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Identifiability analysis in enzyme kinetics using profile likelihood

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The aim of this research was to explore the potential of profile likelihoods for identifiability analysis in the context of real enzyme kinetics data, collected ourselves.

Parameter identifiability concerns the question of whether the type of experimental data we have collected properly determines the parameters of our mathematical models. Identifiability issues arise because not all biological variables involved in the system can be measured, and even those that can be measured can be structurally decoupled from some of the parameters of interest. Although structural non-identifiability is in principle an all-or-nothing concept, in practice parameters may also be only weakly identified or may be practically non-identifiable given finite data. Profile likelihood has proven to be one of the few promising general methods of identifiability analysis that is applicable to multi-parameter, nonlinear problems, but it has not yet been widely adopted in the mathematical/computational biology community. Thus we sought to further explore its usefulness for typical models in this area, and using real experimental (as opposed to synthetic) data.

In this study, we collected data on the activity of the enzyme tissue plasminogen activator (tPA) under variety of scenarios, including different initial substrate and pH levels. We developed a series of simple reaction kinetics models, including both Michaelis-Menten velocity-concentration models and full time-dependent ODE models, and generated profile likelihoods under the various experimental conditions. For the simple Michaelis-Menten model we found that parameters were generally identifiable/weakly identifiable but tended to become less identifiable (approaching practical non-identifiability) at lower pH levels. On the other hand, individual parameters of the full ODE model of enzyme kinetics showed full structural non-identifiability. This led us to consider the identifiability of targeted 'interest' parameters, motivated by the parameters in the simpler system. Using this approach we found that certain combinations of rate parameters, corresponding to those in the simpler Michaelis-Menten model, were better identified in the full model.

Overall we found profile likelihood to be a promising technique for identifiability analysis of enzyme kinetics models. For complex models, however, choosing targeted interest parameters appears to be essential to avoid structural non-identifiability. Further work is needed on systematically motivating these interest parameters based on, for example, simpler models and/or model reduction procedures. In the context of tPA kinetics, more complex reactions involving the inhibitor neuroserpin and interactions of H+ ions with the enzyme should be considered.

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