**379e Boundary Value Formulation for the Sensitivity Analysis of Biological Oscillators with Application to the Circadian Oscillator**

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Many fundamental biological processes exhibit oscillatory behavior. Prominent examples are the cell cycle, circadian rhythm generation, the heart beat, and cAMP and Ca2+ oscillations in neurons. Some oscillatory biological systems provide functions that a static system cannot provide, such as gating mechanisms [1]. Oscillations in signaling molecules are hypothesized to encode more information than possible in a non-oscillatory signal [2]. Other systems show individual, fascinating properties, for example the astonishing robustness of the period of the circadian system in constant darkness conditions, or in different temperature ranges [3]. Several of these processes have been studied extensively, and have been modeled using ordinary differential equations (ODEs) to different levels of mechanistic detail. These dynamic models provide an opportunity to investigate the complex interactions of the different molecular players. One of the most popular methods for such studies is sensitivity analysis. The influence of model parameters and initial conditions on features of the dynamic behavior of the system can be determined. Sensitivity analysis of biological oscillatory systems is challenging due to several characteristics of their sensitivity functions: First, the most commonly modeled biological systems are limit cycle oscillators [4]. Independently of the initial conditions, such systems asymptotically approach a limit cycle, whose shape is determined by the model parameters only. Clearly, it is the limit cycle trajectory which is of interest for parametric sensitivity analysis. We wish to determine the influence of the model parameters on limit cycle features such as period and amplitude of the oscillation. The asymptotic behavior of limit cycle systems creates transients in the sensitivity functions, which will only decay after several (~30) periods, unless we provide a way to find initial conditions that lie on the limit cycle trajectory and initialize the parametric sensitivities accordingly. A second obstacle concerns the derivation of sensitivities for limit cycle properties: the sensitivity trajectories of the state variables (the concentrations in the biological model) with respect to the parameters grow in an unbounded fashion. It is necessary to process these sensitivities in such a way that allows separation of the (bounded) influence of the parameters on amplitude and phase of the system, from the (unbounded) influence of the parameters on the period. Previous work in the area relies on simulating the dynamic system starting from arbitrary initial conditions, until the limit cycle is reached to some tolerance [5,6]. The parametric sensitivities are determined at this point, assuming the transient contributions are negligible. Since it can be shown that the unbounded sensitivity functions grow linearly in time, a periodic function can be derived which relates sensitivities at a given time to those at one period before. This derived function is used to determine the sensitivity of the period with respect to the parameters [5,6].

We have developed a boundary value formulation for the sensitivity problem, which allows us to determine initial conditions for the state variables as well as for their sensitivities with respect to the model parameters. Those initial conditions are a point on the limit cycle, rather than asymptotically approaching it. Consequently, transient terms are avoided, and an exact solution can be calculated after one period of oscillation. Previous work in the area provided such a method, limited to systems with second order dynamics [7]. The present work extends those results to general, oscillating systems, such as those present in models of biological oscillators. We are able to separate the bounded and unbounded terms exactly, and can calculate exact parametric sensitivities for derived functions such as period and amplitude of the oscillation, rather than approximations from truncations of asymptotic processes, as in earlier works. Besides their use in sensitivity analysis itself, exact sensitivities are needed for the analysis of complex systems using optimization techniques. Optimization techniques can be very useful tools to investigate parameter dependencies of features of biological networks on a more global scale, especially when experimental data on the true parameter values is scarce. We applied the method on model systems of different sizes: A small and simple model for the circadian clock in Neurospora crassa

shows some of the interesting characteristics of the circadian system, such as temperature compensation, temperature entrainment and phase responses to different stimuli [8]. A more detailed model of the mammalian circadian clock [9] can also be analyzed efficiently. Sensitivity analysis proves a tool for understanding how network characteristics are encoded in the biological system.

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