

## Joint appointments at the IMB

### RESEARCH FOCUS

The purpose of joint appointments is to foster collaborations in teaching, research and related activities between the IMB and Schools of The University of Queensland. Joint appointments involve a split in salary between the IMB and the relevant UQ School, and a joint appointee's commitment to the research and teaching activities at the IMB is greater than that of affiliate appointees. Joint appointees participate in all Institute activities including laboratory research, supervision of research higher degree students, and attendance at seminars, Divisional meetings and IMB Group Leader retreats.

### Research Group Leaders

Alan Mark  
Geoffrey McLachlan

## Molecular dynamics of biomolecular systems

The group, with members based both at The University of Queensland (UQ) and the University of Groningen (RUG), The Netherlands, concentrates on modelling the structural and dynamic properties of biopolymers such as proteins, nucleic acids and lipid aggregates. In particular, we use computer simulations to understand and predict the macroscopic (experimentally observable) behaviour of complex biomolecular systems based on the interactions between atoms. We develop the software, atomic force fields and theoretical models needed to address a range of fundamental questions.

First, how do proteins fold? Understanding how proteins fold is one of the grand challenges of modern biology and a critical test of our ability to accurately predict interactions in protein systems. The failure of proteins to fold correctly is also linked to a range of debilitating diseases including Alzheimer's Disease, BSE and some forms of Type II diabetes where misfolded proteins form destructive aggregates called amyloid fibrils. Currently, it is not possible to directly simulate the folding of proteins in atomic detail. Dramatic progress has, however, been made in the de novo folding of small peptides and the refinement of some proteins. Research on folding is conducted at multiple levels. Small model systems are used to refine force fields and simulation techniques. On a larger scale we are simulating how multiple copies of certain peptides aggregate in order to understand how amyloid fibrils form.

Second, how do cell surface receptors transmit a signal through the cell membrane? Receptor proteins of the surface of cells play a vital role in cellular communication. However, little is known in regard to the mechanism by which the binding of a molecule to an extracellular receptor transfers a signal across the cell membrane or even how changes in the environment can activate certain cell surface receptors. On one hand we are investigating the mechanism by which low pH triggers

the activation of the Dengue E protein, which plays a critical role in the entry of the virus into cells. We are also investigating the structural changes associated with the binding of human growth hormone to the growth hormone receptor.

Third, how do membrane proteins assemble? Cell membranes are the archetypal self-organised supramolecular structure. Membrane protein complexes also represent a new frontier in structural biology. Using simulations, we are able to directly investigate how bilayers and vesicles form. We are also investigating the assembly of functional structures such as the assembly of anti-microbial peptides into transmembrane pores. This in turn is being used to understand the mechanism by which larger complexes form in heterogeneous environments.

### RESEARCH PROJECTS

- Simulating peptide folding and assembly
- Pore-forming peptides as models for protein assembly
- The nucleation and growth of amyloid fibrils
- Mechanism of activation of the human growth hormone receptor
- New methods in drug design

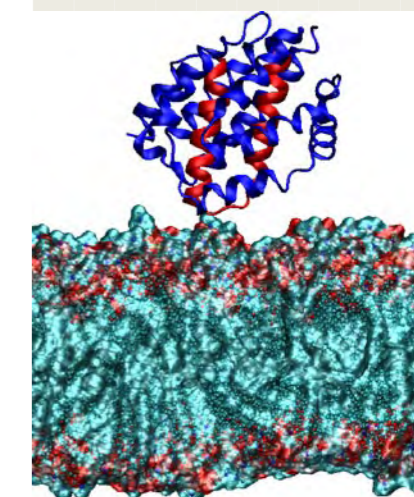
### KEY PUBLICATIONS

van Gunsteren, W.F., Dolenc, J., and Mark, A. E. (2008). Molecular simulation as an aid to experimentalists. *Current Opinion in Structural Biology* **18**: 149-153.

