

Chapter One: Biomedical Engineering

Understanding the Dynamics of Epileptic Seizures: Detection, Prediction, Modelling and Localisation

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Keywords: epileptic seizures; EEG data; bionic technologies

Epilepsy is a neurological disorder which affects approximately 1% of the population (i.e. 50 million people). The disease causes seizures as a result of populations of neurons (brain cells) becoming overly excited. These seizures can have various behavioural manifestations, the most characteristic involving chaotic and uncontrollable movement of the body (i.e. a tonic-clonic seizure). Epilepsy is a global brain disorder because epileptic seizures can involve large portions of the brain, which can have a variety of effects on consciousness. While there are many drugs that can be used to prevent epileptic seizures, 25% of people suffering epilepsy cannot be treated adequately by available pharmacological therapies. Moreover, the exact cause of epileptic seizures in the brain is not well understood.

The research program in epilepsy has a number of objectives.

- Detection of seizures: The reliable and robust detection of the onset of seizures from electroencephalographic (EEG) recordings is still challenging. Part of our research program is involved in developing improved techniques for detecting this seizure onset and characterising epileptic seizures based on EEG data.
- Prediction of seizures: We have an active research program in developing techniques to predict when seizures will occur. The methods used include nonlinear systems theory and electrical probing of the brain state. The development of improved seizure prediction and detection methods will depend on a deeper understanding of the underlying causes of epilepsy through both physiological experiments and neural modelling.
- Neural modelling of brain activity: We are developing and analysing neural models of the brain to understand how epileptic seizures are generated and how they propagate throughout the brain – i.e. how seizures spread from the seizure focus to the rest of the brain.

- Localisation of focus of seizure activity: We are developing improved inverse EEG and simultaneous EEG/fMRI methods to determine the region of the brain that generates epileptic activity.

One potential application for seizure prediction is to activate an implantable device that can prevent or terminate 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 (www.bionicttechnologies.com.au/) to try to make such an implantable seizure control device a reality. Being able to localise the site in the brain that generates epileptic activity is also important for the efficacy of such a device.

In addition to the engineers in the Melbourne School of Engineering, our interdisciplinary team consists of neurologists, neuroscientists, clinicians and software developers at The Bionic Ear Institute (www.bionicear.org) and St Vincent's Hospital Melbourne (www.svhm.org.au).

Patellofemoral Arthritis: Efficacy of Physiotherapy and Understanding the Role of Joint Stress

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Keywords: knee osteoarthritis; biomechanical modelling; patello-femoral joint; physiotherapy

The lateral patellofemoral joint (PFJ) is frequently affected by osteoarthritis (OA), contributing significantly to the morbidity associated with knee OA. This inter-disciplinary project will use a single cohort of individuals with PFJ OA to investigate two distinct, but related questions, using rigorous and innovative methodology. PART A: A randomised controlled trial (RCT) adhering to consolidated standards of reporting trials (CONSORT) guidelines will evaluate the efficacy of physiotherapy compared to health education control. Primary outcomes, pain, physical function and global effect scales, will be evaluated by a blinded examiner at baseline, 12 weeks and 9 months. PART B: Accurate, patient-specific estimates of PFJ stress will be obtained from detailed and innovative biomechanical modelling. Independent predictors of joint stress include pain severity, patellar malalignment, knee malalignment, quadriceps activation, knee flexion and internal rotation range. This research is timely and of major international significance, as the role of joint stress is integral to the pathogenesis of OA and the initiation and continuance of pain. Findings have the potential to foster interventions that are likely to prevent PFJ OA.

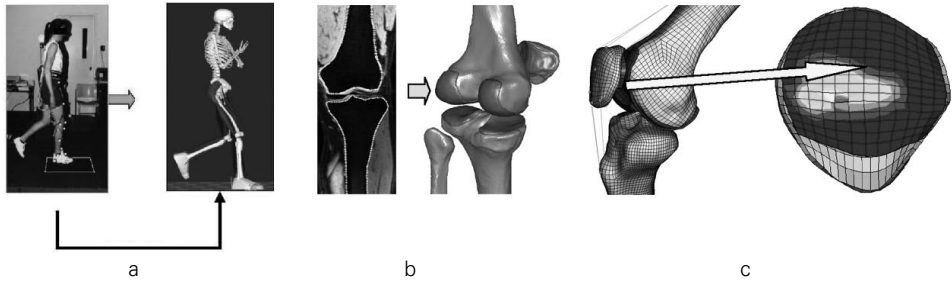


Fig. 1: a) Capture of patient kinematics, calculation of muscle forces, b) Segmentation of bone and cartilage geometry from MR image, c) application of muscle forces and joint kinematics to a patient-specific model.

Biophysics: Protein Aggregation

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Keywords: protein misfolding; protein aggregation; protein therapies

A number of human diseases are associated with protein misfolding, such as Alzheimer's disease, type II diabetes and heart disease. The incidence of Alzheimer's disease increases from 5% to 50% from age 60 to 85, therefore as populations age, the impact these diseases have on the community increases. At the same time, protein therapeutics have become the fastest growth area in biotechnology. Therapeutic proteins are currently produced for vaccines and immune disorders and can be rendered useless or harmful by protein misfolding. The objective of this research is to understand the key factors that cause protein aggregation in processing, which will be critical for the successful commercialisation and subsequent availability of protein therapies. Understanding the mechanism of amyloid formation will optimise protein therapies and define cures for associated diseases.

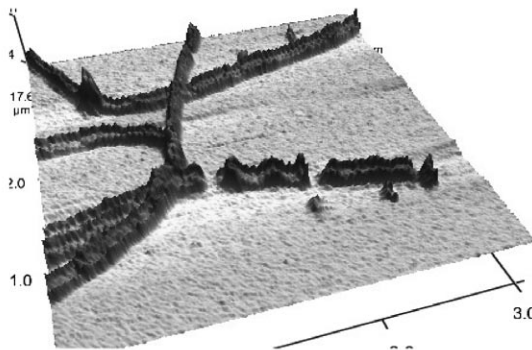


Fig. 1: AFM image of fibrillar aggregate.

Protein Aggregation During Processing

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Keywords: protein aggregation; protein processing; biotechnology industry

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 we have developed in order to understand the mechanisms by which 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.

Site Specific Drug and Vaccine Delivery

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Keywords: targeted drug delivery; novel biopolymers

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.

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Shear-Induced Deformation of Proteins in Couette Flow

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Keywords: protein misfolding; protein aggregation

This project is directed toward understanding the fundamental mechanisms by which proteins undergo conformational deformation in shear flow. A number of the proteins in our bodies are transported in the blood stream. During this circulation the proteins are exposed to a number of hydrodynamic forces. The proteins are degraded during this process and have half lives which are related to the secretion through the kidneys. We are measuring this breakdown in a range of controlled flow geometries. Furthermore, there is evidence to suggest that the aggregation of misfolded proteins is related to disease. This is particularly relevant to the onset of type II diabetes and several other diseases.

Individualised Cochlear Implant Sound Coding: Optimised Algorithms for Better Hearing

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Keywords: cochlear implant sound processing; neural response models; inversion algorithms

One in six Australians are affected by hearing loss. Hearing loss impacts on educational and employment opportunities and has a significant economic impact upon Australia. Over 10% of people with hearing impairment have a severe or profound hearing loss and may be candidates for a cochlear implant. Current cochlear implant sound processing only offers limited benefit to users.

The aim of this project is to develop a method for tailoring the electrical stimulation for an individual cochlear implant user to produce spatio-temporal patterns of neural excitation that optimally match those of normal hearing. This will be done by developing a solution to the "inversion" problem, namely finding the optimum pattern of electrical stimulation that will minimise the difference between the electrical and the target acoustical responses (i.e., the neural response to acoustical stimulation in normal hearing). Because the method takes

account of the way in which electrically-evoked neural responses differ for each cochlear implant user, it offers a means of designing an electrical stimulation strategy that is not only better, but also individually optimised, for each cochlear implant user. The approach is based upon developing models of neural responses and the application of established mathematical inversion and optimisation methods.

This project represents a truly innovative pathway forward in the development of cochlear implant sound coding that could substantially increase the speech perception of users, enabling these people to become and remain active and productive members of our community. A key outcome of the project is an entirely new type of cochlear implant sound coding strategy that could substantially increase the speech perception of users and strengthen Cochlear Limited's international competitiveness.

