**Project title:** Experimental Bifurcation Analysis of Neurons Using Control-based Continuation  
**Main supervisor:** LR, Dr Ludovic Renson (LR) (RAEng Research Fellow in the Dep. of Eng. Math.)  
**Internal co-supervisors:** Dr Lucia Marucci (LM), Prof. Mario di Bernardo (MdB)  
**External co-supervisor:** Prof. Krasimira Tsaneva-Atanasova (KTA), University of Exeter

**Project description**

The behaviour of biological systems is governed by a wide range of complex phenomena that are intrinsically nonlinear and interact on different time and spatial scales. Mathematical modelling currently plays a central role in understanding the dynamic behaviour of these nonlinear systems. Take, for example, neuron models that are studied to unveil the bifurcations underlying the cell’s bursting behaviour [1]. The major caveat with this approach is that discovered bifurcations and other nonlinear features critically depend on the model assumptions (i.e. captured physics) and the model parameter values identified experimentally. As of now, there exist no experimental method that can directly measure nonlinear dynamic features such as bifurcations directly in biological experiments.

Pioneered at Bristol, control-based continuation (CBC) is a non-parametric method that maps out the dynamic features of a nonlinear physical system directly during experimental tests, without relying on the estimation of the parameters of a mathematical model, or a particular model structure. Combining feedback control with numerical continuation algorithms, CBC modifies, on-line, the input applied to the system in order to isolate the nonlinear behaviour of interest. In this way, CBC offers the best conditions to analyse these dynamic features in detail, to follow them as experimentally-controllable parameters are changed, and to detect and track boundaries between qualitatively different types of behaviour (i.e. bifurcations). The fundamental principles of CBC are well established, and the method has been applied to a wide range of non-living (i.e. electro-mechanical) systems. For instance, the method was recently demonstrated by LR on a multi-degree-of-freedom structure exhibiting complex nonlinear phenomena such as mode interaction, quasi-periodic oscillations and isolated response curves [2-3]. CBC proved able to extract dynamic features of the system such as curves of limit-point bifurcations that are key to the understanding of its behaviour (hysteresis, multi-stability, etc.).

This PhD project aims to further develop CBC such that it can be applied to neurons and exploited to experimentally characterise their bursting dynamics. The project is structured around three main objectives:

1) **Develop stabilising feedback controllers for bursting cells.** Feedback control plays a key role in the application of CBC as it allows to rapidly steer the experiment to steady-state and maintain it around a prescribed operating point, thus avoiding stability changes and untimely transitions that could occur due to bifurcations. The first step to address this objective will be to study theoretically and numerically neuron models available in the literature [4] to determine the control strategies and the choice of input(s)/output(s) the most suitable to the application of CBC.

2) **Set-up of a dynamic-clamp experiment to test neurons.** A common way to test excitable cells such as neurons is through a dynamic clamp experiment, which is, in essence, an hybrid experiment (also called real-time dynamic sub-structuring experiment) where an excitable living cell (here a neuron) is interfaced with a model of the membrane or synaptic conductance(s) [5]. Membrane potentials on the living cell are measured using electrodes and fed into the numerical models which computes and outputs the current to be applied to the cell. The dynamic clamp experimental set-up (hardware, software and living cell) will be assembled at Bristol in LM’s laboratory. An existing custom data acquisition system specifically designed for real-time applications and already available at Bristol will be used to connect the model and the physical...
system (i.e. the cell). Cell membrane sensing and actuation will be performed using devices
developed by Dr Despina Moschou, one of LM’s collaborators at the University of Bath. To
guarantee the success of the experiment, trainings with and visits to an experienced
electrophysiologist (KTA) will be arranged.

3) **Combine CBC with the dynamic-clamp experiment to study the bifurcation of neurons.** The
combination of CBC with the dynamic-clamp experiment will enable us to explore the dynamics
of neurons and detect the presence of key dynamic features that must be included in
mathematical models. Dynamic clamp experiments and CBC also share several similarities that
can be exploited to improve the effectiveness and usefulness of both methods beyond the
application considered here. An important difficulty in performing optimal dynamic-clamp
(hybrid) experiments is to complete the cycle of reading the membrane potential, computing the
current and injecting it to the cell at a rate faster than the fastest dynamic rate present in the
system. For long-term behaviours (i.e. steady-states, periodic responses, etc.), CBC allows to
circumvent this difficulty by iteratively modifying the input to the experiment until compatibility
between measured membrane potential and applied current is achieved. Conversely, CBC relies
on the presence of parameters that can be changed, which is easily provided in abundance by the
numerical model used in the dynamic clamp.

Throughout the project, the student will be trained in the groups of the main and co-supervisors in
nonlinear dynamics, control and dynamic-clamp experiments.

**References**