 2a on the following page), and the participation numbers steadily increased in the first four years, while remaining almost constant during COVID-19 (fig. 2b on the next page). High-quality contributions from the community, as well as keynote speakers from world-renowned institutes and the pharmaceutical industry, have undoubtedly helped to fuel this success.

Since 2018, the quality of SysMod contributions has been recognised through various awards. In 2018 in Chicago, Bhanwar Lal Puniya received the best poster award for his contribution to "Systems modelling of phenotypic plasticity of CD4+ T cell differentiation" (Puniya et al., 2018). In 2019 in Basel, three best poster awards recognised the contributions of young researchers: (i) Ulrike Münzner, "A Mechanistically detailed model of the cell cycle in *Saccharomyces cerevisiae*" (Münzner et al., 2019), (ii) Kazunari Kaizu, "Whole Cell Simulation of Bacteria from Genomic Sequence," and (iii) José Américo N. Leva F. de Freitas, "Modelling gene regulatory networks in oncogene-induced senescence." In 2020, the best three virtual posters were awarded to (i) Chaitra Sarathy, "Identifying characteristic features of metabolic states using Genome-Scale Metabolic Models" (Sarathy et al.,
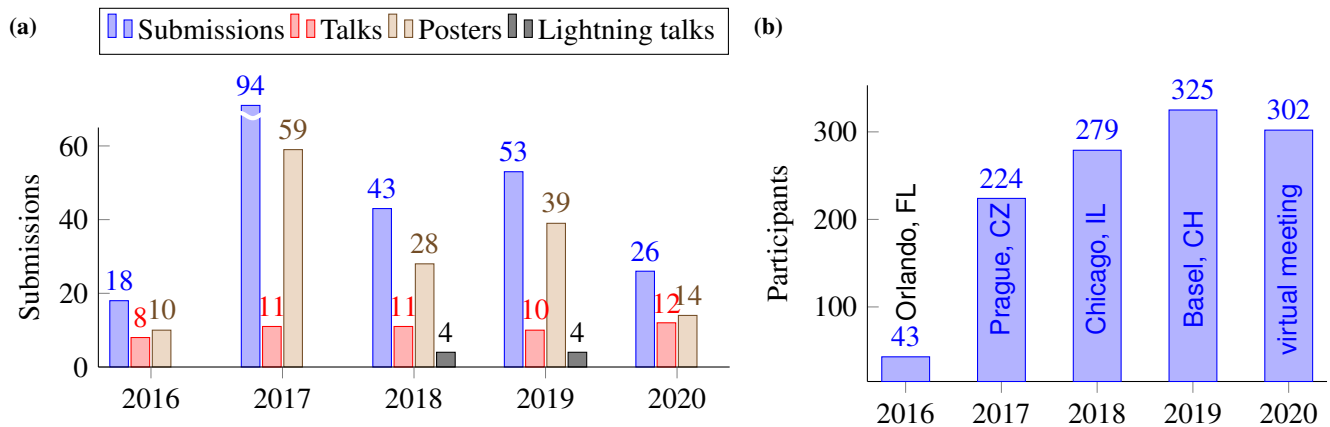
Figure 2 | Contributions and attendance of the SysMod annual meetings. **(a)** Numbers of keynotes, talks, lightning talks and posters contributed to the SysMod meetings. In 2018, the inception of the COSI for Machine Learning in Computational Systems Biology (MLCSB) enabled authors to submit their works to communities with specialised focus areas. **(b)** Numbers of registered conference participants of the SysMod meetings from 2016 to 2020.

2020), (ii) Narasimhan Balakrishnan, "Model reduction and optimal control for multicellular biological oscillator systems," and (iii) Aurélien Pélissier, "Computational model reveals a stochastic mechanism behind germinal center clonal bursts" (Pelissier et al., 2020).