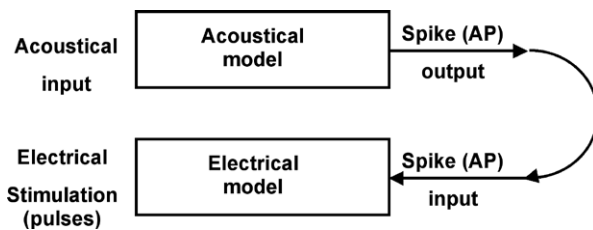


Fig. 1: Diagrammatic illustration of the neural inversion model for generating electrical pulses.

Biological Effects from Extremely Low Frequency Electromagnetic Fields

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Keywords: low frequency electromagnetic fields; biological effects; health risks

Adverse biological outcomes due to the thermal effects of exposure to high-power, low-frequency electromagnetic fields are well understood and are the basis for standards limiting human exposure to such fields. Over the past few decades a controversy has arisen over possible adverse biological effects due to exposure to low-power, low-frequency electromagnetic fields. Epidemiological evidence has been published as well as laboratory based measurements of biological activity. A variety of mechanisms have been proposed to account for such effects. Both the proposed mechanisms and the empirical evidence have been subjected to considerable criticism. Vociferous supporters of both sides of this argument are easy to find. Considerable ongoing research is invested in this area, with the outcomes often used in political battles over the location of power transmission lines, mobile telephony infrastructure and the like, at considerable cost to the community.

This project aims to critically investigate and compare prominent theoretical models, such as the cyclotron resonance model and the ion parametric resonance model, combined with laboratory-based experimental work to test the predictions of these models.

Environmental Effects of Non-Ionizing Radiation and Magnetic Fields

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Keywords: mobile communications; radio frequency fields; biological effects; health risks

The environmental effect of electromagnetic fields is a research area that has generated conflicting results and thus uncertainty regarding possible adverse health effects. The recommendation of the International Committee of Non-Ionizing Radiation Protection (ICNIRP) for exposure limit value for low-frequency electromagnetic fields (EMF) and microwaves aim to protect against nerve stimulation and body heating respectively.

A new third generation of mobile communication is becoming increasingly important, but the impact of this radiation modality is largely unknown. Epidemiological studies will not be able to answer this question until after 10 to 15 years of exposure, therefore it is necessary to study the biological effects that can lead to health impairment, in the laboratory. It is of great importance both to quantify the leakage of albumin through the blood brain barrier (BBB) and to study the toxicological effects of this leakage. This new knowledge can be used as a foundation for new exposure limits that take into account non-thermal biological effects of microwave radiation from mobile telephones and base stations. The results will also lead to safer mobile phone designs. In 2007, there were 1.5 billion mobile phone subscribers globally and 17.2 million users in Australia. To what extent do these new, almost ubiquitous radio frequency fields affect all living organisms? And what will be the effects of many years of continuing exposure?

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Environmental Impact of Low Frequency Electromagnetic Field Exposure – Trams and Trains

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Keywords: transportation systems; low frequency electromagnetic fields; biological effects; health risks

Sources of electric and magnetic fields surround us everywhere, hence investigating long-term exposure of the general public to low frequency electric and magnetic fields caused by transportation systems is of critical importance. In “conventional” transportation systems, energy is supplied as fuel and the internal combustion engine uses a motor with electrical ignition. In “advanced” systems, motors are electrical (AC or DC) and the power supply can also be electrical (AC or DC). People on trains and trams can be exposed to higher static and alternating magnetic fields than background levels.

This project, in collaboration with industry, will quantify the exposure of the general public to low frequency electric and magnetic fields from transportation systems.

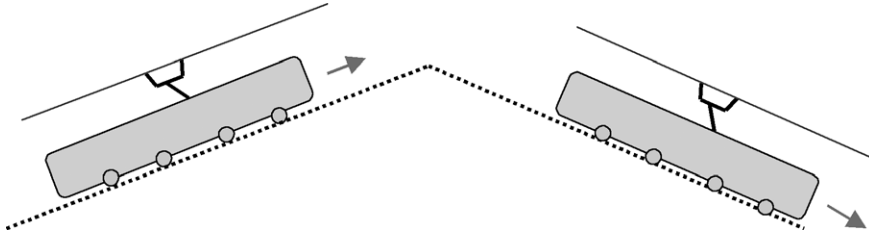


Fig. 1: Tram moving up hill (acceleration) and moving down hill (deceleration). Investigation has focused on occupational exposures (especially for the drivers), as well as passengers.

Sequence Detection for Clustered Regularly Interspaced Short Palindromic Repeats in DNA

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Keywords: CRISPR systems; disease prevention; bioinformatics

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPRs) are widespread in the genomes of many bacteria and almost all archaea. These arrays are repeats separated by similar sized non-repetitive regions (see Fig. 1) called spacers [1]. Experimental results show CRISPR systems provide immunity against bacteriophages for prokaryotic organisms. It works together with a group of associated proteins known as CRISPR Associated Sequence (CAS) [2]. Exploitation of CRISPRs can deliver better techniques for detecting bacteria strains, such as *M. tuberculosis*, in preventing disease outbreak [3]. We can also design valuable bacteria that are insensitive to phage attack for the dairy and wine industries [4]. Since CRISPR arrays are very diverse across different species [5] and errors such as mutation and deletion in sequence, further complicates the detecting process, [6,7] a pattern recognition tool for detecting this system is needed. The aim of this research is to deliver a new method which employs a Hidden Markov Model (HMM) in finding CRISPR array for bacteria and archaea.

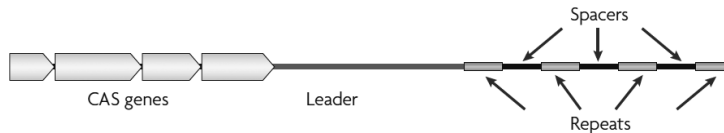


Fig. 1: Structure of CRISPR system (adapted from Sorek et al. 2008).

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Near-Unsupervised Learning Algorithms for the Analysis of Metagenomic Data

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Keywords: near-unsupervised learning algorithms; metagenomic data; pattern mining

Metagenomics is a recent and rapidly growing area of research. It is the study of microbial consortia sampled directly from various environmental niches, and has significantly advanced our knowledge of microbial ecology, diversity and function. The shotgun sequencing methodology of metagenomic surveys is such that the genomic DNA of all constituent microorganisms is sequenced *en masse*, without the need for a pre-cloning step. This enables approximately 99% of Earth's undiscovered microbiota, which resist standard laboratory culturing techniques, to be sequenced and analysed.

As shotgun sequencing requires genomes to be fragmented before sequencing, a fundamental task to downstream analysis of a microbial assemblage is to know which sequenced DNA fragment belongs to which constituent organism (Fig. 1). This is referred to as the binning problem. The methods developed here will rely heavily on unsupervised pattern mining: to minimise dependence on the relatively small number of reference organisms; to develop novel features for *in silico* representation of metagenomic fragments and the careful use of annotated data subject to strict selection and evaluation criteria.

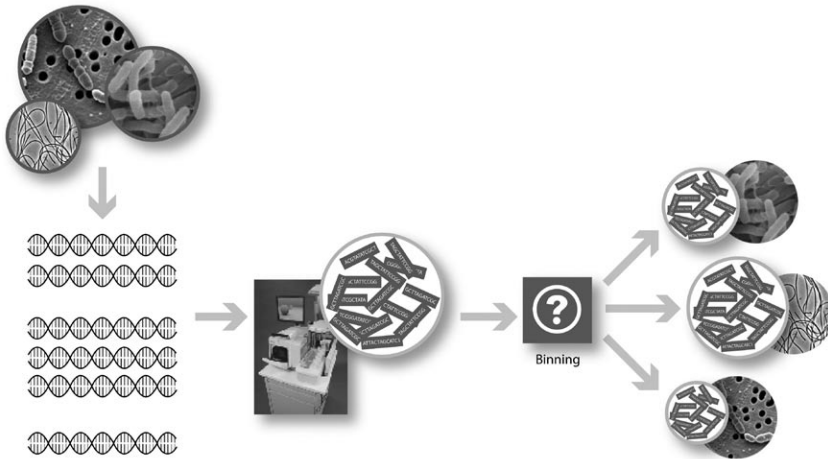


Fig. 1: Sequencing an environmental sample using the metagenomics approach leaves open the question of which sequenced DNA fragment belongs to which organism.

