

# Chapter One: Biomedical Engineering

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## **Learning in Biological-like Neural Networks: Spike-timing Dependent Plasticity in Recurrently Connected Networks**

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Sponsors: National ICT Australia (NICTA)

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This project relates to the mathematical investigation of the impact of a mechanism related to learning (called synaptic plasticity) in neural networks with feedback connections, which are modeled on the brain. The project focuses on a particular mechanism called "Spike-Timing Dependent Plasticity" (STDP), which relies on the correlation (temporal coincidence) between the activities of pairs of neurons, and a mathematical model of the neurons (Poisson neuron).

The aim of the study is to understand the underlying mechanisms behind learning and relate the induced properties of the large-scale activity (at the network scale) to the small-scale parameters of the neurons and connections between them. This should lead to better understanding of information processing in the brain, which will help aid in the development of neural prostheses and machine learning.

Part of this research has been the development of a simulator program in the C++ computer language. This program is used by people involved in computational neuroscience to assess theoretical models of how neurons work using numerical computer simulations.

[1] M. Gilson, A.N. Burkitt, J.L. Van Hemmen, D.B. Grayden, D.A. Thomas, "Spike-timing Dependent Plasticity in Recurrently Connected Networks", *Annual Computational Neuroscience Meeting (CNS\*2007)*, Toronto, (Submitted).

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## **Temporal Pattern Learning and Recognition in Neural Systems**

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The goal of this project is to develop real-time recognition methods for patterns that change with time. These methods are based upon the principles of how biological neural systems learn through modifying the strength of the connection between neurons. By using spiking neurons, the methods are able to capture information that is lost in conventional techniques. The development of a reliable method that is fast and robust to noise will have wide application in many areas, especially computer speech recognition where timing plays a crucial role.

A network that displays reliable recognition of sequences of events of varying durations has been developed and the robustness of the model is being investigated. So far, the ability of the model to learn sequences of events has been demonstrated for a restricted class of sequence patterns. Future work will consider more general sets of sequences modelled on speech.

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## **Neural Gain Modulation and Stability in Biological Neural Systems**

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Gain modulation enables neural systems to transform, combine and compare the information that they carry about the physical world and to accurately control their output responses. Physiological studies have observed gain modulation both in many neural functions and in a number of brain areas, but the underlying mechanisms are only beginning to be understood. This project uses mathematical and computational techniques to discover the underlying mechanisms of gain modulation in neural systems. The stability of networks of such neurons with feedback and recurrent connections is being investigated using methods from complex systems, nonlinear systems analysis and control theory.

Specifically, in this project we are elucidating the mechanisms of neuronal gain modulation and control in biological networks of neurons using mathematical and computational techniques to:

- Develop improved models of neurons and methods for their analysis;
- Investigate mechanisms of gain modulation in a network of conductance-based leaky integrate-and-fire neurons, particularly the role of feedback and correlated synaptic input;

- Analyse the stability of networks involving recurrent and feedback connections;
- Apply these principles to specific questions in auditory processing and cochlear implant speech processing.

The expected outcomes are an understanding and characterisation of gain modulation, control and stability in networks of biologically modelled neurons. The techniques will be applied to models of auditory processing and have implications for artificial neural systems.

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## Biophysics: Protein Aggregation

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Sponsors: ARC

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A number of human diseases are associated with protein misfolding. Alzheimer's disease, type 2 diabetes and heart disease are three significant examples. Ageing of populations will increase the impact of these diseases on the community. The incidence of Alzheimer's disease increases from 5% to 50% from age 60 to 85. Furthermore, protein therapeutics is the fastest growth area in biotechnology. Therapeutic proteins are currently produced for vaccines and immune disorders. Protein therapies and vaccines can be rendered useless or harmful by protein misfolding. The objective of the research is to understanding the key factors that cause protein aggregation in processing and will be critical for the successful commercialisation and their subsequent availability as therapies. Understanding the mechanism of amyloid formation will define cures for the associated diseases and optimise protein therapies.

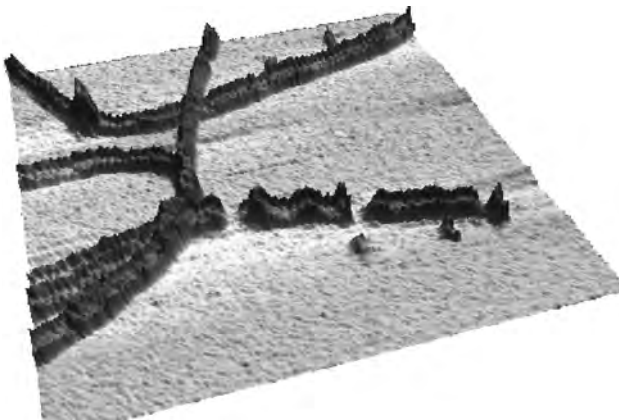


Fig. 1: AFM image of fibrillar aggregate.

## Protein Aggregation During Processing

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A wide range of biochemical processes involve the flow of proteins. The processing of blood plasma and food proteins is of particular interest. The processing of these proteins may cause aggregation to occur. This project will use rheofluorescence methods developed in the group in order to understand the mechanisms by which the aggregation occurs. Novel rheofluorescence and microfluidic methods will be used to identify critical flow and solution conditions that induce protein aggregation. An understanding of the mechanisms by which the aggregation occurs will be developed. The knowledge developed will be used to assess the effects of different unit operations used in the biotechnology industry to improve process efficiency, reduce product loss and improve product quality.

- [1] E.K. Hill, B. Krebs, G.K. Howlett, D.G. Goodall and D.E. Dunstan, "Shear flow induces amyloid formation by b-lactoglobulin", *Biomacromolecules*, **7**, pp. 10-13, 2006.

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## Site Specific Drug and Vaccine Delivery

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Directed drug and vaccine delivery has a number of significant advantages over general administration. Controlled delivery allows reduced levels of the drug to be administered for similar efficacy. In summary, controlled delivery has both improved patient outcomes and significant economic benefits in reduced drug requirements. Several different methods have been researched to control directed delivery. The aim of this project is to develop a novel biopolymer cross linking system which is liquid at room temperature and gelled at body temperature when injected subdermally or to tumour sites where the vaccine/drug is required. The project will quantify the release rates over a range of gel structural conditions.

- [1] S.B. Johnson, G.V. Franks and D.E. Dunstan, "A Novel Thermally Activated Crosslinking Agent for Chitosan", *Colloid and Polymer Science*, **282**, pp. 602-612, 2004.
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## Spectroscopic Determination of Platelet Activity

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The determination of blood platelet activity in the clinic is advantageous. The individual response to clotting drugs is variable. The ability to determine the efficacy of the administered drugs in real time is significant in the effective treatment of such disorders. We aim to develop a real time optical method for the quantification of platelet activity in the clinic.

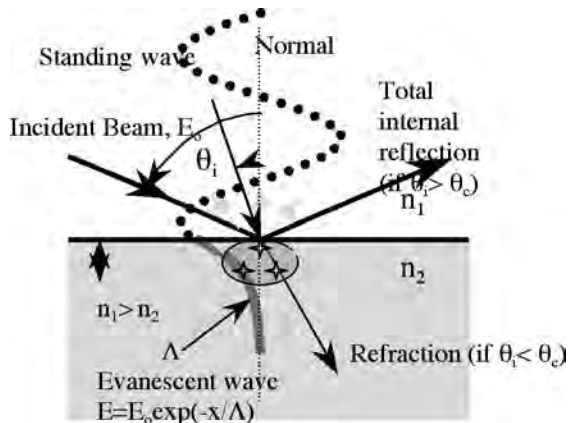


Fig. 1: Method of detection of the platelets.

- [1] L. Jayme, M.L. Gee and D.E. Dunstan, "Time Resolved Polarised Attenuated Total Reflection Spectroscopy of a Protein Film at the Silica/Solution Interface", *R. Soc. of Chem. Gums and Stabilisers for the Food Industry*, **11**, pp. 65-72, 2002.
- [2] T. Smith, L. Bijada and D.E. Dunstan, "Fluorescence Anisotropy Measurements of the Dynamic Behaviour of Biopolymers", *R. Soc. of Chem. Gums and Stabilisers for the Food Industry*, **11**, pp. 54-64, 2002.

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## Cochlear Implant Sound Processing

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This project aims to undertake research, development and evaluation of cochlear implant sound processing strategies. In particular, the Spike-based Temporal Auditory Representation

(STAR) strategy is being investigated by implementing advanced algorithms and then evaluating the effectiveness of these in improving speech perception in noise. Basic research is also being carried out to investigate the possible benefits of incorporating the travelling wave and other aspects of the auditory system in sound processing strategies. The STAR pilot evaluation investigating the most basic implementation of STAR showed it to achieve comparable results to existing commercial strategies. Current investigations are underway to evaluate benefits of STAR with the addition of algorithms for suppression of background noise. Investigations into music perception with the STAR strategy are also due to begin shortly.

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## Detection of Regulatory Regions in Genomic Sequences

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This project aims to develop effective methods for the detection of regulatory signals (e.g. splice sites) in genomic sequences. We proposed several hybrid methods [1], [2] including a hybrid Markov-support vector machine (SVM) method for the identification of regular splice sites. We have also conducted investigations using recently available data to prove that some widely accepted assumptions on SD sequences are incorrect [3].

In future the project will be focussed on the identification of alternative splicing events in the human genome. Alternative splicing is known to be responsible for creating diversity in gene expression and proteins. Identification of alternative exons is one of the most challenging tasks among the alternative splicing events. Extraction of relevant sequence features is regarded as an important step towards the identification of alternative exons. We used an information theoretic approach for the extraction of sequence features which can potentially identify alternative exons.

- [1] A.K.M.A. Baten, B.C.H. Chang, S.K. Halgamuge and J. Li, "Splice site identification using probabilistic parameters and SVM classification", *BMC Bioinformatics* **7**(5), S15, 2006.
- [2] A.K.M.A. Baten, S.K. Halgamuge, B.C.H. Chang and N. Wickramarachchi, "Biological Sequence Data Preprocessing for Classification: A Case Study in Splice Site Identification", *Lecture Notes in Computer Science*, Springer Verlag, 2007.
- [3] B. Chang, S.K. Halgamuge and S. Tang, "Analysis of SD sequences in completed microbial genomes: Non SD-led genes are as common as SD-led genes", *Gene: An International Journal on Genes and Evolution*, Elsevier, **373**, pp. 90-99, 2006.



Fig. 1: Feature extraction and classification of regular and alternative exons.

