

Model transformation of metabolic networks using a Petri net based framework

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Systems Biology modeling approaches:

- top-down
- bottom-up
- middle-out

Models in Metabolic Engineering:

- macroscopic models (used in bioprocess control)
- dynamic large-scale models
- stoichiometric genome-scale reconstructions

Problems with genome-scale modeling:

- network visualization
- pathway analysis
- dynamic simulation

Model reduction approach

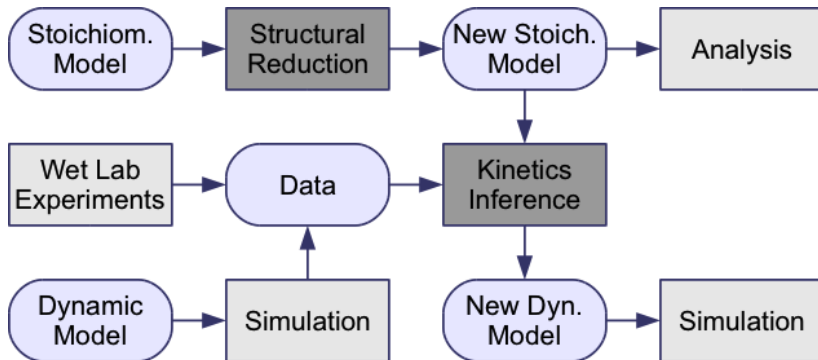
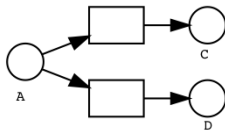
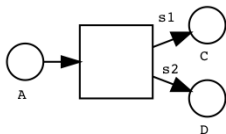
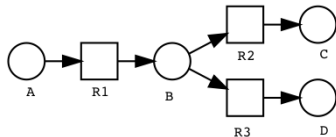


Figure: Overall concept of model reduction and kinetics inference.

Two methods of transition fusion



- Reduction assumes steady-state for the removed metabolites.
- Conjunctive method constrains the flux distribution to a given steady-state ($s_1 = \frac{v_2}{v_1}$, $s_2 = \frac{v_3}{v_1}$).
- Disjunctive method is prone to combinatorial explosion

Limit scenario

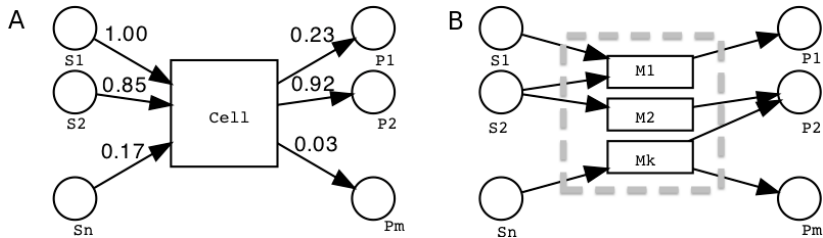


Figure: Limit scenario when all internal metabolites are removed.

Conjunctive method

$$Pn' = \langle P', T', Pre', Post' \rangle$$

$$P' = P \setminus \{p\}$$

$$T' = T \setminus (\bullet p \cup p \bullet) \cup \{t_p\}$$

$$Pre' = \{(p_i, t_j) \mapsto Pre(p_i, t_j) \mid (p_i, t_j) \in dom(Pre) \setminus (P \times (\bullet p \cup p \bullet))\}$$

$$\cup \{(p_i, t_p) \mapsto f_{in}(p_i) \mid p_i \in \bullet(\bullet p \cup p \bullet), p_i \neq p, v'(t_p) \neq 0, f_{in}(p_i) \neq 0\}$$

$$Post' = \{(p_i, t_j) \mapsto Post(p_i, t_j) \mid (p_i, t_j) \in dom(Post) \setminus (P \times (\bullet p \cup p \bullet))\}$$

$$\cup \{(p_i, t_p) \mapsto f_{out}(p_i) \mid p_i \in (\bullet p \cup p \bullet) \bullet, p_i \neq p, v'(t_p) \neq 0, f_{out}(p_i) \neq 0\}$$

$$v' = \{t \mapsto v(t) \mid t \in T \setminus (\bullet p \cup p \bullet)\} \cup \{t_p \mapsto In(p)\}.$$

where

$$f_{in}(p_i) = \frac{\sum_{t \in p_i \bullet \cap (\bullet p \cup p \bullet)} Pre(p_i, t) \cdot v(t)}{v'(t_p)}$$

$$f_{out}(p_i) = \frac{\sum_{t \in \bullet p_i \cap (\bullet p \cup p \bullet)} Post(p_i, t) \cdot v(t)}{v'(t_p)}$$

