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## Multi-timescale systems and fast-slow analysis

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## ABSTRACT

Mathematical models of biological systems often have components that vary on different timescales. This multi-timescale character can lead to problems when doing computer simulations, which can require a great deal of computer time so that the components that change on the fastest time scale can be resolved. Mathematical analysis of these multi-timescale systems can be greatly simplified by partitioning them into subsystems that evolve on different time scales. The subsystems are then analyzed semi-independently, using a technique called fast-slow analysis. In this review we describe the fast-slow analysis technique and apply it to relaxation oscillations, neuronal bursting oscillations, canard oscillations, and mixed-mode oscillations. Although these examples all involve neural systems, the technique can and has been applied to other biological, chemical, and physical systems. It is a powerful analysis method that will become even more useful in the future as new experimental techniques push forward the complexity of biological models.

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## 1. Introduction

Biological systems often feature interacting components that vary on disparate timescales. For example, changes in a cell's environment trigger variations in protein levels through a sequence of protein–protein interactions, leading to changes in gene transcription, followed by translation and often post-translational modification. This process may be followed by translocation of proteins, such as ion channels or hormone receptors, into the cell's plasma membrane, which allows the cell to respond appropriately to its environment. This whole process can take hours, even though the fastest components (such as protein–protein interactions) occur on the timescale of seconds. An even wider gap exists between rapid cellular events such as neuronal electrical activity and much slower circadian rhythms coordinated through the suprachiasmatic nucleus of the hypothalamus and involving rhythms in gene expression.

Such examples are problematic for computer simulations of mathematical models, which are computationally expensive if changes at the fastest timescale are resolved. Fortunately, there are specialized mathematical techniques that can be applied to analyze the behavior of systems in which the separation of timescales is sufficiently large. There is a substantial literature on multiple-

scale asymptotic analysis of systems with timescale separation (e.g., [48]). Alternatively, one can employ geometric methods often denoted as *fast-slow analysis* to simplify the investigation of the system by breaking it into two or more reduced subsystems that are more tractable than the full model. There are two primary goals of this article. The first is to provide an overview of some fast-slow analysis techniques. The second is to illustrate some behaviors that come about in multi-timescale systems and that are best understood from the viewpoint of fast-slow analysis. We use examples that involve the dynamics of electrically excitable cells, but other studies of multiscale dynamics and their analysis focus on chemically reacting systems, intracellular calcium dynamics, ecology, climate dynamics, and other application areas (e.g., [45,55,67,74,75,77]).

A system of ordinary differential equations that evolves on two timescales can be formally written as

$$\frac{d\vec{x}}{dt} = F(\vec{x}, \vec{y}) \quad (1)$$

$$\frac{d\vec{y}}{dt} = \epsilon G(\vec{x}, \vec{y}) \quad (2)$$

where  $\epsilon > 0$  is small. The *fast variables*  $\vec{x}$  evolve on a faster timescale than the *slow variables*  $\vec{y}$ , and we can define a corresponding *fast subsystem*  $d\vec{x}/dt = F(\vec{x}, \vec{y})$ , with  $\vec{y}$  as parameters, and *slow subsystem*  $d\vec{y}/d\tau = G(\vec{x}_f(\vec{y}), \vec{y})$ , where  $\vec{x}_f$  is defined from  $F(\vec{x}, \vec{y}) = 0$  and  $\tau = \epsilon t$  corresponds to a slow timescale. The dimensionality of the two subsystems differs among applications,

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but the general approach of fast-slow analysis is to treat the subsystems separately. The idea underlying this splitting into subsystems is that from a general initial condition, the system will be governed by the fast subsystem and will settle to the neighborhood of a fast subsystem attractor, where  $F = 0$ , that is parameterized by  $\bar{y}$ . Within this neighborhood, the system will evolve slowly, governed by the slow subsystem, unless a boundary of the attractor is reached and the fast subsystem takes over again. Fast-slow analysis is often employed to study relaxation oscillations, such as those that occur in the van der Pol oscillator with strong damping [96,102]. Here, the original second-order nonlinear differential equation can be converted into two first-order differential equations, yielding a single fast variable and a single slow variable. This system has been used to describe a heartbeat [103], and similar planar systems have been used to describe electrical impulses in neurons [40,41,68], intracellular calcium dynamics in a neuron [34], and hourly hormone pulses [105].

More than twenty years after Richard FitzHugh used fast-slow analysis to analyze what is now called the FitzHugh–Nagumo model, John Rinzel adapted the fast-slow analysis technique to understand the dynamics underlying bursting in neurons and pancreatic  $\beta$ -cells [4,78,79,82,83]. *Bursting* is characterized by active episodes of rapid electrical oscillations (also called impulses, spikes, or action potentials) separated by quiescent or silent phases, repeated periodically. It is ubiquitous in neurons and endocrine cells [24,95] and has been shown to be more effective at evoking neurotransmitter and hormone secretion than continuous trains of action potentials [61,104]. The technique developed by Rinzel explains such things as the existence of the bursting oscillation, patterns in interspike interval duration, the duty cycle (the fraction of the period during which the system is spiking), transitions between bursting and continuous spiking, and the roles that various ionic currents play in the bursting pattern. In addition, the bifurcations of the fast subsystem are useful for categorizing bursts; the bifurcation responsible for the transition from silent to active phase and that associated with the transition from active to silent phase determine the type of bursting oscillation [7,51,80]. Fast-slow analysis is now regularly used in the analysis of bursting oscillations, and in the first portion of this article we describe the method and give some applications.

