

Parallel Session
Neuroscience I

**UNDERSTANDING THE HYPOTHALAMIC NETWORK
THAT CONTROLS THE PULSATILE SECRETION OF
REPRODUCTIVE HORMONES: FROM THEORY TO
EXPERIMENTS**

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Keywords: Bifurcation analysis, Relaxation oscillator, Reproductive endocrinology, Neuroendocrinology, GnRH pulse generator.

Reproduction critically depends on the pulsatile secretion of gonadotrophin-releasing hormone (GnRH) from the hypothalamus. This ultradian rhythm drives the secretion of gonadotrophic hormones, which are critical for gametogenesis and ovulation, and its frequency is regulated throughout the life course to maintain normal reproductive health. However, the precise mechanisms controlling the pulsatile GnRH dynamics are unknown. We propose and study a novel mathematical model of a population of neurones in the arcuate nucleus (ARC) of the hypothalamus that co-expresses three key modulators of GnRH: kisspeptin; neurokinin B (NKB); and dynorphin (Dyn). The model highlights that positive feedback in the population exerted by NKB and negative feedback mediated by Dyn are the two key components of the pulse generator, which operates as a relaxation oscillator. Furthermore, our model predicts the response of the system to various neuropharmacological perturbations and reconciles inconsistent experimental observations following such interventions in-vivo. Finally, we use the model to study how external inputs modulate the frequency of the pulse generator. Our model predicts that changes in the level of continuous excitation of the neuronal population should increase pulse frequency; a prediction which we verify in-vivo using optogenetics. Our approach integrating mathematical modelling and experiments provides novel insight into the intrinsic mechanisms controlling GnRH pulse generation.

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A COMPUTATIONAL MODEL INTEGRATING BRAIN ELECTROPHYSIOLOGY AND METABOLISM

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Keywords: Hodgkin-Huxley, Glial potassium cleaning, Multiple time scales, Ischemia.

Several mathematical models have been developed in the recent years to describe the brain activity. The latter is a complex interaction between several dynamics that coexist in a working brain. In particular, we highlight the electrophysiological activity of the neurons, the metabolic cycle of the neuron-astrocyte complex that provides the neurons with the energy needed to produce action potentials, the nutrient supply through the Brain Blood Barrier from the capillaries that irrigate the cerebral tissue, and the blood flow in the circulatory system. These dynamics have been individually the topic of a vast research activity in the last decades, and a large amount of literature is available. A common feature of these studies is a deep analysis on only one of the aforementioned cerebral activities, with only a marginal interest in the others, despite the strongly intertwined roles of these dynamics. We introduce here a lumped model that combines electrophysiology of a neuron-astrocyte complex, its energy metabolism, and the supply of nutrients and oxygen from capillaries. The link between the two models is the energy balance between ATP production by the metabolic network and the energy consumption by the pump action of the sodium-potassium ATPase. The main difficulty in coupling the two models resides in their dramatically different time scales (milliseconds for the electrophysiology and minutes for the metabolism). The electrophysiology acts as a fast time scale driver for the metabolism which represents a slow time scale feedback. We will present the mathematical and computational aspects of the model, and we will show the behaviour of the coupled model for different scenarios: a prolonged resting state, a sustained neuronal activity followed by a return to resting state, and an ischemic episode.

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THE HINDMARSH-ROSE NEURON MODEL: GLOBAL HOMOCLINIC STRUCTURE OF SQUARE-WAVE BURSTERS

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Keywords: Fast-slow dynamics, Neuron models, Homoclinic bifurcations, Higher codimension.

Mathematical neuroscience has a key role today. To understand the functioning of a system as complex as the brain, a convenient step is to delve into the knowledge of neurons as isolated dynamical systems. One of the most studied neuronal models is the Hindmarsh-Rose model, which, among other phenomena, reproduces bursting, a common behaviour in biological neurons. Fast-slow systems are typical in neuronal dynamics, as well as in other areas, such as chemical reactions and lasers. Fold/homoclinic (or square-wave) bursting, following Izhikevich's classification [1], is common in models of this type. However, the overall structure of the involved bifurcation diagram has not been fully understood. For that reason, we provide a global analysis of the bifurcations structure of the Hindmarsh-Rose model, that can be extended to other models with fold/homoclinic bursting. A three-dimensional parameter space is considered [2, 3], the small parameter ε , responsible of the fast-slow dynamics, being one of the parameters. We explore the dynamical changes in the global homoclinic structure, using numerical analysis and continuation techniques. Different homoclinic manifolds with different topologies are studied, as well as codimension-two homoclinic bifurcation curves (namely Belyakov, inclination-flip and orbit-flip curves). Besides, due to the structure of the homoclinic manifolds as tubular-like shapes with very sharp folds, isolas [4] of homoclinic bifurcations appear once ε is fixed. Moreover, isolas of Belyakov points are detected. All these bifurcations are connected with the spike-adding process and canards in fast-slow models, as each spike-adding bifurcation is related with the existence of one homoclinic bifurcation manifold that is exponentially close to the rest of homoclinic bifurcation manifolds. The result is a homoclinic structure that we call "Homoclinic mille-feuille" [3]. Our analysis completes previous partial analysis of fold/hom neuron bursters [5, 6].

This mathematical global structure helps in the dynamical/biological exploration of these neuron models as it gives a detailed "roadmap" in the space of parameters and therefore it provides suitable parameter regions for experimentation and explanations of why several phenomena occur.

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**ELEVATED ICTAL BRAIN NETWORK ICTOGENICITY
ENABLES OPTIMAL EPILEPSY SURGERY
PREDICTION**

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Keywords: Epilepsy surgery, Ictogenic network, Intracranial EEG, Network dynamics, Neural mass model.

Mathematical models are increasingly used to study the dynamics of brain networks inferred from neuroimaging and electrographic brain signals. In the context of epilepsy, we introduced the quantity termed Brain Network Ictogenicity (BNI), which measures how likely a brain network is to generate seizures. The framework consists of placing a mathematical model of seizure transition dynamics onto the nodes of the network in order to then quantify the propensity of the network to be in the seizure state. We have demonstrated that BNI can be used as a practical tool to quantify differences in functional connectivity (FC) networks of healthy individuals and those with epilepsy [1, 2, 3, 4]. More recently, we used BNI to quantify and predict the outcome of epilepsy surgery based on FC extracted from pre-operative ictal intracranial EEG (iEEG) [5, 6]. A key assumption is that the inferred FC provides an appropriate representation of an ictogenic network, i.e. a brain network responsible for the generation of seizures.

However, FC networks have been shown to change their topology depending on the state of the brain, particularly during seizures [7]. We therefore sought to understand how these changes affect BNI. We studied peri-ictal iEEG recordings from a cohort of 16 epilepsy patients who underwent resective surgery and found that, on average, the ictal BNI is higher relative to pre- and post-ictal BNI. However, elevated ictal BNI was not observed in every individual, rather it was typically observed in those who had good post-operative seizure control. We therefore hypothesize that elevated ictal BNI is indicative of an ictogenic network being appropriately represented in the data. We evidence this by demonstrating superior model predictions for post-operative seizure control in patients with elevated ictal BNI [8].

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