

# Effective models of emergent behavior from the manifold boundary approximation method

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Understanding the collective behavior (e.g, signaling or gene regulation) of complex biological systems in terms of their fundamental components (e.g., proteins, genes, reaction rates), is a fundamental problem in systems biology. While a coarse, macroscopic model can describe system level behavior it often comes at the cost of a microscopic, causal explanation for that behavior. Connecting the microscopic to the macroscopic descriptions is particularly important for predicting the outcome of new experiments that directly manipulate the microscopic components. We present a new model reduction method called the Manifold Boundary Approximation Method (MBAM) that derives simple macroscopic models of collective behavior directly from a microscopic description. The result is an effective model of the system that retains the causal explanation in terms of the microscopic components. We illustrate the method with three systems: EGFR signaling, Wnt signaling, and a fully connected network of Michaelis-Menten reactions fit to adaptation behavior. The resulting models have only a few parameters that are statistically identifiable from experimental data (i.e., not sloppy), dramatically highlight the effective control mechanisms, and remain expressed in terms of the microscopic components.

MODELS of complex biological phenomena, are often built by combining several microscopic elements together. This constructionist approach to modeling is a powerful tool, finding widespread use in many fields. Nevertheless, it is not without its pitfalls, most of which arise as models grow in scale and complexity. Overly complex models can be problematic if they are computationally expensive, numerically unstable, or difficult to fit to data [1]. These problems, however, are only manifestations of a more fundamental issue. Specifically, although reductionism implies that the system behavior ultimately derives from the same fundamental laws as its basic components, this does not imply that the collective behavior can easily be understood in terms of these laws [2]. The collective behavior of the system is typically compressed into a few key parameter combinations while most other combinations remain irrelevant [3].

The Manifold Boundary Approximation Method (MBAM) has recently been proposed as a general purpose approximation method for connecting microscopic models with macroscopic theories in complex systems [4]. It is particularly promising for understanding complex biological systems because it identifies the combinations of

microscopic components, i.e., those components that are directly manipulated by experiment or evolution, that control a particular collective behavior.

The idea behind the method is that a model can be interpreted as a manifold of predictions embedded in data space. It has been observed that complex models with many parameters often exhibit a low-effective dimensionality: all but a few of the dimensions of this manifold are very thin [1]. The MBAM operates by approximating this long, narrow manifold by its boundary. Boundaries are identified using computational differential geometry. Geodesics (analogs of straight lines) are constructed numerically along the least-important parameter combination (identified by the eigenvalues of the Fisher Information Matrix). From the geodesic, a limiting approximation is identified that can be analytically evaluated in the functional form of the model.

We illustrate the method with three examples from systems biology: a model of EGFR signaling [5], Wnt signaling [6], and a fully-connected network of Michaelis-Menten reactions fit to adaptation data [7]. In each case, the MBAM identifies a simple effective model of the complex system. Through the sequence of limiting approximations, the parameters of the effective model are identified with nonlinear combinations of parameters in the original model. By connecting the macroscopic and microscopic descriptions in this way, the MBAM characterizes the equivalence class of microscopic systems that are statistically indistinguishable from their collective behavior and predicts which microscopic control knobs govern the system behavior.

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