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Describing saturation phenomena in models of regulated metabolic networks

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1 Abstract

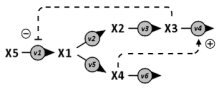
The dynamic modeling of metabolic networks constitutes a major challenge in systems biology. Saturation phenomena are ubiquitous features of there systems given the inherent biochemical processes such as enzymatic cooperativity and gene regulation events. Nonetheless until recently there was no straightforward and systematic way of addressing these aspects when using approximate modeling methods such as the power-law formalism. The further development of mathematical formalisms and numerical tools that appropriately accommodate saturation phenomena is of major importance especially when creating integrated models of biochemical networks.

2 Introduction

In this work we compare three different approaches for including saturations in models of regulated metabolic networks: hybrid modeling with Hill functions embedded in power-laws or power-laws in their piecewice formulation [Savageau MA 2002], and the recently proposed Saturable and Cooperative formalism [Sorribas A et al 2007]. We further compare these three approaches with the S-System framework. A benchmark artificial network that includes regulatory mechanisms of feedback inhibition and feedforward activation is used to establish comparisons regarding accuracy and dynamics prediction, model generalization capacity, mathematical maneuverability of the formalisms and possible biological insights given by the different approaches.

3 Methods

i) BENCHMARK NETWORK TO GENERATE 2 DATASETS

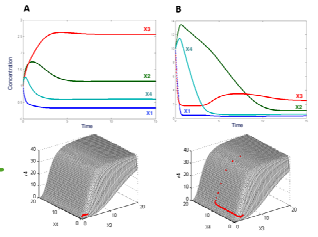


ODE Description:

$$\dot{X}_1 = v_1 - v_2 - v_5$$
$$\dot{X}_2 = v_2 - v_3$$
$$\dot{X}_3 = v_3 - v_4$$
$$\dot{X}_4 = v_5 - v_6$$

$$v_1 = \frac{60\frac{X_5}{0.3}\left(1+\frac{0.05}{1.0}\frac{X_3}{0.15}\right)}{1+\frac{X_3}{0.15}+\frac{X_5}{0.3}\left(1+\frac{X_3}{1.0*0.15}\right)} \quad ; \quad v_2 = \frac{15X_1}{2+X_1} \quad ; \quad v_3 = \frac{4X_2}{1+X_2}$$

$$v_4 = \frac{40\left(\frac{X_3}{15}\right)^3}{\left(\frac{X_3}{15}\right)^3 + \frac{1.0+\left(\frac{X_4}{1.0}\right)^3}{1.0+60\left(\frac{X_4}{1.0}\right)^3}} \quad ; \quad v_5 = \frac{15X_1}{1+X_1} \quad ; \quad v_6 = \frac{10X_4}{1+X_4}$$



Synthetic datasets A: generated from initial conditions [1.0, 1.0, 1.0, 1.0], all fluxes have a dynamic range in the non-saturated region; **B** generated from initial conditions [10.0, 10.0, 10.0, 10.0], fluxes have wider dynamic ranges

ii) MODELING APPROACHES

S-SYSTEM (SS)

$$\dot{X}_1 = \alpha_1 X_5 X_3^{g_{13}} - \beta_1 X_1^{h_{11}}$$
$$\dot{X}_2 = \alpha_2 X_1^{g_{21}} - \beta_2 X_2^{h_{22}}$$
$$\dot{X}_3 = \beta_2 X_2^{h_{32}} - \beta_3 X_3^{h_{33}} X_4^{h_{34}}$$
$$\dot{X}_4 = \alpha_4 X_1^{g_{41}} - \beta_4 X_4^{h_{44}}$$

PIECEWISE POWERLAWS (PWPL)

$$\dot{X}_1 = \begin{cases} \alpha_{1A} X_5, & \alpha_{1B} X_3^{g_{13}} < \alpha_{1A} \\ \alpha_{1B} X_5 X_3^{g_{13}}, & \alpha_{1A} < \alpha_{1B} X_3^{g_{13}} < \alpha_{1C} \\ \alpha_{1C} X_5, & \alpha_{1C} < \alpha_{1B} X_3^{g_{13}} \end{cases} - \beta_1 X_1^{h_{11}}$$

$$\dot{X}_2 = \alpha_2 X_1^{g_{21}} - \beta_2 X_2^{h_{22}}$$

$$\dot{X}_3 = \beta_2 X_2^{h_{22}} - \begin{cases} \beta_{3A} X_3^{h_{33}}, & \beta_{3B} X_3^{h_{33}} X_4^{h_{34}} < \beta_{3A} X_3^{h_{33}} \\ \beta_{3B} X_3^{h_{33}} X_4^{h_{34}}, & \beta_{3A} X_3^{h_{33}} < \beta_{3B} X_3^{h_{33}} X_4^{h_{34}} < \beta_{3C} X_3^{h_{33}} \\ \beta_{3C} X_3^{h_{33}}, & \beta_{3C} X_3^{h_{33}} < \beta_{3B} X_3^{h_{33}} X_4^{h_{34}} \end{cases}$$

