Title: *Describing saturation phenomena in models of regulated metabolic networks*

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Abstract:

Objectives: The dynamic modeling of biochemical networks constitutes a major challenge in systems biology. Saturation phenomena are ubiquitous features of these systems given the inherent biochemical processes such as enzymatic cooperativity and gene regulation events. Nonetheless until recently there was no straightforward and systematic way of addressing these aspects when using approximate modeling methods such as power-laws or the lin-log and the log(linear) formalisms.

We herein compare three different approaches of including saturations in models of regulated metabolism: power-laws in their piecewise formulation [1], mixed modeling with Hill functions embedded in power-laws, and the recently proposed Saturable and Cooperative formalism [2]. A benchmark artificial metabolic network [3] that includes feedback inhibition and feedforward activation regulation is used to establish comparisons regarding the mathematical maneuverability of the formalisms, their associated computational and numerical aspects and the possible biological insights given by the different approaches.

Results: The piecewice power-law method has the advantages widely acknowledged for these approaches although some interpretability is lost for the additional model parameters. The mixed modeling with embedded Hill functions is useful when *a priori* understanding exists on the saturable variables of the system and can have the advantages of the power-law formalism through recasting methodologies. The Saturable and Cooperative formalism allows better insights into the dynamic features of the networks through numerical simulation results.

Conclusion: The further development of mathematical formalisms and numerical tools that appropriately accommodate saturation phenomena is of major importance especially when creating integrative models for metabolic and regulatory networks.

References:

[1] Savageau M., *Alternative designs for a genetic switch: Analysis of switching times using the piece-wise power-law representation*. Math Biosci 2002. 180: 237-253

[2] Sorribas A., Hernández-Bermejo B., Vilaprinyo E., Alves R., *Cooperativity and Saturation in Biochemical Networks: A Saturable formalism Using Taylor Series Approximations*. Biotechnol Bioeng 2007. 97(5): 1259-1277

[3] Marino S., Voit EO., *An automated procedure for the extraction of metabolic network information from time series data*. J Bioinform Comp Biol 2006. 4(3): 665-691