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TOWARDS COMPOSING ML-RULES MODELS

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ABSTRACT

In cell biology, particularly to describe intra-cellular dynamics, network centered models prevail. Reusing those models requires additional effort as it often prevents a traditional black box based composition, i.e., aggregation, but asks for a fusion of models, where the internals of the models to be composed (not only their interfaces) are accessible as well. This is particularly the case if multi-level models, as those defined in ML-Rules, shall be composed. Still declarative interfaces that are separated from the concrete models help in retrieving suitable models for composition, whether those are aggregated or fused at the end. Here, we present a concept for composing multi-level network centered models.

1 MODEL COMPOSITION AND HIERARCHICAL MODELS

Component-based modeling refers to building models from predefined model components, i.e., the reuse of existing models. In many technical applications areas (e.g., modeling vehicles), we can find widely accepted model repositories. However, some application areas such as cell biology lack those widely accepted, modular building blocks so far. Although cells can be viewed as reactive systems (Fisher et al. 2011) with a clear boundary to their environment (and thus lend themselves to the metaphor of building blocks), most cell biological modeling focus on intra-cellular dynamics and describing signaling or metabolic pathways as reaction networks (Barabási and Oltvai 2004). Consequently, if existing reaction-based models shall be reused and composed, certain efforts are required to compose those (Randhawa et al. 2009). The situation is aggravated when composing reaction-based models with hierarchically nested structures.

2 COMPOSITION OF ML-RULES MODELS

ML-Rules is a rule-based, multi-level modeling formalism for cell biological systems (Maus et al. 2011). Models comprise attributed *species* that are organized in populations and can be hierarchically nested. Such as the number of species, the species hierarchy can change during simulation by applying reactions, which are defined as rules. These hierarchical structures reflect the organization of the modeled system, e.g., a cell comprising cytosolic compartments that again can comprise lysosomes and so on. Composing hierarchically and dynamically nested ML-Rules models faces further problems. The composition needs to assemble the initial structure of the composed model. Moreover, as each compartment in the hierarchical structure forms a context for rules, the consistency of these contexts needs to be addressed, as rules may or may not be applied in specific contexts.

Therefore, we distinguish between two kinds of composing models: *fusion* and *aggregation*. Similar to (Randhawa et al. 2009), the internal structure of model components is accessible in fusion. Thus, all species

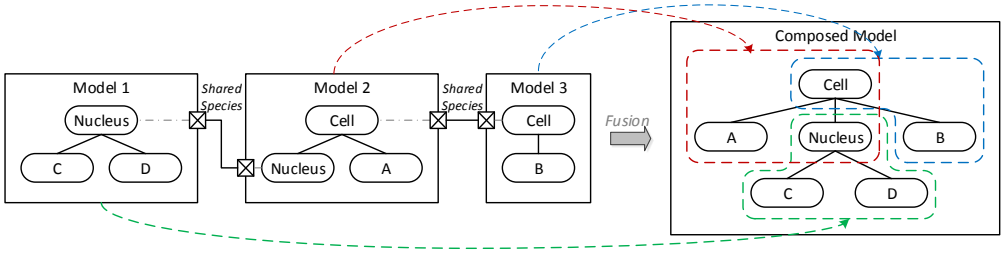

Figure 1: (Left) Three models that shall be composed. (Right) The result of this composition.

can be matched in principle. Currently, species with the same name are matched by default (if attributes and structure are equal). If the naming slightly differs, having the same attributes and nested structure may be another way of identifying suitable candidates for matching. To prevent that rules are applied in inconsistent contexts, a set of rules with a minimally constrained context can be created. However, in both cases, name matching and providing a context for rules, it is important that the user checks the fused model. The result of the fusion is a single model replacing the initial models in the simulation. In contrast to (Randhawa et al. 2009), this model is not flat, but preserves the structure of the initial models (see Figure 1). Aggregation can be viewed as restricted and controlled variant of fusion, but may likely be less applicable. As aggregation only allows accessing the interfaces of components but not their internal structure, it resembles a "classic" composition of reusable model components where all interaction points are declared in the interface.

Declarative, formalism independent interfaces, which are separated from the concrete model definition, can be exploited to support a composition of models (Röhl and Uhrmacher 2008). Our interfaces include model parameters and interaction points in terms of species. In addition, interfaces can be annotated with further metadata to support reusing models (see (Novère et al. 2005)). However, the interfaces have different meanings in fusion and aggregation. Whereas in fusion interfaces are merely used for retrieving suitable model components and their initialization (via parameters), in aggregation the interfaces additionally declare the exclusive points of interaction of these model components. Currently, we are exploring additional means to support a semantically valid composition of ML-Rules, inspired by Szabo and Teo (2009).

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REFERENCES

Barabási, A.-L., and Z. N. Oltvai. 2004, February. "Network biology: understanding the cell's functional organization". *Nature Reviews Genetics* 5 (2): 101–113.

Fisher, J., D. Harel, and T. A. Henzinger. 2011. "Biology as Reactivity". *CACM* 54 (10): 72–82.

Maus, C., S. Rybacki, and A. M. Uhrmacher. 2011. "Rule-based multi-level modeling of cell biological systems". *BMC Systems Biology* 5 (166).

Novère, N. L., A. Finney, M. Hucka et al. 2005. "Minimum information requested in the annotation of biochemical models (MIRIAM)". *Nature Biotechnology* 23 (12): 1509–1515.

Randhawa, R., C. A. Shaffer, and J. J. Tyson. 2009, October. "Model aggregation: a building-block approach to creating large macromolecular regulatory networks". *Bioinformatics* 25 (24): 3289–3295.

Röhl, M., and A. M. Uhrmacher. 2008. "Definition and analysis of composition structures for discrete-event models". In *Proc. of the 2008 Winter Simulation Conference*, 942–950.

Szabo, C., and Y. M. Teo. 2009. "An Approach for Validation of Semantic Composability in Simulation Models". In *Principles of Advanced and Distributed Simulation (PADS 2009)*, 3–10.