Mathematical models of glucosinolate metabolism in plants

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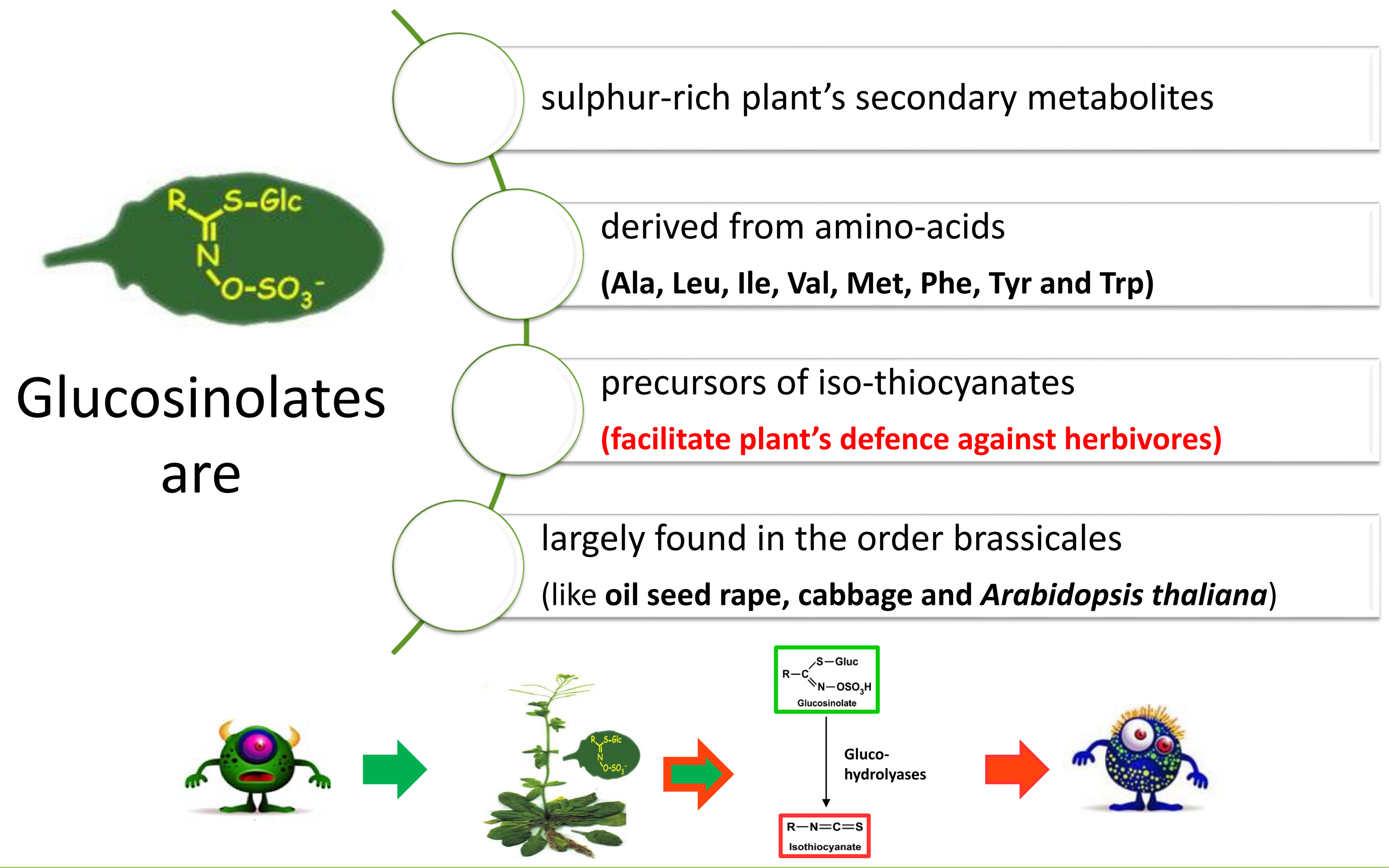
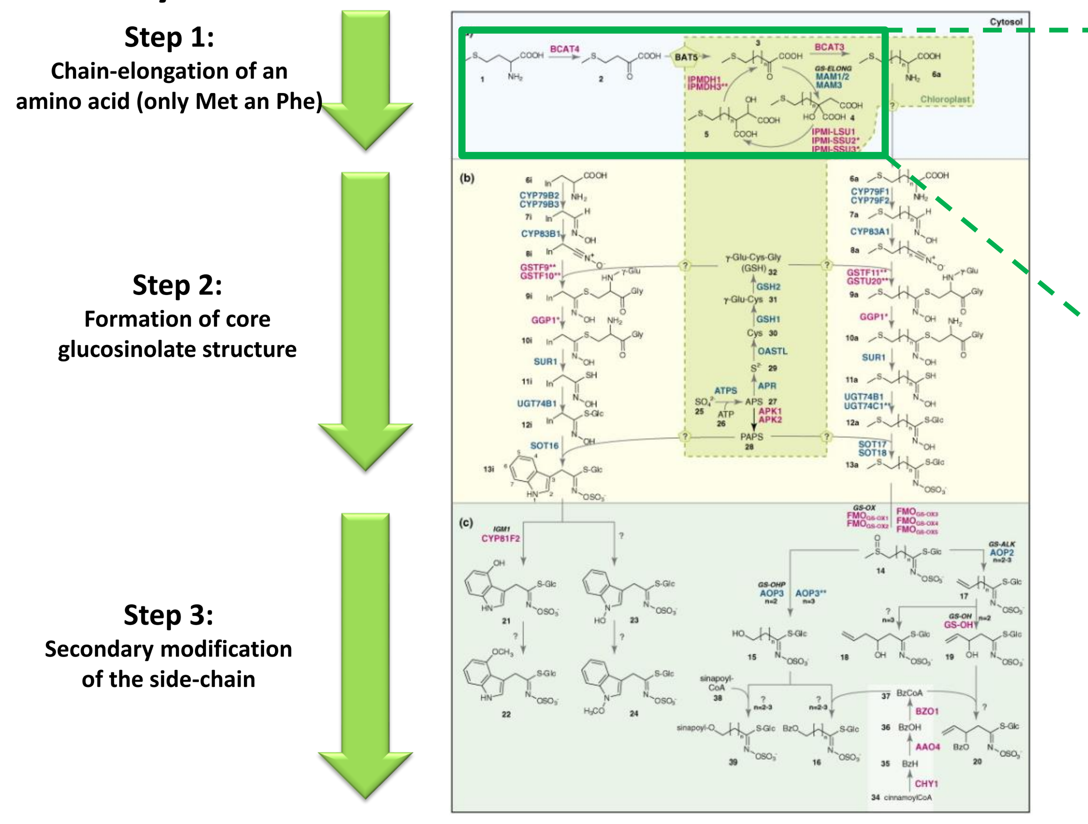
Significance

