Workshop ANAR-REGATE

Dynamical Systems & Neuroendocrinology

Friday, October 16th 2009, Paris

Lecture hall of the Jacques Monod Institute, Jussieu Campus :

8:45	-	9:15	*Welcome*	
9:15	-	9:30	*Introduction*	
9:30	-	10:30	Richard Bertram	"A mathematical study of electrical bursting in pituitary cells"
10:30	-	11:00	*Break*	
11:00	-	12:00	Alfredo Ulloa-Aguirre	"GnRH resistance and congenital hypogonadotropic hypogonadism in humans: A GPCR conformational disease"

Esclangon cellars, Jussieu Campus, UPMC : Lunch buffet

Lecture hall Durand, Esclangon Building, Jussieu Campus, UPMC :

1:30	-	2:30	Krasimira Tsaneva-Atanasova	"A mathematical model for regulation of gonadotrophins secretion"
2:30	-	3:30	Gareth Leng	"Modelling neuroendocrine systems"
3:30	-	4:00	*Break*	
4:00	-	5:00	Jacques Young	"Pulsatile GnRH secretion in human physiology and pathology"
5:00	-	5:30	*Workshop conclusion*	

Website : http://alx.vidal.googlepages.com/ANAR-REGATE.htm

Abstracts

Prof. Richard Bertram
Department of Mathematics and Programs in Neuroscience and Molecular Biophysics,
Florida State University,
Tallahassee, Florida.

A Mathematical Study of Electrical Bursting in Pituitary Cells.

Pituitary lactotrophs, somatotrophs, and corticotrophs often exhibit electrical bursting patterns, consisting of periodic episodes of electrical impulses followed by periods of quiescence. Unlike bursting observed in nerve cells and pancreatic islets, the impulses in pituitary bursts have a small amplitude, and the burst frequency is high. Mathematical models of bursting are typically analyzed using geometric singular perturbation analysis, often called fast/slow analysis. This analysis has been applied to pituitary bursting and contrasted with square wave bursting, a typical type of bursting in neurons and pancreatic islets. The analysis highlights the many differences in the dynamics of these two forms of bursting. In this talk, we describe these dynamics and demonstrate that, although the two seem very different, it is possible to transform one to the other through variation of a single parameter. Moreover, parameters that can achieve this transformation are biologically plastic, so it is reasonable that they could vary from one cell type to another.

Prof. Alfredo Ulloa-Aguirre
Research Unit in Reproductive Medicine,
Instituto Mexicano del Seguro Social,
Mexico D.F., Mexico.
Invited STUDIUM Professor at INRA Tours, France.

GnRH resistance and congenital hypogonadotropic hypogonadism in humans:
A GPCR conformational disease.

The mammalian gonadotropin-releasing hormone receptor (GnRHR) belongs to the superfamily of G-protein coupled receptors, specifically the family related to the rhodopsin- and β_2-adrenergic-like receptors. Unlike other members of the GPCRs superfamily, the GnRHR exhibits several unique futures, including the lack of the carboxyl-terminal extension into the cytosol and, in the case of primate GnRHRs, the presence of Lys at position 191 in the second extracellular loop, which restricts cell surface plasma membrane expression of the receptor by hindering formation of the Cys14-Cys200 disulfide bridge, which is necessary to stabilize the receptor in a conformation compatible with endoplasmic reticulum export.
Point mutations in cell surface receptors may result in the production of misfolded proteins that are translated but do not reach their proper destination in the cell. This is the case of loss-of-function mutations in the human GnRHR, which are a rare cause of hypogonadotropic hypogonadism in humans, a disease leading to reproductive failure due to partial or complete inability of the pituitary gonadotrops to respond to agonist. The majority of these mutant GnRHRs are trafficking-defective receptor proteins, whose function can be restored *in vitro* by genetic or pharmacologic means. We have recently applied a combined strategy (mutagenesis and functional studies as well as computational modeling and molecular dynamics simulations) to analyze some structure-function relationships of the human GnRHR and the mechanism(s) whereby mutations lead to misfolded receptor proteins. In this talk I will describe how application of these strategies have contributed to elucidate the conformational effects of Lys191 in the human GnRHR and the role of the Cys14-Cys200 disulfide bridge in receptor cell surface plasma membrane expression.

