

## MINISYMPOSIUM

MULTI-SCALE MATHEMATICAL MODELS IN  
ENDOCRINOLOGY**Organizer**

MARGARITIS VOLIOTIS  
Research Fellow  
Living Systems Institute  
University of Exeter, UK  
M.Voliotis@exeter.ac.uk

**Co-organizer**

EDER ZAVALA  
Research Fellow  
Living Systems Institute  
University of Exeter, UK  
E.Zavala@exeter.ac.uk

**Minisymposium Keywords:** Mathematical endocrinology, Multi-scale modelling,

Neuroendocrine axes are complex systems regulating core bodily functions from energy homeostasis to reproduction to stress responses. In the brain-endocrine pancreas axis, for example, beta cells continuously monitor and control sugar levels by regulating insulin secretion, a hormone that also modulates feeding behaviour and body energy stores in the brain. Similarly, the hypothalamic-pituitary-adrenal axis mediates stress responses by regulating levels of glucocorticoid hormones through the coordination of molecular, cellular, and multi-organ processes.

Thus, a major biomedical challenge is to quantitatively understand endocrine systems and their dynamics at different organisational levels: from single cells, tissues and organs to systems-level coordination. Mathematical modelling captures the complex dynamics of these homeostatic systems by successfully accounting for key properties such as non-linearity, feedback regulation, and modularity. However, more needs to be done in order to develop models that bridge the gap between organisational levels and increase the impact of biomedical modelling in healthcare. Such multi-scale quantitative understanding is crucial to develop insight into physiological scenarios, understanding disease (e.g., metabolic syndromes, hormone imbalances, stress-related disorders) and design better clinical interventions.

This mini-symposium brings together experts in mathematical modelling of endocrine systems at different levels of organisation. We aim to develop a common understanding of the major challenges in studying the dynamic aspects of hormone regulation and outline future directions on key biomedical questions.

*Minisymposium: Multi-scale mathematical models in endocrinology*

# STOCHASTIC TRANSCRIPTIONAL DYNAMICS AND SPATIAL SIGNALLING FOR THE PROLACTIN GENE IN SINGLE CELLS AND TISSUE.

DAVID RAND

d.a.rand@warwick.ac.uk

University of Warwick, UK

*Keywords:* Stochastic transcriptional dynamics, Multi-scale modelling.

I will review recently developed mathematical methods for reconstructing stochastic transcriptional dynamics from imaging time series and describe how these have been used to characterise the bursting structure of the prolactin gene. This has revealed general principles that have now been shown by many labs to be ubiquitous for genes. I will then describe how this has been used to study the coordination of transcription in tissue (the pituitary) and discuss mathematical methods that enable us to identify signalling and characterise the nature of the signals.

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## MIDDLE-OUT MULTI-SCALE MODELLING OF THE DEVELOPMENT OF OVARIAN FOLLICLES

FRÉDÉRIQUE CLÉMENT

frederique.clement@inria.fr

INRIA Paris, France

*Keywords:* Multi-scale modelling, Follicle development.

Ovarian follicles are the basic anatomical and functional units sustaining gametogenetic and endocrine functions in ovaries. The development of ovarian follicles is a tightly-controlled physiological and morphogenetic process, which can be investigated from a middle-out approach starting at the cell level. Our modeling approach calls to the generic formalism of structured cell populations, that allows us to make mechanistic links between the control of cell fate (proliferation, differentiation or apoptosis) and that of the follicle fate (ovulation or degeneration) or to investigate how the functional interactions between the oocyte and its surrounding cells shape the follicle morphogenesis.

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## DEVELOPING A MULTISCALE MATHEMATICAL UNDERSTANDING OF THE HPA AXIS

EDER ZAVALA

E.Zavala@exeter.ac.uk

Living Systems Institute, University of Exeter, Stocker Rd. EX4 4QD, Exeter, United Kingdom

Joint work with F. Spiga (University of Bristol, UK), J. Walker (University of Exeter, UK), Z. Zhao (University of Bristol, UK), J. Terry (University of Exeter, UK), and Stafford Lightman (University of Bristol, UK)

*Keywords:* Multi-scale modelling, HPA axis.

