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GLOBAL *A PRIORI* IDENTIFIABILITY OF MODELS OF FLOW-CELL OPTICAL BIOSENSOR EXPERIMENTS

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Ideally, a parametric model for a biological system enables prediction of system behaviour for conditions where we lack observations. This necessitates first estimating parameters from some limited data series subject to random error, that is, solving an 'inverse problem'. A solution is some parameter vector that optimises an objective function. For example, a solution may minimise a sum of squared errors. Multiple (equally valid) solutions may result in unresolvable uncertainty over which is the actual parameter vector.

This is problematic as predictions for a system's observable features—and the unobservable 'state variables' influencing these—may vary drastically with the parameter vector employed. Hence, we cannot confidently use our model to predict system behaviour. Consequently, the effort and resources expended in collecting data provide no benefit.

We may anticipate this problem prior to data collection. We achieve this by testing the combination of a model and proposed experimental conditions for the property of (global *a priori*) identifiability. Testing occurs in an idealised setting which assumes that an infinite, error-free data record is available. It determines those parameter vectors for which model output exactly reproduces such 'idealised data'.

Commonly, errors do not provide information on the model parameters. In this case, it is almost certain that the inverse problem's solution set cannot be smaller than that found by the identifiability test. That is, if the test returns uncountably infinitely many solutions, we are almost guaranteed an uninformative study. A test returning a

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unique solution shows the diametrically opposite outcome; it is at least possible for proposed experiments to yield a decisive result.

Our interest in identifiability pertains to the modelling of flow-cell optical biosensor experiments. These indirectly monitor the formation and dissociation of complexes of biochemical species. Experimentalists use data with an assumed model for the estimation of parameters representing rate constants.

Often experiments have multiple stages, delineated by an abrupt change in experimental conditions. Accordingly, in certain situations, experimental data is suitably modelled by a type of linear switching system (LSS). As experiments indirectly measure the transfer of mass between forms, and this mass is conserved, suitable models are also 'compartmental'. There is a scant literature on testing LSSs for identifiability, in particular for those which evolve in continuous-time.

Our application leads us to focus on the analysis of continuous-time uncontrolled compartmental LSS of one switching event (ULSS-1). These may suitably model data from a common ('kinetic') type of biosensor experiment having two stages. We propose an appropriate definition for the identifiability of ULSS-1 models and proceed to formulate approaches to testing these for the property. Through use of the symbolic algebra capabilities of Maple^{TM}, the theory we develop is able to classify each of three test cases. The first two test cases are alternative models for data resulting from the 'simple bimolecular interaction' mechanism. Our results demonstrate the influence of the parameterisation and experimental conditions used in model formulation on the classification obtained. The third—and most complex—test case models data obtained under the 'two-state conformational change' mechanism. Our methods result in the first classification of this model.

The definitive classifications of the test cases demonstrate the viability of our methods for testing ULSS-1 models for global *a priori* identifiability. We give brief consideration to special cases of experiments for which appropriate models are classified more easily. We note future avenues for extension of our methods, including the consideration of experiments having three or more stages.

Some of the results of the thesis have been published in [1, 2].

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