Dr. Krasimira Tsaneva-Atanasova
Department of Engineering Mathematics,
University of Bristol,
Bristol, United Kingdom.

A Mathematical Model for Regulation of Gonadotrophins Secretion.

Gonadotrophin-releasing hormone (GnRH) is a hormone released from the brain to control the secretion of reproductive hormones. Like many other chemical messages it is released in brief pulses. Pulsatile GnRH can increase fertility (e.g. in IVF programmes) whereas sustained GnRH reduces fertility (and is used to treat hormone-dependent cancer) but the ways in which the GnRH receptor and its intracellular signalling cascade decode these kinetic aspects of stimulation are essentially unknown. Given that clinical use of GnRH agonists relies on avoidance or exploitation of this effect, it is remarkable how little is known about the way gonadotrophs decode stimulus kinetics. In this talk we present a biophysical model of the key players that govern GnRH signalling. The model results are closely related to experimental data.

Prof. Gareth Leng
School of Biomedical Sciences,
University of Edinburgh, College of Medicine and Veterinary Sciences,
Edinburgh, United Kingdom.

Modelling neuroendocrine systems.

Peptides in the hypothalamus are not like conventional neurotransmitters; their release is not particularly associated with synapses, and their long half-lives mean that they can diffuse to distant targets. Peptides can act on their cells of origin to facilitate the development of patterned electrical activity, they can act on their neighbours to bind the collective activity of a neural population into a coherent signalling entity, and the co-ordinated population output can transmit waves of peptide secretion that act as a patterned hormonal analogue signal within the brain. At their distant targets, peptides can re-programme neural networks, by effects on gene expression, synaptogenesis, and by functionally rewiring connections by priming activity-dependent release.
My lab has studied mainly the oxytocin and vasopressin neurones of the hypothalamus, these neurones fire in distinctive patterns that govern and in turn are governed by the peptide secretion that they induce. Oxytocin cells display remarkable synchronised bursts that arise through emergent properties of an interactive network; vasopressin cells also burst, but asynchronously in a very different way and for very different reasons. In their different ways, these two neuronal systems have become important model systems in neuroscience; in this talk I will talk about modelling these model systems.

Prof. Jacques Young
Service d'Endocrinologie et des Maladies de la Reproduction, INSERM U 693,
Université Paris Sud-11, APHP, CHU de Bicêtre,
Paris, France.

Pulsatile GnRH secretion in human physiology and pathology.

GnRH is the central regulator of the reproductive hormonal cascade and was first isolated from mammalian hypothalami as the decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly.NH2). GnRH is processed in hypothalamic neurons from a precursor polypeptide by enzymic processing and packaged in storage granules that are transported down axons to the external zone of the median eminence. The peptide is released in

synchronized pulses from the nerve endings of about 1000 neurons into the hypophyseal portal system every 30120 min to stimulate the biosynthesis and secretion of LH and FSH from pituitary gonadotropes. Each GnRH pulse stimulates a pulse of LH release, but FSH pulses are less distinct. The frequency of pulses is highest at the ovulatory LH surge and lowest during the luteal phase of the ovarian cycle. The asynchronous patterns of LH and FSH release result from changes in GnRH pulse frequency, modulating effects of gonadal steroid and peptide hormones on FSH and LH responses to GnRH, and differences in the half-lives of the two hormones.
Low doses of synthetic GnRH delivered in a pulsatile fashion to simulate the endogenous GnRH levels in the portal vessels restore fertility in men and women with hypogonadotropic hypogonadism. However, high doses of GnRH or agonist analogs desensitize the gonadotrope with resultant decrease in LH and FSH and a decline in ovarian and testicular function. This desensitization phenomenon is extensively applied in clinical medicine for the treatment of a wide range of diseases among which prostate cancer and precocious puberty.
Isolated GnRH deficiency is the clinical syndrome that results from failure of this normal pattern of episodic GnRH secretion to occur. It is characterized by complete or partial absence of any endogenous GnRH-induced LH pulsations and normalization of pituitary and gonadal function in response to physiological regimens of exogenous GnRH replacement.
Clinically, the diagnosis of GnRH deficiency is made in adolescence when there is failure of pubertal development and absence of appearance of secondary sex characteristics. In isolated GnRH deficiency, a variety of aberrant gonadotropin secretory patterns have been observed, indicating a spectrum of defects in GnRH secretion in keeping with the diverse clinical presentation. These different pulsatile abnormalities will be discussed.