## Interpretation and Classification of Viral Genomic Data by Statistical Data Mining

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This project aims to exploit the use of statistical data analysis techniques to decipher the rich and complex content of viral genomic sequence data. Viruses, including those that infect bacteria, are the most abundant biological entities on earth and they make up most of the unknowns in our environment. To interpret their genetically diverse and mosaic content, which consists of tens of millions of DNA molecules, we utilise large-scale data analysis techniques including Support Vector Machines [1] and statistical subspace clustering. These techniques enable us to infer relationships between viral species and predict the functions of unknown DNA sequences. We have also developed a system capable of inspecting gene arrangement patterns among all the currently available bacterial virus data in the public domain [2]. Outcomes from large-scale viral data analysis can bring implications for microbial ecology and potentially environmental remediation and modulation of the global climate.

- [1] R. Saad, S.K. Halgamuge, J. Li, "Polynomial Kernel Adaptation and Extensions to the SVM Classifier Learning", *Neural Computing and Applications*, 2007.
- [2] J. Li, S. Tang, S.K. Halgamuge and C.I. Kells, "Gene function prediction based on genomic context clustering and discriminative learning: An application to bacteriophages", *BMC Bioinformatics*, **8**(4),S6, 2007.



Fig. 1: Classification and Interpretation of Viral Genomic Data

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## Separation of Microorganisms based on DNA Sequence Data Clustering

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Microorganisms form part of the foundation of the biosphere. Since they cannot be easily cultivated in the laboratory, the traditional DNA sequencing which requires cell cultivation, cannot be used. Therefore, despite their ubiquity, only less than 1% of them are known. A fundamental limit of Whole Genome Shotgun (WGS) sequencing is that only the genomes of high-abundance species can be assembled. The presence of large amounts of DNA fragments from the low-abundance species poses a problem for assembling genomes. In order to infer the biological functions of a microbial community from sequences, a process named 'binning' is used to group these unassembled DNA sequence fragments into biologically meaningful 'bins', such as phylogenetic groups.

This project aims to implement suitable data clustering algorithms to effectively separate DNA sequences according to their phylogenetic groups [1], [2]. We extend the dynamic clustering algorithm, Growing Self-Organizing Maps (GSOM), to perform this task. An example of the developed GSOM for DNA data clustering is shown in Fig. 1.

- [1] C. Chan, A.L. Hsu, S. Tang and S.K. Halgamuge, "Improving the clustering strategy for the binning process in environmental whole genome shotgun sequencing", *Journal of Biomedicine and Biotechnology*, Hindawi Publishing, 2007.
- [2] J. Reinhard, C.K.K. Chan, S.K. Halgamuge, S.L. Tang and R. Kruse, "Region Identification on a Trained Growing Self-Organizing Map for Sequence Separation between Different Phylogenetic Genomes", *BIOINFO2005*, Busan, Korea, 2005.

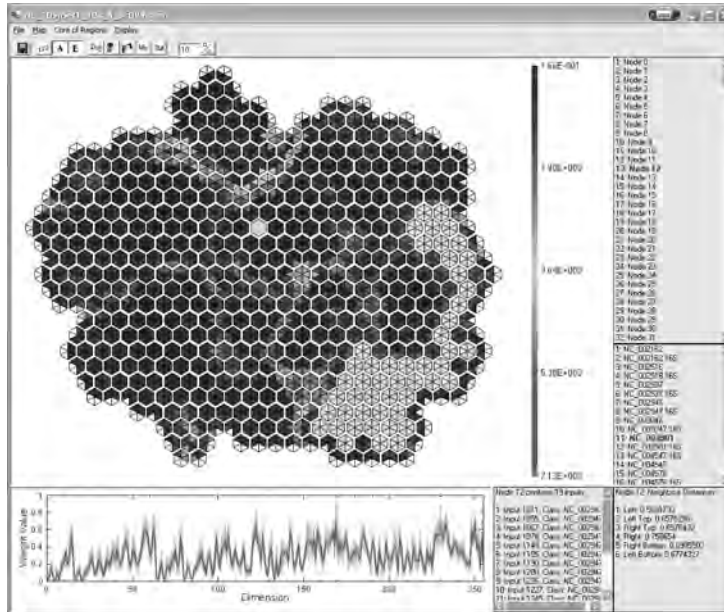


Fig. 1: A generated Growing Self Organising Map for Species Separation.

## Mathematical Modelling of Sodium Ion Channels

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Voltage-gated ion channels (also known as sodium channels) are transmembrane proteins that conduct sodium ions ( $\text{Na}^+$ ) and are responsible for the rising phase of action potentials in excitable cells such as neuron and myocytes. Sodium channels play an important role in propagating the electrical excitable impulse in nerve, muscle fibres, and the heart. It contains charged amino acid residues that serve as the primary voltage sensors of the channel that will move from inside the pore to the extracellular side of the pore when an activation potential is applied as shown in Fig. 1.

This project aims to model sodium channels and their mutants in three spatial scales for assessing the distinguishable physiological properties triggered by distinct genetic mutations. The main components of this research project are:

- Kinetic Modelling of channel gate using Hidden Markov Model [1-3],
- Ion transport modelling using Poisson-Nernst-Planck with Markov Models [4], and
- Ventricular cell modelling for simulating cardiac action potential by incorporating Markov currents due to mutation.

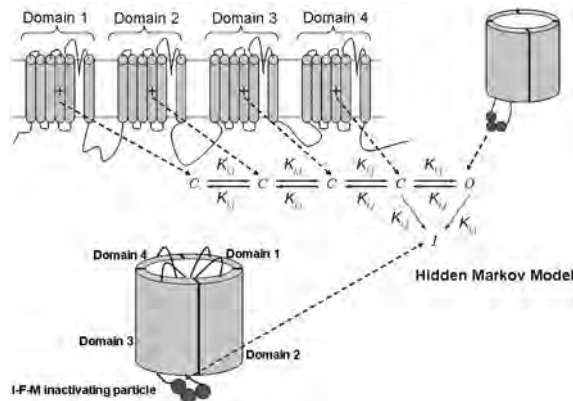


Fig. 1: Molecular structure of sodium ion channel –  $\alpha$  subunit

- [1] K-F. Ho, S.K. Halgamuge, D. Smith, B.C-H. Chang, "Optimization of S-system GRNs", *Computational Methodologies in Gene Regulatory Networks*, IGI Global Publishing, 2007.
- [2] Y.-K. The, J. Fernandes, M.O. Popa, A.K. Alekov, J. Timmer, and H. Lerche, "Modeling of Single Noninactivating Na<sup>+</sup> Channels: Evidence for Two Open and Several Fast Inactivated States," *Biophysical Journal*, **90**, pp. 3511-3522, May 2006.
- [3] L. Venkatatamanan, J. Walsh, R. Kuc, and F. Sigworth, "Identification of Hidden Markov Models for Ion Channel Currents – Part I: Colored Background Noise", *IEEE Trans. Signal Processing*, **46**(7), pp. 1901-1915, Jul 1998.
- [4] U. Hollerbach, D-P. Chen, and R.S. Eisenberg, "Two- and Three-Dimensional Poisson-Nernst-Planck Simulations of Current Flow Through Gramicidin A", *Journal of Scientific Computing*, **16**, pp. 373-409, Dec 2001.

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## Signal Processing Techniques for Structural and Diffusion MRI

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Magnetic Resonance Imaging is a non-invasive technique of vast neuroscientific benefit, owing to its ability to image the internal structure of the brain. We propose the application of signal processing techniques for improvement in MR signal acquisition, contrast enhancement in the reconstructed image volumes, and development of robust image processing

methods, motivated by potential impact on both neuroscience research endeavours and improved clinical and public health outcomes.

Increasingly higher field strength MRI scanners are permitting detection of more detailed brain structures, for example via cortical parcellation algorithms validated on histology datasets (Fig.1) [1]. Similarly, recent modalities like diffusion MRI are rapidly advancing the ability to non-invasively study brain structure. Diffusion MRI is sensitive to the directional diffusivity of water, detected via application of magnetic field gradients. White matter fibres, comprised of myelinated axon bundles, are now identifiable in both location and direction. We are developing diffusion MRI analysis methods and tractography algorithms for use in characterisation, and ultimately early detection, of neurological diseases such as Multiple Sclerosis and Huntington's disease.

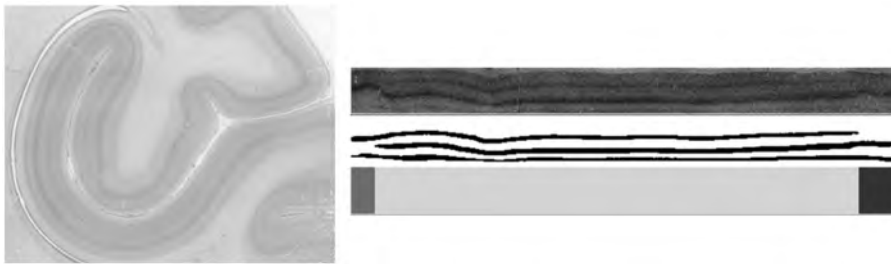


Fig. 1: Automated parcellation of a post-mortem histological slice of baboon cortex. Left: Haematoxylin & eosin stained slice. Right: Flattened segment of cortex (top), Map of posterior probability of dark band (middle), Cortical parcellation result (bottom).

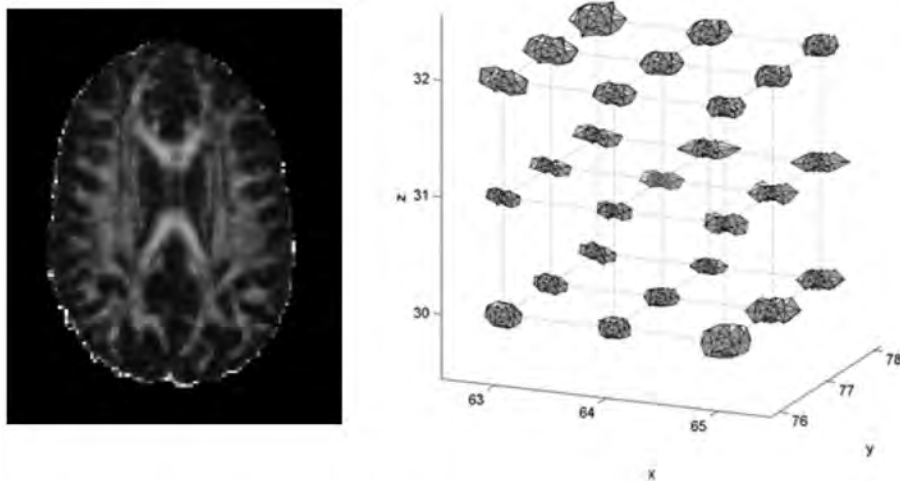


Fig. 2: Visualisation of local white matter structure as determined by water diffusivity, in 32-direction diffusion MR image of a Huntington's disease patient.