In addition to relaxation and bursting oscillations, one other class of oscillations that comes up in fast-slow systems is called *mixed-mode oscillations* (MMOs). These consist of small-amplitude oscillations mixed with large-amplitude oscillations, often repeated periodically. MMOs have been identified and analyzed using mathematical models in chemically reacting systems [55,75], voltage dynamics of neurons [10,30,33,44,50,62,65,85–87] and electrically excitable pituitary cells [107,108], intracellular calcium dynamics [45], and elsewhere [67]. The small-amplitude oscillations are often due to *canards*, which are orbits that follow a curve or sheet of attracting equilibria as well as a portion of a repelling curve/sheet of equilibria of the fast subsystem. Though originally studied in a system with one fast and one slow variable [31,37], canards can be generic in systems with two or more slow variables, so they occur over much larger regions of parameter space in the latter case (see [29] for an excellent review of canards and MMOs). In the context of neurons, the small oscillations are subthreshold voltage oscillations, while the large oscillations are action potentials. Thus, the canard orbits have the effect of increasing the time between spikes, and thereby reducing the spike frequency [87]. In electrically excitable pituitary cells the canard orbits themselves are the “spikes”, which are typically quite small, and the large oscillations are repolarizations that occur between bursts [106]. In the second portion of this article we illustrate how canard orbits come about in the context of MMOs and discuss some applications of MMOs in electrically excitable neurons and pituitary cells.

We note that when the first issue of *Mathematical Biosciences* was published in 1967, little of what we discuss in this article had been discovered. Relaxation oscillations had been around for half a century, but bursting oscillations, canards, and mixed-mode oscillations were all in the future. The future is now!

## 2. Relaxation oscillations and canards in a planar fast-slow system

*Planar systems allow us to illustrate how the basic interplay between fast and slow variables can give rise to a characteristic form of oscillations. Furthermore, they provide a clear view of transitional phenomena that arise as a parameter is varied such that a bifurcation from steady state to oscillatory behavior occurs. We will illustrate these points with a single model system, noting that qualitatively similar phenomena occur in other systems with similar mathematical structure.*

As mentioned above, the van der Pol oscillator with strong damping is the canonical fast-slow system with a single fast and a single slow variable. For purposes of continuity with later sections, we begin with a fast-slow system that describes membrane potential oscillations in an electrically active cell and that captures the dynamic features of the van der Pol oscillator. This is based on the “s-model” for pancreatic  $\beta$  cells [91]. This model has a variable for the membrane potential or voltage ( $V$ ), an *activation variable* for the fraction of activated delayed rectifier  $K^+$  channels ( $n$ ), and an activation variable for the fraction of activated  $K^+$  channels of another type ( $s$ ). These latter  $K^+$  channels could be  $Ca^{2+}$ -activated  $K^+$  channels, for example. The dynamics of the variables are described by the following differential equations:

$$\frac{dV}{dt} = -(I_{Ca} + I_{Kdr} + I_{KATP} + I_{Ks} + I_L)/C_m \quad (3)$$

$$\frac{ds}{dt} = \frac{s_\infty(V) - s}{\tau_s} \quad (4)$$

The change of voltage depends on several ionic currents reflecting ion flux through different ion channels. The  $V$ -dependent  $Ca^{2+}$  current,  $I_{Ca}$ , is an inward current that is responsible for the upstroke of a spike. It is similar to the  $Na^+$  current in neurons, although its inactivation is much slower and is not included in the s-model. (A  $Na^+$  current is also not included, since  $Na^+$  channels are inactivated in mouse  $\beta$  cells.) Like the  $Na^+$  current, the  $Ca^{2+}$  current activates very rapidly, and in the s-model it is assumed to adjust instantaneously to changes in  $V$ . This is called a *quasi-equilibrium* or *quasi-steady-state approximation* and is often used in multi-timescale models [42]. Using this assumption, the  $Ca^{2+}$  current is  $I_{Ca} = g_{Ca} m_\infty(V)(V - V_{Ca})$ , where  $g_{Ca}$  is the maximum conductance (the conductance when all channels are activated),  $V - V_{Ca}$  is the *driving force* that powers ion flux through open channels, and  $m_\infty(V)$  is the equilibrium activation function, given by the increasing sigmoid function

$$m_\infty(V) = \frac{1}{1 + e^{-\frac{v_m - V}{s_m}}} \quad (5)$$

This function, which ranges from 0 to 1, is half-maximal at  $V = v_m$  and the steepness of the curve is determined by  $s_m$  (the curve is steeper when  $s_m$  is small). The other inward or depolarizing current is  $I_L$ , which is a constant-conductance leakage current that groups together the effects of various ion-specific flows and takes the form  $I_L = g_L(V - V_L)$ .

Model (3) and (4) includes three outward or hyperpolarizing currents, all carried by  $K^+$ . The first,  $I_{Kdr}$ , is the standard delayed rectifier that is responsible for the downstroke of an action potential. Activation of this current is considerably slower than that of the  $Ca^{2+}$  current (otherwise there would be no spike), so the

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