Simulating the Proline-Glutamate pathway in *Trypanosoma cruzi* with an *in silico* metabolic model

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Introduction

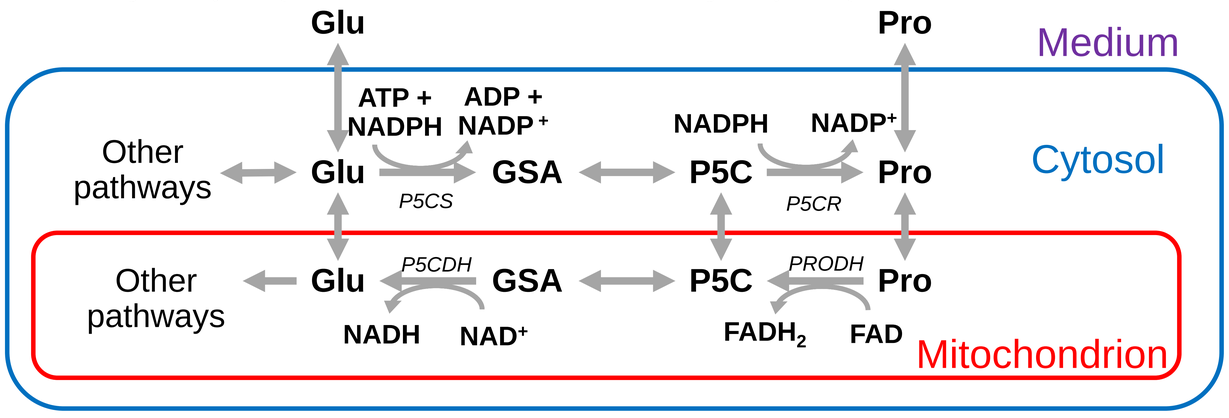
T. cruzi relies on Pro for several processes, such as cellular invasion, differentiation, osmoregulation, and this amino acid can sustain energetically the parasite, by transferring electrons to FAD and NAD^+ which can further feed the Electron Transport Chain. The steady state concentration of Proline differs largely between stages of the parasite, and the activities of enzymes involved in this pathway are also finely regulated. Here, we show an *in silico* kinetic metabolic model of the Pro–Glu pathway in *T. cruzi*.

Goals

The aim of this project is to develop and validate a metabolic model of the Pro-Glu pathway. The final model should be able to predict accurately the steady state concentration of both amino acids and intermediaries across compartments, given a set of conditions: extracellular amino acid and cofactor concentrations, enzyme activity levels and pH (within physiological range).

Overview of the model

Main metabolites are Proline, Glutamate and their intermediaries, Δ^1-Pyrroline-5-carboxylate (P5C) and Glutamate-5-semialdehyde (GSA).



Modeling the enzymes

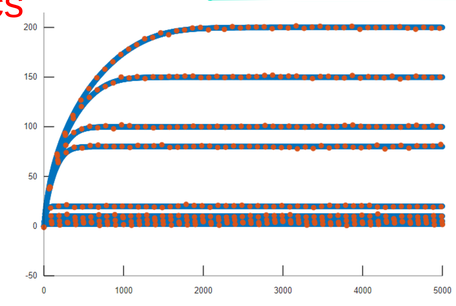
Enzymes were modeled using the Reversible Hill Equation[1]. It is a generic rate law that contains less parameters than Bi-Bi models, but usually matches their behavior closely. An algorithm was developed to infer the parameters from concentration time courses obtained through kinetic assays.

$$A + B \leftrightarrow P + Q$$

Kinetics Thermodynamics

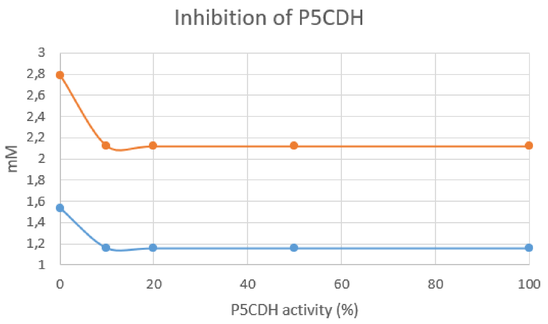
$$v = \frac{V_f \left(\frac{ab}{K_A K_B}\right)\left(1 - \frac{pq}{ab}\cdot\frac{1}{K_{eq}}\right)}{\left(1 + \frac{a}{K_A} + \frac{p}{K_P}\right)\left(1 + \frac{b}{K_B} + \frac{q}{K_Q}\right)}$$