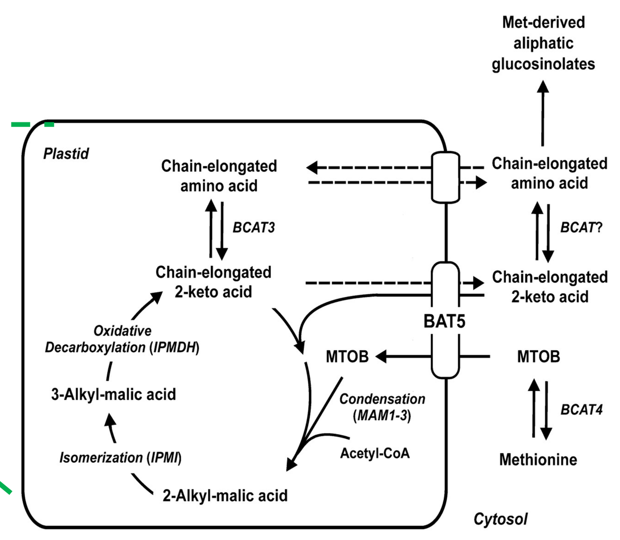
Glucosinolates are plant secondary metabolites which play an important role in plant's defense against herbivores. Therefore, **understanding the regulation of glucosinolate production is key for understanding plant-microbe interactions**. A major difficulty in the analysis of secondary metabolites is the vast diversity of different chemical structures. Considering the types of biochemical transformations involved in the biosynthesis of secondary metabolites, in principle an infinite number of chemical structures could be produced.



