Project title:	**Developing Mathematical Modelling Techniques to Determine Protein Structure**
Project duration:	Up to 8 weeks (between 4 – 8 weeks)
Description:	This research project will develop mathematical methods to determine protein structure using a set of experimental distance constraints measured between pairs of spin labels attached to a protein of interest. The experimental data is already available for a Non-Ribosomal Peptide Synthetase (NRPS), and our interest in this system is to understand how its structure-function relationship enables it to produce antibiotics – a very important goal for medical applications. The project will generate a large set of trial NRPS structures in silicon which will be spin labelled in silicon and the set of distance distributions between the spin labels computed and stored. This data will then be fitted to the corresponding experimental distance distributions to define an optimal set of structures for the NRPS protein. To determine the optimal set regularisation techniques will be examined, for example, $A(\mathbf{p}) = \Sigma\,\|(\mathbf{y}_{exp}-\underline{\mathbf{Y}}_{sim}.\mathbf{p})\|^2$, (Eq. 1) where $\mathbf{y}_{exp}$ are the experimental distance distributions, $\underline{\mathbf{Y}}_{sim}$ is a matrix of distance distributions generated from the trial protein structures, and **p** is the population probability of each conformation. As this is an under-determined problem, meaningful solutions can only be obtained by imposing additional regularisation constraints, $Q = A(\mathbf{p}) + \lambda R(\mathbf{p})$, with $p_i \geq 0$ (Eq. 2) where λ is a Lagrange multiplier that defines the relative weight of a regularisation function. In the case of a maximum entropy approach, $R(\mathbf{p}) = -\Sigma p_i \log(p_i)$, where it is shown that minimizing the objective function Q (eq. 2) with respect to **p** produces a unique significant solution. ***About the EPR group:*** Associate Professor Jeffrey Harmer is a principal research fellow and Electron Paramagnetic Resonance Group Leader at the Centre for Advanced Imaging. His research focuses on the development and application of Electron Paramagnetic Resonance (EPR) spectroscopy to determine molecular structure, dynamics and function of molecules containing unpaired electrons (paramagnetic materials). A main focus is understanding the structure and function of proteins. Alongside experimental data, the group works on computation methods to determine structural models of proteins by e.g. combining molecular dynamics simulation with experimental distance constraints measured by EPR on spin labelled proteins.

Expected outcomes and deliverables:	The candidate will gain basic laboratory skills, as well as skills in both electrospray ionisation (ESI) and matrix assisted laser desorption ionisation (MALDI) based mass spectrometry, mass spectrometry imaging, proteomics, enzyme assays, histology, and light microscopy. The candidate will gain basic skills in running a magnetic resonance spectrometer, as well as skills in structural biology, molecular modelling, methods of optimisation and computer programming with Matlab.
Suitable for:	This project would suit someone interested in mathematical modelling and computer programming (we use MatLab). It would be an advantage but not essential to have Biophysics knowledge.
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