2019 MATHEMATICS OF PHYSIOLOGICAL RHYTHMS

Creswick, Ballarat VIC
Australia

9-13 September 2019

ABOUT THE PROGRAM

The aim of the research program is to unite and combine current trends in dynamical systems and time series analysis for solving problems in physiology which are governed by repeating processes. Examples are circadian rhythms, cardio-dynamics, sleep processes, glucose-insulin regulation and many others. The importance of the circadian clock to human health was recognized by the 2017 Nobel prize in medicine. The invited participants are experts in mathematics, physics and computer sciences working in applications of dynamical systems and time series in physiology, biology and medicine. The program will explore the state-of the-art mathematics underlying periodic and periodic-like processes in human physiology.

The retreat will focus on models based on deterministic and stochastic differential equations and delay differential equations, dynamical system approaches to time series, statistical mechanics, phase transitions and mean field approaches. The mathematical models of regulatory processes are often informed by data-driven models, derived from spectral analysis and signal processing. Furthermore, the large number of parameters can be difficult to measure. Machine learning and statistical approaches will be explored to estimate parameters. The models are based on real data measured from humans (ECG, EEG, actigraphy, eye movements, glucose levels, insulin sensitivity), and the processes for building models from such data will be discussed.

Organisers:

- Maia Angelova, Deakin University
- James Sneyd, Auckland University
- Aneta Stefanovska, Lancaster University
- Plamen Ch Ivanov, Boston University and Harvard Medical School

Local Organising Committee:

- Dr Sergiy Shelyag, Deakin University
- Dr Sutharshan Rajasegarar, Deakin University
- Dr Chandan Karmakar, Deakin University
- Dr Ye Zhu, Deakin University

Participant List:

- Maia Angelova (Deakin University)
- Aneta Stefanovska (Lancaster University)
- Plamen Ch. Ivanov (Boston University)
- Anne Skeldon (University of Surrey)
- Krasimira Tsaneva-Atanassova (University of Exeter)
- Adelle Coster (UNSW)
- Andrew Phillips (Monash University)
- David Liley (Melbourne University)
- Ruben Fossion (National Autonomous University of Mexico)
- Chandan Karmakar (Deakin University)
- Ye Zhu (Deakin University)
- Sutharshan Rajasegarar (Deakin University)
- Christopher Stephens (National Autonomous University of Mexico)
- Sergiy Shelyag (Deakin University)
- Shitanshu Kusmakar (Deakin University)
- Jyotheesh Gaddam (Deakin University)
- Mohammad Abdul Motin (University of Melbourne)
- Emerson Keenan (University of Melbourne)
- Shreyasi Datta (University of Melbourne)
- Md Ahsan Habib (Deakin University)
- Jason Whyte (University of Melbourne)
- Tania Pencheva (Bulgarian Academy of Sciences)
- Anuroop Gaddam (Deakin University)

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Keynote Abstracts

The new Frontier of Network Physiology: from Temporal Dynamics to Synchronization and Principles of Integration in Networks of Physiological Systems

9 Sep
9:30-10:15
Lecture Theatre

Plamen Ivanov

Boston University and Harvard Medical School

The human organism is an integrated network where complex physiological systems continuously interact to optimize and coordinate their function. Organ-to-organ interactions occur at multiple levels and spatiotemporal scales to produce distinct physiologic states. Disrupting organ communications can lead to dysfunction of individual systems or to collapse of the entire organism. Yet, we do not know the nature of interactions among systems and sub-systems, and their collective role as a network in maintaining health. The new field of Network Physiology aims to address these fundamental questions.

Through the prism of concepts and approaches from statistical and computational physics and nonlinear dynamics, we will present a new framework to identify and quantify dynamic networks of organ interactions. We will demonstrate how physiologic network topology and systems connectivity lead to integrated global behaviors representative of distinct states and functions.

The presented investigations are initial steps in building a first Atlas of dynamic interactions among organ systems and the Human Physiolome, a new kind of Big-Data of blueprint reference maps that uniquely represent physiologic states and functions under health and disease.

*We acknowledge support from W M Keck Foundation.

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9 Sep
10:45-11:30
Lecture Theatre

The interplay of periodic stimulation and translocation in the insulin signalling system

Adelle Coster
UNSW

The action of insulin on cell metabolism falls into two broad categories, the translocation of components and their biochemical activation via phosphorylation. Often the location of synthesis/storage and activation are dissimilar, and so translocation needs to precede phosphorylation (activation) of the component.

Insulin is synthesised and stored in the β-cells of the pancreas. Even in the fasted state, small quantities of insulin are released into the blood stream in a pulsatile fashion with a period of 510 minutes. The amplitude of the pulse, however, increases dramatically within a few minutes of a rise in blood sugar, something which also occurs periodically, with the ingestion of food.

The periodic stimulation by insulin causes the translocation of Akt. We have developed a compartmental model of Akt translocation, and, using the conservation relation inherent in the model, we can show that this system is equivalent to a heavily damped harmonic oscillator. Here I explore some of the ramifications of the hysteresis observable in the system response when subjected to pulsatile and periodic forcing, both of which are ubiquitous in biological signalling networks.

