

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. Unfortunately, the effort required for comprehensive simulation studies with complex multi-level models is often prohibitive. Equation-free analysis reduces the demand for simulations and facilitates numerical analysis of the macroscopic behavior of a system.

We present the integration of equation-free analysis through control-based continuation into the simulation language SESSL to analyze multistability of biochemical models. It combines ideas from numerical continuation and feedback-control to stabilize the system state and track unstable phenomena. The resulting bifurcation diagram divides parameter space into regions of qualitatively different behavior and is a key element in understanding nonlinear dynamics. We use a Wnt shuttling model as a case study.

Wnt signaling is imperative for embryonic development and homeostatic self-renewal in a number of adult tissues [2]. It has been shown that multistability that arises within the cross-talk of Wnt and other signaling pathways such as Notch is related to cell fate selection [5]. Since β -catenin acts as intracellular signal transducer, it is the primary protein to observe.

Experimental Design

- Biochemical model defined in the multi-level modeling language ML-Rules [4]
- Declarative description with Simulation Experiment Specification via a Scala Layer (SESSL) [3]
- SESSL takes care of stochasticity of the model and model observation
- Automated bifurcation analysis

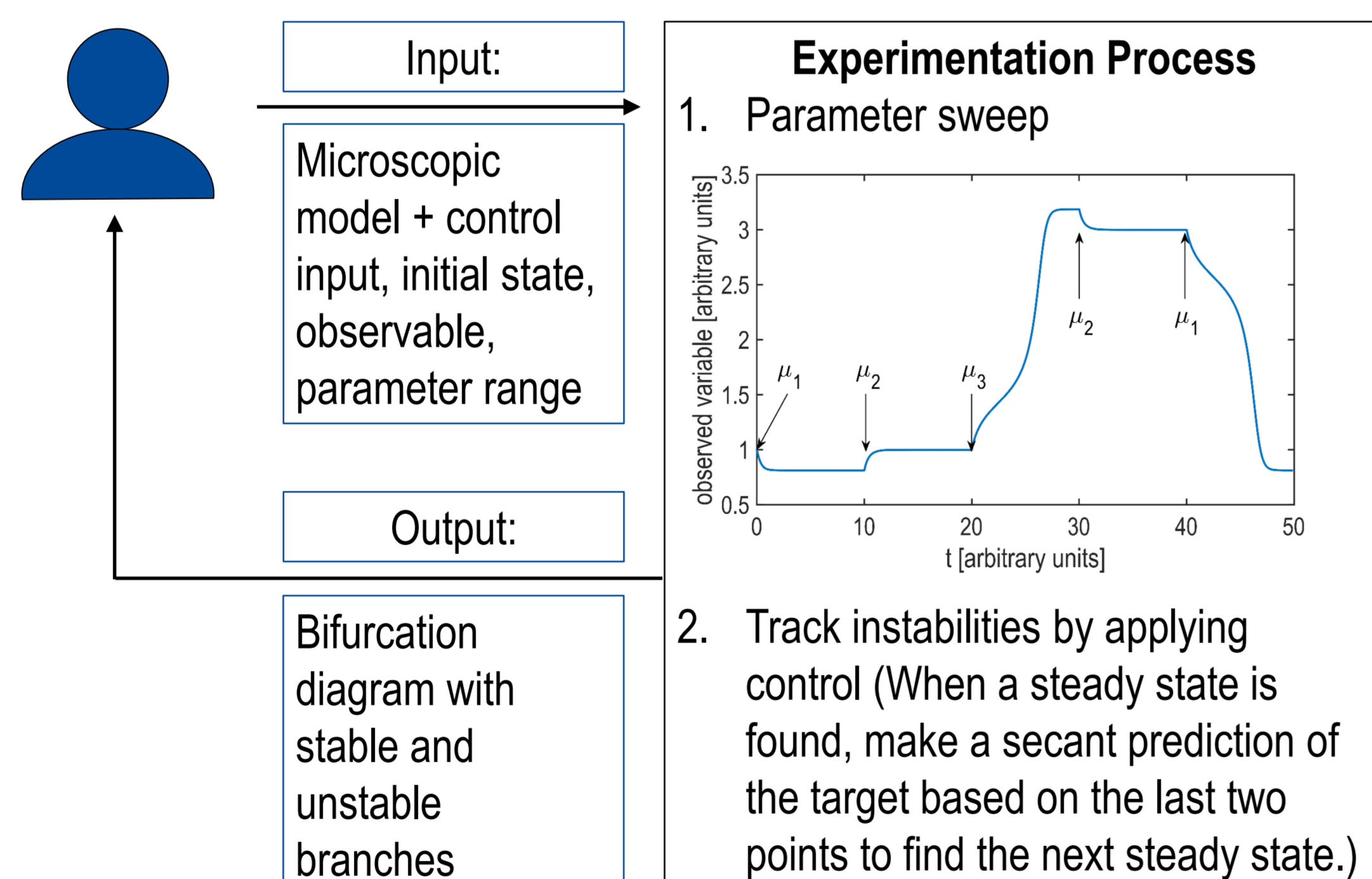


Fig. 1: Outline of the equation-free analysis with SESSL. The plot (inside the experimentation process) shows an example parameter sweep with hysteresis.