Disjunctive method

$$Pn' = \langle P', T', Pre', Post' \rangle$$

$$P' = P \setminus \{p\}$$

$$T' = T \setminus (\bullet p \cup p \bullet) \cup \{t_{xy} \mid (x, y) \in (\bullet p \times p \bullet)\}$$

$$Pre' = \{(p_i, t) \mapsto Pre(p_i, t) \mid (p_i, t) \in dom(Pre) \setminus (P \times (\bullet p \cup p \bullet))\} \\ \cup \{(p_i, t_{xy}) \mapsto Pre_0(p_i, x) \cdot Pre(p, y) + Pre_0(p_i, y) \cdot Post(p, x) \\ \mid (x, y) \in (\bullet p \times p \bullet), p_i \in \bullet\{x, y\}\}$$

$$Post' = \{(p_i, t) \mapsto Post(p_i, t) \mid (p_i, t) \in dom(Post) \setminus (P \times (\bullet p \cup p \bullet))\} \\ \cup \{(p_i, t_{xy}) \mapsto Post_0(p_i, x) \cdot Pre(p, y) + Post_0(p_i, y) \cdot Post(p, x) \\ \mid (x, y) \in (\bullet p \times p \bullet), p_i \in \{x, y\} \bullet\}$$

where

$$Pre_0(p, t) = \begin{cases} Pre(p, t) & \text{if } (p, t) \in dom(Pre) \\ 0 & \text{if } (p, t) \notin dom(Pre) \end{cases}$$
$$Post_0(p, t) = \begin{cases} Post(p, t) & \text{if } (p, t) \in dom(Post) \\ 0 & \text{if } (p, t) \notin dom(Post) \end{cases}$$

Marked continuous Petri net ($m_0 : P \rightarrow \mathbb{R}_0^+$):

$$Pn = \langle P, T, Pre, Post, m_0 \rangle$$

Define a firing speed $v : T \rightarrow \mathbb{R}_0^+$, using GMA kinetics:

$$v(t) = k_t \prod_{p \in \bullet t} m(p)^{a_{p,t}}$$

or linlog kinetics:

$$v(t) = v_0(t) \left(1 + \sum_{p \in \bullet t} \varepsilon_{p,t}^0 \ln \left(\frac{m(p)}{m_0(p)} \right) \right)$$

where v_0 is the reference steady-state.

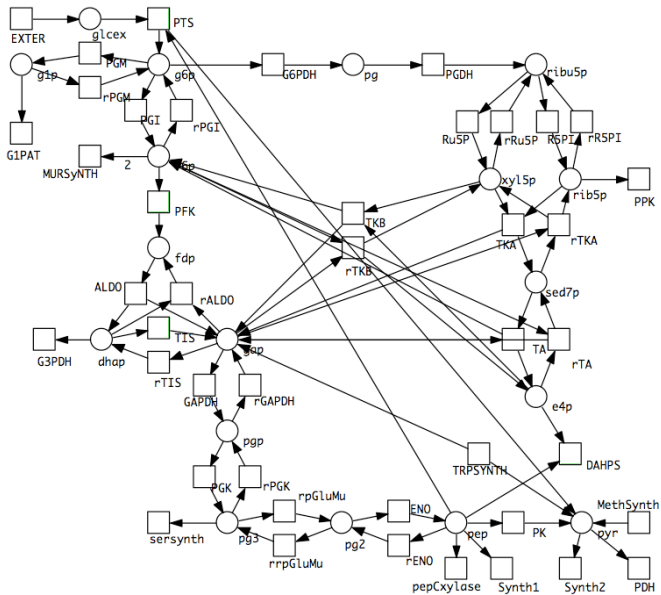
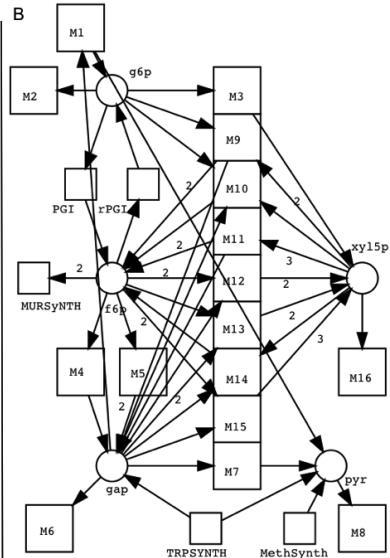
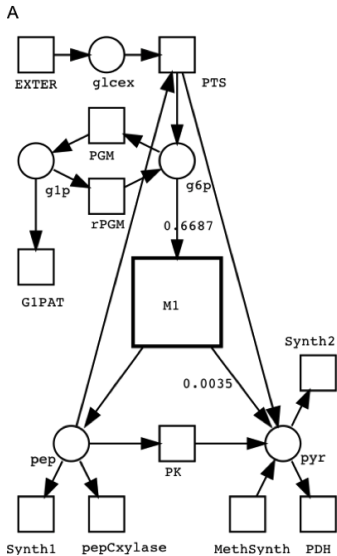


