Improved Enzyme Kinetics Model for Simulating Complex Biochemical Networks

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***Short Abstract* — Quasi steady-state enzyme kinetic models are commonly used in systems modelling. Current models require the reactant stationary assumption (also known as the low enzyme concentration assumption), which may not always be valid *in vivo*. We have developed the differential quasi-steady state approximation (dQSSA) kinetic model, which eliminates the reactant stationary assumption while only requiring two kinetic parameters to model irreversible enzyme action. We validated the dQSSA *in silico* and found that it is consistent with mass action kinetics and correctly replicated *in vitro* kinetics of the enzyme LDH. This presents an accurate method of modelling complex biological systems.**

***Keywords* — Systems Biology, Enzyme Kinetics, ODE Modelling, Biochemical Networks, Quasi-steady state assumption.**

I. Enzyme Kinetic Models

Enzyme kinetic models are integral parts of chemical kinetic models as many biochemical networks are enzyme mediated [1]. However, modelling of large networks leads to a high dimensionality model of many unknown kinetic parameters, which increases the amount of data required to tune unambiguously [2]. As such, the Michaelis Menten model is commonly as it simplifies the mass action model by reducing the required parameter number by one per reaction [3]. However, this model requires two assumptions: the quasi-steady state assumption and the reactant stationary assumption. These may not always be satisfied in complex biochemical networks under *in vivo* conditions.

The total quasi steady state approximation (tQSSA) model proposed by Tzafriri overcomes the reactant stationary assumption by using total concentrations as the state variable [4]. Which this approach is viable for the simplest biochemical networks, it becomes mathematically intractable to apply when an enzyme targets more than two substrates [5]. To address these issues, we set out develop an improved model that improves accuracy by overcoming the reactant stationary assumption [5].

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II. Results

The new dQSSA enzyme kinetic model was derived by explicitly modelling the complex concentration as functions of its constituent substrate and enzymes. The evolution of the complex concentration was then determined using a linearized form of the differential equation to avoid the use of simultaneous equations.

We found the dQSSA to replicate the mass action model when on a hypothetical complex network that includes negative feedbacks and substrates competitively targeted by multiple enzymes. Furthermore, we found the dQSSA and Michaelis Menten model to differ when predicting the kinetics of pyruvate to lactate reaction by LDH when NAD^+ is present. It was found that the dQSSA made the correct prediction, thus showing that the dQSSA is a model that is accurate enough to be able to replicate kinetic behaviors in *in vitro* scenarios.

III. Conclusion

The dQSSA is an enzyme kinetic model that can model complex biochemical networks with improved accuracy of *in vitro* scenarios by overcoming the reactant stationary assumption.

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