Open Questions & Outlook

- How to automate the entire analysis process?
 - How to generate control-terms automatically?
 - How to find regions (initial state and parameter values) of multistability?
 - How to track the branch around fold bifurcation points?
- How to adapt the control-based continuation method in order to work with dynamically nested multi-level models?

Next steps:

- Develop a set of benchmark models
- Application and comparison of other methods of equation-free analysis (e.g. using lifting and restriction operators)
- Test realistic model that combines intra- und intercellular dynamics to predict behavior on cell population level

Method: Control-Based Continuation

- Consider a microscopic model $\dot{\mathbf{u}} = \mathbf{f}(\mathbf{u})$ in the form of a high-dimensional system of N differential equations (or described by reaction rules), which quickly converges to a low-dimensional object (macroscopic system)
 - Goal: Track unobservable (unstable) steady states of macroscopic system F (depending on parameter μ) with assumed model:

$$\dot{x} = F(x, \mu)$$
 - Add control term [1] (shown in red) to stabilize unstable steady states:

$$\dot{x} = F(x, \mu) + a(y - x)$$
 - Add control target equation [7, 8] to have an adaptive, reference-free control technique for locating unknown steady states:

$$\dot{y} = b(y - x)$$
- If a steady state is observed \rightarrow control term vanishes \rightarrow steady state of the original system found
- Requirements to track unstable ('un-observable') steady states: $0 < b \ll a$
- In our case:
 - β -catenin is part of the microscopic model, but it behaves on a different time scale than the other variables \rightarrow good choice for a macroscopic variable