## Modelling Brain Development

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We seek to understand the processes by which the brain develops, through mathematical modelling based on MRI and confocal laser microscopy data of the mammalian brain. This research is motivated by a desire to provide insight into neurodevelopmental disorders, and to provide methods for studying individualised structure-function mapping as an alternative to current atlas-based methods. This project focuses on two aspects of brain development: neuron migration and cortical folding.

During embryonic development, populations of neurons migrate from their places of birth, and in a seemingly miraculous manner, determine their eventual residence in layers in the cortex. We study the migrational dynamics of the neuron subpopulations in the embryonic mouse brain via confocal laser microscopy, biomechanical modelling and the creation of software to track the migratory paths (Fig.1).

The human neocortex is a highly convoluted sheet with surface area of some 2500cm<sup>2</sup>, folded to occupy the space within the skull. We observe the cortical folding process in fetal lamb brain using diffusion MRI, a modality that indicates preferential directional water diffusivity, thus providing a cue to white matter fibre directionality. Our research shows that diffusion MRI measures of fractional anisotropy and tensor directionality change over the gestational period in a manner consistent with fibre-regulated folding (Fig.2). We are currently investigating the integration of diffusion MRI measures with a biomechanical finite element model that is able to faithfully reproduce the developmental folding process.

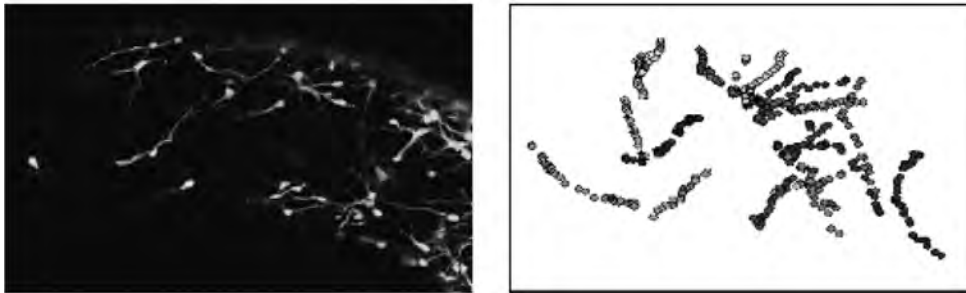


Fig. 1: Left: Interneuron migration in GAD-67 mouse brain slice culture at embryonic day 12. Right: Labelled neuron trajectories.

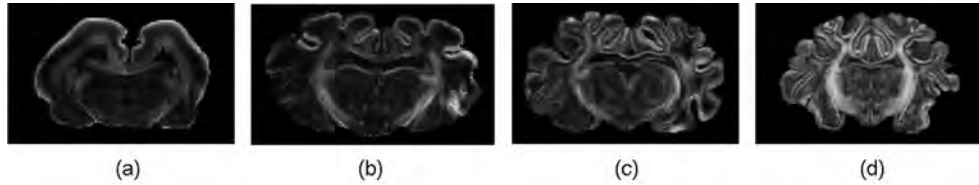


Fig. 2: Fractional anisotropy-weighted principle diffusion tensor eigenvalue in slice of fetal lamb brain at a) 70 days, b) 90 days, c) 110 days, d) 130 days gestation.

## Analysing Brain Activation Patterns Through Functional MRI

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Functional Magnetic Resonance Imaging (fMRI) provides an indirect measure of neuronal activity. The neuronal response to a stimulus in a particular brain region elicits a hemodynamic response in the surrounding capillary networks, due to increased demand for oxygenated blood. The resultant interactions between cerebral blood flow, volume and metabolic rate of oxygen cause local MR signal perturbations, termed the Blood Oxygenation Level Dependent (BOLD) effect.

We are interested in the formulation of mathematical models that describe the BOLD effect, and the analysis of these models for the interpretation of fMRI experimental results. The typically employed linear hemodynamic response model is unable to take into account the marked variability in response shape known to exist across cortical regions and between individuals [1]. We aim to develop biologically meaningful nonlinear models of the BOLD response and are applying statistical signal processing techniques for the inference of hidden physiological variables [2]. A second focus of this project is the development of rigorous and reliable methods for estimating connectivity between brain regions as detectable from fMRI experiments. This research advances fundamental understanding of brain function, and is applicable in the development of fMRI-based cognitive neuroscience and pre-surgical planning tools.

- [1] E. Duff, J. Xiong, B. Wang, R. Cunnington, P. Fox and G. Egan, "Complex spatio-temporal dynamics of fMRI BOLD: A study of motor learning", *NeuroImage*, **34**, pp.156-168, 2007.
- [2] L. Johnston, E. Duff and G. Egan, "Particle filtering for nonlinear BOLD signal analysis", *9th International Conference on Medical Image Computing and Computer Assisted Intervention*, **2**, pp. 292-299, 2006.

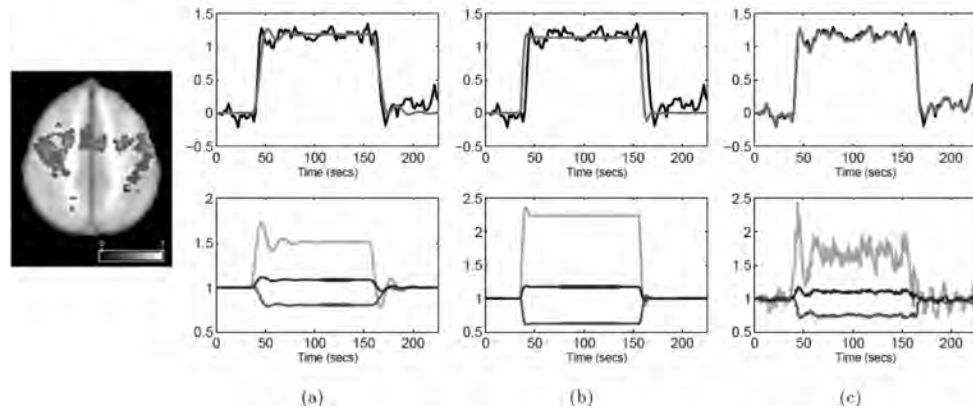


Fig. 1: Observed BOLD signal (right) in the primary motor cortex (left). Particle filter estimates of BOLD signal and normalised cerebral blood flow, volume and deoxyhemoglobin content, for a) optimal, b) underfitting and c) over-fitting of system parameters.

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## A Statistical Dynamics Model of Interactions Between Nephrons in the Kidney

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Students: Robert Moss

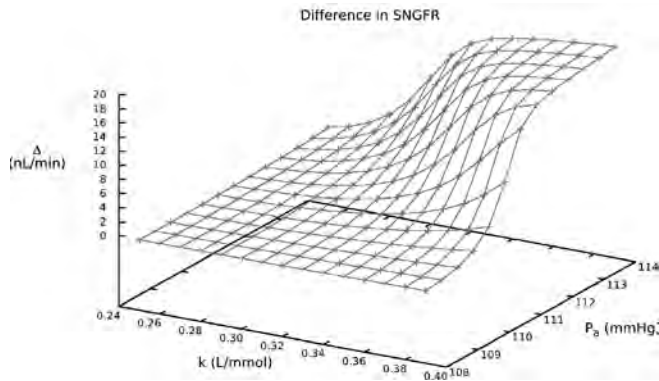
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The human kidney performs a number of very important functions in the human body including the excretion of wastes produced by metabolism, hormone secretion, and maintenance of the extra-cellular environment. The main functional units of the kidney are *Nephrons*, and there are approximately 800,000 to 1,000,000 nephrons in a human kidney. Nephrons are twisted tubules that adjust the solute and electrolyte levels of the body's blood plasma. They are immersed in renal fluid and are surrounded by a complicated network of capillaries that also exchanges solutes and electrolytes with the surrounding renal fluid. The behaviour of individual nephrons can fluctuate widely and coupled systems of nephrons can behave chaotically. However, the overall behaviour of the kidney remains stable even under extreme conditions.

The aim of this project is to model the behaviour of clusters of nephrons by studying connections and interactions between nephrons. Specifically, we wish to answer questions about how the stability of *Global Kidney Behaviour* arises from the interactions of the individual nephrons, and tubules that may behave chaotically. Further, we aim to create models that are capable of predicting kidney function and the effects of renal disease.

We approach this problem assuming that the kidney is a complex network, and we model individual nephrons as dynamic networks where each node models a tubule segment and difference equations model solute transport between tubule segments, the surrounding renal fluid, and peri-tubular capillaries.



A two-nephron model has been constructed which reproduces known behaviours, such as synchronisations between the two nephrons (shown on the right, over a 2D subset of our parameter space) and responses to changes in pressure and sodium chloride concentration. This model is currently being extended to much larger clusters of nephrons.

We can use our model to simulate larger clusters. Currently only one paper has examined a system of more than two nephrons, and we are not aware of any work that attempts to measure the stable behaviour of nephron clusters, nor the stability of nephron clusters in response to renal diseases. From this experiment, we will provide an estimate of the stability of an entire kidney.

## Visuo-Haptic Environments for Dental Drilling

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This is a collaborative project with the Department of Dentistry and is a part of the University of Melbourne's MUVES project [1], that investigates the development and use of virtual environments in medicine and medical education.

In the current climate of increased public expectations of health care professionals, the apprenticeship model, where the variety of clinical situations cannot be controlled, is fast becoming outmoded. Consequently, virtual reality simulators have an increased role in training and education in medicine, dentistry, and physiotherapy. Simulators have been shown to be particularly useful in situations where the following factors pertain:

- There are high-risk tasks, combined with low tolerance of failure, for example, surgical procedures;
- There is low availability of training materials, for example, lack of human bones and teeth or cadavers;
- Real-life situations appropriate for training are infrequent, for example, rare procedures;

- The cost of real training is high, for example, when surgical theatre time is required;
- There is restricted availability of expert tuition, for example, specialist surgeons whose time for training is limited.

In addition, expert surgeons and dentists need to maintain a high level of expertise for infrequently encountered situations and the capacity to retrain in response to changing external demands.

The objective of this project is to create a set of realistic virtual environments in which students can learn and practice dental techniques. The environment is based on realistic visuo-haptic tooth and jaw models that capture both visual detail and material properties, providing an environment in which students get sensory feedback about different anatomical materials, such as enamel, dentine, bone, as they drill and develop expertise in how to drill those materials.



Fig. 1: Phantom 1.5 Haptic Probe from SensAble Technologies.

Current experiments use force sensing devices to measure the forces exerted when drilling through teeth and jaw material and reproduce those forces in a haptic probe. Concurrently, simulators are being developed to create models that align visual and haptic sensory information. Methods for evaluating the effectiveness of the virtual environment for training dentists will be developed as the next phase of the project. Once shown to be effective, the environment will be integrated into dental school curricula.

