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EXPLOITING EQUATION-FREE ANALYSIS FOR MULTI-LEVEL, AGENT-BASED MODELS IN CELL BIOLOGY

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ABSTRACT

Multi-level modeling approaches have been successfully applied in systems biology to model complex systems with different levels of organization. They allow for straightforwardly integrating upward and downward causation as well as compartmental dynamics. This makes multi-level models powerful, but also expensive to simulate. Consequently, the effort required for comprehensive simulation studies with complex multi-level models is often prohibitive. One way to decrease the demand for simulations is to apply analysis methods. However, most approaches focus on differential equations models and cannot handle models with stochasticity or dynamical nesting. Among the new approaches that allow for analysis of complex systems is *equation-free analysis*, which has been applied to perform coarse level bifurcation analysis in various areas. We present the integration of an equation-free method into the simulation language *Simulation Experiment Specification on a Scala Layer (SESSL)* to analyze bi- or multistability of biochemical models, defined in the multi-level modeling language *ML-Rules*, and its role in cell fate selection.

1 INGREDIENTS AND INTERACTION

ML-Rules (Helms et al. 2017) is a rule-based modeling language for dynamically nested biochemical reaction networks. It allows for concisely describing executable multi-level models that can be simulated with a number of algorithms. The *Simulation Experiment Specification on a Scala Layer (SESSL)* (Ewald and Uhrmacher 2014) is the premier way to run complex simulation studies with ML-Rules. SESSL is an internal domain-specific language that permits to specify executable experiments with a declarative look-and-feel. Experiment specifications in SESSL are valid Scala code, but maintain readability and succinctness due to SESSL's syntactical shortcuts. SESSL does not perform actual computations, but serves as a common interface to heterogeneous tools. Bindings connect SESSL to other software components, for example simulation packages like ML-Rules. Being an internal domain-specific language, SESSL can be extended with user-provided Scala code on-the-fly. This facilitates the rapid development of complex experimentation strategies, such as integrating the actual simulation in another algorithm (e.g. simulation-based optimization).

Equation-free analysis utilizes the fact that many complex systems defined on a microscopic level show a relatively low-dimensional macroscopic behavior due to a time-scale separation. The fast time scales quickly converge to the so-called slow manifold representing the macroscopic behavior. The method facilitates numerical analysis on the macroscopic level even though there are no equations explicitly given on this level (Kevrekidis and Samaey 2009). Short simulation bursts and subsequent suitable numerical evaluations combined with so-called lifting and restriction operators allow switching between the microscopic simulation level of the complex model and the macroscopic level of the numerical analysis. Examples of coarse level analyses are continuation methods and numerical bifurcation analysis as well as coarse level integration. Implicit methods allow minimizing the numerical error of this approach, which is mainly due to the problem that the lifting operator cannot be constructed to map precisely on the low-dimensional

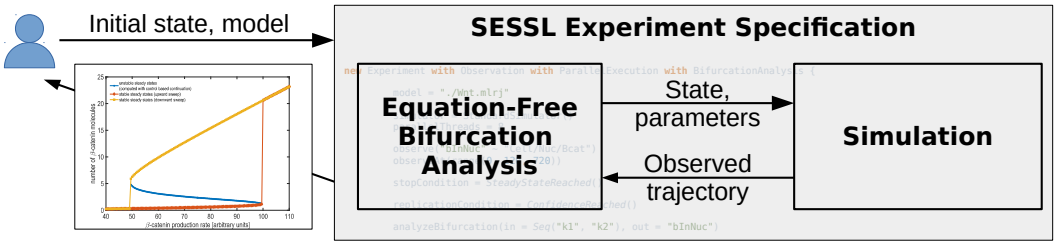

Figure 1: Integration of the equation-free bifurcation analysis method with ML-Rules in SESSL.

manifold representing the macroscopic behavior (Marschler et al. 2014). The obtained results allow for a systematic parameter-dependent analysis, which could not be achieved by brute-force simulation as these were too costly in time.

The *integration* of the equation-free analysis in SESSL is depicted in Fig. 1. Both the analysis and the simulation are components in a SESSL experiment, which contains some model-specific initial conditions and the description of an observable. The equation-free analysis iteratively triggers the execution of relevant simulation set-ups and receives the trajectories of the observable as results. To produce these results, the simulation component might detect and determine the steady state of a run, execute several replications of the run and compute a mean trajectory to return to the analysis component.

2 BIFURCATION ANALYSIS FOR BIOCHEMICAL MODELS

The differentiation of cells into specialized tissues involves a series of cell fate decisions within which signaling pathways, such as the Wnt signaling pathway, its regulation, and interaction with other pathways play a central role. It has been shown that bistability or multistability that arises within the cross-talk of Wnt and other signaling pathways such as Notch acts akin to cell fate selection (Kay et al. 2017). In extending our current ML-Rules model of the Wnt signaling pathway (Haack et al. 2015) toward a multi-cellular model the interaction with other signaling pathways requires specific care. Here, the systematic bifurcation analysis of ML-Rules models as enabled by our new architecture will be an essential method to be included into the modeling process. Figure 1 (left) indicates bistability by an up- and down-sweep for a test problem, which shows the necessity of a systematic bifurcation analysis.

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