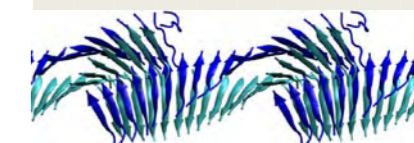
Wassenaar, T.A., Quax, W.J., and Mark, A.E. (2008). The conformation of the extracellular binding domain of Death Receptor 5 in the presence and absence of the activating ligand TRAIL: A molecular dynamics study. *Proteins: Structure, Function, and Bioinformatics* **7**: 333-343.



ALAN E. MARK



The initial stage of the binding of the pore-forming toxin Colicin to a model membrane.



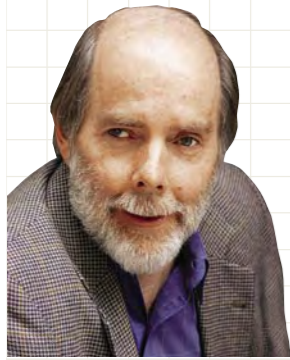
The lateral assembly of the amyloid-forming peptide SUP-35.

### LAB MEMBERS

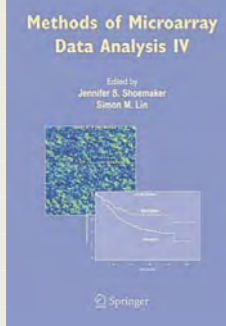
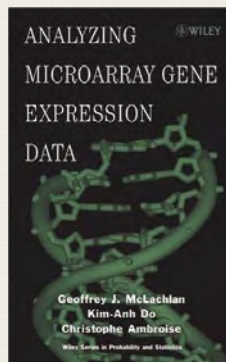
**Research Officers:** Dr David Poger (UQ), Dr Itamar Kass (UQ), Dr Aldo Rampioni (RUG), Dr Semen Yesylevskyy (RUG), Dr Alpesh Malde (UQ), Dr Maria Ratajczak (UQ), Dr Zuo Le (UQ)

**Administration:** Sophie Turner (UQ)

**PhD/Masters Students:** Ajinkya Joshi (UQ), Matthew Breeze (UQ), Daniela Mueller (RUG), Ying Xue (RUG), Jelger Risselada (RUG)



GEOFFREY MCLACHLAN



Covers from books to which Professor McLachlan has contributed.

## Applied statistics and bioinformatics

My research in applied statistics is in the related fields of classification, cluster and discriminant analyses, data mining, image analysis, intelligent systems, machine learning, neural networks, and pattern recognition, and in the field of statistical inference. The focus in the latter field has been on the theory and applications of finite mixture models and on estimation via the E(expectation)-M(maximization) algorithm.

I am also actively involved in the field of bioinformatics with the focus on the development of methods and software for the analysis of data from high-throughput genomics projects, with particular emphasis on gene-expression profiles. The limitations of conventional methods of cancer classification and diagnosis based on the site and appearance of the tumour or organ are well-known. With microarrays allowing genome-scale measures of gene expression, attention has turned to using differences in the activity of the gene expressions (gene profiling) to classify and diagnose tumours. However, the complexity of tumours makes it likely that a diagnostic test will be based on marker profiles rather than individual markers. But the identification of relevant subsets of the genes has its challenges, because typically thousands of gene expression levels are available from only tens of patients. It means that off-the-shelf methods of statistical analysis cannot be implemented, at least not without serious modifications. Thus, there is a need for new methodologies to be able to process thousands of genes with the aim of finding those genes that are biologically heterogeneous and therefore potential markers for cancer type, treatment therapies, or clinical outcomes.

### RESEARCH PROJECTS

- Statistical modelling via finite mixture models, including methods for the detection of differentially expressed genes in different treatment classes or in time-course studies

- Analysing the statistics of microarray gene-expression data for the development of disease diagnostics
- Developing diagnostic methods for cancer, using multiple molecular indices in conjunction with clinical factors
- Developing statistical methodology for the next generation of high-throughput technology with fast sequencing platforms

### KEY PUBLICATIONS

McLachlan, G.J., *et al.* (2008). Clustering of microarray data via mixture models. In *Statistical Advances in Biomedical Sciences: Clinical Trials, Epidemiology, Survival Analysis, and Bioinformatics*, A. Biswas, *et al.* (Eds.). Hoboken, New Jersey: Wiley, pp. 365-384.

