Canard- and Hopf-induced bursting in pituitary cells

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The electrical activity of endocrine pituitary cells regulates diverse functional characteristics such as the release of prolactin, growth hormone and ACTH in lactotrophs, somatotrophs and corticotrophs, respectively. The combination of ionic currents mediated by various ion channels in the cellular membrane determines the pattern of electrical activity exhibited by these cells [9]. One particular pattern of electrical activity commonly seen in pituitary cells is pseudo-plateau bursting [7], which consists of alternating periods of small-amplitude oscillations in the active (depolarized) phase followed by silent phases. The calcium concentration in these cells increases more when the cell is bursting than when it is spiking, resulting in higher levels of hormone and neurotransmitter secretion [8], [12]. In this way, the hormone secretion from pituitary cells is, to a large extent, controlled by the electrical activity of the cell.

Pituitary cells express a variety of ion channels and establishing the role of a single channel type can be difficult since many different channel types contribute to any given electrophysiological property. However, it has been proposed that large conductance potassium (BK) channels [9] primarily determine whether a pituitary cell spikes or bursts [8]. In [10], a hybrid computational/experimental approach was used to study how the kinetic properties of BK channels affect bursting in pituitary cells. One of the key results from [10] is that BK current promotes bursting, provided it is fast activating. If the BK activation is too slow, then the BK current becomes inhibitory to bursting and the cell is in a spiking state. The primary aim of the current article is to provide a mathematical explanation of the key physiological observations of [10]. Namely, to understand why BK activation must be fast in order to promote bursting.

The dependence of the electrical activity on the activation rate of the BK channels highlights the importance of timescales in cellular excitability. Experimental recordings and model simulations of pituitary cell bursting support this notion by

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showing that the dynamics evolve on multiple timescales. There are fast epochs where the cell switches between active and silent phases and slow epochs where the small oscillations of the bursting can occur. Typically, pituitary cell models are described by singularly perturbed problems, making them amenable to singular perturbation methods. One particular singular perturbation technique that has been used with great success is geometric singular perturbation theory [3], [5], which combines asymptotics with dynamical systems techniques. Using geometric singular perturbation theory, it has been shown that the pseudo-plateau bursting is a mixed mode oscillation (MMO) [11], [13]. An MMO is an oscillatory trajectory featuring small amplitude oscillations sitting on top of large amplitude, relaxation-type oscillations. Two common mechanisms for MMOs are canard dynamics [1], [15] and slow passage through a dynamic Hopf bifurcation [2], [4].

In [14], we analyze a pituitary cell model to address the question of why BK activation must be fast to promote bursting. Using our geometric singular perturbation analysis, we explain the bursting behaviour via canard- and Hopf-induced MMOs. In particular, we demonstrate that both MMO mechanisms are affected by the BK conductance, however, only the Hopf mechanism generates MMOs that depend on the BK activation rate. That is, we show that sensitivity to variations in the BK activation rate is an useful diagnostic in identifying the burst mechanism. We test our geometric analysis experimentally by injecting artificial BK conductance into spiking GH4 cells (a lacto-somatotroph cell line) using the dynamic clamp technique [6]. As we decrease the activation time constant of BK channels, we observe longer bursts with smaller oscillations during the active phase, consistent with the Hopf mechanism.

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Theo Vo was born and raised in Sydney and completed a Bachelor of Science degree at the University of Sydney. Theo is currently in the final year of his PhD and is very much looking forward to a long break when it's over!