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10 Sep
9:30-10:15
Lecture Theatre

The origin of GnRH pulse generation: An integrative mathematical-experimental approach

Krasimira Tsaneva-Atanassova
University of Exeter

Fertility critically depends on the gonadotropin-releasing hormone (GnRH) pulse generator, a neural construct comprised of hypothalamic neurons co-expressing kisspeptin, neurokoinin-B and dynorphin. Here, using mathematical modelling and in-vivo optogenetics we reveal for the first time how this neural construct initiates and sustains the appropriate ultradian frequency essential for reproduction. Promted by mathematical modelling, we show experimentally that robust pulsatile release of luteinizing hormone, a proxy for GnRH, emerges abruptly as we increase the basal activity of the neuronal network using continuous low frequency optogenetic stimulation. Further increase in basal activity markedly increases pulse frequency and eventually leads to pulse termination. Additional model predictions that pulsatile dynamics emerge from non-linear positive and negative feedback interactions mediated through neurokinin-B and dynorphin signaling respectively are confirmed neuropharmacologically. Our results shed light on the long-elusive GnRH pulse generator offering new horizons for reproductive health and wellbeing.

Modelling living systems with nonautonomous phase oscillator networks

10 Sep
10:45-11:30
Lecture Theatre

Aneta Stefanovska

Lancaster University

Most of the models of living systems assume conservation of mass and energy. Differential equation are formulated in terms of parameters related to e.g. concentrations or masses. However, living systems operate far from equilibrium and are inherently open in character. So, a new approach is needed as will be described in this talk.

From neurons to mean fields: modelling the genesis of brain oscillatory activity

11 Sep
9:30-10:15
Lecture Theatre

David Liley

Melbourne University

The thin rind of the cerebrum that comprises the cortex of humans is densely populated with neurons that interact with each other over a range of temporal and spatial scales. The collective activity emerging from these 100 billion neurons interacting by the 1000 trillion or so connections forms the basis for human behaviour. To date the most familiar approach to studying such activity has been directed towards enumerating, characterising and simulating these vast neural networks. However there exist empirically and computationally much less burdensome approaches to studying such collective activity that rely on a range of insights derived from mathematical physics. Such approaches, variously referred to as mass action or mean field approaches, replace individual interactions between neurons by effective averages known as mean fields. The dynamical activity of this system is then approximated by the evolution of these mean fields.

The aim of this talk will be to outline one mean field approach to modelling brain activity that has been particularly successful in articulating the genesis of rhythmic electroencephalographic activity, developing forward models of simultaneous EEG and fMRI activity in the context of realistic cortical connectivity and geometry, and in modelling the macroscopic electrocortical effects of anaesthetic action.

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11 Sep
10:45-11:30
Lecture Theatre

Light and its role in human sleep and circadian rhythms: mathematical modelling and open questions

Anne Skeldon

University of Surrey

Sleep is fundamental to human health. Extensive laboratory research has led to a good understanding of the core processes that drive sleep-wake regulation. Translating that understanding to the irregularities of the real world is challenging since sleep-wake cycles depend not only on our biology. For example, we may get up earlier than we would like because we have to go to school or work. We may go to bed long after we feel ready for sleep because of work or social factors. Our light environment is also critical. Light plays a fundamental role because our internal clock typically run a little slow, with the accepted human average natural period being 24.2h. This means that, in the absence of clocks or of natural time cues, most people would drift gradually later, each day getting up a little later and going to bed a little later than the day before. Historically, it was the periodic forcing from the natural light-dark cycle that kept us to a 24h rhythm.

Unpicking the effect of these three elements: biological, sociological and environmental is difficult and is a place where mathematical models have an important part to play.

In this talk I will give an overview of some existing mathematical models but then focus on the role of light in particular as an entraining signal, including the role of self-selection.

I will discuss how we measure light, what typical light exposure patterns look like, the effect of different light exposure patterns, how we combine time series of light data with mathematical models and some of the many open challenges around quantifying the effect of light on the human circadian clock.

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12 Sep
9:30-10:15
Lecture Theatre

Sleep regularity – linking metrics and models

Andrew Phillips

Monash University

The circadian clock evolved under a stable light/dark cycle. Today, however, individuals often live on irregular schedules and are exposed to irregular light/dark patterns. We have developed a time series analysis approach called the Sleep Regularity Index (SRI) to quantify the regularity of an individual's sleep/wake patterns, as a proxy for circadian disruption. The SRI has recently been shown to associate with a variety of health outcomes, including mental health, cardiometabolic, and school performance outcomes. Using a mathematical model of human circadian timing and sleep/wake regulation, we investigate the causes or irregular sleep/wake patterns and the approaches by which irregular sleep/wake patterns can be realistically modelled.