McLachlan, G., *et al.* (2008). Clustering. In *Bioinformatics, Vol. 2: Structure, Function, and Applications*, J.M. Keith (Ed.). Totowa, New Jersey: Humana Press, pp. 423-439.

McLachlan, G.J., and Krishnan, T. (2008). *The EM Algorithm and Extensions*. Second Edition. Hoboken, New Jersey: Wiley.

Wu, X., Kumar, V., Quinlan, J.R., Ghosh, J., Yang, Q., Motoda, H., McLachlan, G.J., *et al.* (2008). Top 10 algorithms in data mining. *Knowledge and Information Systems* **14**: 1-37.

Zhu, J.X., McLachlan, G.J., *et al.* (2008). On selection biases with prediction rules formed from gene expression data. *Journal of Statistical Planning and Inference* **38**: 374-386.

Baek, J., Son, Y.S., and McLachlan, G.J. (2007). Segmentation and intensity estimation of microarray images using a gamma-t mixture model. *Bioinformatics* **23**: 458-465.

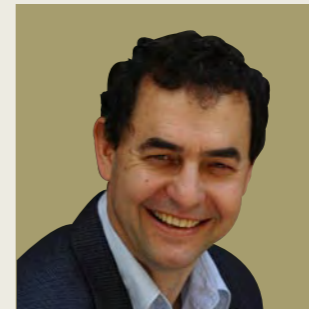
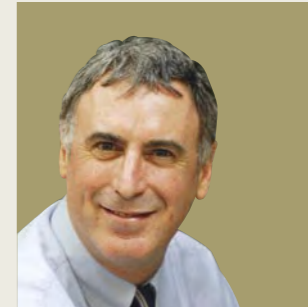
McLachlan, G.J., *et al.* (2006). A simple implementation of a normal mixture approach to differential gene expression in multiclass microarrays. *Bioinformatics* **22**: 1608-1615.

### LAB MEMBERS

**Research Officers:** Dr Kim-Anh Le Cao, Dr Lloyd Flack

**PhD Students:** Justin Zhu, Katrina Monico, Leesa Wockner

## AFFILIATE APPOINTMENTS



The purpose of affiliate appointments is to foster collaborations in teaching, research and related activities between the Institute for Molecular Bioscience (IMB) and Schools at The University of Queensland. Affiliate appointees to the IMB contribute through active involvement with relevant IMB Groups, facilities or research programs and through joint supervision of research higher degree students. Affiliate appointees contribute to the intellectual life of the Institute through attendance at IMB seminars, Divisional meetings and IMB Group Leader retreats. Salary for affiliate appointees is paid by the relevant University of Queensland School.

### PROFESSOR MATT BROWN

Diamantina Institute for Cancer, Immunology and Metabolic Medicine

### PROFESSOR IAN FRAZER

Diamantina Institute for Cancer, Immunology and Metabolic Medicine

### ASSOCIATE PROFESSOR STUART KELLIE

School of Molecular and Microbial Sciences

### PROFESSOR BOSTJAN KOBE

School of Molecular and Microbial Sciences

### ASSOCIATE PROFESSOR FRED MEUNIER

Queensland Brain Institute

### ASSOCIATE PROFESSOR JOE ROTHNAGEL

School of Molecular and Microbial Sciences

### PROFESSOR ISTVAN TOTH

School of Molecular and Microbial Sciences

### DR JON WHITEHEAD

Diamantina Institute for Cancer, Immunology and Metabolic Medicine

### ASSOCIATE PROFESSOR PAUL YOUNG

School of Molecular and Microbial Sciences