Complexity Science mini-project proposal 2010-11

Project title: Modelling antibody binding to antigens immobilised on a surface and application to Surface Plasmon Resonance experiments

Project outline

Background: A strategy of increasing live donor transplantation for renal failure faces the problem of patients with preformed donor-specific antibodies. Traditionally a positive crossmatch vetoes the transplant. However, pretransplant antibody removal can now be used to overcome this barrier [1], but this is immunologically very high risk, with early rejection and dysfunction being characteristic. In order to manage this risk, a better understanding of how much antibody a transplant can tolerate, what antibody types are important when considering rejection, and how these are modulated by the transplant process and immunosuppression is needed. Characterisation and identification of rejection risk in individual patients will allow tailored immunosuppression and improved risk management. To be able to tackle these issues it is necessary to quantify antibody binding characteristics associated with transplantation, rejection and immunosuppression [2].

In order to quantify antibody binding characteristics it is necessary to determine reaction constants (such as binding affinity) from quantitative measurements of the underlying biological process. Surface plasmon resonance (SPR) provides convenient real-time measurement of the reaction that enables subsequent estimation of the reaction constants. Three mathematical (ODE-based) models are typically applied to represent the binding reaction between an analyte in a flow and an immobilised surface receptor; these are: the Langmuir model, which models the reaction as though it were between two well-mixed substrates; a modified Langmuir model that incorporates the effects of transport [3]; and the Effective Rate Constant approximation, which can be derived from consideration of the fluid dynamics of the analyte in the flow and the receptor layer, and the subsequent binding [4]. The latter model enables quantification of the error associated with a lumped (ODE-based) approach compared with a distributed (PDE-based) fluid dynamics approach.

In order to be applicable in a clinical diagnostic setting it is necessary to be able to quantify binding kinetics of a heterogeneous sample; that is, a sample that contains an unknown number of types with different (unknown) binding rates. For example, human serum contains *polyclonal antibodies* of different types (e.g., IgG, IgA, IgM, IgD, IgE).

Objectives: The principal objective is to determine the most appropriate modelling approach for considering heterogeneous binding reactions involving antibodies, in order to be able to provide (ultimately) reliable and robust estimates for binding affinities and/or characteristics in human serum from SPR. To achieve this, a suitable mathematical representation of the experiment will be derived from consideration of the fluid dynamics of the analyte with the reaction taking place on the boundary.

What the student will do: The student will assess (homogeneous) modelling approaches from the literature and compare them to the models typically applied by software provided with SPR platforms. The most appropriate form of model will then be extended in order to account for the heterogeneity in binding kinetics inherent in polyclonal antibody samples. All models considered must then be analysed with respect to the available measurements in order to determine *a priori* to what extent binding affinities can be uniquely determined. This *structural identifiability analysis* [5] relates to the uniqueness of the mapping from model parameters to *measured* model response (the part of the model to be compared with the experimental data).

In light of the results from the structural identifiability analysis the models will be applied to experimental data provided by University Hospitals Coventry and Warwickshire. The quality and reliability of the parameter estimates will be assessed in the usual ways and an analysis of residuals will be performed to assess the quality of the model fits. Model fits will be compared in order to suggest which of the models is best suited to determining the antibody kinetics.

Scope for continuation: The project will limit itself in the early stages to *monoclonal* samples (ie antibodies of a single type and subclass), looking to extend to *polyclonal* samples (ie antibodies of a single type but different subclasses) by the end. Ultimately the project needs to be extended to reflect human serum, which comprises different antibody types (e.g. IgA, IgE, IgG, IgM), with multiple different subclasses of unknown contributions from each.

Typically for distributed parameter systems (i.e., those modelled using PDEs) a numerical analysis is performed in order to approximate a truly structural identifiability analysis, which is inherently symbolic in nature (i.e., carried out respect to generic parameters rather than specific numerical values). Truly structural approaches are needed and an opportunity exists to consider this problem.

References: [**1**] R. Higgins et al. *Transplantation* **84**:876–884, 2007. [**2**] R. Higgins et al. *Transplantation* **87**:882–888, 2007. [**3**] D. Myszka et al. *Biophys. J.*, **75**:583–594, 1998. [**4**] D.A. Edwards. *B. Math. Biol.*, **63**:301–327, 2001. [**5**] J.A. Jacquez. *Compartmental Analysis in Biology and Medicine* (BioMedware), 1996.