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Semi-Supervised Learning of Multiple Biomechanical Systems

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Keywords: multiple biomechanical systems; mathematical system modelling; urban rescue operations; landmine detection

Robotic technologies have many limitations in areas where human intervention is either dangerous, or not possible, due to environmental conditions. For example, searching for victims in unstructured environments, such as, in buildings after an earthquake [1]. A similarly dangerous area for humans to work is in the detection and removal of landmines. Identification of the exact location of landmines is time-consuming with currently available sensing technologies, because they are designed for concealment [2].

The aim of this research project is to analyse the cognitive learning of multiple biomechanical human-robot-animal integrated systems (Fig. 1) through mathematical system modelling. The three sub-systems: human, robot and animal, each have unique abilities. For example,

rodents have tuned physical morphology to navigate in highly unstructured environments and have good olfactory capacities that can be used to detect the location of human victims. Robots, on the other hand, can be programmed and can communicate with humans in a predictable manner. Humans have higher cognitive capability and the ability to interpret visual information better; hence humans can arbitrate the animal-robot system. Effective cognitive learning between the three systems can overcome the bottlenecks of each. Application of such multiple biomechanical systems can be especially beneficial in urban and rescue operations, as well as in landmine detection for human re-settlement.

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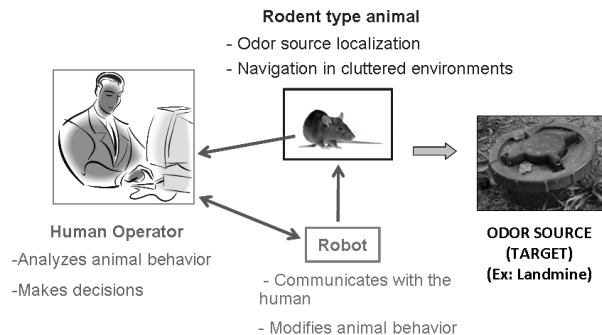


Fig. 1: Multiple biomechanical systems for odor source localisation.

Bio-Inspired Cable Driven Parallel Robots

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Keywords: cable driven parallel mechanisms; human joint simulation

A Cable Driven Parallel Mechanism (CDPM) is a type of parallel robot, where cables are used instead of rigid links, with a number of promising advantages. A variation of the CDPM with the rigid serial-link structure actuated through cable drives, is a bio-inspired arrangement analogous to the bone and muscle structure of a human. The system possesses compliance that conventional rigid parallel and serial robots lack. For an n degrees of freedom (DOF) task to be realised, the CDPM mechanism has to be actuated with at least $n+1$ number of cables, as cables can only pull and not push. Actuation through $n+1$ cables produces a

unique mapping between actuation and task space, while actuation through more than $n+1$ cables causes the system to be redundantly restrained (redundantly actuated). Redundant actuation means that there are more than one set of cable tensions that can produce the same motion/force seen at the end-effector of the mechanism. The fundamental research issues for CDPM systems include kinematics, dynamics, workspace, control, mechanism design and optimisation.

CDPMs possess the high structural stiffness associated with parallel mechanisms and are light in weight. As a result, higher motion speeds can be obtained with less energy consumption. Another advantage of CDPMs is that the cable setup can be portable and reconfigurable for different purposes. These properties make CDPMs useful in the areas of high speed manipulation, haptic devices, and robot rehabilitation.

In this project, a 3 DOF spherical manipulator is investigated. The manipulator is articulated through a ball-socket joint, structurally similar to a simplified human shoulder. The strategy for the generation of force and motion, resulting workspace and optimisation strategy for redundantly constrained cases will be studied, with the outcomes utilised to better understand the mechanisms of human joints, such as the shoulder and the hip.

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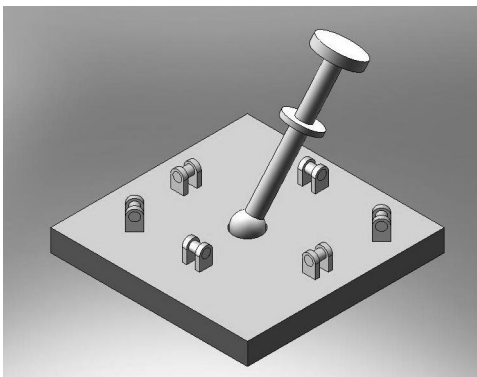


Fig. 1: 3 DOF human shoulder structured spherical manipulator.

Computational Modelling of In Vivo Contact Stresses in the Equine Fetlock Joint

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Sponsors: Rural Industries Research and Development Corporation

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Keywords: gait analysis; equine fetlock joints; 3D stress models

Over 70% of equine fatalities on Victorian racetracks are due to catastrophic joint injury. Of these cases, injury to the fetlock joint is the most common. An understanding of the loads imparted on the structures in this joint will improve our understanding of the consequences of interventions and treatments. Previous studies in human biomechanics provide a reliable pathway to determining these loads.

Gait analysis involves the use of motion capture systems and force transducers to determine both the positions of all of the joints of an animal in motion and the reaction load observed when limbs are in contact with the ground (Fig. 1a). The results of gait analysis allow the estimation of the net torques about each joint.

A separate 3D model of the musculoskeletal system (Fig. 1b) is then forced to behave in the same manner as the experimental results, yielding an estimate of the loads in each separate muscle structure. Finally these muscle forces are employed in a detailed 3D stress model of the joint to predict contact stresses (Fig. 1c).

This project will yield three such joint stress models, highly specific to three racehorses. These models will be able to predict some of the causes of tendon and bone failures, as well as the outcomes of preventative measures.

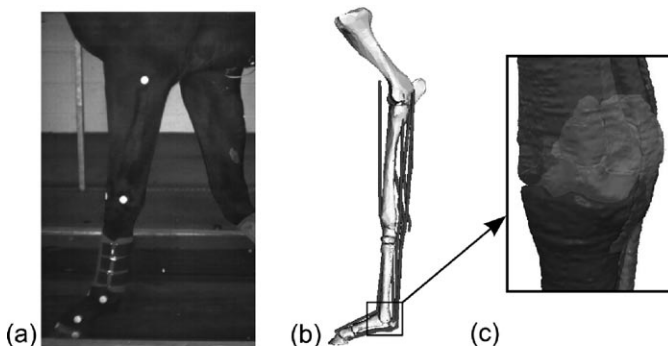


Fig. 1: (a) Equine forelimb with motion capture markers in place, (b) musculoskeletal model, (c) geometry of the fetlock including bones, ligaments and tendons for the 3D contact stress model.

Signal Processing Techniques for Structural and Diffusion MRI

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Keywords: signal processing; disease detection; magnetic resonance imaging

Magnetic Resonance Imaging is a non-invasive technique of vast neuroscientific benefit because of 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.

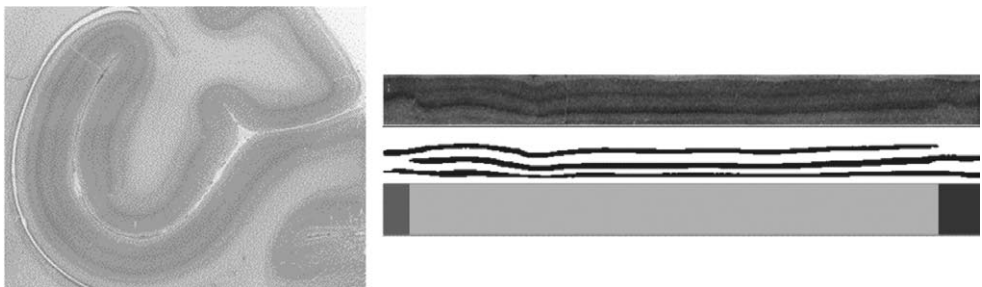


Fig. 1: Automated parcellation of a post-mortem histological slice of baboon cortex. Left: Haematoxylin & eosin stained slice. Right: Flattened segment of cortex (top), Map of posterior probability of dark band (middle), Cortical parcellation result (bottom).