Framework for Mathematical Modelling of Insomnia

12 Sep
10:45-11:30
Lecture Theatre

Maia Angelova, Chandan Karmakar, Ye Zhu, sean Drummond and Jason Ellis
Deakin University

We spend a considerable part of our lives sleeping and the sleep is a very important part of human existence and wellbeing. Sleep disorders can significantly reduce the quality of our lifes and pose a threat to our health.

In this talk we present our latest work on the challenges of modelling sleep disturbances such as acute and chronic insomnia using data driven models and phenomenological concepts.

We have two case studies: Case Study 1 - acute insomniacs compared to healthy controls and Case Study 2 chronic insomniacs and their sleep partners.

I will show results derived only from actigraphy measurements of these two groups.

This work is in collaboration with psychologists - Jason Ellis, Northumbria University, Newcastle upon Tyne, UK, and Sean Drummond, Monash University, Australia, computer scientists - Chandan Karmakar and Ye Zhu, Deakin University, Australia, computational scientists Sergiy Shelyag, and physicists Ruben Fossion and Ana Leonor Rivera, Universidad National Autonoma de Mexico, Mexico.

Homeostasis from a time-series perspective

12 Sep
14:00-15:00
Lecture Theatre

Ruben Fossion
National Autonomous University of Mexico

Although homeostasis is a key concept of physiology and the basis to understand chronic- degenerative disease and human ageing, it is difficult to quantify in clinical practice. Time series resulting from continuous and non-invasive physiological monitoring is conjectured to reflect the underlying physiological regulatory processes, but it is not clear why the variability of some variables such as heart rate gives a favourable health prognosis whereas the variability of other variables such as blood pressure implies an increased risk factor. Homeostasis suggests that different physiological variables may play distinct roles in their respective regulatory mechanisms and one can distinguish between regulated variables, such as blood pressure or core temperature, and physiological responses, such as heart rate and skin temperature. We give evidence that in optimal conditions of youth and health the former are characterized by Gaussian statistics, low variability and represent the stability of the internal environment, whereas the latter are characterized by non-Gaussian distributions, large variability and reflect the adaptive capacity of the human body; in the adverse conditions of ageing and/or disease, adaptive capacity is lost and the variability of physiological responses is diminished, and as a consequence the stability of the internal environment is compromised and its variability increases. We conclude that time-series analysis allows to quantify homeostasis in the optimal conditions of youth and health and the degradation of homeostasis or homeostenosis in the adverse conditions of ageing and/or disease and may offer an alternative approach to diagnosis in clinical practice.

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12 Sep
14:00-15:00
Lecture Theatre

On Application of InterCriteria Analysis Approach

Tania Pencheva

Bulgarian Academy of Sciences

Recently developed InterCriteria analysis (ICrA) has being intensively gained popularity as quite promising approach to support decision making process in biomedical informatics studies. ICrA has been elaborated to discern possible similarities in the behaviour of pairs of criteria when multiple objects are considered. The approach is based on mathematical formalisms of intuitionistic fuzzy sets and index matrices thus relying on methodology different from the classical correlation analysis. Up to now, ICrA has been successfully applied in different areas economics, ecology, crude oil analysis, e-learning, metaheuristic algorithms performance, neural networks, etc. ICrA has been demonstrated as promising also in studies related to medicine, i.e. blood plasma thermograms dataset analysis, oncological data analysis, electrocardiography signals analysis, as well as in in silico studies of complex biomolecular systems. In all applications so far, ICrA shows prerequisites to assist in decision making processes in order to guide the selection of the most appropriate choice among many.

Acknowledgements: Funding from the National Science Fund of Bulgaria, under grant DN 17/6 A New Approach, Based on an Intercriteria Data Analysis, to Support Decision Making in in silico Studies of Complex Biomolecular Systems, is gratefully acknowledged.

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13 Sep
9:30-10:15
Lecture Theatre

From Evolution to Daily life: The Importance of Timescale in Network Physiology

Christopher Stephens

National Autonomous University of Mexico

In physics, the question of scale is of fundamental importance in establishing and theoretical framework for understanding phenomena. In particular, understanding the natural time scale of variability and the feedback mechanism from one space/time scale to another is vital. Fortunately, in physics there is relatively little cross-talk between the different fundamental scales - nuclear, atomic, molecular etc. and their associated effective degrees of freedom. However, in biology there is substantial cross-talk and this cross-talk is driven by much longer term processes, with the ultimate level being evolution itself. Thus, the processes of interest in this workshop - Sleep, Brain, Diabetes, Network Physiology - although having an intrinsic scale that is short term, more or less a day, have important, very different, time scales that affect them. An important one is simply the long term friction due to lifestyle and, of course, simply the aging process. Thus, physiological systems are subject to wear and tear that has both a quantitative (length of time) and qualitative (lifestyle) aspect. Moreover, the expected wear and tear and our physiological ¿ response to it is something that has been tuned by evolution itself. In this talk I will present data that offers support for these assertions and discuss the challenges of obtaining data from human populations that gives a more holistic framework for understanding the interactions between biological phenomena at different scales.

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