The University Of Sheffield.

*Department of Automatic Control and Systems Engineering*

# IEEE UK&RI Chapter
# Colloquium on Control in Systems Biology

Programme

09:30-10:00: Arrivals and Refreshments

10:00-11:00: Glenn Vinnicombe
"Fundamental limitations on noise reduction in the cell"

11:00-11:40: Mustafa Khammash
"Noise in Gene Regulatory Networks: Biological Role and Mathematical Analysis"

11:40-12:20: Antonis Papachristodoulou
"Methods and Algorithms for Biological Networks Analysis"

12:20-13:00: Lunch

13:00-13:40: Declan Bates
"Feedback Control Mechanisms in the Tryptophan Operon: Modelling, Analysis and Design"

13:40-14:20 Visakan Kadirkamanathan
"Metabolic Network Analysis: Flux Estimation from Noisy and Missing Data"

14:20-14:40 Tea

14:40-15:20 Hong Yue
"Sensitivity Analysis and Experimental Design of a Stiff Signal Transduction Pathway"

15:20-16:00 Aidan O'Dwyer
"Biotechnology, Life Sciences and Control Engineering – Some Synthesis Issues"

16:00 Round Table Discussion at the Local Pub

# Abstracts

## Glenn Vinnicombe

### Fundamental limitations on noise reduction in the cell

It is well known that, for a molecule being produced in an unregulated manner and degraded exponentially (constitutive gene expression for example) the intrinsic noise in the molecule number will be such that variance equals the mean. This talk will establish fundamental limits on the amount of noise reduction that can be obtained by regulation when delays in the mechanism (due to transport and the finite time required to synthesize intermediate molecules) and when that mechanism has limited information carrying capacity in the sense of Shannon (due to itself involving finite numbers of molecules). Examples where these limitations might have influenced "design" will be given.

## Mustafa Khammash

### Noise in Gene Regulatory Networks: Biological Role and Mathematical Analysis

The cellular environment is abuzz with noise. Generated by random molecular events, cellular noise not only results in random fluctuations within individual cells but it is also a source of phenotypic variability among clonal cellular populations. In some instances fluctuations are suppressed downstream through an intricate dynamical network that acts to filter the noise. Yet in other instances, noise induced fluctuations are exploited to the cell's advantage. Intriguing mechanisms that rely on noise include stochastic switches, coherence resonance in oscillators, and stochastic focusing. While mathematical models of genetic networks often represents gene expression and regulation as deterministic processes with continuous variables, the stochastic nature of cellular noise necessitates an approach that models these variables as discrete and stochastic. In this framework, probability densities of the system states evolve according to a (usually infinite dimensional) Chemical Master Equation (CME). Until recently, sample trajectories have been computed almost exclusively with Kinetic Monte Carlo methods, such as Gillespie's Stochastic Simulation Algorithm. In this talk we present a new direct approach for computing the relevant statistics, which involves the projection of the solution of the CME onto finite subsets. We illustrate the algorithm underlying our Finite State Projection approach and introduce a variety of systems theory based modifications and enhancements that enable large reductions and increased efficiency with little to no loss in accuracy. Model reduction techniques based on linear perturbation theory allow for the systematic projection of multiple time scale dynamics onto a slowly varying manifold of much smaller dimension. The proposed projection approach is illustrated on few important models of genetic regulatory networks.

## Antonis Papachristodoulou

### Methods and Algorithms for Biological Networks Analysis

Modeling complex biological networks presents a number of mathematical challenges. For the models to be useful from a biological standpoint, they have to represent available data or be systematically invalidated by existing data. Quantifying the robustness of these models is key for biological understanding

including both the deterministic stability and performance in the presence of parametric uncertainties and their stochastic behavior in the presence of noise. In this talk, we present mathematical and algorithmic tools to address such questions. These tools are rooted in robust control and dynamical systems, but with important recent developments. At the same time, they have great practical promise and relevance, which we explore through a series of biologically meaningful examples.

Declan Bates

Feedback Control Mechanisms in the Tryptophan Operon: Modelling, Analysis and Design

The various feedback mechanisms used by prokaryotes such as *E. coli* to regulate the expression of proteins involved in the production of the amino acid tryptophan combine to form an extremely complex, but highly effective, feedback control system. In this talk, I will briefly explain the biology behind the various forms of negative feedback employed by the tryptophan operon, before summarising the work done to date on the development of mathematical models for this system. Tools based on global optimisation algorithms will be introduced for the analysis of such models, which are often of high-order, strongly nonlinear and include significant time-delays. I will show how the use of such tools can help to resolve doubts about model validity, and provide a more rigorous comparison between experimental data and model outputs. Finally, given the current interest from the biotechnology community in using genetic engineering to maximise production rates of tryptophan for commercial purposes, I will show how advanced control system analysis techniques may assist in this tricky, and safety-critical, process.

Visakan Kadirkamanathan

Metabolic Network Analysis: Flux Estimation from Noisy and Missing Data

Metabolomics is the study of cellular metabolic activity and its relation to function and behaviour of the cell. It involves the analysis of metabolic networks, with a view to identifying and quantifying metabolic pathways. The quantification problem is the metabolic flux estimation problem and this is addressed in this presentation. Metabolic flux analysis is carried out under steady state conditions and use flux balance analysis and is aided by carbon isotope tracer experiments. Difficulties in flux estimation arise from the fact that the measurements are noisy as well as obtaining many intracellular metabolite data are difficult. The presentation outlines the problem formulation and discusses methods that have been proposed to estimate metabolic fluxes.

Hong Yue

Sensitivity Analysis and Experimental Design of a Stiff Signal Transduction Pathway

We aim to understand a complex signal transduction pathway system with sensitivity analysis techniques. Both time-dependent local sensitivity analysis and global sensitivity analysis is carried out for the IKK-NF-
The study shows the links and difference between these two analyses. Based on the global sensitivity rankings, we re-estimate those important parameters with the simplified I
obtained compared with the results published in literature. Local sensitivity

coefficients have been taken to formulate the Fisher information matrix and then used to realize the optimal experimental design which determines the best step input for the IKK activation.

Aidan O'Dwyer

Biotechnology, Life Sciences and Control Engineering – Some Synthesis Issues

The synthesis of biotechnology, life sciences and control engineering is receiving increasing interest. The purpose of this contribution is to raise awareness of some of this synthesis work, and report some of the authors work in the area. Though relevant synthesis examples have been reported for almost forty years (e.g. the dynamical modelling of genetic feedback control systems and the control of enzyme activity, the application of control and systems theory to biology (now labelled systems biology) has received increasing impetus in the past five years. A number of strands of activity are outlined.