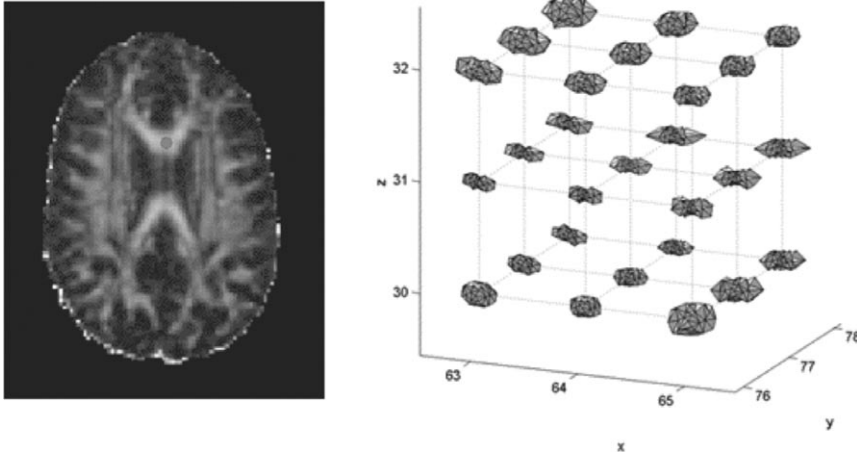


Fig. 2: Visualisation of local white matter structure as determined by water diffusivity, in 32-direction diffusion MR image of a Huntington's disease patient.

Modelling Brain Development

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Keywords: mathematical modelling; magnetic resonance imaging; brain development

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 2500cm², 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.

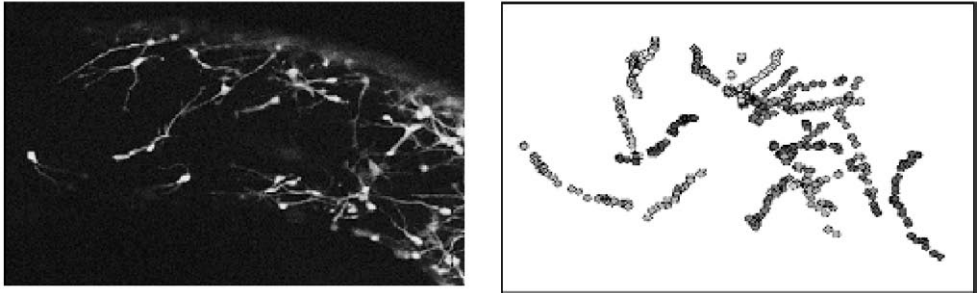


Fig. 1: Left: Interneuron migration in GAD-67 mouse brain slice culture at embryonic day 12. Right: Labelled neuron trajectories.

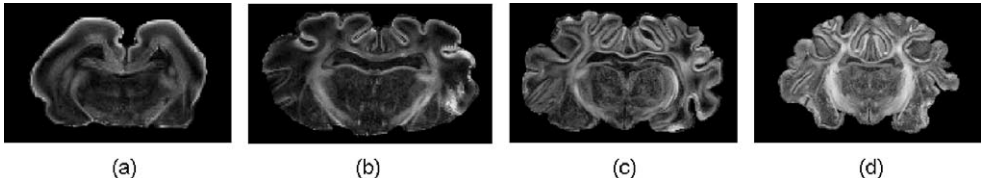


Fig. 2: Fractional anisotropy-weighted principle diffusion tensor eigenvalue in slice of fetal lamb brain at a) 70 days, b) 90 days, c) 110 days, d) 130 days gestation.

Analysing Brain Activation Patterns Through Functional MRI

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Sponsors: National ICT Australia (NICTA)

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Keywords: brain function; functional magnetic resonance imaging (fMRI)

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.

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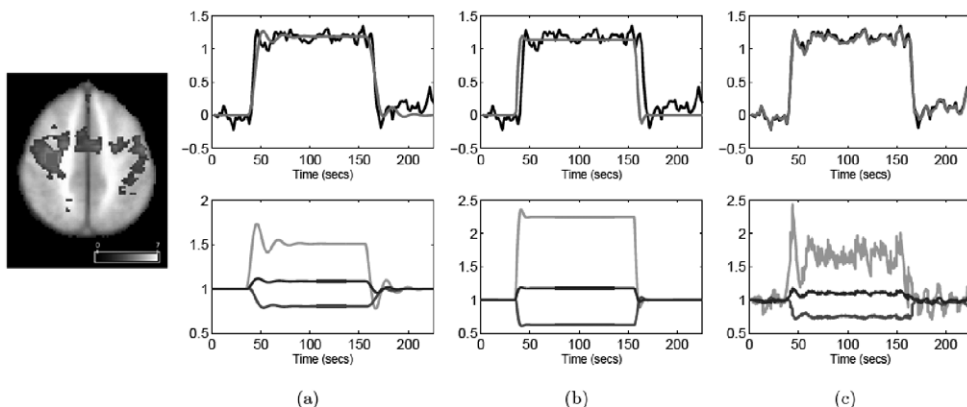


Fig. 1: Observed BOLD signal (right) in the primary motor cortex (left: square). Particle filter estimates of BOLD signal and normalised cerebral blood flow, volume and deoxyhemoglobin content for a) optimal, b) underfitting and c) over-fitting of system parameters.

Investigating Evidence of Control System Dynamics in Visuomotor Skill Acquisition Using Multimodal Functional Magnetic Resonance Imaging

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Keywords: motor skill acquisition; multimodal functional magnetic resonance imaging

This project brings together mathematical and engineering methods with cognitive neuroscience in a novel way to better understand the fundamental processes associated with brain imaging and the acquisition of motor skills. An improved understanding of the function of regions within the motor network will have a direct benefit for the rehabilitation of patients suffering motor deficits from developmental causes, following traumatic brain injuries, and after stroke and other neurodegenerative diseases. The outcomes of the research will also contribute to our understanding of the complexity of brain networks involved in motor skill acquisition.

A Statistical Dynamics Model of Interactions Between Nephrons in the Kidney

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Keywords: renal modelling; complex systems; emergent dynamics

The human kidney performs a number of 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. The behaviour of individual nephrons can fluctuate widely and coupled systems of nephrons can behave chaotically. However, the overall behaviour of the kidney remains remarkably 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, the project aims 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, it aims to create models that are capable of predicting kidney function and the effects of renal disease.

To achieve this, we will need to model the shape and size of structures within the kidney such as arteries, veins, urine ducts and renal pyramids in a generalised manner with variable parameters such as the organ's size. These models are to be used with physiological models to produce a whole kidney model of varying size and condition for simulation.

Early work on this project has produced exciting and groundbreaking results [1]. The kidney is modelled as a complex network, with individual nephrons as dynamic networks in which each node models a tubule segment and difference equations model solute transport between tubule segments, the surrounding renal fluid, and peri-tubular capillaries. Models consisting of 2, 8, and 72 nephrons have been constructed, and these models reproduce known behaviours, such as responses to changes in pressure and sodium chloride concentration.

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Visuo-Haptic Environments for Dental Drilling

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Keywords: virtual dental surgery; haptic probe

This is a collaborative project with the Department of Dentistry and is a part of the University of Melbourne's MUVES project, which 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 and bone, as they drill and develop expertise in how to drill those materials.

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.



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

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

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Keywords: gait disorder; detection systems

This research aims to investigate computational intelligence methods to detect gait characteristics depictive of a disorder. Gait disorders, which result in falls in the elderly, are a 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 for 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); and
- 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.

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Automated Recognition of Obstructive Sleep Apnoea Syndrome from Electrocardiogram Recordings

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Keywords: sleep apnoea; electrocardiogram signals

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. Using the 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.

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New Algorithms for Screening Cardiac Autonomic Neuropathy in Diabetic Patients

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The prevalence of diabetes mellitus is currently estimated at 200 million people worldwide and exceeding 360 million patients by 2030. The majority of these patients will have type II diabetes. As many as 22% of people with type II diabetes suffer from cardiovascular autonomic neuropathy (CAN) which leads to impaired regulation of blood pressure, heart rate and heart rate variability (HRV). Silent ischaemia is significantly more frequent in patients with CAN than in those without (38% vs 5%). Around 75% of people with diabetes die from cardiovascular disease such as heart attack and stroke. Early sub-clinical detection and intervention are of prime importance for risk stratification in preventing the potentially serious consequences of CAN. However, existing screening techniques using cardiovascular reflex responses are subject dependent and likely to detect CAN at the advanced stage, once symptoms are visible, rather than at an earlier stage of progression. The aim of this project is to develop sophisticated but simple algorithms for early detection of CAN in diabetic patients and monitor its progression.

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Diagnosis of Foetal Heart Defects using ECG and Doppler Ultrasound

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Keywords: foetal heart defects; electrocardiogram; Doppler ultrasound

Good health in the developing human foetus is critical to the future well-being of an adult. At least 8 in 1,000 infants born each year have a heart defect and congenital cardiovascular defects are present in about 1% of live births. This project proposes a novel non-invasive system to recognize the timings of foetal cardiac events on the basis of analysis of electrical (foetal ECG) and mechanical (Doppler ultrasound signals) heart activity to enable obstetricians to detect an early stage of prenatal cardiac dysfunction. The outcome of this project will improve the prenatal cardiovascular risk assessment tools in Australia.