Case Study: Wnt Shuttling Model

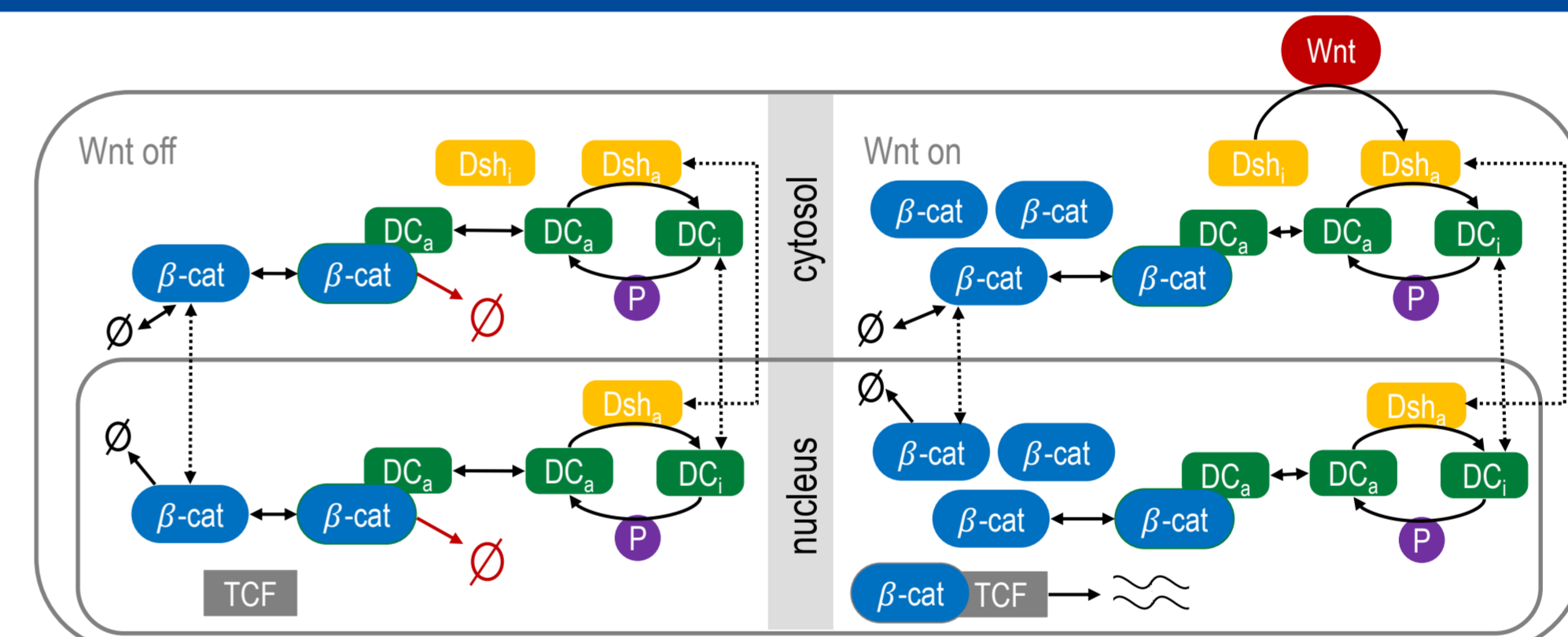


Fig. 2: Wingless and INT-1 (Wnt) model (19 ordinary differential equations / 31 reaction rules) with focus on the processes of shuttling and degradation [6]. Wnt is turned on for simulation.

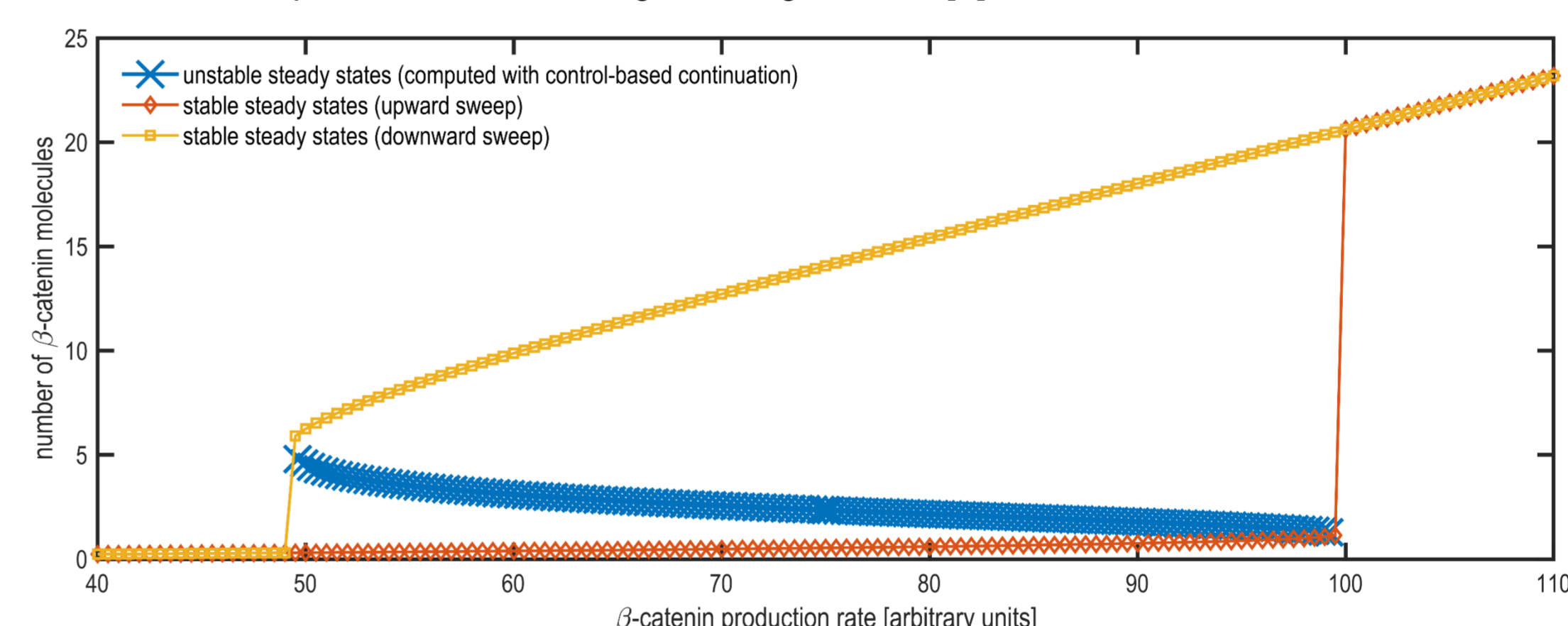


Fig. 3: Bifurcation diagram of hysteresis behavior of β -catenin depending on its production rate, which shows bistability of Wnt shuttling model. The unstable branch (blue) was tracked by using control-based continuation with $a=50$, $b=0.01$.

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