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Effects of quasi-steady-state reduction on biophysical models with oscillations

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HIGHLIGHTS

- Quasi-steady-state reduction can destroy oscillations in biophysical models.
- Some mechanisms for the onset of oscillations are robust under QSSR.
- Systematic risk mitigation for QSSR in systems with multiple timescales.
- QSSR can introduce new bifurcations of equilibria and periodic orbits.

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ABSTRACT

Many biophysical models have the property that some variables in the model evolve much faster than others. A common step in the analysis of such systems is to simplify the model by assuming that the fastest variables equilibrate instantaneously, an approach that is known as quasi-steady state reduction (QSSR). QSSR is intuitively satisfying but is not always mathematically justified, with problems known to arise, for instance, in some cases in which the full model has oscillatory solutions; in this case, the simplified version of the model may have significantly different dynamics to the full model.

This paper focusses on the effect of QSSR on models in which oscillatory solutions arise via one or more Hopf bifurcations. We first illustrate the problems that can arise by applying QSSR to a selection of well-known models. We then categorize Hopf bifurcations according to whether they involve fast variables, slow variables or a mixture of both, and show that Hopf bifurcations that involve only slow variables are not affected by QSSR, Hopf bifurcations that involve fast and slow variables (i.e., singular Hopf bifurcations) are generically preserved under QSSR so long as a fast variable is kept in the simplified system, and Hopf bifurcations that primarily involve fast variables may be eliminated by QSSR. Finally, we present some guidelines for the application of QSSR if one wishes to use the method while minimising the risk of inadvertently destroying essential features of the original model.

1. Introduction

For well over 50 years, oscillations in cell biology have been of major interest to both theoreticians and experimentalists. In neurons, for example, oscillation of the membrane potential is one of the fundamental behaviours that underlie neuronal function, while in almost every cell type oscillations in the concentration of cytoplasmic calcium control a wide variety of cellular behaviours, including secretion, water transport, movement, gene expression and differentiation. These are but two examples from many of current interest to scientists.

In addition to their physiological interest, models of oscillations in cell physiology often have interesting mathematical properties. In particular, they commonly contain variables that operate on different timescales; thus, mathematical analyses of these models require the use of mathematical techniques that can cope with multiple, widely varying, timescales.

One method that has commonly been used to study such multiple timescale systems is quasi-steady state reduction (QSSR), also sometimes referred to as pseudo-steady state reduction or adiabatic elimination. In this approach, one or more fast variables

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are assumed to be at quasi-steady state, so transient response in these variables is ignored and the differential equations for their evolution are replaced by algebraic equations, thereby reducing the dimension of the model. QSSR was introduced by Michaelis and Menten over 100 years ago to simplify a mathematical description of enzyme kinetics (Michaelis and Menten, 1913). The simplification was also discussed by Briggs and Haldane (1925) and, more recently, in great detail in Segel and Slemrod (1989). An extension to QSSR, named *total quasi-steady-state reduction* (tQSSR), was introduced in Borghans et al. (1996), and further developed in Ciliberto et al. (2007) and Pedersen et al. (2008). In tQSSR, a coordinate transformation is first applied, followed by regular QSSR; the coordinate transformation effectively attempts to align model variables more closely with timescales, and thereby to overcome difficulties arising when the evolution equation for a physical variable contains terms corresponding to a mix of timescales.

The approach of equilibrating some variables instantaneously is intuitively satisfying, but it is only justified if the model under consideration possesses a globally attracting slow manifold to which the dynamics are confined after the initial transient phase (Segel and Slemrod, 1989). Most studies of QSSR (or tQSSR) are devoted to studying the accuracy of the simplified system in comparison to the full system when the system has a globally attracting, slow invariant manifold. Some recent papers note that application of QSSR can lead to qualitatively different predictions compared with the original model, especially with regard to oscillations (Erneux and Goldbeter, 2006; Flach and Schnell, 2006; Pedersen et al., 2008; Zhang et al., 2011), but a comprehensive understanding of what can go wrong, and why, is still lacking.

Because of the widespread use of QSSR resulting from its ease of use and its ability to present understandable and simplified versions of complex models, it is important to know, as precisely as possible, when a QSSR approach is valid and when it is not. We address this issue in detail in this paper.

The remainder of the paper is organised as follows. In Section 2, we motivate our interest in this issue by showing the effect of QSSR on a selection of well-known biophysical models, all which have oscillatory solutions arising in Hopf bifurcations. In some cases, the dynamics of the original model is minimally disrupted by QSSR but in other cases substantial dynamical changes are induced by QSSR. In Section 3 we look in more mathematical detail at the effect of QSSR and state our main result about the consequences of QSSR for Hopf bifurcations; this result is proved in Appendix A. Section 4 presents some guidelines for the application of QSSR if one wishes to use the method while minimizing the risk of inadvertently destroying essential dynamics of the original model. Some concluding remarks are presented in Section 5.