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Human Gait Pattern Analysis and Modelling

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Keywords: gait control; human movement; diagnostic assessment methods

Understanding the underlying mechanisms and associated deficits in movement dynamics across the lifespan and the effects of pathological conditions, such as falls, will lead to many applications in the design and evaluation of diagnostic and assessment methods for

human movement. For example, these methods could assess age-related decline in gait control, the associated risk of sustaining a fall, and could determine the effect of exercise intervention and treatment. Falls and injuries during walking in older adults are a major public health issue and cost Australia \$498 million per annum. These costs are projected to triple by 2051, if fall rates remain unchanged, however they may be preventable if risk factors can be identified. This project addresses the following research questions:

1. What are the key features and variability indices (statistical and nonlinear, e.g., Poincaré plots, approximate entropy, detrended fluctuation analysis, wavelet based fractal correlations etc.) that characterise dynamic steady-state control during locomotion?
2. How are these features and indices influenced by more challenging gait tasks, such as walking on inclined surfaces?
3. How do gait variability and control mechanisms change due to ageing and pathology, for example, in falling behaviour?

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A Low-Cost Pulse Oximeter for Developing Countries using a Cell Phone for Processing and Display

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Keywords: pulse oximetry; pneumonia diagnosis; cell phone

Pneumonia kills at least 2 million people each year, including many children in Africa. Sadly, most of these deaths could be avoided if the disease was properly diagnosed and treated. In a modern hospital setting, physicians can use chest X-rays, lab tests, blood oxygen measurements and other diagnostic tools to distinguish between the many causes of respiratory illness. In a remote African village, few such tools are available to determine if a child's fever and shortness of breath are caused by pneumonia, malaria or some other infectious disease.

Pulse oximeter plethysmography (PPG) (sometimes referred to simply as "pulse oximetry" or "photo-plethysmogram") is a standard method of obtaining blood oxygenation data in a non-invasive and continuous manner. An oximeter uses two wavelengths of light to determine hemoglobin saturation. Waveforms are created by the absorption produced by pulsatile arterial blood volume, which represents the alternating current (AC) signal. The absorption produced by nonpulsatile blood, venous and capillary blood, and tissue absorption is depicted by the direct current (DC) signal. An oximeter measures the oxygen content in red blood cells by measuring the absorption of red and infrared light waves as they pass through a patient's fingertip or ear lobe. Hemoglobin, the oxygen-carrying component of blood, is often in a depleted state in people with severe pneumonia. The LEDs (light-emitting diodes) needed for an oximeter sensor are widely available and inexpensive.

The aim of the study is to create: 1) a prototype \$20 oximeter sensor that health workers can simply plug into their mobile phone using USB; and 2) software that can be installed on smartphones to extract respiratory information from the varying oximeter wavelength readings obtained from inexpensive LED fingertip sensors.

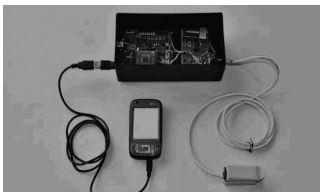


Fig. 1: Most health workers in Africa carry mobile phones. This prototype device allows health workers to use their mobile phones to better diagnose and treat pneumonia and other health issues.

Novel Retinal Analysis Algorithm to Predict the Risk of Cardiovascular Diseases

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Keywords: cardiovascular disease; retinal analysis; early diagnosis; risk prediction

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 below). 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.

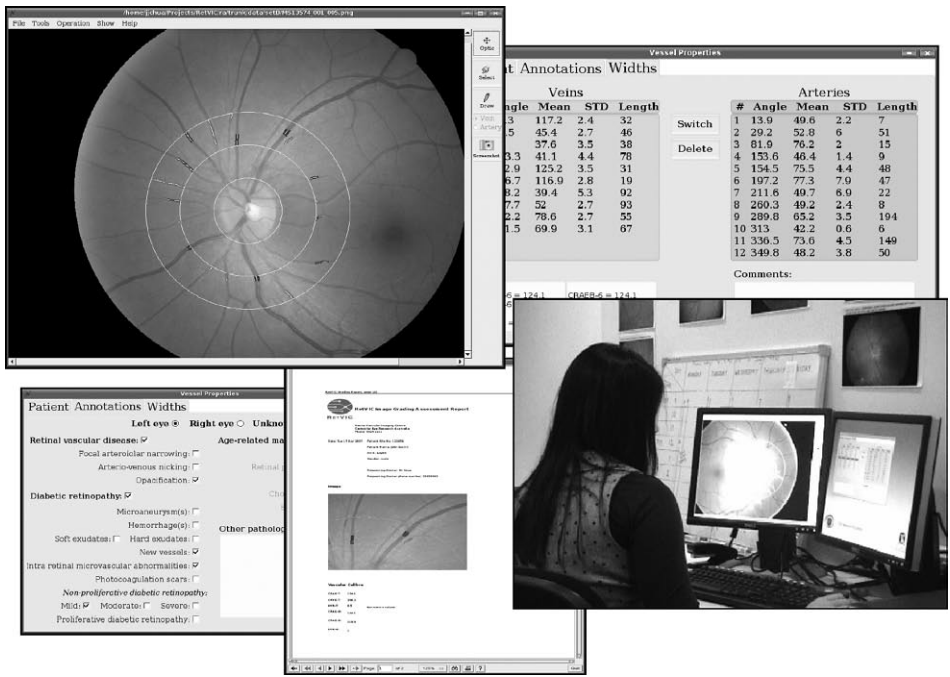


Fig. 1: Retinal image analysis software.

Longitudinal Data Mining for Neuropsychiatry Research

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Sponsor: AE Rowden Foundation

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Keywords: first episode psychosis; magnetic resonance imaging; longitudinal data mining

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. 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.

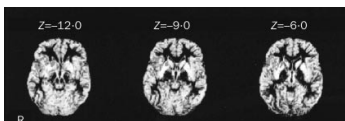


Fig. 1: Some of the areas with reduced grey matter volume in those who developed psychosis (Pantelis, *Lancet* 2003).

Image Processing for the Assessment of Skin Conditions

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Keywords: automated skin assessment; signal processing algorithms

This project involves devising signal processing algorithms and software, which compares photographs of patients with facial skin problems, such as acne, to determine rate of recovery or deterioration, over time. The key objective is to assess whether a patient's skin is getting better or worse with treatment and to develop an objective method for assessing the performance of medications and skin care products, which doctors use to treat disorders such as acne and redness. We have developed programs which take photographs of people's faces and do transformations and processing to identify skin disorders and give indications of severity.

To date, the assessment of clinical trials of skin medications and products has been done in a subjective manner, using human judgement to determine whether skin is getting better or worse. The benefit of automating this task is that skin assessments will be more objective and the amount of data used can be greatly increased.

Optimisation and Filtering on Manifolds

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Keywords: signal processing; non-linear problems; optimisation problems; manifolds

Traditionally, the main tool in signal processing has been linear algebra. For non-linear problems, researchers have either devised clever transformations to make problems linear or have adopted an adhoc approach. However, recently it has been shown that it is possible to tackle non-linear problems directly using powerful mathematical methods including differential and algebraic geometry.

The main focus of this project is to determine ways for taking existing algorithms in Euclidean space, extending them to manifolds, taking non-linear problems in signal processing and developing systematic solutions to solve them. The outcomes to date include a new framework for solving optimisation problems on manifolds. Within this framework any optimisation algorithm (without memory) on Euclidean space can be transformed to a manifold and it can be shown that the local rate of convergence is the same on the manifold as it is for the original algorithm in the Euclidean space.

The potential benefits are that many problems in the real world are formulated, for example, on manifolds, indeed the collection of all rotations in three dimensions form a manifold known as the special orthogonal group. Being able to solve optimal and near optimal non-linear problems will have wide-ranging applications.

A Systems Engineering Approach to Neuroscience

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Collaborators: Shiro Ikeda (Institute of Statistical Mathematics, Japan), Mark McDonald (University of South Australia), Steven Petrou (Howard Florey Institute, Melbourne), Evan Thomas (Howard Florey Institute, Melbourne), Joel Bornstein (Physiology, The School of Medicine) and John Furness (Neurosciences Victoria)

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Keywords: systems engineering; neural engineering

This is a new project, which has received funding through the education infrastructure fund to set up a Centre for Neural Engineering. It aims to bring together researchers from the Faculties of Engineering, Medicine and Science, in line with the world-wide convergence of the physical and life sciences. The project seeks to take a cross-disciplinary approach to understanding how networks of biological neurons work. Specifically we want to use ideas from mathematics and systems engineering to try to determine: how the brain works; how to repair it when it goes wrong; and how to communicate with it, which will allow us to develop devices, such as the bionic eye.