Biosynthesis



Met-derived glucosinolate biosynthesis. Figure from [1]

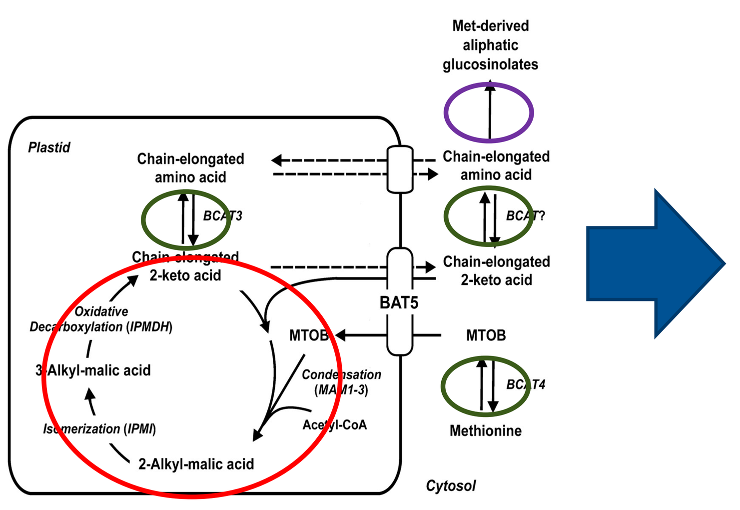


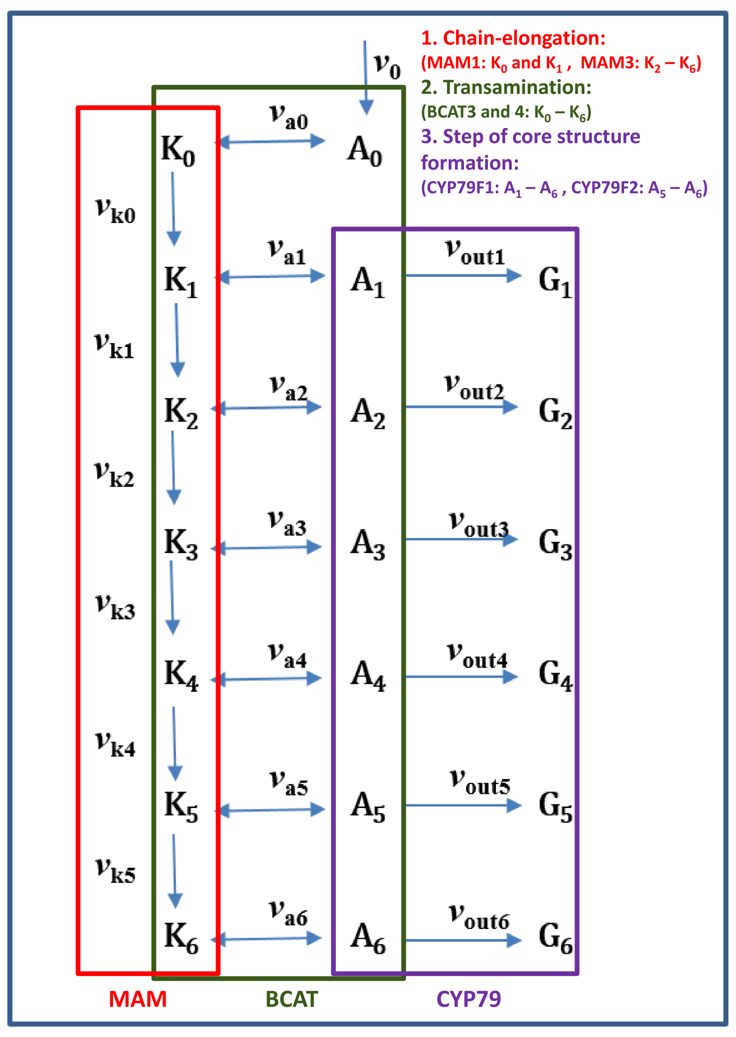
Chain-elongation process. Figure from [2]

Together with chain elongation, secondary modification results in 120 known glucosinolates [3], of which Arabidopsis has 40, mainly derived from Met and Trp [4].

