Mathematical biology of signaling and metabolism at synapses

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Life is based on energy conversion by which cells and organisms adapt to the varying environment. The human brain weighs only 2% of the body weight but consumes 20% of the energy. Synaptic plasticity and neural computation are energy-intensive processes; the impairment of molecular processes related to energy conversion leads to diseases, including Parkinson's disease and Alzheimer's disease. The underlying biological processes are intrinsically multiscale phenomena since they are based on molecular interactions on the small scale of microdomains, such as presynaptic boutons and dendritic spines, leading to the emerging behavior of neurons, astrocytes, and neural networks. Multiscale mathematical models have played a critical role in helping us understand the underlying regulation and to dissect the mechanisms that control synaptic and neuron behavior. Such models not only offer the opportunity to test different mechanisms but can also address current experimental technology gaps giving us distinct views of the phenomena, and could inform possible treatments for diseases. In this mini-symposium, we aim to highlight how the combination of different computational modeling strategies can address diverse aspects of synaptic plasticity with a focus on the interplay between neuronal signaling and metabolism at different temporal and spatial scales. This will lay the foundation to understand the implications of neuronal signaling in brain energy homeostasis in healthy and disease states. Particularly, the speakers of this mini-symposium will give a nanoscale description of the underlying mechanisms of synaptic plasticity (Erik De Schutter). Followed by a detailed derivation of ATP production in mitochondria (Guadalupe C. Garcia). Then the relationship between stimulus-induced calcium spikes and ATP production in mitochondria, will be presented (Geneviève Dupont). The mini-symposium will close with a discussion of how the brain trades information for energy savings (Renaud Jolivet).

Diversity, equality, and inclusion

The organizers of this mini-symposium represent a number of disciplines and minorities in the scientific community. We have a very diverse background in Mathematics, Engineering, and Physics, and diverse cultural backgrounds from India, Mexico, and Argentina, which give us very particular perspectives. We believe enhancing the visibility of female scientists from underrepresented minorities is key to shaping the landscape of future scientific generations, and increasing the participation of women in historically male-dominated fields. We know representation matters. Giving the chance to young scientists of underrepresented minorities to have a leading role in this conference is an excellent way to increase diversity and inclusion.

Modeling the tripartite synapse at the nanoscale

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Classic descriptions of the synapse include only the presynaptic terminal and postsynaptic density, often located on a spine. It is now generally accepted that astrocytic processes form an integral part of a structure called the tripartite synapse. Our long-term goal is to build detailed nanoscale models of tripartite synapses. At present, we have detailed separate models of each component and have combined simplified versions of these models into a preliminary tripartite synapse model.

This work builds on the STEPS software (http://steps.sourceforge.net) for stochastic reaction-diffusion simulations in irregular meshes. Recently we have expanded STEPS to model all key aspects of vesicle

structure and function, including: vesicle diffusion; the accumulation and diffusion of proteins on the vesicle surface; inter-vesicle protein-protein interactions (vesicle clustering); vesicle-cytosolic protein-protein interactions; vesicle-surface protein-protein interactions (docking); regulated endocytosis (recycling) and exocytosis (fusion and neurotransmitter release).

Using this technology, we were able to model all major phases of the synaptic vesicle cycle in a realistic hippocampal pyramidal cell synaptic bouton morphology at unprecedented levels of molecular and spatial detail, from docking and priming to fusion and recycling. Our model reveals highly dynamic and robust recycling of synaptic vesicles able to maintain stable and consistent synaptic release over time, even during high frequency and sustained firing and assuming full vesicle collapse followed by dispersal and retrieval of vesicle proteins. We also reveal how synapsin and the cytosolic protein tomosyn-1 can cooperate to regulate the recruitment of vesicles from the reserve pool during sustained periods of synaptic activity. We are also using the vesicle technology to simulate AMPA receptor recycling and its regulation in hippocampal spines during the expression of synaptic plasticity. Finally, we have been building detailed models of how calcium release in astrocytic processes depends on nanoscale morphology of the astrocyte and of its organelles like ER and mitochondria.

A thermodynamically-consistent model for ATP production in mitochondria

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Life is based on energy conversion. In the nervous system, in particular, significant amounts of energy are needed to maintain synaptic transmission and homeostasis. To a large extent, neurons depend on oxidative phosphorylation in mitochondria to meet their high energy demand. To develop a comprehensive understanding of the metabolic demands in neuronal signaling, accurate models of ATP production in mitochondria are required. Here, we present a thermodynamically-consistent model of ATP production in mitochondria based on previous work[1,2,3,4]. The significant improvement of the model is that the reaction rate constants are set so detailed balance is satisfied. Moreover, using thermodynamic considerations the dependence of the reaction rate constants on membrane potential, pH, and substrate concentrations are explicitly provided. These constraints assure us the model is physically-plausible. We provide a complete and detailed derivation of ATP production in mitochondria. Furthermore, we explore different parameter regimes to understand in which conditions ATP production or its export are the limiting step in making ATP available in the cytosol. The outcomes reveal that, under physiological conditions, ATP production is the limiting step and not its export. Finally, we analyze the portion of the total volume taken up by the membranes and study the functional effect this can have on the availability of ATP in the cytosol. A compression of approximately 50% of the Intermembrane space or the matrix can increase the amount of ATP in the cytosol by 2-6%. This model lays the foundation for future studies of the internal mitochondrial physiology and metabolism in neurons using Monte-Carlo techniques to simulate the biochemical interactions that take place in the mitochondrial compartments.

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Reciprocal regulation of cytosolic Ca^{2+} signalling and mitochondrial metabolism

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Stimulus-induced Ca^{2+} spikes represent a widespread mode of intracellular signalling. These Ca^{2+} increases are transmitted to mitochondria, which stimulates the production of ATP to allow cells to cope with the increased energy demand created by the stimulus. However, the metabolic status of mitochondria also affects their rates of Ca^{2+} exchanges. This two-way relationship plays a crucial role in cellular signalling and metabolism. We developed mathematical models describing at the same time intracellular Ca^{2+} dynamics, the Krebs cycle, the electron transport chain and the activity of the F1FO ATPase. These models allowed to investigate how the activities of the main cytosol-mitochondria transporters, namely the mitochondrial Ca^{2+} uniporter (MCU), the mitochondrial sodium-Ca^{2+} exchanger (NCLX) and the mitochondrial permeability transition pore (mPTP), regulate Ca^{2+} signalling and mitochondrial metabolism. Simulations led to experimentally validated predictions related, for example, to the crucial role of the MCU in shaping Ca^{2+} signals or to the possible bistable behaviour of the mPTP, corresponding to the well-known low and high conductance modes of this cell-death controlling mitochondrial pore.

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Energy-efficient information transfer in brain circuits

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The nervous system consumes a disproportionate fraction of the resting body's energy production. In humans, the brain represents 2% of the body's mass, yet it accounts for 20% of the total oxygen consumption. Expansion in the size of the brain relative to the body and an increase in the number of connections between neurons during evolution underpin our cognitive powers and are responsible for our brains' high metabolic rate. Despite the significance of energy consumption in the nervous system, how energy constrains and shapes brain function is often under-appreciated. I will illustrate the importance of brain energetics and metabolism, and discuss how the brain trades information for energy savings in the visual pathway. Indeed, a significant fraction of the information those neurons could transmit in theory is not passed on to the next step in the visual processing hierarchy. I will discuss how this can be explained by considerations of energetic optimality. Finally, I will briefly discuss how energetic constraints might impact coding strategies in neural networks and how this provides an elegant approach for a more holistic view of brain circuits.