Sensitivity Analysis in Systems Biology Research: New Perspectives and Considerations

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Utilising ordinary differential equation (ODE) models within systems biology (SB) allows for a more comprehensive representation of biological systems and their dynamics on a global scale, which may not be feasible with higher-order representations. By "global-scale dynamics," we refer to the ability of ODE models to capture the behaviour of entire biological systems over time, considering interactions across multiple scales—from molecular to cellular, and even organ-level processes [1]. For instance, an ODE model of the cardiovascular system might simultaneously account for the dynamics of heart muscle contraction, blood flow through arteries, and the regulation of blood pressure by the nervous system. This integrated approach enables researchers to understand how changes at the molecular level, such as alterations in ion channel function, can affect overall heart function and lead to systemic conditions like hypertension or heart failure. SB research in recent years has focused on the personalisation of these models in order to negate the need for invasive tests and predict patient outcomes.

The personalisation process utilises ODE models as virtual representations of specific biological processes [2], such as predicting a patient's metabolic response to a meal, personalising medical treatment based on tumour growth, or identifying cardiac pathophysiology through abnormal parameter values. The personalisation problem has gained popularity alongside the rise of the "digital twin" concept [3]. In drug discovery and the development of less invasive medical tests, the ability to personalise ODE models to inform medical decisions and predictions is increasingly crucial. With the adoption of such practices in the medical field, it is essential to quantify the uncertainty associated with any information inferred from these models. In the personalisation problem, the focus is often on a select set of model outputs that correspond to the available experimental data, which are used to calibrate the model parameters. In order to identify which parameters can be used to inform medical decisions one often performs a global sensitivity analysis [4]. In doing this the influential input parameters present themselves which are responsible for causing the largest variation in the outputs. However, this talk examines if this is sufficient enough for personalisation.

Figure 1 is a proposal for the personalisation of a standard ODE based systems biology model which emphasises the recursive nature of the personalisation process. For example, once a personalisable subset of parameters have been obtained, if said subset does not contain the biomarkers (input parameters), one must work with clinicians to establish what additional data can be obtained for a patient and thus GSA and subset selection can be iterated. In order to obtain a subset of input parameters which are likely to be identifiable. From figure 1 we propose that the personalisation process should be a largely offline process to obtain the best case personalisable set of input parameters. This stage is informed by GSA and subset selection methods. Then one performs an uncertainty analysis to examine if the parameter bounds prescribed are sufficient. Once we subsequently begin to constrain the model with experimental data, to personalise the model, this stage involves the optimisation and calibration of the model parameter values. Also, one can then begin to examine the practical identifiability of the model parameters which allows one to examine the uniqueness of the personalisable subset of model parameters given noisy clinical data.

The proposed workflow below defines a novel approach to quantifying the uncertainty associated with systems biology.

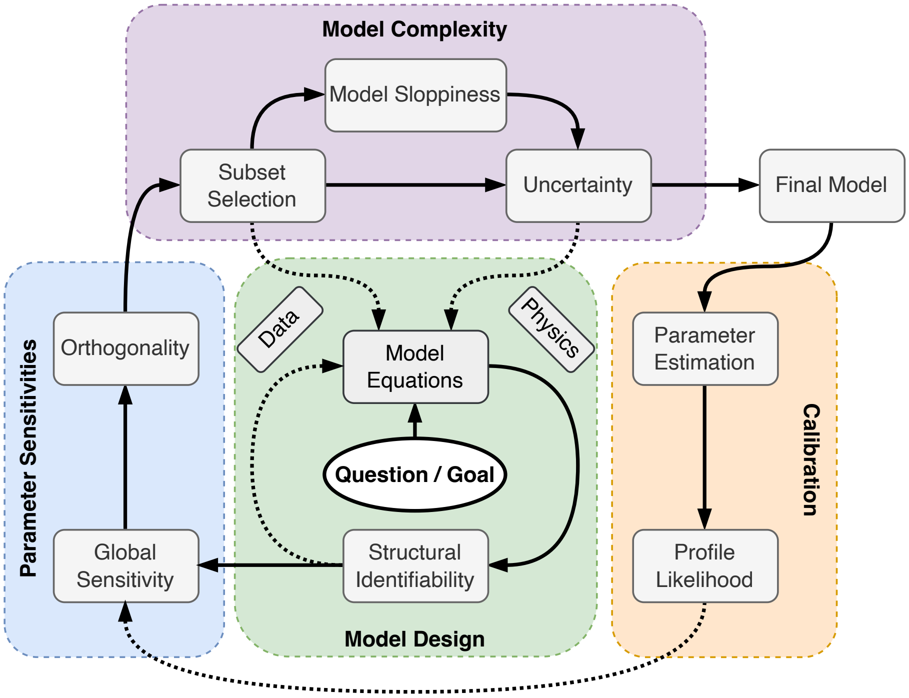

Figure 1: **The Personalisation Process**: Schematic highlighting the vital uncertainty quantification and sensitivity analysis stages involved in the personalisation of a systems biological model.

Conclusion/Main Contribution

In this talk, we propose and evaluate an extended workflow, centred on performing a comprehensive global sensitivity analysis, to improve the personalisation of models of systems biology. We compare this novel approach with previous personalisation methodologies, emphasising new considerations and highlighting the importance of offline model investigations involving global sensitivity analysis to ensure that the identified parameters are both identifiable and experimentally informative. The talk concludes with a discussion of the key challenges associated with sensitivity analysis in systems biology research.

References:

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