Model development

Objective: To explain which factors govern the chain-elongation of Met-derived glucosinolates





Model assumptions

- The irreversible steps of chain-elongation are lumped together as one reaction (K_i to K_{i+1})
- The model doesn't include inter-compartment transport mechanisms
- Acetyl-CoA and CO_2 are provided externally

If one enzyme can catalyse different substrates, then all the substrates will compete for the binding site

Based on rapid-equilibrium assumption [5] and conservation of total enzyme concentration, we derived the steady-state rate equations which has the general form:

Reversible reaction

$$A_n + E \underset{k_{-n,1}}{\overset{k_{+n,1}}{\rightleftharpoons}} EA_n \underset{k_{-n,2}}{\overset{k_{+n,2}}{\rightleftharpoons}} K_n + E$$

$$v_{rev\_i} = \frac{V_m^{i+} A_i / K_m^{i+} - V_m^{i-} K_i / K_m^{i-}}{1 + \sum_{j=0}^{6} A_j / K_m^{j+} + \sum_{j=0}^{6} K_j / K_m^{j-}}$$

$$V_m^{i+} = k_{+i,2} E_{total}; V_m^{i-} = k_{-i,1} E_{total};$$

$$K_m^{i+} = \frac{k_{-i,1} + k_{+i,2}}{k_{+i,1}} \text{ and } K_m^{i-} = \frac{k_{-i,1} + k_{+i,2}}{k_{-i,2}}$$

Irreversible reaction

$$K_n + E \underset{k_{-n,1}}{\overset{k_{+n,1}}{\rightleftharpoons}} EK_n \xrightarrow{k_{n,cat}} K_{n+1} + E$$

$$A_n + E \underset{k_{-n,1}}{\overset{k_{+n,1}}{\rightleftharpoons}} EA_n \xrightarrow{k_{n,cat}} G_n + E$$

$$v_{irr\_i} = \frac{V_m^i S_i / K_d^i}{1 + \sum_{j=1}^{6} S_j / K_d^j}$$

S can be A or K ;

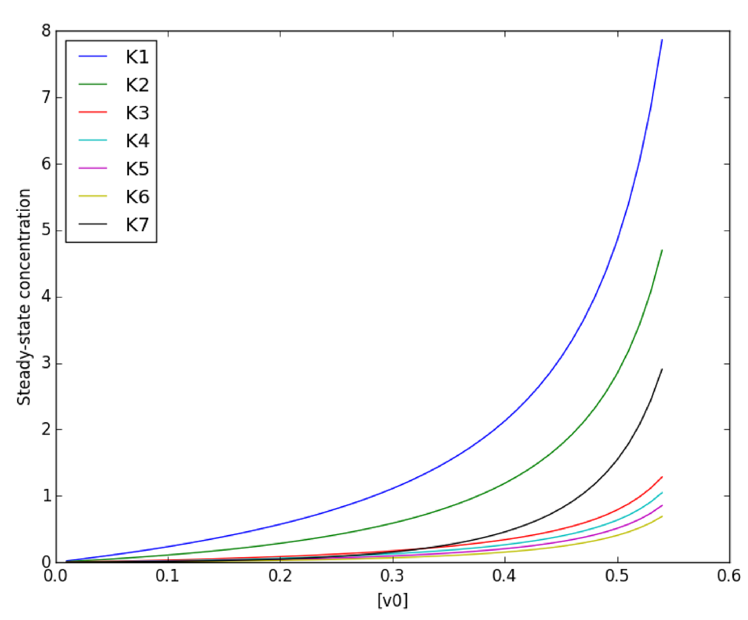
$$V_m^i = E_{total} k_{n,cat} \text{ and } K_d^i = \frac{k_{+i,1}}{k_{-i,1}}$$

We could see from these equations that production of anything is affected by everything else.

