Using logic programming for modeling the one-carbon metabolism network to study the impact of folate deficiency on methylation processes

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SUPPLEMENTARY MATERIAL

Illustration of parameters identification.

For illustration purpose, we propose herein to perform the parameter estimation on the Methionine Synthase (MS) reaction**.** It implies three BK describe as follow: BK_1: *"healthy human plasma homocysteine amount extended between 5 and 15 µM "* (53)

$$F_1 = \{Organism(human), State(healthy), Param(Hcy), ValP(Hcy,15,\mu M)\},$$

which expresses five distinct facts: (i) human is an organism, (ii) healthy is a state, (iii) Hcy (homocysteine) is a parameter, (iv) Hcy can take value 5µM or (v) 15 µM.

$$R_1 = \begin{Bmatrix} [Organism(human), Organ(Blood), Tissu(Plasma), State(healthy)] \\ \Rightarrow [ValP(Hcy) \le 15\mu M] \end{Bmatrix}$$

R_1 suggest to express these facts by the following semantic, "*if* the cell is from a healthy human organism and plasma tissue, *then* homocysteine amount extend between 5 and 15µM".

From now, KB contains the first knowledge BK_1 with fact base FB=F_1; and rule base RB=R_1). If we take a second biological knowledge BK_2 in literature, we obtained:

BK_2:"In human crude cell, specific activity of methionine synthase reaction (MS) is 2.53µmol/min/mg at 37°C temperature"

$$F_2 = \begin{Bmatrix} Organism(human), Temperature(37), Cell(crude), Reaction(MS), \\ Param(Kcat_{MS}), ValP(Kcat_{MS}, 2.53, mol*(\min * mg)^{-1})) \end{Bmatrix}$$

$$R_2 = \begin{Bmatrix} [Organism(human), Temperature(37), Cell(crude), Reaction(MS)] \\ \Rightarrow ValP(Kcat_{MS}, 2.53, mol*(\min * mg)^{-1}))] \end{Bmatrix}$$

Then the rule base RB become

$$RB \vee R_2 = \begin{Bmatrix} [Organism(human), Temperature(37), Cell(crude), Reaction(MS) \\ \Rightarrow ValP(Kcat_{MS}, 2.53, mol*(\min * mg)^{-1}))]; \\ [Organism(human), Organ(Blood), Tissu(Plasma), State(healthy)] \\ \Rightarrow [ValP(Hcy) \le 15\mu M] \end{Bmatrix}$$

By now, KB contains 5 facts and 3 rules extracted from the literature. For consolidation, we add anothe constraint from the Michaelis and Menten kinetic reaction stipulating that

$V_m=K_{cat}*E_0$ where V_m , K_{cat}, and E_0 are respectively the maximal velocity, the catalytic constant and the initial amount of the enzyme which catalyse the given reaction. We then have:

BK_3: "Reaction MS is Michaelis Menten reaction type, $V_{m\_MS}=K_{cat\_MS}*E_{0\_MS}$"

F_3={Param(V_{m_MS}), Param(E_{0_MS})}

R_3= {$V_m=K_{cat\_MS}*E_{0\_MS}$}

At the end, we obtain KB= $BK_1+BK_2+BK_3$ = {FB: $F_1 \vee F_2 \vee F_3$, RB: $R_1 \vee R_2 \vee R_3$}

Experimental condition is a five item given row concerning in order, the organism name, organ name, cell type, physiological state, the optimum pH value, and temperature. For example:

ExpCond=(Organism,Organ,Cell,State,pH,Temperature)

$ExpCond_1$=(human,liver,HepG2,healthy,7.5,37).