Hydrocephalus Hydrodynamics: Realistic Numerical Modelling using Neuroimaging

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Sponsor: Early Career Researcher grant, The University of Melbourne

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Keywords: ventriculomegaly; numerical simulation; MRI ; neuroimaging

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.

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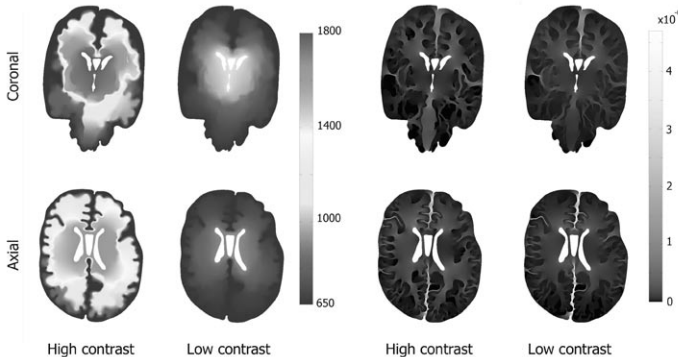


Fig. 1: Pressure [Pa] (a) and velocity [m/s] (b) fields for a coronal and an axial slice.

Tissue Distraction: A Novel Approach to Enhance Tissue Growth for Soft Tissue Engineering

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Sponsor: Australian Research Council

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Keywords: tissue engineering; tissue mechanics; cell proliferation; cell differentiation

All tissues have measurable characteristic mechanical properties and forces naturally experienced between the tissue cells and their extra-cellular matrix. If we alter the tension applied to tissues, precursor cells within the tissue can be stimulated to multiply, or to differentiate into a committed cell type. By replicating the mechanical properties of tissue inside our patented tissue engineering chamber and manipulating tissue tension, we have proof of the principle that tissue can be stimulated to grow faster. We believe these principles can be applied to many tissues and organs. This device has the potential to replace prosthetic devices, organ transplantation and many reconstructive surgical procedures.

Nonlinear Behaviour of Bubbles Subject to an Acoustic Field

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Sponsor: Commonwealth Scientific and Industrial Research Organisation (CSIRO)

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Keywords: targeted microbubbles; nonlinear behaviour of bubbles; acoustic field

Experiments will be conducted on the nonlinear behaviour of bubbles subjected to an acoustic field, utilising CMIT's new laboratory facilities. This involves 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.

Analysis of Non Linearity in Poincare Maps and Detection of Sleep Apnoea

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Keywords: Poincare plot; sleep apnoea; electrocardiogram

A Poincare plot is one of the important techniques used for visually representing heart rate variability. It is valuable due to its ability to display nonlinear aspects of data sequence. However, the problem lies in capturing temporal information of the plot, quantitatively. The standard descriptors used for quantifying a Poincare plot (SD1, SD2) measure gross variability of time series data. Determination of advanced methods for capturing temporal properties poses a significant challenge. In this area, we have developed a new efficient method to define asymmetry and modified the existing measures of asymmetry with respect to the new definitions. The resulting definition is shown to perform better than the earlier techniques using real life case studies in detecting pathology. A new descriptor for Poincare plots, uniquely representing the temporal variation, is currently under development.

Healthy sleep is an essential mechanism for maintaining good mental and physical health. An irregular breathing pattern during sleep causes daytime fatigue and impaired cognitive functioning leading to memory loss, hence easy and early detection of sleep disordered breathing is critical in maintaining good health. This project addresses a challenging problem in detecting sleep apnoea from electrocardiogram recordings. A novel multi-stage classification based on wavelet feature extraction is developed and is shown to perform better than the existing techniques. Efforts are being made to integrate the system with a portable ECG machine.

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Computational Methods for Protein Structure Prediction

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Keywords: protein structure; molecular biology; enterprise grids

Proteins are of primary importance to the normal functioning of a living organism. Understanding the way proteins function is arguably the most important aim of molecular biology. There has been a consensus in the molecular biology community that the function of protein depends on its three dimensional structure, therefore solving the three dimensional structure of a protein becomes a very important issue. Knowledge of protein structure helps us to understand the way proteins interact with other molecules and the way abnormal proteins function to cause disease. Abnormal function is due to change in the three dimensional structure of the protein. Efficient design of drugs (also protein) is only possible when we understand the structure of abnormal proteins.

Apart from efficient drug design, knowledge about protein structure helps us to understand the evolutionary relationships between proteins. This research is based on using an enterprise grid model, which will assist in the development of protein structure prediction algorithms developed by our group to be universally accessible. The development of computational methods in designing new drugs has improved the entire process in terms of quality and time taken to generate new drugs. This is essentially due to structure based drug design, which depends on knowledge of the three dimensional structure of diseased protein and the drug. Due to large improvements in computational methods for protein structure prediction, the time taken for rational drug design has dropped considerably.

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.

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Tumor Detection and Computer Based Medical Image Retrieval

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Keywords: breast cancer; tumor detection; medical image retrieval

Breast cancer is the most common cause of cancer-related death in Australian women. The risk of developing cancer before the age of 75 has risen to 1 in 9, from 1 in 11 in 2000. Encouragingly, the mortality rate fell by an average rate of 3% between 2001 and 2005. This is directly attributable to widespread screening and early detection, together with improved treatment techniques.

Radiation therapy is one of the most widely used therapies for lung cancer. Radiotherapy aims to deliver the necessary therapeutic dose of ionizing radiation to tumor tissue, while minimizing irradiation of normal tissue. To spare normal tissues, such as skin or organs, which radiation must pass through in order to treat the tumor, shaped radiation beams are aimed from several angles of exposure to intersect at the tumor, providing a much larger absorbed dose, than in surrounding healthy tissue. In order to ensure safe and effective radiotherapy treatment for tumors several factors must be considered, such as: accurate target or tumor

volume delineation; proximity of sensitive structures to the tumor; respiratory motion of the target and normal structures such as heart and lung; and presence of tissues with non-uniform densities, such as lung and bone, in the treatment volume. The main aim of this project is to develop a method that can accurately delineate a tumor and track it from lung PET images using calculated volume as a constraint. This will lead to accurate, fast and effective radiotherapy treatment planning. Specific objectives are to devise an automatic scheme to detect and track the tumor in lung PET images using Active Contour Models and to test the system on at least 25 patients; and to modify level set methods to choose appropriate termination criterion using wavelet features. Currently the system is being tested on cardiac gated images and extensions are being made to automatically analyse full body PET images.

Specific limitations of the current digital mammography systems for breast cancer are the inability of current systems to detect architectural distortion and bilateral asymmetry in mammograms. These are critical aspects of early screening for breast cancer. Current systems do not have the capability to learn from their mistakes (false positives and false negatives). This is mainly due to the absence of incremental learning methods and a retraining procedure that is very time consuming. Hence an incremental and adaptive learning scheme is a vital requirement in today's learning machines. In addressing these technical challenges and delivering new capabilities in low cost breast cancer screening systems, the project offers genuine commercial opportunities for industry partners to deliver locally produced technology, which can be commercialised for a global market.

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Studies of Polysomnographic Signals in Obstructive Sleep Apnoea

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Student: Chandan Karmakar

Collaborators: Neela Khan (Swinburne), Pasi Franti, (Finland)

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Keywords: sleep apnoea; polysomnographic signals

Obstructive sleep apnoea (OSA) is characterised by periodic hypoxia/reoxygenation owing to repetitive collapse of the upper airway during sleep. It is a serious disorder with increased risk of a large number of comorbid conditions. Polysomnogram (PSG) is the current gold standard in the assessment of OSA. In addition to signals from the brain, heart, eyes, nose and thoraco-abdominal sites, it also records surface submental electromyography (sSM EMG) signals. This research utilises sSM EMG signals, and revolves around the neurological characterisation in general, and myoneural perturbations, in particular, during differing stages of this diseased condition. A number of novel features uncovered are being evaluated, with the hope that some important pathophysiological causes of OSA severity will be discovered.