$$\dot{X}_4 = \alpha_4 X_1^{g_{41}} - \beta_4 X_4^{h_{44}}$$

S-SYSTEMS+ HILL (SSH)

$$\dot{X}_1 = \alpha_1 X_5 \frac{t_{13}^{hc_{13}}}{t_{13}^{hc_{13}} + X_3^{hc_{13}}} - \beta_1 X_1^{h_{11}}$$
$$\dot{X}_2 = \alpha_2 X_1^{g_{21}} - \beta_2 X_2^{h_{22}}$$
$$\dot{X}_3 = \beta_2 X_2^{h_{32}} - \beta_3 X_3^{h_{33}} \frac{X_4^{hc_{34}}}{t_{34}^{hc_{34}} + X_4^{hc_{34}}}$$
$$\dot{X}_4 = \alpha_4 X_1^{g_{41}} - \beta_4 X_4^{h_{44}}$$

SATURABLE & COOPERATIVE (SC)

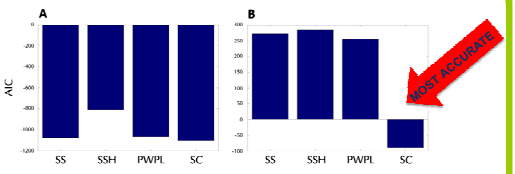
$$\dot{X}_1 = V_1 X_5 \frac{X_3^{n_{13}}}{(K_{13} + X_3^{n_{13}})} - \frac{V_2 X_1^{n_{21}}}{(K_{21} + X_1^{n_{21}})} - \frac{V_5 X_1^{n_{51}}}{(K_{51} + X_1^{n_{51}})}$$
$$\dot{X}_2 = \frac{V_2 X_1^{n_{21}}}{(K_{21} + X_1^{n_{21}})} - \frac{V_3 X_2^{n_{32}}}{(K_{32} + X_2^{n_{32}})}$$
$$\dot{X}_3 = \frac{V_3 X_2^{n_{32}}}{(K_{32} + X_2^{n_{32}})} - \frac{V_4 X_3^{n_{43}} X_4^{n_{44}}}{(K_{43} + X_3^{n_{43}})(K_{44} + X_4^{n_{44}})}$$
$$\dot{X}_4 = \frac{V_5 X_1^{n_{51}}}{(K_{51} + X_1^{n_{51}})} - \frac{V_6 X_4^{n_{64}}}{(K_{64} + X_4^{n_{64}})}$$

iii) PARAMETER ESTIMATION (TOP-DOWN APPROACH)

1. Calculate fluxes from synthetic datasets → 2. Parameterization (gradient-based or direct search optimization algorithms) → Model describing dataset (least sum of squared errors)

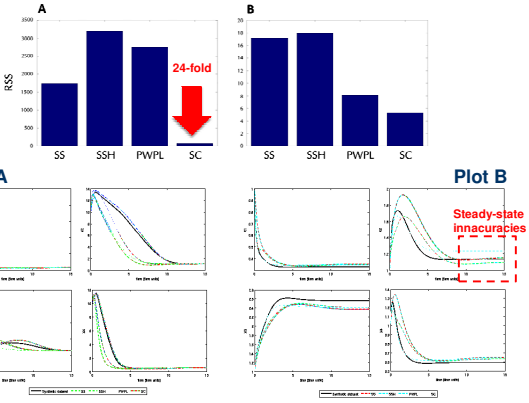
4 Results

FORMALISM ACCURACY



Akaike Information Criterion (AIC) for comparison of the 4 formalisms; *AIC = 2k + n[ln(2πRSS/n) + 1]* where *k* is the number of model parameters, *n* is the number of observations and *RSS* is the residuals sum of squares of the fitting; from different alternative models the one having the smaller AIC values should have the highest preference rank. **(A)** and **(B)** are models derived from datasets A and B, respectively

GENERALIZATION CAPABILITY



Generalization capability of the different formalisms (cross-prediction): the barplots represent the RSS of the different approaches when predicting dataset B with models inferred from dataset A (**plot A** below) and predicting dataset A with models inferred from dataset B (**plot B** below)

OTHER COMPARISONS

Formalism	Steady-States	Biological Interpretation
SS	Analytical	Net rate constants and kinetic orders
SSH	Numerical	Same as above with local information on Hill coefficients and thresholds
PWPL	Analytical	It may be difficult to interpret some of the additional rate constants
SC	Numerical	Direct interpretation of a single variable SC approximation when the remaining variables are fixed

5 Conclusions

- The SSH and PWPL approaches may be interesting modeling tools when prior information on the systems saturations are available
- The SC formalism although being a local approximation, is the most accurate for wider dynamic ranges in the data

References

[1] Savageau MA 2002 Math Biosci. 180: 237-253
[2] Sorribas A et al 2007. Biotechnol Bioeng. 97(5): 1259-1277

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