The benefits to society include increasing the quality of dental practice by exposing students to a variety of normal and abnormal anatomy and providing them with the opportunity for repeated practice of dental techniques.

[1] <http://www.muves.unimelb.edu.au>

## **Automated Recognition of Obstructive Sleep Apnoea Syndrome from Electrocardiogram Recordings**

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Obstructive sleep apnoea syndrome (OSAS) is a common problem defined by frequent cessation of breathing due to the partial or complete obstruction of the upper airway for short periods during sleep. Undiagnosed OSAS is now regarded as an important risk factor for the development of cardiovascular diseases. In this study, we apply a machine learning technique [support vector machines (SVM)] for automated recognition of OSAS types from their nocturnal ECG recordings. A total of 104 sets of nocturnal ECG recordings acquired from normal subjects (OSAS-) and subjects with OSAS (OSAS+), each of approximately eight hours in duration, were analysed. Features extracted from successive wavelet coefficient levels after wavelet decomposition of signals due to heart rate variability (HRV) from RR intervals and ECG derived respiration (EDR) from QRS amplitudes were used as inputs to the SVM to recognize OSAS+/- subjects (Fig.1). Using leave-one-out technique, the maximum accuracy of classification for 83 training sets was found to be 100% for a SVM using a subset of selected combination of HRV and EDR features. Independent test results on 21 subjects showed that it correctly recognized 14 out of 15 OSAS+ subjects and 5 out of 6 OSAS- subjects. For estimating the relative severity of OSAS, the posterior probabilities of SVM outputs were calculated and validated with respective Apnoea/hypopnea index (AHI).

The significance of this study is that it provides a simple scheme for diagnosis of OSAS based on ECG signals, which could be suited to Holter monitors, as no additional hardware is required. Ideally, Holter recordings would be routinely screened for apnoea and this may allow a significant reduction in the costs associated with the detection of OSAS. This would be a step toward addressing the serious public health issue caused by under-diagnosis of OSAS. However, significantly more clinical experience with the technique, and a detailed cost-benefit analysis, would be required to evaluate its true clinical utility as a screening tool.

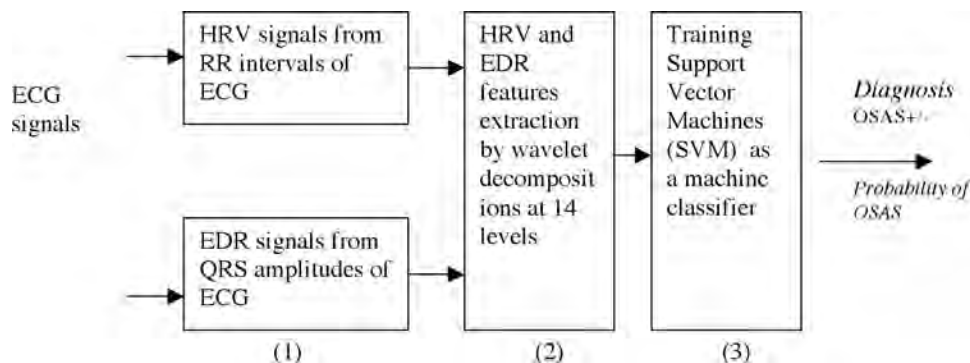


Fig.1. Schematic representation of an automated diagnostic system for recognizing obstructive sleep apnoea syndrome (OSAS+) based on ECG signals.

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## Novel Retinal Analysis Algorithm to Predict the Risk of Cardiovascular Diseases

Staff: Ramamohanarao Kotagiri, Joey Chua

Students: Mohammed Alauddin Bhuiyan

Collaborators: Tien Wong, Gabriella Tikellis (Dept. Ophthalmology)

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Epidemiological research conducted at the Retina Vascular Imaging Centre (RVEEH) has shown that early stages of cardiovascular diseases (hypertension, stroke and diabetes) cause observable damage to the small blood vessels inside the eye many years before the disease can be diagnosed clinically. The aim of this multi-disciplinary project is to translate this knowledge into a routine, non-invasive early-diagnostic technology that could help reduce the incidence of cardiovascular diseases, which currently affect 3.67 million Australians.

We have developed software for the analysis of vascular characteristics in retinal photographs (Fig. 1). Current work involves improving the techniques for measuring other subtle abnormalities in the retina, and developing a risk prediction model for cardiovascular diseases. The risk prediction model will be validated on an existing database of 30,000 clinical cases.

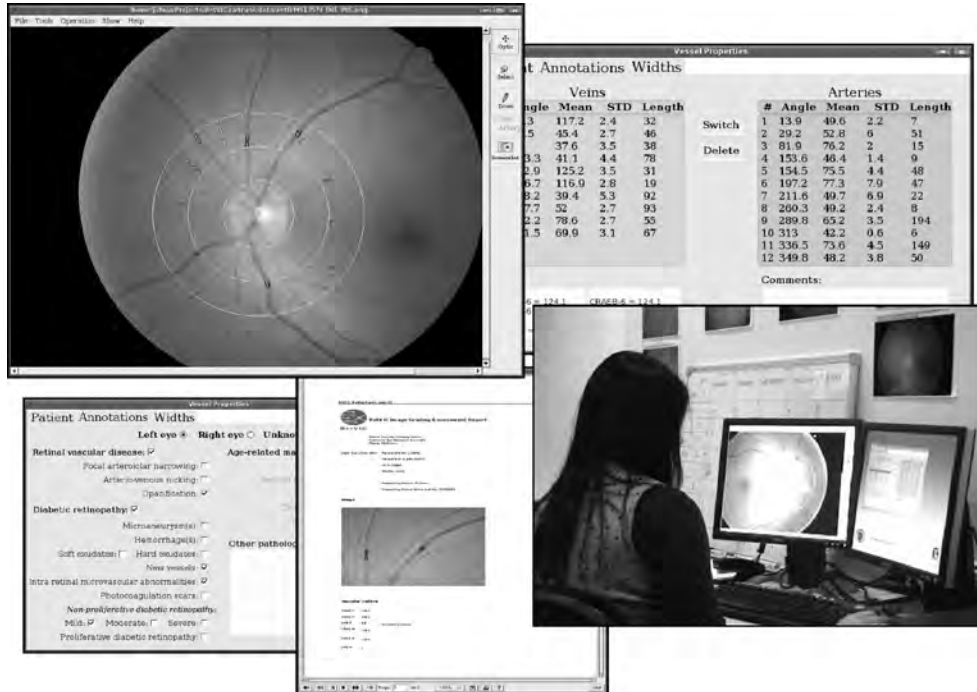


Fig. 1: Retinal image analysis software.

## Longitudinal Data Mining for Neuropsychiatry Research

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Sponsors: AE Rowden Foundation

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Schizophrenia is a debilitating mental illness. In 2001, Access Economics estimated that the real financial cost of schizophrenia totalled \$1.85 billion. Over a third of this cost is borne by people with the illness and their carers. This cost is expected to increase to \$10 billion per year by 2010. Even more alarming is the human cost: people with schizophrenia are 12 times more likely to die by suicide compared to the general population.

Pioneering research conducted at the Melbourne Neuropsychiatry Centre (MNC) used magnetic resonance (MR) imaging to show that schizophrenia is associated with abnormalities in the brain structure. These abnormalities are present even before the patient suffers a first psychotic episode. Despite this, some people who suffer their first psychotic episode can recover and lead normal lives, whereas others deteriorate and develop chronic

schizophrenia. It is thought that a patient's risk of developing schizophrenia after a first-psychotic episode is determined by many risk factors, including precursors that can be detected by MR imaging of the brain. Ability to predict a patient's risk of developing schizophrenia after a first-psychotic episode can have a huge impact in the management of the patient's condition.

The aim of this multi-disciplinary project is two-fold: (1) to develop techniques for longitudinal data mining studies over a collection of clinical and brain imaging data which have been accumulated over several studies; and (2) to use data mining techniques to find structural markers and clinical indicators that can be associated with the predisposition to develop schizophrenia after a first psychotic episode. The MNC has a large collection of clinical and brain imaging data, including follow-ups of patients over time. Data mining techniques can be used to find risk prediction models from these data, although to date, a large part of the available data has been accumulated over time without prior data-mining structure. A major part of this project involves developing techniques that would automate the conversion of the qualitative clinical data, and the MR images of varying quality and resolution, into some canonical form suitable for longitudinal data-mining studies.

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## **Automated Morphometric Analysis of Human Spermatozoa**

**Staff:** Ramamohanarao Kotagiri, Joey Chua

**Collaborators:** Gordon Baker (Obstetrics and Gynaecology), Claire Garrett (Obstetrics and Gynaecology)

**Sponsors:** Microptic S.L. (Barcelona)

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In Australia, male infertility affects 1 in 20 men. It is the main reason for half of all infertility problems in relationships, and accounts for 40% of couples who used assisted reproductive technology (ART). In 2006, a Federal Government Review Committee estimated that the average cost of an ART live birth is close to \$33,000, of which 80% is now covered by Medicare. Between 2003 and 2005, the Medicare expenditure for ART services doubled from \$50 million to \$108.4 million, and the cost is expected to continue to rise.

A major frustration for clinicians is that in almost 40-50% of cases of male infertility, no specific cause can be found. Three quarters of infertile men are actually "subfertile"—that is, they have sperm present in the semen, so natural pregnancies may happen, but at lower rates than usual. The question is whether to advise those couples to resort to ART, or to suggest that they continue trying to conceive naturally.

The aim of this multi-disciplinary project is to develop an assessment protocol that can give clinicians better information for managing cases involving subfertile men. The protocol will be based on clinical data and sperm morphometric analysis. We have already developed software that can automatically analyse the morphometry of sperm samples in order to determine whether they are capable of binding to an oocyte naturally. The next step is to develop a success-rate prediction model that includes both morphometric and clinical data. The model will be validated on a longitudinal database consisting of hundreds of case studies at the Royal Women's Hospital.

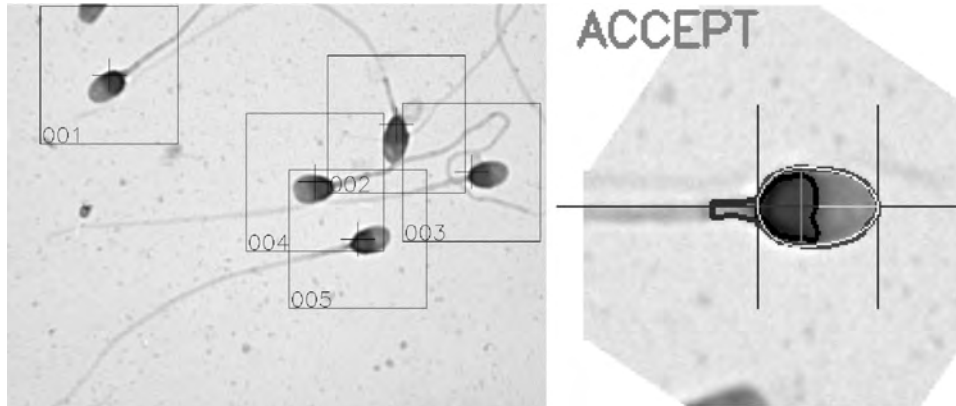


Fig 1. Automated morphometry analysis: target detection, alignment and measurement.