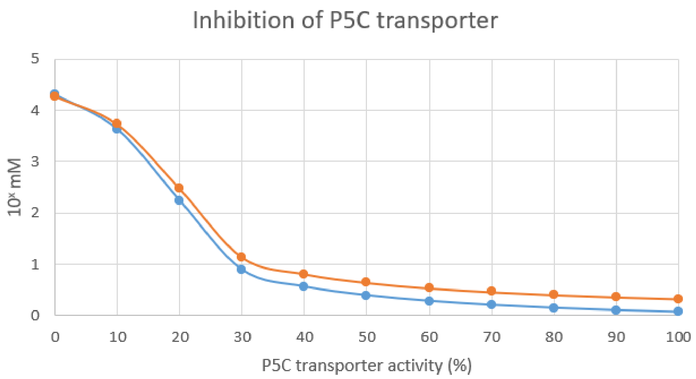
Affinities

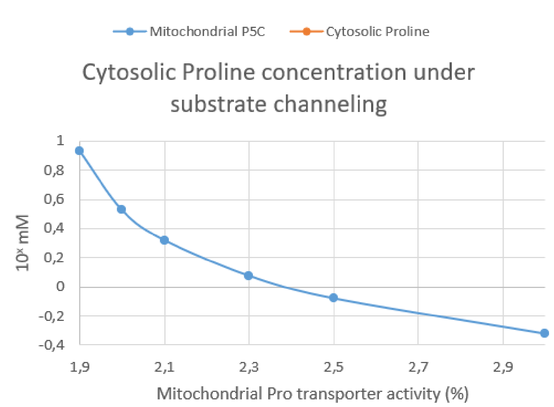


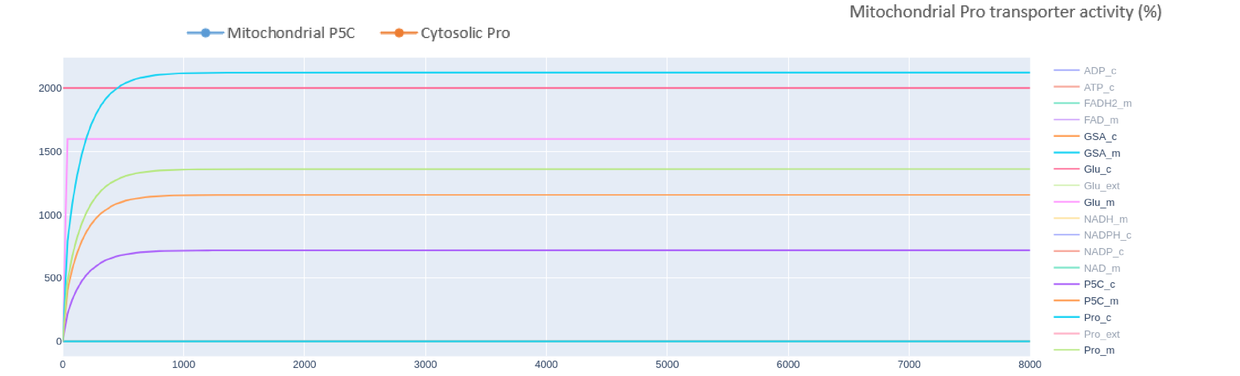
Results

Preliminary results show a stable system with steady state values within physiological range. Simulations point to the necessity of substrate channeling in the mitochondrial pathway or a high-capacity P5C transporter to avoid toxic P5C concentration levels.









Future work

In the future we will collect experimental data on fluxes and concentrations, and use artificial intelligence techniques to estimate the parameters of the equations and infer other interactions between elements in the network.

Reference

[1] Rohwer *et al*. Evaluation of a simplified generic bi-substrate rate equation for computational systems biology. Syst Biol. PMID: 16986312.

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