Organizers

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Sponsors

ANAR : *Analyse Non linéaire et Application aux Rythmes du vivant*, funded by the ANR.

REGATE : *REgulation of the GonAdoTropE axis*, Large-Scale project INRIA.

Participants

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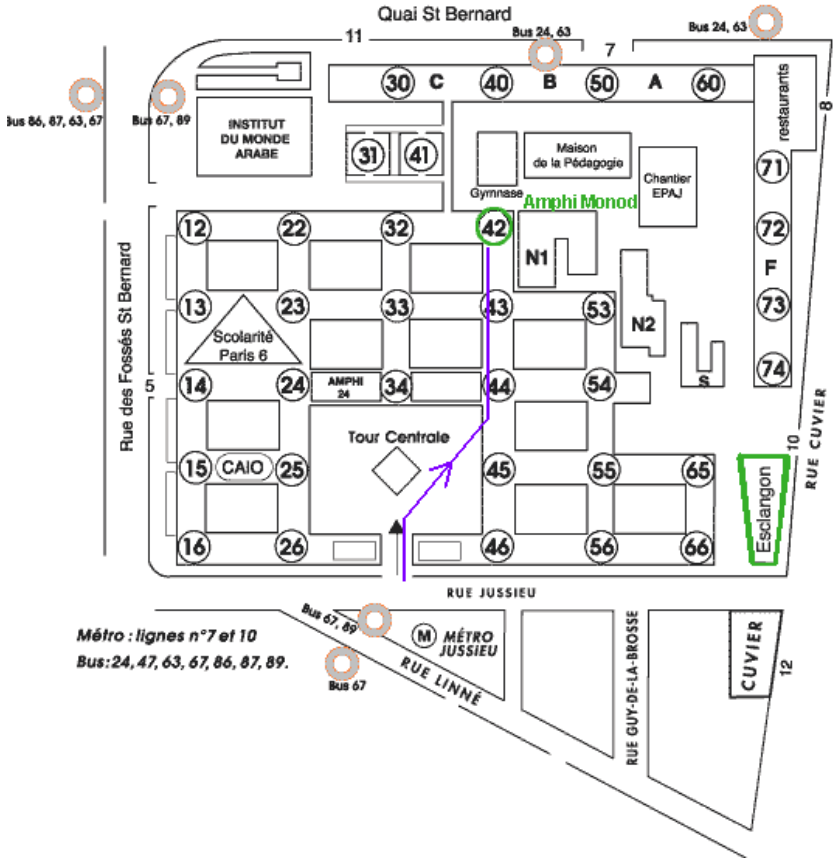
Practical Information

The workshop will take place in the Jussieu Campus (University Pierre & Marie Curie, UPMC), in the heart of Paris (see neighborhood map on the next page). It is accessible with the metro, station "Jussieu" on lines 7 and 10, and many bus lines (see the Campus schema below).

During the morning, the workshop will take place in the lecture hall of the Jacques Monod Institute, Tower 42 (level -1). Afterwards, there will be a lunch-buffet set in the original cellars of the "Halle aux Vins", in the Esclangon Building. Then, during the afternoon, the workshop will continue in the lecture hall Durand (Esclangon Building).

The registration is free but mandatory. If you intend to participate in the workshop, please send an e-mail to: alexandre.vidal@univ-evry.fr



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