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## Cancer Genomics (CG)

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[http://www.nicta.com.au/research/projects/cancer\\_genomics](http://www.nicta.com.au/research/projects/cancer_genomics)

The aim of the Cancer Genomics project is to develop software techniques and tools enabling conversion of genetic profiles of tissue into clinically useful knowledge assisting oncologists and pathologists.

The project is developed in close collaboration with the Peter MacCallum Cancer Centre (PMCC). It aims to address knowledge extraction challenges arising from a series of cancer genomic datasets generated at the PMCC. In particular, we build software tools which can utilise molecular tissue markers for cancer diagnosis, detection of site of the origin, prediction of response to treatment, understanding/discovery of specific molecular processes and discovery of novel treatments.

Cancer genomics aims to alter the way that people with cancer are diagnosed, staged, and treated. The field is currently in transition: major sites world-wide, including the PMCC, are now generating high-quality datasets involving hundreds of samples with detailed clinical information that have been analysed on complex microarrays (30,000+ elements). This includes arrays that generate different types of information such as gene expression, gene copy number and chemical modification of the DNA (methylation). Such datasets provide an excellent opportunity to develop and apply innovative approaches to data analysis and mining.

The project involves three streams of activity:

1. Discovery and development of IT methodology for discerning biologically meaningful and

medically useful knowledge from microarray profiles of tissue, with a focus on cancer diagnosis and treatment:

- Learning from a very small number of samples (VSS-learning)
  - Kernel machines and regularisation techniques
  - Learning from structured data
  - Feature Selection
2. Development of practical algorithms and development of software tools for operational testing, demonstration and operational implementation of the discovered solutions.
  3. Application of the results to cancer research and clinical oncology. Here we have identified a few separate sub-projects which will generate separate streams of data (this list will inevitably proliferate):
    - Carcinoma of Unknown Primary
    - Response to Chemoradiotherapy for Oesophageal Cancer
    - Cancer Cell Micro-environment
    - Gastric Cancer
    - Ovarian Cancer
    - Sarcoma
    - Breast Cancer

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## Computational Intelligence in the Identification of Risk of Falls in the Elderly

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Collaborators: Victoria University

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This research aims to investigate computational intelligence methods to detect gait characteristics depictive of a disorder. Gait disorders, for example, falls in the elderly are the major cause of injury and death and cost the U.S. government USD 18 billion annually in healthcare cover. The major challenge here is to design a system that is robust and general enough to reliably screen gait patterns and make accurate diagnosis. Currently, we are investigating automated detection of:

- Tripping falls in the elderly.
- Knee disorders such as patellofemoral pain (PFPS) and knee osteoarthritis (OA).
- Gait events such as sitting, walking, running from single gait measures.

Future work will focus on intelligent gait detection systems integrated with sensing capabilities for improved detection.

- [1] R.K. Begg and M. Palaniswami (eds.), "Computational Intelligence for Movement Sciences: Neural Networks and other Emerging Techniques", IGI Publishing: Hershey, USA., 2006.
  - [2] R.K. Begg and M. Palaniswami, "Recognition of gait patterns using support vector machines", *Computational Intelligence for Movement Sciences*, IGI Publishing, Hershey, Pennsylvania, pp. 243-262, 2006.
  - [3] H. Ahsan A. Khandoker, M. Palaniswami and R.K. Begg, "Comparison of Approximate Entropy Measure and Poincaré Plot Indexes for the Study of Gait Characteristics in the Elderly", *Proceeding of workshop on Biosignal Processing and Classification*, Portugal, pp 144-151, 1-5 August 2006.
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## **Prediction of Epilepsy Seizures using Nonlinear Analysis of EEG Recordings**

**Staff:** Iven Mareels, Margreta Kuijper, Anthony Burkitt, Mark Cook, David Grayden, Levin Kuhlmann

**Students:** Andre Peterson, Dean Freestone, Andrea Varsavsky, Elma O'Sullivan-Greene, Craig Savage

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Approximately 1% of the world's population (50 million people) suffer from epilepsy. Epilepsy is a neurological disorder where seizures arise in populations of neurons (brain cells) that become overly excited, through both electrical and chemical mechanisms. These seizures can have various behavioural manifestations, the most famous being the chaotic and uncontrollable movement of the body (i.e. a fit). Given that epileptic seizures can involve large portions of the brain, it is a global brain disorder, and can have a variety of effects on consciousness. While there are many drugs that can be used to prevent epileptic seizures, 25% of epileptics cannot be treated sufficiently by available therapies. Moreover, the exact cause of epileptic seizures in the brain is not well understood.

This project will develop the theory and algorithms for reliable and robust prediction and detection of the onset of epileptic seizures and the characterisation of epileptic seizures based on EEG data. Our interdisciplinary team consists of neuroscientists and systems engineers supported with clinicians and software developers. The team will develop the theory and design, implement and evaluate decision support software that is able to interpret EEG data and present epilepsy relevant information to clinicians and patients. Our methods are based on statistical signal processing, nonlinear dynamics (bifurcation and time-series methods) and systems engineering (system identification, adaptive methods).

One potential application for seizure prediction, is to use it to activate an implantable device that can prevent or abort epileptic seizures. Possible means of seizure prevention include direct electrical stimulation of the epileptic brain region, or local drug delivery to the site of the seizure in the brain. Our group is working closely with Bionic Technologies Australia to try to make such an implantable seizure control device a reality.

In addition to working on seizure prediction and detection, our group is also trying to understand the underlying causes of epilepsy through both physiological experiments and neural modelling. Our basic research interests are currently aimed at (1) understanding the relationship between seizures and high frequency content in the EEG, and (2) analysing how seizures spread from the seizure focus to the rest of the brain. Insights gained from this more fundamental research will hopefully drive the development of improved seizure prediction and detection algorithms.

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## Hydrocephalus Hydrodynamics: Realistic Numerical Modelling using Neuroimaging

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Sponsors: ECR – The University of Melbourne

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Hydrocephalus is a condition where abnormal flow of cerebrospinal fluid (CSF) leads to increase in intracranial pressure causing brain expansion and damage. It affects thousands of people living in Australia, and millions around the world as a result of birth defects (common in preterm births), accidents, haemorrhaging, tumours or infections. The health care cost for hydrocephalus exceeds \$33 millions dollars per year in Australia.

For the first time, actual brain and skull geometries obtained from MRI scans can be incorporated into the numerical simulations of CSF flow in obstructive hydrocephalus. Velocity and intracranial pressure fields will be calculated based on sophisticated hydrodynamic models [1], [2]. These mappings may demonstrate conditions leading to hydrocephalus. Moreover, better understanding of the hydrodynamic of this condition may lead to better planning for surgical intervention and development of innovative treatments.

- [1] X. Shen, G. Narsilio, H. Wang, D. Smith, G. Egan, "Using Numerical Model to Predict Hydrocephalus Based on MRI Images", *Joint Meeting of the 6<sup>th</sup> International Symposium on Noninvasive Functional Source Imaging of the Brain and Heart & the International Conference on Functional Biomedical Imaging*, October 12-14, Hangzhou, 2007.
- [2] G. Narsilio, X. Shen, H. Wang, D. Smith, G. Egan, "Hydrocephalus: A Realistic Porous-Media Model with Geometry Based on Neuroimaging", *1<sup>st</sup> International Conference on Cognitive Neurodynamics and the 3<sup>rd</sup> Shanghai International Conference on Physiological Biophysics - Cognitive Neurodynamics*, November 17-21, Shanghai, 2007.

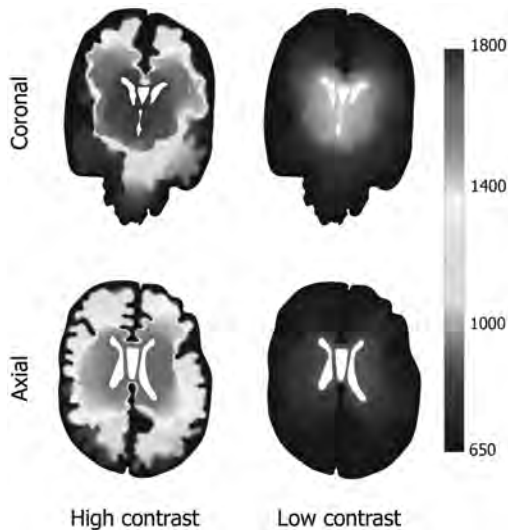


Fig. 1: Pressure [Pa] fields for a coronal and an axial slice of the brain. Comparison between high hydraulic conductivity impedance with  $k_w=1.542 \cdot 10^{-7}$  m/s and  $k_g=1.542 \cdot 10^{-9}$  m/s (*high contrast*); and lower contrast when  $k_g=1.542 \cdot 10^{-8}$  m/s (*low contrast*).

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## Nonlinear Behaviour of Bubbles Subject to an Acoustic Field

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Sponsors: CSIRO

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Experiments will be conducted on the nonlinear behaviour of bubbles subjected to an acoustic field, utilising CMIT's new laboratory facilities. This would involve exciting the bubbles near their resonance frequency and studying their complicated nonlinear behaviour. Investigations of different arrangements of microbubbles near, or attached to, rigid and semi-rigid boundaries are planned. Bubbles may be free or coated in a shell. Supporting theory and/or numerical calculations will also be made. If the nonlinear microbubble behaviour can be accurately modelled, the outcomes will be invaluable to the successful implementation of diagnostic tools. Work may be done with microbubbles coated in proteins.

The key novel element would be the development of a physical technology for either the early detection in-vivo of specific markers of colorectal cancer or the in-vivo imaging of metastatic lesions. The expected outcome is a prediction of ultrasound signatures specific to targeted microbubbles bound to their target. However, other useful outcomes may arise, for example, the creation of appropriate microbubbles for the experiments or the development of numerical or analytic techniques to analyse the results.

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## **Solving Protein Structures from Diffraction Patterns using the Method of Molecular Replacement**

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Students: Jayavardhana Gubbi

Collaborators: Michael Parker (St. Vincent's Institute of Medical Research)

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Very little progress has been made by the bioinformatics community in automating protein structure prediction by experimental methods. The literature available in model building using diffraction patterns (output of x-ray crystallography) is comparatively limited. This project designs new methods using machine learning to help model building process in the molecular replacement stage of x-ray crystallography research.