The stress response depends on the coordination of the hypothalamus, the pituitary and the adrenal glands for the rapid synthesis and secretion of glucocorticoid hormones. The biosynthesis of these steroid hormones is regulated by remarkably dynamic processes that are critical for an efficient response to stress. Though many key factors involved in these processes have been identified and studied in isolation, the way in which these factors interact with one another as a dynamic network has not been investigated.

Here, we develop a mathematical model of the interactions between the pituitary gland and the adrenal Steroidogenic Regulatory Network (SRN) that accounts for key regulatory processes occurring at different time scales. We postulate how steroidogenic factors respond collectively to ACTH stimuli from the pituitary, and used our model to predict the time evolution of steroidogenesis in response to a range of physiological ACTH perturbations, including basal and acute stress scenarios. We discuss the implications of the model predictions in the light of recent *in vivo* experiments in the rat.

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## POPULATION-BASED SIGNAL PROCESSING AND STIMULUS-RESPONSE IN OXYTOCIN NEURONES

DUNCAN J. MACGREGOR

duncan.macgregor@ed.ac.uk

Centre for Discovery Brain Science, University of Edinburgh, UK

Joint work with Maicas-Royo (University of Edinburgh, UK) and G. Leng (University of Edinburgh, UK)

*Keywords:* Cellular heterogeneity, Oxytocin neurone.

The magnocellular oxytocin neurones of the hypothalamus are well known for their role in milk-ejection and in the homeostatic systems that maintain osmotic pressure, but they also function as part of appetite regulation, signalling satiety in response to the gut hormone CCK1. Thus oxytocin neurones respond to multiple signals, secreting oxytocin both peripherally into plasma, from axonal terminals in the posterior pituitary, and centrally, via dendritic secretion. Blood plasma oxytocin levels give the most accessible measure of oxytocin neuronal activity, but the relationship between input stimulus and plasma output response is complex and highly non-linear. In milk-ejection, where a large short pulse of oxytocin is required, the neurones act as a coordinated network, but in other roles spiking activity is independent, and the heterogeneous neurones act as a population of independent cells producing a summed output signal. The input signals consist of many small excitatory and inhibitory pulses from thousands of input neurones. The oxytocin neurones must act individually and as a population to process a noisy input signal into a robust output signal. We have previously developed an integrated input, spiking, secretion, and plasma diffusion single oxytocin neurone model, accurately simulating in vitro and in vivo response. This model showed how intrinsic mechanisms such as the after-hyperpolarisation (AHP) act to reduce signal noise. Here we study a model neurone population, with varied levels of heterogeneity and independence of input signals in order to understand the relationship between single cell properties and action as a population in producing a robust signal response.

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# MULTIPLE SCALE ANALYSIS AND PERIODIC SOLUTIONS IN A MODEL OF ULTRADIAN GLUCOSE REGULATION

BENOIT HUARD

benoit.huard@northumbria.ac.uk

Department of Mathematics, Physics and Electrical Engineering, Northumbria University, UK  
Joint work with A. Bridgewater (Northumbria University, UK) and M. Angelova (Deakin University, Melbourne, Australia)

*Keyword:* Glucose regulation.

Glucose regulation is an essential function of the human body which allows energy to be distributed to the brain, organs and muscles. This regulation operates in a cyclic manner, perhaps as a mechanism for increasing robustness in the presence of sustained glucose stimulations. A model for these oscillations in the ultradian regime was devised in [Li, Kuang, Mason, *Jour Theor Biol*,2006] where it was shown that the presence of two delays in glucose and insulin secretion times provide a pathway for explaining these oscillations. The efficacy of this control is typically reduced in the presence of diabetes.

In this contribution, we employ a multiple scale approach to obtain approximate expressions for the limit cycle in this two-delay model corresponding to this feedback loop. The resulting equations allow to quantify the joint contribution of delays and diabetic parameters (such as insulin resistance) to the production and accurate tuning of the oscillatory regimes. This provides a novel technique for estimating the efficacy of glucose regulation in pre- and diabetic individuals.