5. Related events and partnerships

In addition to the annual meeting, SysMod partners with other modelling communities to provide opportunities to engage in scientifically relevant events throughout the year. For example, during the BC2 conference in Basel in 2019, SysMod, in partnership with the Consortium for Logical Models and Tools (CoLoMoTo, colomoto.org; (Naldi et al., 2015), organised a workshop focused on developing guidelines and best practices for annotation and curation of logical models (Niarakis et al., 2020). During the ECCB in 2020, two additional SysMod-related events took place: (i) hands-on tutorial on modelling software tools ("Computational modelling of cellular processes: regulatory vs metabolic systems") and (ii) the workshop on "Advances in computational modelling of cellular processes and high-performance computing" with the two SysMod coordinators, María Rodríguez Martínez and Jonathan R. Karr, as keynote speakers, and one SysMod coordinator, Anna Niarakis, as a

co-organiser. Additional public outreach activities include the monthly Online Cell Modelling Seminar organised by the Center for Reproducible Biomedical Modelling (reproduciblebiomodels.org/ dissemination-training/seminar/), the hackathons and conferences on Integrative Collaborative modelling in systems Medicine (INCOME) organised by Jan Hasenauer, Wolfgang Müller, and Olaf Wolkenhauer (www.integrative-pathway-models.de), and the COVID-19 disease map initiative (Ostaszewski et al., 2020a,b) with its weekly online presentation series.

6. Conclusion

SysMod has grown to a vital element of the ISMB/ECCB, complementing an already wide range of bioinformatics topics with systems biology modelling. This integration is only possible thanks to a remarkably agile computational and systems biology community that presents and actively proposes and discusses the latest developments of the field. SysMod provides a unique platform for a wide range of related activities, through which its members benefit from a regular exchange.

The fundamental principle that brings together the SysMod community is the increasing interest in *mech-*

anistic computational models as the key to gain new *knowledge* about biological processes. The SysMod community focuses on models that explicitly include the principles of natural sciences, such as biophysics and thermodynamics, interaction mechanisms, or spatiotemporal dynamics. Models are developed as computational tools that incorporate a wide range of quantitative data to predict and understand how biological systems function. Driven by this core value, SysMod regularly fosters discussion among experts from various fields who contribute to transforming biology from a qualitative and descriptive scientific discipline to a quantitative science based on engineering and computational analysis. As such, SysMod has contributed to the development of systems biology as a young field. With regards to global challenges such as the COVID-19 pandemic or climate change, SysMod with its virtual and personal conferences and forums paves the way for the establishments of new forms of friendly and cooperative interactions, which will determine the future of our global networking.

A. Appendix

A.1. Authors' contributions

AD, TH, and JT drafted the first version of the manuscript, which was finalised with significant contributions from MBa, CC, JRK, AN, and MRM, as well as input from all authors. JRK designed the SysMod branding (incl. the logo, poster, and presentation templates, etc.) and created the website sysmod.info which has been hosted and maintained by AD with support by TH and JRK. MBa, LC, AD, CC, and JSR invited or interacted with the keynote speakers. AD, TH, and MBa interacted with the ISCB team. JRK and AD wrote the annual meeting reports to ISCB. AD, TH, and JRK managed and reviewed this COSI's finances. AD reviewed student travel fellowship applications and initiated the poster prizes. AD, JRK, and JT mainly interacted with the community via mailing lists, social media platforms, and online forums such as ISCB connect. Scientific contributions to the SysMod program were delivered by MBa, followed by JT, and CC, AD, JSR. JRK, AD, and LC gave opening speeches and TH, CC, and AD closed SysMod events with their remarks. AD, LC, TH, JRK, MBa, CC, AN, MRM, JSR, and JT chaired individual sessions during annual events. AD followed by LC as well as CC, TH, JRK, MRM, JSR, and JT acted as program chairs for annual events. All SysMod coordinators jointly reviewed submitted scientific contributions. All authors read and approved the final manuscript.

Conflict of interest: none declared.

A.4. Abbreviations

BioVis	Biological Data Visualisation
BONITA	Boolean Omics Network Invariant-Time Analysis
CoLoMoTo	Consortium for Logical Models and Tools
COVID-19	Corona Virus Disease 2019
COSI	Community of Special Interest
DFG	*Deutsche Forschungsgemeinschaft*
ECCB	European Conference on Computational Biology
EPFL	École Polytechnique Fédérale de Lausanne
ETH	Eidgenössische Technische Hochschule
H2020	Horizon 2020
INCOME	Integrative Collaborative modelling in systems Medicine
ISB	Institute for Systems Biology
ISCB	International Society for Computational Biology
ISMB	Intelligent Systems for Molecular Biology
MIDD	Model-Informed Drug Development
MLCSB	Machine Learning in Computational Systems Biology
NetBio	Network Biology
NIH	National Institutes of Health
PBMC	Peripheral Blood Mononuclear Cell
QSP	Quantitative and Systems Pharmacology
SIB	Swiss Institute of Bioinformatics
SysMod	Computational Modelling of Biological Systems
UCSD	University of California, San Diego

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