Figure: Petri net model of the central carbon metabolism of *E.coli* (from Chassagnole *et al*, 2002) built with the SNOOPY tool.

Metabolite properties (topological and dynamic)

Metabolite	$\#(\bullet p)$	$\#(p\bullet)$	$\#(\bullet p \times p\bullet)$	m_0 (mM)	I_n (mM/s)	τ (s)
glcex	1	1	1	0.0558	0.0031	18.099
pep	1	6	6	2.6859	0.3031	8.8603
g6p	3	3	9	3.4882	0.2004	17.406
pyr	4	2	8	2.6710	0.2418	11.044
f6p	3	5	15	0.6014	0.1423	4.2266
g1p	1	2	2	0.6539	0.0023	278.62
pg	1	1	1	0.8092	0.1397	5.7929
fdp	2	1	2	0.2757	0.1414	1.9495
sed7p	2	2	4	0.2761	0.0454	6.0757
gap	7	6	42	0.2196	0.3661	0.5997
e4p	2	3	6	0.0986	0.0454	2.1684
xyl5p	3	3	9	0.1385	0.0839	1.6503
rib5p	2	3	6	0.3994	0.0558	7.1626
dhap	2	3	6	0.1682	0.1414	1.1892
pgp	2	2	4	0.0080	0.3207	0.0251
pg3	2	3	6	2.1437	0.3207	6.6851
pg2	2	2	4	0.4014	0.3031	1.3241
ribu5p	3	2	6	0.1114	0.1397	0.7974

Reduced model (conjunctive and disjunctive versions)



Parameter fitting

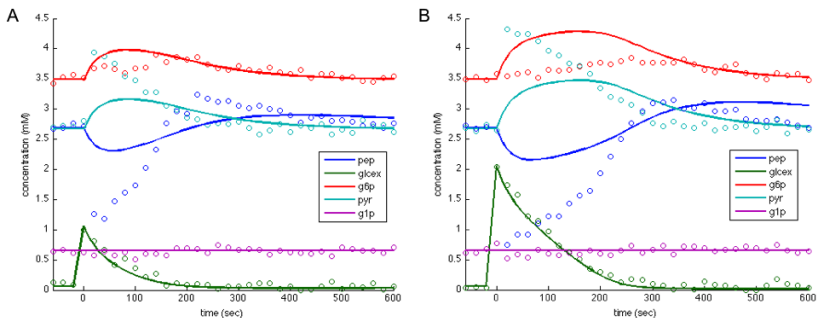


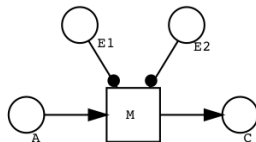
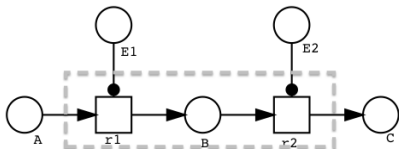
Figure: (A) Parameter fitting with pseudo experimental data (1mM extracellular glucose pulse). (B) Validation with different experimental set (2mM extracellular glucose pulse).

Conclusions

- Modeler faces two options when reducing a network.
- Choice of method and nodes to remove depends on purpose of model and assumptions made.
- Inferred model better at simulating extracellular dynamics.

Future work . . .

- Build a genome-scale reduced dynamic model.
- Consider read and inhibitor arcs for enzymatic regulation.
- Consider hierarchical petri nets (after SBML level 3).
- Use read-arcs to integrate regulatory network.



Thank you for your attention.

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