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A model integration approach linking signalling and gene-regulatory logic with kinetic metabolic models

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ABSTRACT

Systems biology has to increasingly cope with large- and multi-scale biological systems. Many successful *in silico* representations and simulations of various cellular modules proved mathematical modelling to be an important tool in gaining a solid understanding of biological phenomena. However, models spanning different functional layers (*e.g.* metabolism, signalling and gene regulation) are still scarce. Consequently, model integration methods capable of fusing different types of biological networks and various model formalisms become a key methodology to increase the scope of cellular processes covered by mathematical models. Here we propose a new integration approach to couple logical models of signalling or/and gene-regulatory networks with kinetic models of metabolic processes. The procedure ends up with an integrated dynamic model of both layers relying on differential equations. The feasibility of the approach is shown in an illustrative case study integrating a kinetic model of central metabolic pathways in hepatocytes with a *Boolean* logical network depicting the hormonally induced signal transduction and gene regulation events involved. *In silico* simulations demonstrate the integrated model to qualitatively describe the physiological switch-like behaviour of hepatocytes in response to nutritionally regulated changes in extracellular glucagon and insulin levels. A simulated failure mode scenario addressing insulin resistance furthermore illustrates the pharmacological potential of a model covering interactions between signalling, gene regulation and metabolism.
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1. Introduction

Model integration is emerging as a key methodology in modern systems biology since mathematical modelling frameworks are increasingly forced to cope with complex physiological and phenotype-driven issues spanning a multitude of intra- and intercellular organisation scales as well as environmental conditions (Dada and Mendes, 2011; Goncalves et al., 2013; Karr et al., 2012). According to a natural "intracellular task sharing" concept, three major cellular process layers can be distinguished with each featuring distinct physiological and functional characteristics: (i) cell signalling is essentially mediated by interacting proteins generating and transducing flows of information from the cell surface to the nucleus; (ii) gene regulation, by contrast, comprises transcriptional regulation of gene expression and post-transcriptional modification mechanisms that further control and fine-tune protein abundances, whereas (iii) metabolism comprises enzyme-catalysed reactions, transforming substrates into biomass and product metabolites. A cell's phenotype results from the interplay of all these processes described above – a fact stressing the layers' interdependencies.

Integrative models linking the associated information and material flows across all three cellular process layers will therefore provide a more complete representation with increased predictive power. Such models are, nevertheless, an exception as most modelling studies in systems biology focus on single layers only. Presumably, this could, on the one hand, be caused by the complexity of integrated models implying a potentially high number of parameters to be measured or estimated and, on the other hand, by the large variety of different (quantitative *vs.* qualitative) modelling concepts and implementation strategies

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Abbreviations and symbols

AKT	Protein kinase B (also PKB)
cAMP	Cyclic adenosine monophosphate
CBP	CREB binding protein
ChREBP	Carbohydrate response element binding protein
CREB	cAMP responsive element binding protein
ENO1	Enolase 1
F-1,6-P2	Fructose-1,6-bisphosphate
F-2,6-P2	Fructose-2,6-bisphosphate
G6P	Glucose-6-phosphate
GSK3	Glycogen synthase kinase 3
GYS2	Glycogen synthase 2
HNF4α	Hepatocyte nuclear factor 4 α
IR	Insulin receptor
IRS1	Insulin receptor substrate 1
ITT	Incomplete truth table (operator)
LIH	Logical interaction hypergraph
LSS	Logical steady-state
LXRα	Liver X receptor α (also NR1H3)
ODE	Ordinary differential equation
PDHK2	Pyruvate dehydrogenase kinase isoform 2
PDHP2	Pyruvate dehydrogenase phosphatase 2
PDK1	3-Phosphoinositide-dependent kinase 1
PFK1	Phosphofructokinase 1 (also PFKL)
PFK2	Phosphofructokinase 2
PKA	Protein kinase A
PKLR	Pyruvate kinase (liver-type; also LPK)
PP2A	Protein phosphatase 2A
PPARα	Peroxisome proliferator-activated receptor α (also NR1C1)
SOP	Sum of products (notation)
SREBP1c	Sterol-regulatory-element-binding protein 1c
TORC2	Transducer of regulated CREB protein 2 (also CRTC2)
TRB3	Tribbles homolog 3 (also neuronal cell death-inducible putative kinase / NIPK)
V	Index set of all species in the integrated model