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Modelling and Simulation of Human Locomotion

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Sponsor: Australian Research Council

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Keywords: human locomotion; biomechanics of walking; modelling and simulation

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 support the body against gravity and provide forward propulsion 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 or which neural pathways are involved in feedback control, primarily because neural excitations and muscle forces cannot be measured directly. This applies to normal walking, and virtually nothing is known about neuromuscular control under other conditions, such as walking on inclines, walking up and down stairs and running.

This project will use biomechanical experiments and computational methods to quantitatively assess muscle function during human locomotion. The aim is to address the following questions:

1. Which muscles provide support, forward propulsion and stability during walking?
2. How does neuromuscular function change with gait modality (i.e. from normal walking to walking on inclines, walking up and down stairs and running)?

Computational Tools for Studying Gait Disorders in Children with Cerebral Palsy

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Sponsor: Australian Research Council

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Keywords: gait analysis; cerebral palsy; computational tools; childhood disability

Cerebral palsy (CP) is the most common cause of childhood disability in Australia and throughout the developed world. It results from damage to the brain at or around the time of birth, and as the child grows, leads to muscle and bone deformities that require surgery. Orthopaedic surgery for children with CP has improved greatly over the last 20 years, since

the introduction of non-invasive force and motion measurement techniques commonly referred to as gait analysis. Gait analysis has the capacity to evaluate the biomechanics of gait abnormalities and provide quantitative information on limb motion, ground reaction forces, and net joint torques. However, only half the children operated upon show clear benefits from the use of these measurements, and some get worse. This is because gait analysis provides very limited information on leg muscle function during walking. More sophisticated tools are required to determine muscle function and plan orthopaedic surgeries more precisely, so that the best possible results can be obtained for all patients.

The overall goal of this project is to combine data from gait analysis experiments with medical imaging and advanced computational modelling to improve the diagnosis and treatment of gait disorders in children with CP. A computer model of each patient's lower limbs will be built from high-resolution images of the muscles, bones, and joints acquired from magnetic resonance imaging (MRI). Gait analysis data recorded for each patient will be input into the patient-specific model and used to perform large-scale dynamic simulations of walking. Analyses of the model simulations will allow a quantification of leg muscle function on a patient-specific basis. This information will increase our understanding of the biomechanical causes of movement abnormalities in CP patients.

Evaluating Functional Performance of Total Knee Replacements in vivo

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Keywords: osteoarthritis; total knee replacement; biomechanics; gait analysis

Osteoarthritis is the leading cause of musculoskeletal pain and disability in our community and is a designated National Health Priority. Total knee replacement (TKR) surgery is the established treatment for end-stage osteoarthritis and is the most common joint replacement surgery performed in Australia and worldwide. Accurate knowledge of joint loading during functional activities, like walking, is critical for evaluating the functional performance of TKRs in vivo and for quantifying the effects of implant design and surgical alignment on TKR performance. Unfortunately, there is no direct method for measuring joint loading non-invasively in humans. This is because muscle forces contribute substantially to joint loading, and there is no method available for measuring muscle forces non-invasively.

The overall goal of this project is to combine patient-specific data from biomechanical gait experiments with medical imaging and advanced computational modelling to non-invasively evaluate the functional performance of TKRs in vivo. Time histories of muscle and joint loading for walking will be entered into a 3D, deformable, finite-element model of the TKR to determine joint contact pressures and stresses produced in the implant. This information will increase our understanding of the biomechanical performance of current TKR designs during functional tasks such as walking.

Designing the Next Generation of Hydrogel-Based Scaffolds for Soft Tissue Regrowth

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Sponsor: Melbourne University (Growing Innovation Fund)

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Keywords: hydrogel-based scaffolds; soft tissue engineering

This project will provide a timely and unique opportunity to develop biodegradable and biocompatible hydrogel-based 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. The technology developed in this project will make a significant contribution to biomaterial science and manufacture in Australia.

This project synthesises a biocompatible and biodegradable hydrogel with desirable properties for tissue engineering applications including: good mechanical strength; non-toxic nature to biological environment; and interconnected and appropriate pore sizes to promote cell proliferation.

The following figure shows the results from two weeks of an *in vivo* trial. It was evident that no major inflammation had occurred. The formation of tissues and blood vessels within the interconnected pores of the hydrogels was observed. This indicates that the hydrogels with improved and interconnected pores have promoted the regeneration of new tissues.

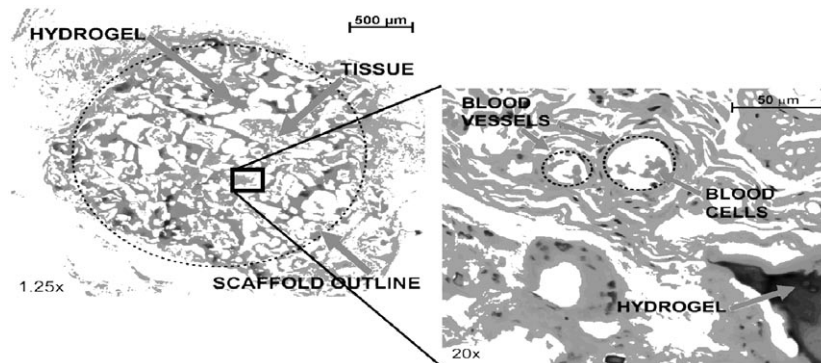


Fig. 1: Images from hydrogels stained with Hematoxylin and Eosin (H & E) after two weeks of an *in vivo* trial.

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Hamstring Muscle Biomechanics During Sprinting

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Keywords: hamstring muscle strain injuries; biomechanics; musculoskeletal modelling

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, for example, 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.

The first objective of this research program was to analyse a unique dataset captured from a single subject while walking, jogging and sprinting in a laboratory, prior to, and immediately following, a right hamstring muscle strain injury. The details of the case history, along with preliminary analyses relating to joint kinematics and inverse dynamics, have been published [1, 2]. Recently, this data was entered into a computer-based musculoskeletal model to calculate hamstring muscle force, velocity and power pre and post injury. Results are displayed in Fig. 1.

The second objective is to collect experimental data (joint kinematics, ground reaction force and muscle activity) from a large cohort of subjects across the full spectrum of locomotion speeds (walking through to maximal sprinting). Such data will be used to determine the effects of increasing running speed and gender, on hamstring muscle biomechanics (muscle length, velocity, force, power and work done). The program will involve a joint collaborative venture between the Department of Mechanical Engineering at the University of Melbourne and the Sports Science Sports Medicine Department at the Australian Institute of Sport. Outcomes will have significant clinical implications for the development of effective rehabilitation and prevention strategies for hamstring muscle strain injuries.

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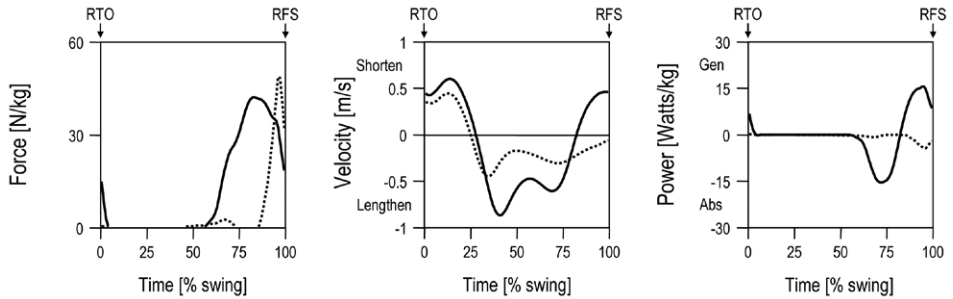


Fig. 1: Hamstrings force (left panel), velocity (middle panel) and power (right panel) during sprinting ($\sim 7\text{m/s}$), time normalised as a percentage of the swing phase. Data are for the right leg for a single representative pre-injury trial (solid line) compared to the injury trial (dotted line). RTO, right toe-off; RFS, right foot-strike. Positive hamstrings muscle-tendon velocity represents shortening; negative hamstrings muscle-tendon velocity represents lengthening. Positive hamstrings muscle-tendon power represents generation (Gen); negative hamstrings muscle-tendon power represents absorption (Abs).

Algorithms for Analysis of Genomic Data

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Keywords: genomic sequences; pattern detection; structural pattern matching

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.

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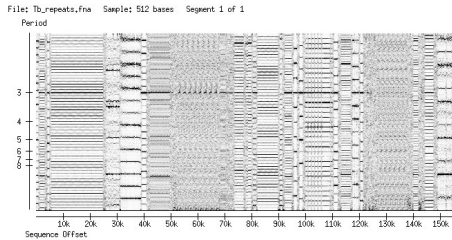


Fig. 1: Visualisation of repetitive regions in *T. brucei* genome using Fast Fourier Transform.