We approach the problem by reducing the search space of diffraction patterns for predicting numerous structures in proteins. This is accomplished by secondary structure prediction, solvent accessibility prediction, disulphide bridge prediction and finally, topology prediction. The search space of diffraction pattern at the topology level is thereby reduced drastically. We finally propose to create "fragment datasets" of diffraction patterns for solving the structure.

- [1] G.L. Jayavardhana Rama, M. Palaniswami, D. Lai, and M.W. Parker, "A study on the effect of physico-chemical properties in protein secondary structure prediction", *Applied Artificial Intelligence*, pp. 609-616. World Scientific, 2006.
- [2] J. Gubbi, D. Lai, M.W. Parker and M. Palaniswami, "Protein secondary structure prediction using support vector machines and a new feature representation", *International Journal of Computational Intelligence and Applications*, 2007.
- [3] J. Gubbi, A. Shilton, M.W. Parker and M. Palaniswami, "Real value solvent accessibility prediction using adaptive support vector regression", in *2007 Proceedings of IEEE Symposium on Computational Intelligence in Bioinformatics and Computational Biology*, IEEE Press, 2007.
- [4] J. Gubbi, A. Shilton and M. Palaniswami, "Kernel methods in protein structure prediction", In Y. Zhang and J. Rajapakse, eds., *Machine Learning in Bioinformatics*. Wiley, 2007.

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## **Muscle Function in Human Locomotion**

Staff: Marcus Pandy, Richard Baker, Hyung Joo Kim

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Sponsors: CCRE, ARC

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Walking is a task that most of us perform with ease. Although seemingly simple, it is an extraordinarily complex skill that takes years to develop. The various actions of the leg muscles are exquisitely timed to provide support against gravity and to maintain forward progression and balance from step to step. Thousands of experiments have been undertaken to better understand the biomechanics of walking, yet little is currently known about the way individual muscles coordinate body movement, primarily because experiments provide very limited information on muscle function. This applies even for walking at the self-selected speed, and virtually nothing is known about muscle function under other conditions, such as walking at different speeds, walking up and down inclines, and running.

This research project uses biomechanical experiments and novel computational methods to address fundamental questions related to muscle function during human locomotion. For example: How do muscles move our limbs during walking? How do the nervous system and muscles work together to control movement? Answers to these questions will provide insight into the biomechanical mechanisms underlying balance and stability during locomotion. Understanding how the nervous system and muscles cooperate to control movement is important to such applications as clinical gait analysis and gait rehabilitation, sports medicine (injury prevention), sports training, and the video/digital games industry.

[1] F.C. Anderson and M.G. Pandy, "A dynamic optimization solution for vertical jumping in three dimensions", *Computer Methods in Biomechanics and Biomedical Engineering*, **2**, pp. 201-231, 1999.

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## **Numerical Investigation of Signal Mechanotransduction of Bone Cells – Application to Bone Remodeling**

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Sponsors: ARC

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Mechanical forces modulate skeletal tissues such as bone, cartilage, and tendon. However, the mechanism by which bone cells are activated in order to start resorption/formation of bone mass remains poorly understood. Particular bone cells (osteocytes) are emphasized as being the mechanosensory cells of bone. Osteocytes are connected by a fluid-saturated network. Fluid flow through this network appears to mechanically activate osteocytes. To better understand mechano-signal transduction, a new state-of-the-art mathematical model including coupled electrochemical, chemomechanical, and electromechanical effects, is formulated. The findings will give new insights into the prognosis of osteoporosis and development of bone implants.

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## Numerical Investigation of Cell-Cell Communication: Application to Bone Remodeling

Staff: Peter Pivonka, David Smith, Bruce Gardiner

Students: Jan Zimak

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In this project we formulate a bone cell population dynamics model, which allows simulation of bone remodeling by basic multi-cellular units (BMUs, see Fig. 1a). One major output variable of this model is *bone volume*, which is the integrated resorption-formation response over time (see Fig. 1b). Depending on different disease states associated with changes in bone microenvironment, different bone volume responses may be obtained, ranging from overall bone volume loss to overall bone volume gain. Effects related to mechanical stimulation can be taken into account by adjustment of differentiation and apoptosis rates of cells in the BMUs. This integrated approach allows investigation of various mechanisms related to bone diseases. Findings of this project will give new insights into prognosis and treatment of bone diseases such as osteoporosis, and may help develop new strategies for bone implant design.

- [1] P. Pivonka, D. Smith, B. Gardiner and C. Dunstan, "Numerical investigation of bone cell remodeling by means of a cell population dynamics model", *Engineering and Physical Science in Medicine (EPSM)*, Queensland, Australia, 11-21 September 2006.
- [2] P. Pivonka, D. Smith, B. Gardiner and C. Dunstan, "Role of mathematical modeling in bone biology: from intracellular signaling to tissue level", *16<sup>th</sup> Annual Meeting of the Australian and New Zealand Bone and Mineral Society*, Queensland, Australia, 23-26 October 2006.
- [3] P. Pivonka, D. Smith, B. Gardiner and C. Dunstan, "Hierarchical model describing bone cell dynamics: application to bone remodelling", *Proceedings of the 15<sup>th</sup> International Conference on Mechanics in Medicine and Biology*, pp. 225-226, 2006.

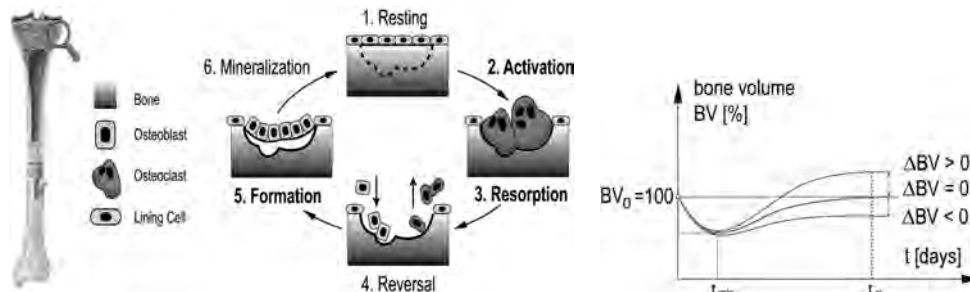


Fig. 1: Bone remodeling: (a) Activation, resorption, formation (ARF) sequence and (b) bone volume vs. time curves for different disease states.

## Synthesis of Functionalised, Biosorbable Biopolymers with Novel Architecture for Soft Tissue Engineering

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Students: Zuratul Ain Abdul Hamid

Sponsors: ARC

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This project will provide a timely and unique opportunity to develop biodegradable and biocompatible polymeric scaffold materials for use in soft tissue engineering. The project forms an essential part of the research strategy established at the University of Melbourne to develop a system for cell transplantation and organ recreation. The success of the project will provide a significant contribution to the solution of organ shortage for organ transplantation both in Australia and the world. As a result of the technology developed in this project, a significant contribution in biomaterial science and manufacture in Australia will be achieved.

So far, biodegradable and biocompatible functionalised polymers have been developed. Films cast (Fig. 1) from this polymer showed enhanced cell growth, which is essential for their application in tissue engineering and biomaterials.

This project also involves the development of soft tissue scaffold based on chemically cross linked hydrogels with increased mechanical strength and elasticity. By using fused salt emplates it has been possible to produce porous hydrogels that swell in water and possess suitable biochemical properties. Currently the elasticity and biogradability of these hydrogels are being improved through the development of hydrogels comprised of hydrophobic synthetic polymers.

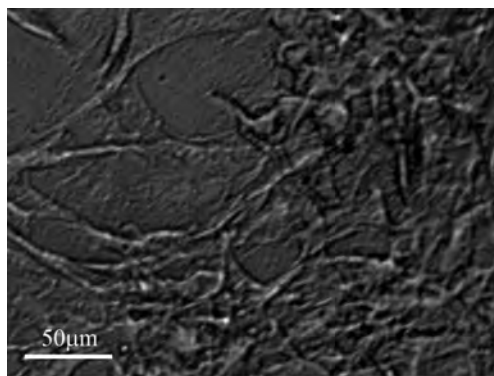


Fig. 1: This image shows the promotion of cell growth via adhesion and spreading of a 3T3 fibroblast cell on the film produced by using poly(lactic acid) film functionalized with GRGS on its surface.

- [1] E.L. Prime, J.J. Cooper-White and G.G. Qiao, "Coupling Hydrophilic Amine-Containing Molecules to the Backbone of Poly( $\epsilon$ -Caprolactone)", *Aus. J. Chem.*, **59**(8), pp. 534-538, 2006.

- [2] E.L. Prime, Z.A.A. Hamid, J.J. Cooper-White and G.G. Qiao, "Addition of Biological Functionality to Poly(e-Caprolactone) Films", *Biomacromolecules*, **8**(8), pp. 2416-2421, 2007.
- [3] E.L. Prime, J.J. Cooper-White and G.G. Qiao, "Conjugation of bioactive groups to poly(lactic acid) and poly(lactic-co-glycolic acid) films", *Macromolecular Biosciences*, 2007, (in press).

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## Hamstring Muscle Biomechanics during Sprinting

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Collaborators: Sports Science Sports Medicine Department, the Australian Institute of Sport

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The aim of this research program is to investigate the biomechanical mechanisms behind hamstring muscle strain injuries. Hamstring muscle strain injuries are common and highly prevalent in sports that involve rapid accelerations and maximal sprint efforts e.g. Australian Rules football. There is currently limited knowledge about the mechanical loads inflicted upon the hamstring muscles during sprinting and the likely factors leading to muscle strain. One of the key objectives of the program is to determine the effect of increasing running speed on hamstring muscle biomechanics (muscle length, velocity, force). An additional objective is to reanalyse a highly unique data set previously obtained from a single subject sprinting in a laboratory whereby a minor hamstring muscle strain injury occurs. Preliminary results to date demonstrate that quite marked biomechanical adaptations occur at the hip and knee joints immediately post hamstring muscle strain injury (Fig 1). Outcomes will have significant clinical implications for the development of effective rehabilitation and prevention strategies.

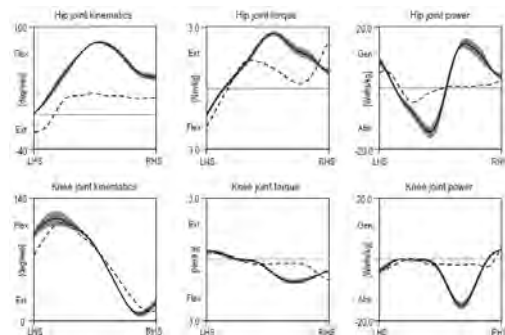


Fig 1: Hip and knee joint biomechanics during the mid and terminal swing phase of sprinting (7.5m/s). Mean curve and SD (grey bands) for normal trials (N=3). Dashed line indicates hamstring strain trial.

