Interdisciplinary approaches to calcium dynamics and secretory processes in cells

As stated in the title of the book by [Whitfield and Chakravarthy \(2001\)](#), calcium is the “grand-master cell signaler” used as messenger in a large number of vital processes such as secretion of hormones and neurotransmitters and muscle contraction and genetic transcription, among others ([Whitfield and Chakravarthy, 2001](#); [Augustine, 2001](#)).

Regarding the release of neurotransmitters, the vast majority of synapses in the central nervous system are chemical as are all synapses between nerves and muscles. When an action potential invades the terminal, the depolarization opens voltage-sensitive calcium channels, allowing calcium ions to enter the nerve terminal and trigger the transmitter release process. This model, established by [Katz and Miledi \(1965, 1967\)](#) for the release of neurotransmitter in the frog neuromuscular junction, was extended to release processes in neurons, endocrine cells, and many other cell types.

Synaptic transmitter is stored in small membrane-bound packets called synaptic vesicles. Transmitter release occurs when vesicles fuse with the nerve terminal membrane and empty their contents into the synaptic cleft. The transmitter release is monitored by recording synaptic potentials in the post-synaptic cell. These result from the summed post-synaptic effect of the transmitter from one or several of these releases.

A quantitative understanding of all processes involved greatly benefits from modeling studies of the system in order to confront different experimental data and to test hypothesis that lie far beyond present experimental possibilities. Because of the tiny structures of the synaptic terminals, following the pre- and post-synaptic response is only possible in a very limited number of

these structures as, for example, the squid giant synapse and the calyx of Held ([Neher, 1996](#)). However, although sharing the same basic mechanisms, the phenomenology of synaptic transmission varies from one to another terminal.

In comparison to the release of neurotransmitter by presynaptic terminals, secretion by neuroendocrine or endocrine cells is a relatively slow process with long latencies ([Augustine et al., 1985](#); [Llinas et al., 1981](#)). For instance, secretion by chromaffin cells persists for dozens of milliseconds after a short pulse ceases ([Chow et al., 1992](#)); these long latencies have also been observed in pancreatic betacells ([Eliasson et al., 1997](#)). The existence of endogenous buffers is a plausible explanation for this fact; buffers bind calcium, which is the agent responsible of triggering secretion, delaying in this way the response of secretory vesicles. This hypothesis is confirmed by the effect of exogenously added buffers on the secretion time course in chromaffin cells ([Chow et al., 1996](#)) and in betacells ([Bokvist et al., 1995](#)). Also, the spatial organization of calcium channels and secretory vesicles has a key influence on the secretory response. In synaptic terminals, the distance between calcium channels and synaptic vesicles is small and the channel actually becomes part of the molecular release machinery ([Clapham, 1995](#)). Neuroendocrine cells show a similar calcium dependence of release as synapses but a strongly different organization of channels and vesicles, biophysical and biochemical properties of large dense core vesicle release in neuroendocrine cells, suggest that the vesicles and channels are separated by a distance of 100–300 nm.

The papers of this special issue deal with different aspects of calcium-

induced processes in particular cell prototypes, which can be seen as representative of systems having responses with different time scales.

The perspective review of [Soria et al. \(2010\)](#) presents an interesting overview of what is known about pancreatic alpha-, beta-, and deltacells. These cells are found in the islets of Langerhans, which are responsible of glucose homeostasis. The word homeostasis makes reference to the maintenance of the constant physiological state and this is, of course, one of the fundamental characteristics of life. The islets of Langerhans are formed by alphacells, which increase the blood glucose level; betacells decrease it; and deltacells, where the precise role of which still needs identifying. Studies on the secretory response of pancreatic cells have a deep impact in public health because its malfunctioning can cause diabetes mellitus, among other diseases.

On the other hand, the review by [Dupont and Croisier \(2010\)](#) pointed out a fundamental aspect about calcium: the organization, both in time and space, of the calcium signal inside the cell is crucial in order to determine its specific role. In hepatocytes, for example, a hormone-induced increase in calcium can lead both to the production of glucose but also to apoptosis or necrosis. How is the cell able to decide between such drastically different responses? The specific organization of the intracellular calcium signal seems to be the answer. A modeling approach to this aspect in electrically non excitable cells in which InsP3 receptors are the most important calcium channels, is considered in the clarifying Dupont and Croisier's paper.

In the contributed paper by [Haller-mann et al. \(2010\)](#), the authors presented a nice analysis, both theoretical

and experimental, of several models of presynaptic vesicle dynamics at the *Drosophila* neuromuscular junction, evaluating their impact on short-term plasticity at this synapse. Additionally, the authors apply these models to synapses lacking the active zone component Bruchpilot in order to understand the role of this active zone on short-term plasticity. “Plasticity” means how a particular synapse modulates the release of neurotransmitters: some synapses transmit strongly to action potentials but weaken with repeated activation; others transmit weakly at first but strengthen with sustained activity. This is the reason many synapses can be *grosso modo* classified as facilitating (having a low probability of initial transmitter release and exhibiting facilitation of release during trains of stimuli) or depressing (with high probability of initial release and depression of release during trains).

Representative of “moderately slow” secretory processes (neuroendocrine cells) is the paper by Villanueva *et al.* (2010), which proposed a model of cytoskeletal cages in bovine chromaffin cells, where the secretory machinery associated with its borders. In this way, the organization of cytoplasm in excitable cells, which has been a factor usually ignored in mathematical models describing the role of intracellular calcium in neuroendocrine cells, provocatively emerges as a possible key factor for the understanding of the secretory response in these cells.

Finally, an interesting theoretical study on the betacell (the slowest of the party, from a secretory point of view)

activity in islets is presented in the paper by Meyer-Hermann and Benninger (2010). Pancreatic betacell communications in the Langerhans islet at the electrical level is mainly mediated by gap-junctions of connexin 36. The authors combine a mathematical model of betacell electrophysiology with a model for gap-junctions in order to explain experimental observations.

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