First results

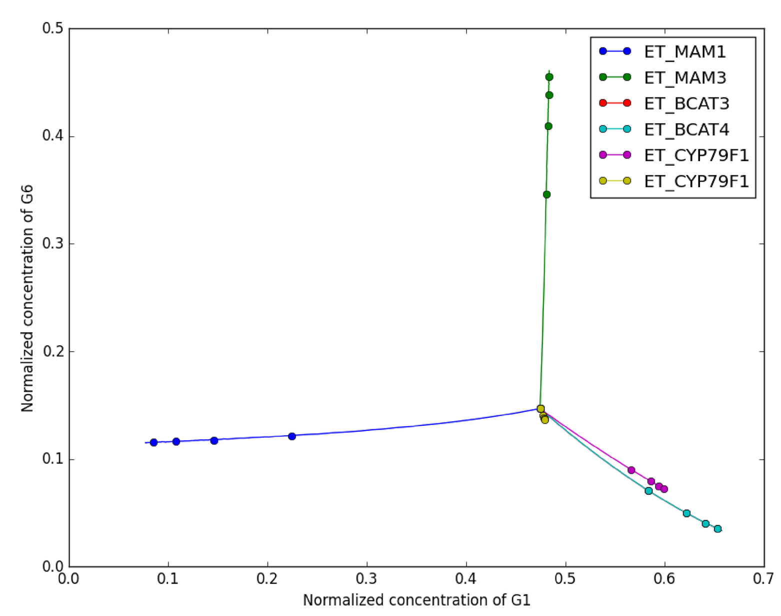
With steady-state rate equations, we simulated our model where all the enzymes compete, for their respective substrates, with equal efficiency and:

- **Varied influx v_0**



* where $E_t = 1.0$

- **Varied total Enzyme concentration $[Et]$**



- where $v_0 = 0.3$
- MAM1: $K_0 - K_1$; MAM3: $K_2 - K_6$; BCAT3: $A_0 - A_6$; BCAT4: $A_0 - A_6$; CYP79F1: $A_1 - A_6$ and CYP79F2: $A_5 - A_6$

Current stage:

- **Parameter estimation using genetic algorithm**

Error function:

$$\Delta = \sum_{i=1}^{n} (\hat{G}_{exp} - \hat{G}_{model})^2$$

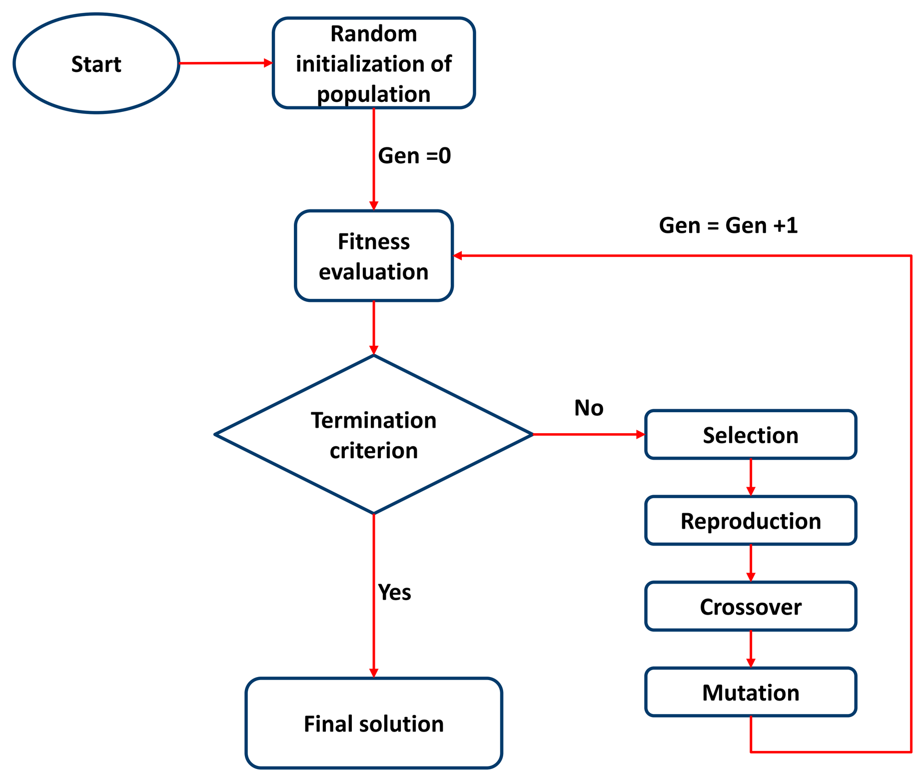
Fitness function:

$$J = \frac{1}{(1 + \Delta)}$$

Constraints for crossover and mutation:

1. Satisfaction of Haldane relation,

$$K_{eq} = \frac{V_{max}^{+} K_m^{-}}{V_{max}^{-} K_m^{+}}$$



Future work

- Find/estimate the values of the kinetic parameters to fit the observed production of the different Met-derived GSL levels in Arabidops
- Study inter-compartment transport of metabolites
- Study feed- back/forward loops regulating the biosynthesis

Acknowledgement

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