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## Computational Models for Cartilage Physiology in Health and Disease

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Articular cartilage is a thin layer of connective tissue covering the end of long bones in flexible joints. The composition and structural organization of articular cartilage gives its low-friction, wear-resistant and load-bearing properties. Arthritis is a highly prevalent and painful disease, characterised by the destruction of cartilage through release of macromolecular constituents from the tissue, and subsequent loss of tissue integrity and mechanical properties. Approximately 3.4 million (16%) Australians have arthritis and 60% of these people are of working age. It has been estimated that arthritis costs the Australian community \$11.2 billion, or 1.4% of GDP (Access Economics *Report on Arthritis*, 2005).

Our research team, which includes Alan Grodzinsky (MIT), aims to understand the biological systems maintaining healthy cartilage, and those that lead to cartilage disease. We have developed a computational model that couples the mechanical and growth factor transport processes in cartilage (including binding to cell receptors and to multiple binding protein families embedded in the cartilage matrix), the biochemical and biomechanical stimulation of cartilage cells to produce new cartilage matrix, and the matrix degradation processes. Our current research offers a means of understanding, as an integrated system, the competing factors contributing to cartilage health and disease.

- [1] B.S. Gardiner, D.W. Smith, P. Pivonka, A.J. Grodzinsky, E.H. Frank and L. Zhang, "Solute transport in cartilage undergoing cyclic deformation", *Computer Methods in Biomechanics and Biomedical Engineering*, **10**, pp. 265-278, 2007.
  - [2] L. Zhang, B.S. Gardiner, D.W. Smith, P. Pivonka and A.J. Grodzinsky, "The effect of cyclic deformation and solute binding on solute transport in cartilage", *Archives of Biochemistry and Biophysics*, **457**, pp. 47-56, 2007.
  - [3] L. Zhang, B.S. Gardiner, D.W. Smith and P. Pivonka, "Solute Transport in Cartilage: Effects of Cyclic Deformation and ECM Binding", *15th International Conference on Mechanics in Medicine and Biology (ICMMB-15)*, Singapore, pp. 171-172, 2006.
  - [4] D.W. Smith, L. Zhang, B.S. Gardiner, P. Pivonka and A.J. Grodzinsky, "Effects of ECM binding on solute transport in cyclically deformed cartilage", Paper No. 0101, *The 53rd Annual Meeting of the Orthopaedic Research Society*, San Diego USA, 11-14 February, 2007.
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## Preterm Birth Prediction

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Students: Damien McCormack

Sponsors: National Health and Medical Research Council (NHMRC)

Collaborators: Roger Smith (University of Newcastle)

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<http://www.civenv.unimelb.edu.au/research/groups/biomed/prem.html>

Premature birth complicates 6-10% of births, is associated with 70% of neonatal mortality, and often leads to other diseases that have substantial long-term consequences for neonates. In the last 30 years there has been no change in the incidence of premature birth. A major difficulty has been the absence of effective methods for identifying those women destined to deliver preterm. Even when a woman presents in preterm labour, she has less than 50% chance of a preterm delivery. Our research is aimed at developing a more effective method of predicting preterm delivery, well before the onset of preterm labour. In the future, this may allow the testing and initiation of new therapies earlier than is currently possible.

Working with Prof. Roger Smith (University of Newcastle), we have recruited 420 subjects, and had their blood and ultrasound samples collected at monthly intervals from 16 weeks until delivery. A computer program using Matlab is being developed to facilitate analysis of the data, which allows presentation of individual subjects data and enables the estimation of risk for an individual woman. The best current predictor can identify up to 50% of women likely to give birth prematurely, with a certainty of about 50% (see Fig. 1).

- [1] X. Shen, D. Smith, R. Smith, J. Smith, "Computer Visualization of Interrelationships Between Multiple Variables Across Human Pregnancy," *IEEE Biomedical Visualization*, pp. 60-68, 2007.

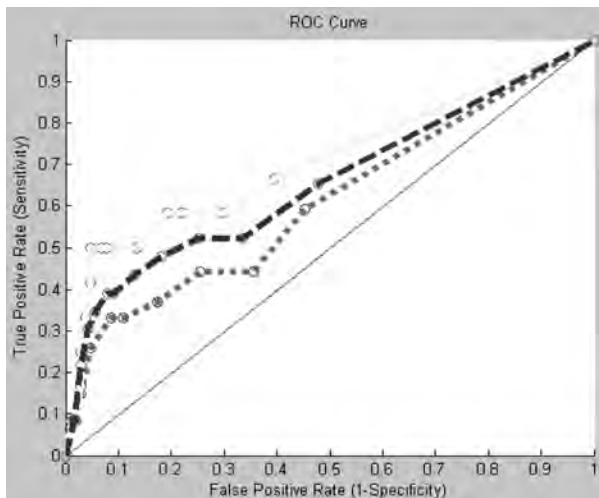


Fig. 1: ROC Curve of Predicted Results (X-Axis: 1-Specificity; and Y-Axis: Sensitivity). Red dot line: CRH; Blue segment line: CRH-ALP; and Yellow solid color: CRH-Prog.

## Wnt Signaling Pathway in Colorectal Cancer

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Cells are able to sense their environment through cell surface receptors and respond through intracellular communication (signalling) pathways leading to the cell nucleus. The Wnt/ $\beta$ -Catenin signaling pathway has an important role in cell fate decisions, such as cell survival, growth, proliferation and differentiation. It is unsurprising that this pathway is deeply implicated in a range of cancers and diseases (e.g. Alzheimer's disease), with inappropriate Wnt signaling prevalent in all stages of cancer development. Colorectal cancer is the second leading cause of cancer death in the western world and over 80% of colorectal cancers involve mutations in the key elements in the Wnt/ $\beta$ -Catenin pathway. Victoria leads the world in incidence rates of colorectal cancer. To develop effective strategies for modifying or treating colorectal cancers (and others) we need a model that integrates known information. It is highly important that we collectively achieve a greater understanding of this pathway, not only for cancer treatment but also for research into development and regenerative medicine.

Previously a minimal computational model of the canonical pathway was developed by Lee *et al.* (2003) [1], with experimental verification conducted in cell-free systems using *Xenopus* extracts. The current project aims to build on this study by converting it to a mammalian system relevant to colon cell-lines and extend it to include connecting pathways through hub molecules like  $\beta$ -Catenin. The project is a collaboration between the University of Melbourne Engineering Faculty and the Ludwig Institute of Cancer Research (Melbourne), working closely with the Director Prof Antony Burgess on the establishment of an experimental and computational model for the pathway. A systemic approach to achieve this is to determine key elements of the pathway and formulate a mathematical model and characteristic set of equations, when are calibrated and verified with experimental data.

The expected outcome is a well-tested experimental and mathematical model of the mammalian system to explore/understand the Wnt signaling network, upon which further experiments can be designed. One aim is to develop anti-cancer strategies for a colon cancer cell-line. Furthermore, due to the pathway's role in development, it is expected that a greater understanding will lead to advances in the fields of developmental systems biology, and the related area of regenerative medicine.

- [1] E. Lee, A. Salic, R. Krüger, R. Heinrich and M.W. Kirschner, "The Roles of APC and Axin Derived from Experimental and Theoretical Analysis of the Wnt Pathway", *PLoS Biology*, **1**(10), pp. 116-132, 2003

## Arterial-venous Shunting of Oxygen in the Kidneys

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Collaborators: Roger Evans (Physiology, Monash University), Paul O'Connor (Physiology, Medical College of Wisconsin)

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Chronic kidney disease and acute renal failure are major causes of morbidity and mortality in Australia and internationally. There is an ongoing epidemic of chronic kidney disease in indigenous Australians. Tissue hypoxia (inadequate supply of oxygen) makes major contributions to the pathogenesis of both acute and chronic renal diseases. Over the last three decades we have made dramatic advances in the treatment of acute and chronic hypoxia in the heart, but the same cannot be said for the treatment of kidney disease. This limited success in the kidney is due, in part, to our relatively limited understanding of the delivery of O<sub>2</sub> to the kidney. Delivery of O<sub>2</sub> to the heart is mainly dependent on coronary artery blood flow, so treatments that replace or dilate diseased vessels have proved to be highly effective. By contrast, regulation of oxygenation of kidney tissue is complex and poorly understood, with the process complicated by the functional requirement of the kidney to filter the entire blood volume and remove waste products.

One hypothesis we are currently exploring both computationally and experimentally, in collaboration with Dr Roger Evans (Monash University, Physiology) and Paul O'Connor (Medical College of Wisconsin, Physiology), for how kidney tissue oxygen levels are regulated, is through a process of *oxygen shunting*, where oxygen short-circuits the kidney circulation by diffusing through the arterial wall into nearby veins. The main objective of this proposed study is to explore the role of oxygen shunting the spatial arrangement of kidney blood vessel structure and oxygen consumption have, in regulating kidney tissue oxygen. The outcome will be better understanding of the factors that that may make a kidney more prone to hypoxia, and therefore, aid our early identification of kidneys at risk.

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## Towards the Optimum Design of a Glaucoma Drainage Device

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[http://www.civenv.unimelb.edu.au/research/groups/biomed/theme\\_3.html](http://www.civenv.unimelb.edu.au/research/groups/biomed/theme_3.html)

Glaucoma is a common and serious long-term eye-disease that affects up to 2.5% of the Australian population over the age of 40 years. Its incidence is higher in remote and third world countries, where treatment is relatively expensive. Glaucoma is the second most common cause of world blindness. Its treatment can be difficult and there are sometimes side-effects. Successful treatment of glaucoma relies on lowering the abnormally high

intraocular pressure. For these reasons developing an inexpensive and practical way of lowering intraocular pressure is envisioned to have a high impact on patient morbidity.

One method of treating glaucoma is by using ocular implants that drain and absorb aqueous solution from the eye, thereby returning intraocular pressure to the normal range. The focus of this project is to model hydraulic flow from the eye, through the implant, and into the surrounding tissues. The main objective is on the optimal design of a pressure release system for the eye. We require a permeable implant that can allow the eye to drain at a rate sufficient to maintain a normal eye pressure. Too high a drainage rate may result in the eye not being able to maintain its shape. Too low a drainage rate may result in a higher than desirable eye pressure. Another key design constraint involves the tissue next to the eye, where the fluid drains. If this tissue experiences too high a fluid pressure necrosis of the surrounding tissue can occur. A mathematical model developed for this project will help understand this system further, and assist in the design of a suitable implant.