Metabolic model context

c	Vector of metabolite concentrations [μM] (*cf.* Step 1)
c_{norm}	Normalised metabolite concentration [n.u.] (*cf.* Eq. (4)/Step 4)
e	Total number of metabolites (*cf.* Step 1)
K	Normalisation parameter defining normalisation threshold [μM] (*cf.* Eq. (4)/Step 4)
l	Total number of metabolites in subset M^S (*cf.* Step 1)
M	Index set of metabolites ($M \subset V$; *cf.* Step 1)
M^S	Index subset of metabolites regulating signalling species ($M^S = S^M = S \bigcap M$; *cf.* Step 1)
N	Stoichiometric matrix (*cf.* Step 1)
N	Normalisation parameter defining normalisation sharpness [n.u.] (*cf.* Eq. (4)/Step 4)
Q	Metabolic network (*cf.* Step 1)
p	Total number of reactions (*cf.* Step 1)
q	Total number of reactions in subset R^S (*cf.* Step 1)
R	Index set of reactions (*cf.* Step 1)
R^S	Index subset of reactions involving enzymes under signalling control (*cf.* Step 1)
r	Vector of kinetic rates [μM/h] (*cf.* Step 1)
t	Time [h] (*cf.* Step 1)

Signalling model context

B	Set of *Boolean* functions (*cf.* Step 2)
$\tilde{B}$	Set of continuous function homologues (*cf.* Step 3)
b	*Boolean* function (*cf.* Eq. (2)/Step 2)
$\tilde{b}$	Continuous function homologue of a *Boolean* function (*cf.* Eq. (3)/Step 3)
d	Confidence level of a logical transition (*cf.* Step 2 and Table S6)
j	Running index for signalling effectors affecting species i ($j \in [0;z_i]$); see Step 3 and Supplementary Table S4)
k	Transformation parameter defining the normalised signalling species activation threshold [n.u.] (*cf.* Step 3)
L	Logical network (*cf.* Step 2)
$\tilde{L}$	Transformed logical network (*cf.* Step 3)
n	Transformation parameter defining the normalised transformation sharpness [n.u.] (*cf.* Step 3)
S	Index set of signalling species ($S \subset V$; *cf.* Step 2)
S^A	Index subset of signalling species reflecting effector activation levels
S^E	Index subset of signalling species reflecting signalling outputs to metabolism and therefore metabolic key-enzyme activation or gene expression levels ($S^E \subset S^A \bigcup S^G$) with $S^E \bigcap S^M = \emptyset$ (*cf.* Step 2)
S^G	Index subset of signalling species reflecting effector gene expression levels ($S^G \subset S$; *cf.* Step 2)
S^H	Index subset of signalling species reflecting levels of external hormonal inputs to signalling ($S^H \subset S$; *cf.* Step 2)
S^M	Index subset of signalling species reflecting levels of metabolic inputs to signalling ($S^M = M^S = S \cap M$; *cf.* Step 2)
S^P	Index subset of signalling species reflecting effector modification levels ($S^P \subset S$; *cf.* Step 2)
S^U	Index subset of signalling species reflecting basal effector activity or gene expression level ($S^U \subset S$; *cf.* Step 2)
w	Total number of signalling species (*cf.* Step 2)
$\tilde{\mathbf{x}}$	Vector of continuous state variables (defining the normalised species activation levels) [n.u.] (*cf.* Eq. (3)/Step 3)
y	Relevance parameter of a logical transition (*cf.* Table S6)
z	Total number of upstream effector species (*cf.* Eqs. (2) and (3)/Steps 2 and 3)
τ	Time constant (defining signalling species response rate) [h] (*cf.* Eq. (3)/Step 3)

independently developed and tailored to the nature of the respective biological process under investigation (Goncalves et al., 2013).

Adequate model integration, moreover, exceeds pure coupling, as dimensions of the integrated model must not exceed a tractable scale whereas individual sub-model features might be worth being preserved in the course of model reduction. Karr et al. achieved a recent breakthrough by assembling a whole-cell model of *Mycoplasma genitalium* (Karr et al., 2012) which integrates different biological processes by means of mathematical formalisms specifically adapted to each of the 28 sub-modules considered. The metabolism was, for instance, represented using a genome-scale metabolic model and simulated *via* flux balance analysis (FBA), whereas RNA and protein degradation were modelled by *Poisson* equations. The sub-modules work autonomously for a small time scale (*e.g.* one second), subsequently exchanging information according to predefined rules. Related methods such as integrated (iFBA) (Covert et al., 2008) or integrated dynamic FBA (idFBA) (Lee et al., 2008) have been described within the context of linking metabolic models with gene regulatory networks. Simeonidis et al. (Simeonidis et al., 2013) presented another FBA-based concept with focus on

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