Poster presentation

How to formalise the meaning of a bio-model: a case study
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Introduction

Systems biology reconstructs biological phenomena in order to develop explanatory models of living systems. These models are represented precisely in terms of mathematical expressions. However, the meaning of a model usually is not formally specified but only described in natural language. This is something which hampers the development of computer-aided modelling in systems biology. Here, we discuss a framework for specifying the meaning of bio-models. We show that semantics appears on different levels: the meaning of the model as a whole, the meaning of the model's components, and the meaning of the model's behaviour. Each level has an intrinsic and extrinsic facet. We illustrate our framework by sketching what must be considered for a formal semantics of two simple numerical models of the cell cycle.

Conceptual framework

A bio-model can be seen as a binary relation between a formal (mathematical or computational) expression and the modelled biological reality. This introduces two sides of the meaning of the bio-model: The mathematical expression bears meaning by itself without referring to the biological reality. It can be interpreted, analysed, and used in computational simulations without knowing what it represents. We call this side the intrinsic meaning of the bio-model. However, a bio-model is more than a pure syntactical formal expression: it describes a piece of biological reality and thereby also exhibits an extrinsic meaning. For both meaning sides of a bio-model three pragmatic meaning levels can be identified: (1) The mean-

ing regarding the model as a whole accounts for its intention. (2) The meaning regarding the components of the model accounts for its structure. (3) The meaning regarding the dynamics of the model accounts for its behaviour. The extrinsic/intrinsic sides of the three levels together form the six **meaning facets**. The meaning facets are views at the meaning of a bio-model from different perspectives. We claim that a formal semantics of a bio-model has to incorporate all of these meaning facets and the relations between them.

In order to make the notion of the meaning facets of bio-models more concrete Table 1 shows typical questions for each of the meaning facets. The answers to these questions have to be formalised in order to arrive at a semantic description of a bio-model.

Case Study

In order to illustrate the conceptual framework of the meaning facets we sketch the meaning of two cell cycle models by Tyson [1]. The first model consists of a set of ordinary differential equations (ODEs) where each equation models the temporal evolution of the concentrations of one of the involved substances wrt. the concentrations of the other substances. The second model is a mathematical abstraction of the first model under certain additional biological assumptions. The variables in the second models do not represent concentrations of biological molecular species but rather are aggregated abstractions of specific concentration variables from the first model. Thus the variables of the second model can not be assigned

Table 1: Typical questions to answer in order to account for the meaning facets of a bio-model.

Intrinsic	Extrinsic
Intentional	
Which mathematical **formalism** is used? How is the formalism interpreted and executed? How is the formalism used to simulate the behaviour?	Which biological **system** is addressed? What does the model stand for in the biological reality? What is the aim of the model?
Structural	
What is the structure of the mathematical **expression**? What are the mathematical entities of the model (equations, terms, variables, rules)?	Which biological **components** are addressed by model? What are the modelled biological objects and relations? How do model entities map these biological components?
Behavioural	
Which **simulation** results does the model show? What are characteristic types of dynamical behaviour (e.g. attractors)? Which parameter settings are used therefore?	Which biological **phenomenon** correlates with which type of dynamical behaviour of the model? Which experimental data are reproduced by simulation results?

directly to molecular species as it is possible for the first model. This shows that the reconstruction of the meaning of a bio-model has to incorporate the mathematical structure of the model.

In [3] we show how the BioModels Database [2] entry for the first Tyson cell cycle model can be extended according to our meanings facets. This extension incorporates the mathematical model structure and accounts for the modes of behaviour of the model. In the current stage of the project we possess a semi-formal specification of the semantics of both Tyson models. This specification makes reference to and contributes part of a proposed *Model Ontology* (MO) that formally describes concepts typically used in biological modelling. Like in the BioModels Database [2] the grounding of the biological meaning is carried out by means of external references (hyperlinks) to bioinformatic databases. For details and results of this case study see the project homepage: http://www.infor matik.uni-jena.de/csb/prj/sembiotics/.

Summary
The meaning facets suggested here can serve as a guideline to arrive at reasonable formal semantics of bio-models. We illustrated this using Tyson's cell cycle models. Our meaning facets can be seen as a methodological commitment that should be followed when modelling biological processes. They offer a set of criteria for systematically constructing bio-models and for reconstructing their meaning. Our approach also addresses aspects of the meaning that existing approaches did not, e.g. the meaning of behaviours and the meaning of aggregated abstract model variables. It therefore seems appropriated as a basis for a new class of knowledge-based modelling tools that helps the working biologist to understand bio-systems.

References
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