

Preface

In the world of cell biology, there is a myriad of oscillatory processes, with periods ranging from the day of a circadian rhythm to the milliseconds of a neuronal action potential. To one extent or another they all interact, mostly in ways that we do not understand at all, and for at least the past 70 years, they have provided a fertile ground for the joint investigations of theoreticians and experimentalists. Experimentalists study them because they are physiologically important, while theoreticians tend to study them, not only for this reason, but also because such complex dynamic processes provide an opportunity to use, as their tools of investigation, the methods of mathematical analysis.

In this volume, we are concerned with two of these oscillatory processes: calcium oscillations and bursting electrical oscillations. These two are not chosen at random. Not only have they both been studied in depth by modellers and mathematicians, but we also have a good understanding – although not a complete one – of how they interact, and how one oscillatory process affects the other. They thus make an excellent example of how multiple oscillatory processes interact within a cell, and how mathematical methods can be used to understand such interactions better.

The theoretical study of electrical oscillations in cells began, to all intents and purposes, with the classic work of Hodgkin and Huxley in the 1950s. In a famous series of papers they showed how action potentials in neurons arose from the time-dependent control of the conductance of Na^+ and K^+ channels. The model they wrote down, a system of four coupled nonlinear ordinary differential equations, became one of the most influential models in all of physiology. It was quickly taken up by other modellers, who extended the model to study oscillations of electric potential in neurons, and over the last few decades the theoretical study of neurons and groups of neurons has expanded to become one of the largest and most active areas in all of mathematical biology.

More traditional applied mathematicians were also strongly influenced, albeit at one remove, by the Hodgkin-Huxley equations. The simplification by FitzHugh in the 1960s led to the FitzHugh-Nagumo model of excitability (Nagumo, a Japanese engineer, derived the same equation independently at the same time, from entirely

different first principles) which formed the basis of more theoretical studies of excitability across many different areas, both inside and outside cell biology.

Oscillations in the cytosolic concentration of free Ca^{2+} (usually simply called Ca^{2+} oscillations) have a more recent history, not having been discovered until the development of Ca^{2+} fluorescent dyes in the 1980s allowed the measurement of intracellular Ca^{2+} concentrations with enough temporal precision. But since then, the number of theoretical and experimental investigations of Ca^{2+} oscillations has expanded rapidly. Calcium oscillations are now known to control a wide variety of cellular functions, including muscular contraction, water transport, gene differentiation, enzyme and neurotransmitter secretion, and cell differentiation. Indeed, the more we learn about intracellular Ca^{2+} , the more we realize how important it is for cellular function. Conversely, the intricate spatial and temporal behaviors exhibited by the intracellular Ca^{2+} concentration, including periodic plane waves, spiral waves, complex whole-cell oscillations, phase waves, stochastic resonance, and spiking, have encouraged theoreticians to use their skills, in collaboration with the experimentalists, to try and understand the dynamics of this ubiquitous ion.

Many cell types, however, contain both a membrane oscillator and a Ca^{2+} oscillator. The best-known examples of this, and the most widely studied, are the neuroendocrine cells of the hypothalamus and pituitary, as well as the endocrine cells of the pancreas, the pancreatic β cells. In these cell types, membrane oscillators and calcium oscillators are indissolubly linked; fast oscillations of the membrane potential open voltage-gated Ca^{2+} channels which allow Ca^{2+} to flow into the cell, which in turn activates the exocytotic machinery to secrete insulin (in the case of pancreatic β cells) or a variety of hormones (in the case of hypothalamic and pituitary cells). However, in each of these cell types, cytosolic Ca^{2+} also controls the conductance of membrane ion channels, particularly Ca^{2+} -sensitive K^+ and Cl^- channels, which in turn affect the membrane potential oscillations. In these endocrine cells, it is thus necessary to understand both types of cellular oscillator in order to understand overall cellular behavior.

Thus, this current volume. In it we first see how the interaction of Ca^{2+} cytosolic with membrane ion channels can result in the complex patterns of electrical spiking that we see in cells. We then discuss the basic theory of Ca^{2+} oscillations (common to almost all cell types), including spatio-temporal behaviors such as waves, and then review some of the theory of mathematical models of electrical bursting pituitary cells.

Although our understanding of how cellular oscillators interact remains rudimentary at best, this coupled oscillator system has been instrumental in developing our understanding of how the cytosol interacts with the membrane to form complex electrical firing patterns. In addition, from the theoretical point of view it has provided the motivation for the development and use of a wide range of mathematical methods, including geometric singular perturbation theory, nonlinear bifurcation theory, and multiple-time-scale analysis.

It is thus an excellent example of how mathematics and physiology can learn from each other, and work jointly towards a better understanding of complex cellular processes.

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