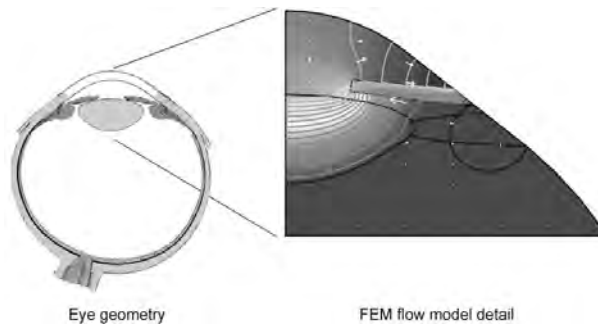


Fig. 1: Finite element aqueous flow model, based on normal eye geometry. Pressure and velocity field for the model are shown to the right. A drainage device would be inserted in the cornea, close to the iris in the anterior chamber, and drains towards the conjunctival tissue in order to reduce the intraocular pressure.

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## Algorithms for Analysis of Genomic Data

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Recent developments in biological sequencing techniques have led to an explosion in the amount of genomic sequence data publicly available. Despite the large volume of data, interpretation is not always straightforward, and new computational tools are needed for analysis. The length of genomic sequences dictates that tools must use algorithms that are efficient if they are to be practical.

The aim of this project is to develop efficient algorithms to find significant patterns in genomic sequence data. One such algorithm uses a Fast Fourier Transform (FFT) of a genomic sequence and a novel visual representation of the FFT that makes features readily visible [1]. This algorithm runs in time proportional to sequence length, and shows approximate locations of coding sequences, non-coding sequences, and repetitive regions. Used

as a filter, the algorithm can greatly speed up the process of exact delineation of region edges using algorithms with less favourable time complexity.

Another algorithm searches for families of non-coding RNA. These RNAs have been in the spotlight recently, with publication this year of experimental evidence for their role in regulating gene expression. Within an RNA family, the 2-dimensional structure will be quite similar, although not necessarily identical. The challenge in identifying families is that the 1-dimensional sequences may not be related. In this project we have developed a linear-time, heuristic algorithm for searching for structurally related, but not necessarily identical, RNA molecules, i.e. potential members of an RNA family.

Genomic sequence analysis algorithms are important tools in basic molecular biology research, which in recent years have made significant contributions to our knowledge and management of human health and disease.

- [1] R.Hall and L.Stern, "A rapid method for illustrating features in both coding and non-coding regions of a genome", *Bioinformatics*, **20**, pp. 982-982, 2004.

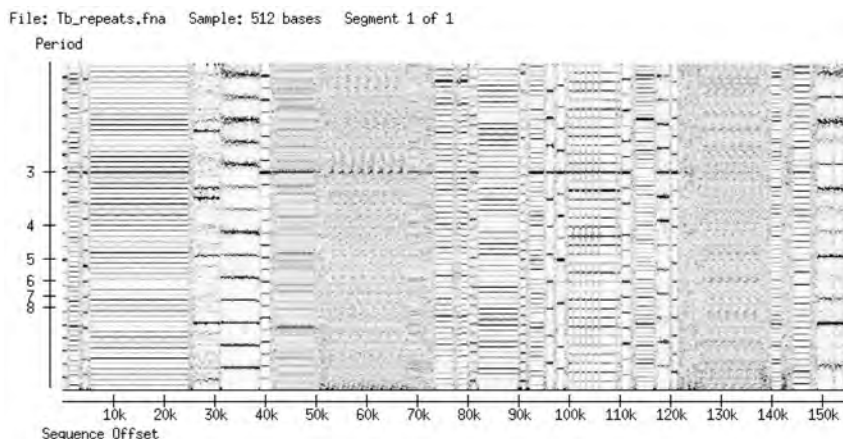


Fig. 1: Visualisation of repetitive regions in *T.brucei* genome using Fast Fourier Transform.

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## Protein Structure Determination and Visualization

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This project investigates methods for improving the structural understanding of proteins using visualisation and matching techniques. MUSTANG is a tool for multiple protein structural alignment producing alignments which are comparable in quality to hand-curated

alignments. Fig. 1 illustrates alignments of globins and serine proteinases performed by MUSTANG. It has been used in a molecular replacement pipeline to help determine the structure of eight new proteins. It was part of three entries to the CASP protein structure determination competition in 2006. Apart from structural alignment we are investigating structural lookup of proteins, and the visualization of secondary structure of proteins in order to notice similarities.

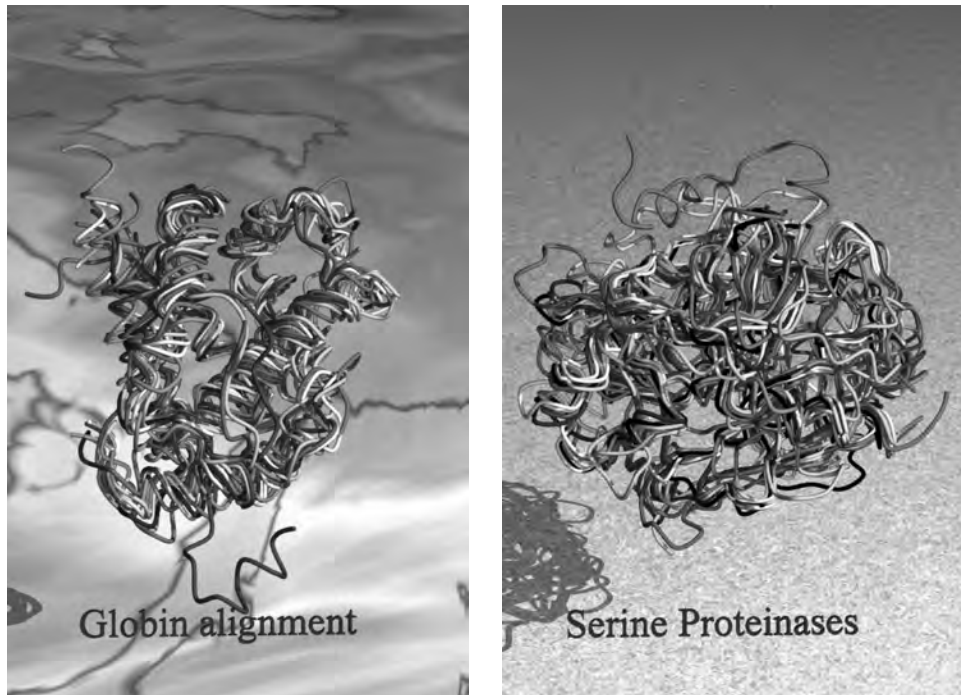


Fig. 1: Examples of multiple structural alignment of proteins by MUSTANG.

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## Damage Analysis of Osteoporosis in Human Bone

Staff: John Williams, John Clement

Collaborators: David Thomas (Dental School), John Williams

An analysis of multi-axial bending and compression in the human femur including bone imaging data for determining the reduction in cross-sectional properties has been undertaken to assess the vulnerability of patients to bone fracture depending on the degree of osteoporosis present in the bone structure.

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## Accelerated Wound Healing

Staff: John Williams

Collaborators: Eugene Athan (Geelong Hospital)

Students: Wen Shan

The occurrence over recent years of lower leg ulcers associated with the “Bairnsdale Ulcer” has prompted research, in conjunction with the Department of Infectious Diseases at Geelong Hospital, to develop methods for improving wound healing rates following surgery. A biomedical device has been designed and is currently being built in order to achieve successful outcomes in this and other aspects of wound healing.

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## Genomic Signal Processing

Staff: Justin Zobel, Adam Kowalczyk, Noel Faux, Bryan Beresford-Smith, Christopher Leckie, James Bailey, Ramamohanarao Kotagiri

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Recent breakthroughs in methods for analysis of the genome have triggered the development of novel approaches to investigation of the inner workings of biological cells. These approaches have fuelled a rapid and fundamental shift in genomics, away from a focus on individual genes, to the study of multivariate gene and protein activity within the framework of cellular pathways. In this context, of particular interest to NICTA, is the area of genomic signal processing (GSP). This is broadly understood as analysis, processing, and use of, genomic signals for gaining biological knowledge, and the translation of that knowledge into systems-based biotechnology and medical applications. Several major clinically relevant goals are: to understand genes and their products (proteins, messenger RNA) for disease diagnosis, prognosis, and selection of personalized treatment; to understand the underlying biology, including the cell regulatory system such as non-coding RNA; and to contribute to the development of more efficient techniques for sequencing of other organisms, such as commercial crops.

There are many issues that must be addressed for effective GSP. Resolving these issues requires fusion of deep biological and mathematical knowledge, as biological cell systems are inheritably non-linear, have highly distributed regulation mechanisms, and depend on large number of parameters. Dealing with these limitations is one of the main research directions in Life Sciences in this area. We focus on selected wet-lab projects in our partner’s laboratories and are developing knowledge extraction techniques as a background for the core research objectives, which range from gaining of fundamental scientific insights to development of practical (clinical) solutions. These techniques include literature search tools and custom built database searches. The prototype examples here are current projects on prediction of response to treatment in esophageal cancer, identification of critical DNA aberrations in ovarian cancer (Fig. 1), development of a diagnostic system for carcinoma of unknown primary, and identification of genome regions that determine commercially significant traits in barley and other crops.

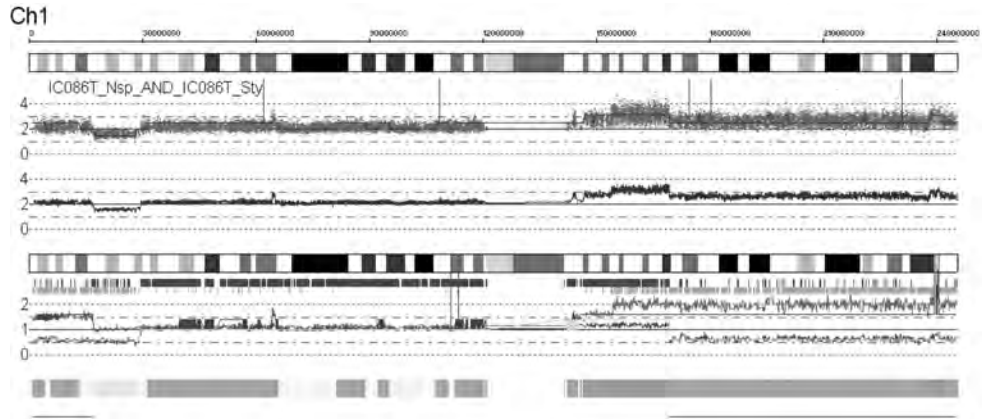


Fig. 1: Chromosome 1, SNP profiles of DNA copy number of an ovarian cancer sample obtained with GeneChip® Human Mapping 500K Array technology from Affymetrix (produced by PMCC).