2. Motivating examples

In this section we show the effect of QSSR on the dynamics of a selection of well-known ordinary differential equation models, all of which have the feature that oscillatory solutions are introduced via one or more Hopf bifurcations as a bifurcation parameter is varied. It is not *a priori* clear how QSSR affects the onset of oscillations, the interval of parameter values for which the emanating branch of periodic orbit exists, or characteristics of the periodic orbits such as frequency and amplitude. As these examples will demonstrate, it turns out that in some cases the dynamics is minimally disrupted by the application of QSSR but in other cases significant qualitative changes are induced by the reduction.

All the numerical investigations in this section were done with the bifurcation and continuation software AUTO (Doedel et al., 2007).

2.1. Hodgkin–Huxley model

The first example is the well-known Hodgkin–Huxley (HH) model (Hodgkin and Huxley, 1952) for the membrane action potential in the squid giant axon. The version of the model we use is formulated as a system of four ordinary differential equations (Rubin and Wechselberger, 2007):

$$C_m\frac{dv}{dt} = I - g_{Na}m^3h(v-E_{Na}) - g_K n^4(v-E_K) - g_L(v-E_L), \tag{1}$$

$$\frac{dm}{dt} = \frac{1}{\tau_m t_m(v)}(m_\infty(v)-m), \tag{2}$$

$$\frac{dh}{dt} = \frac{1}{\tau_h t_h(v)}(h_\infty(v)-h), \tag{3}$$

$$\frac{dn}{dt} = \frac{1}{\tau_n t_n(v)}(n_\infty(v)-n), \tag{4}$$

where v represents the membrane potential, m represents the activation of the sodium channel, h describes the inactivation of the sodium channel and n the activation of the potassium channel. The parameter I represents the applied current, and will be used as the main bifurcation parameter. Expressions for the functions $m_\infty(v)$, $h_\infty(v)$, $n_\infty(v)$, etc. and the values of constants used are given in Appendix B.

Since sodium channel activation is observed in experiments to occur more rapidly than sodium channel inactivation or potassium channel activation, m is usually regarded as a faster variable than either n or h. It is common to assume, therefore, that m relaxes instantaneously to its quasi-steady state value, $m_\infty(v)$, (Moehlis, 2005; Rinzel, 1985; Keener and Sneyd, 2009; Ermentrout and Terman, 2010; Rubin and Wechselberger, 2007) and to replace m by $m_\infty(v)$ in Eq. (1). Then the HH equations reduce to a three-dimensional system of ordinary differential equations for v, h and n:

$$C_m\frac{dv}{dt} = I - g_{Na}(m_\infty(v))^3h(v-E_{Na}) - g_K n^4(v-E_K) - g_L(v-E_L), \tag{5}$$

$$\frac{dh}{dt} = \frac{1}{\tau_h t_h(v)}(h_\infty(v)-h), \tag{6}$$

$$\frac{dn}{dt} = \frac{1}{\tau_n t_n(v)}(n_\infty(v)-n). \tag{7}$$

A careful nondimensionalization and comparison of the timescales, over the physiologically relevant range of $v \in (-77\text{ mV}, 50\text{ mV})$, reveals that v, not m, is the fastest variable in the HH equations (Rubin and Wechselberger, 2007). From a mathematical point of view, therefore, v might be a more natural candidate for removal via QSSR than m, although this is not usually done. If we assume that v equilibrates instantaneously so that $dv/dt = 0$, then we can set the right hand side of Eq. (1) to zero and use this expression to write v as a function of the remaining variables:

$$\overline{v}(m,h,n) = \frac{I + g_{Na}m^3hE_{Na} + g_K n^4E_K + g_L E_L}{g_{Na}m^3h + g_K n^4 + g_L}.$$

Substituting this expression into the remaining three equations, we get an alternative simplified form of the HH equations:

$$\frac{dm}{dt} = \frac{1}{\tau_m t_m(\overline{v})}(m_\infty(\overline{v})-m), \tag{8}$$

$$\frac{dh}{dt} = \frac{1}{\tau_h t_h(\overline{v})}(h_\infty(\overline{v})-h), \tag{9}$$

$$\frac{dn}{dt} = \frac{1}{\tau_n t_n(\overline{v})}(n_\infty(\overline{v})-n). \tag{10}$$