Investigation of the Functional Role of IGFBPs in Modulating the Uptake of Growth Factors by Biological Tissues

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Keywords: IGF-I; IGFBPs; degradation; concentration of growth factors

Insulin-like growth factors (IGF-I and -II) belong to a family of peptide hormones that regulate cell growth and development. IGF is produced by the liver, resulting in tissues being bathed in a constant background concentration of IGF throughout the body, in different tissue concentrations. Recent studies have suggested that the proteolysis of Insulin-like Growth Factor Binding Proteins (IGFBP) may contribute to the exposure of a tissue to IGFs. For example, the degradation of IGFBPs by their proteases (e.g. matrix metalloproteases) could potentially change the ratio of IGFBPs for IGFs, and thereby may change the bioavailability of free IGFs to IGF receptors. However, the actual functional roles of IGFBPs in modulating IGF uptake in a biological tissue are still not fully understood or quantified due to the limitation of current experimental techniques either in vitro or in vivo. Therefore, the purpose of current study is to conduct a series of "mathematical experiments" to explore the roles of a range of key factors related to IGFBPs (e.g. diffusivity, degradation rate, and binding affinity) in regulating the free IGF concentration in biological tissues.

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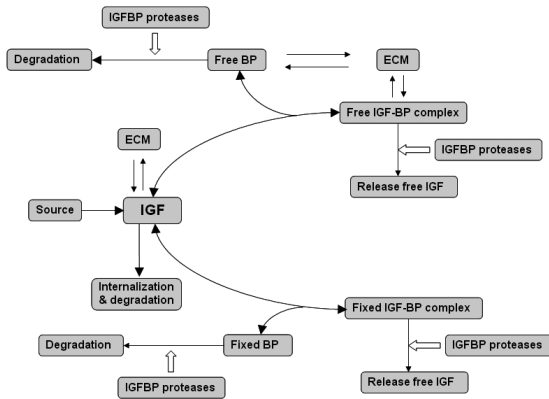


Fig. 1: Model of potential functional roles of IGFBPs on actions of IGFs. The majority of IGFs are contributed by synovial fluid. The bioavailability of IGFs is widely thought to be regulated by IGFBPs (either free or bound in ECM). IGFBP proteases degrade IGF-BP complexes, resulting in releasing of IGFs.

Understanding the Roles of Physical Activities in Cartilage Homeostasis

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Keywords: cartilage behaviour; arthritis; computer modelling

Nearly one in five Australians (approximately 3.85 million) have arthritis and more than 60% of these people are of working age. The understanding of cartilage behaviour in vivo is challenging, but absolutely vital to the maintenance of healthy cartilage and improvement of the repair process. The central aim of this project is to develop a computational state-of-the-art model to understand the cartilage microenvironment in vivo in a large variety of physical activities and induced joint motions undertaken in daily life. The research outcomes may help to reduce the risk of cartilage damage by overuse, and identify new strategies for cartilage recovery by employing adequate physical therapies.

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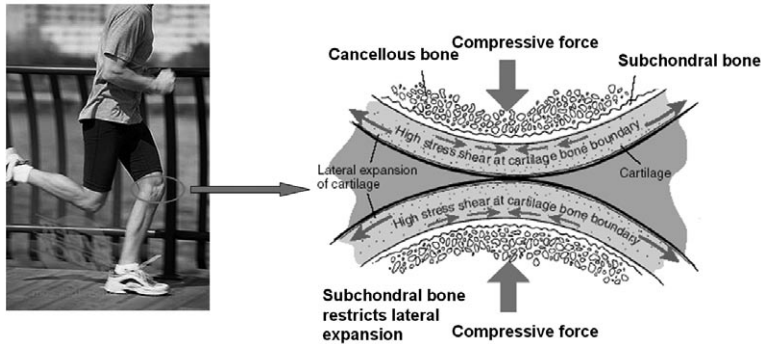


Fig. 1: The composition and structural properties of cartilage allow it to provide a smooth, low-friction and wear resistant bearing. In vivo chondrocytes regulate cartilage homeostasis by responding to their chemical and mechanical 'microenvironment'.

Classifying Microarray Data using Gene Sets

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Keywords: gene expression microarray; analysing gene sets; machine learning; breast cancer

Recent technologies, such as gene expression microarray, measure the expression of tens of thousands of genes in tissue specimens. Many studies have used this data to find interesting associations between genes and their phenotypes, such as cancer and metastasis. The results are lists of genes which are highly associated with the phenotype and can be used for predicting patient outcomes, for example, which breast cancer patients are at higher risk of metastasis. At the same time, different studies of the same cancers

result in different lists of genes, indicating that large numbers of genes are associated with this phenotype. Genes do not work in isolation, but form highly-interconnected networks. Therefore, it has been suggested that the reason for the differing gene lists is that they represent the same underlying biology, and are in more agreement than is otherwise apparent. These results have sparked a growing interest in examining genes as sets or networks (pathways) rather than individually.

The aim of this research is to continue moving away from examining single genes, towards using biologically meaningful sets of genes, which can be used both for clinical prognosis of patients, and to provide insight into the underlying biological mechanisms of cancer. We are comparing different approaches to analysing gene-set information, and to using knowledge of the network structure to guide the process of finding meaningful and consistent associations with metastasis. The approach is applied to breast cancer microarray data, trying to classify patients according to their risk of metastasis. Results so far indicate that we can find gene sets that are as predictive of metastasis as lists of genes, but are stable across different datasets, and represent known biological processes related to cancer, such as the cell cycle process.

DNA Sequence Assembly of Short Read Data

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Keywords: DNA sequencing; high-throughput sequencing; DNA assembly

New DNA sequencing techniques have revolutionized the field of molecular biology. The speed and low costs of new sequencing platforms make the technique broadly available, opening new possibilities for research and application, but they also pose new challenges. Fragments of data are smaller and less accurate than those of traditional techniques, which makes the process of assembling or mapping them a huge computational challenge, or even unsolvable. In addition, the characteristics of these data are widely unknown – the chemical process of preparing and reading the DNA fragments is highly complex and potential biases for or against certain patterns unknown.

This project deals with a general analysis of the difficulties of the assembly process. We assess the quality of output of available programs and try to determine a set of necessary parameters to obtain good results and the general strengths and weaknesses of these tools. Approaching the field from another direction, we assess the quality of the sequencing data itself and assess the general assumptions made about it. The project focuses on taking the results and optimising the usage of information contained in the data and thus the overall assembly quality.

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Efficient Algorithms for Specialised Search in Biomedical Data

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Keywords: DNA; genomic datasets; compression algorithms

New sequencing activities are leading to changes in the kinds of genetic data that are being gathered and stored. The falling cost of high throughput sequencing is enabling more ambitious activities such as the 1000 Genomes Project, which aims to sequence DNA from at least one thousand humans to obtain a more accurate understanding of human genetic variation. Similar projects are proposed for other organisms and other human variations, such as cancer genomes.

These activities are leading to massive growth in the size of DNA datasets, motivating investigation into techniques for effective compression. They are also providing opportunities for novel compression techniques that take advantage of the characteristics of this new data. In particular, the potential for high level of similarity between sequences introduces a high level of redundancy. The aim of this research is to exploit the redundancy to achieve space savings as well as to create more efficient search and alignment algorithms for large DNA datasets.

We have created a DNA compression algorithm known as COMRAD that is able to efficiently detect and compress the redundancy in large datasets. Using this method, we were able to compress the largest datasets so far to be attempted by a DNA compression algorithm (a dataset of 1023 mutated copies of the chicken genome amounting to approximately 130Giga-bases) with promising results [1].

We plan to extend the redundancy detection method into improving the efficiency of search algorithms for large DNA datasets as well as for sequence clustering and alignment algorithms.

Genomic Data Sharing and Compression

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Keywords: genomic data; compression techniques

Transmission of genomic data creates a significant bottleneck in sharing new information from international research collaborations. Advances in genome sequencing automation and the advent of personalised genome sequencing for clinical use are expected to generate genomic data at an accelerating rate.

We are investigating ways to reduce the size of genome data transmissions by exploiting the similarity with data already held by both receiver and sender, which share large quantities of common information. One line of investigation is extending generic encoding and compression techniques to overcome memory limits and improve efficiency of coding with respect to a multi-terabyte data collection. Also, we are investigating search methods to identify existing data in a collection which are highly similar to a target file and would yield improved compression using existing techniques.
