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► To cite this version:

Pierre Millard, Kieran Smallbone. Multi-scale modelling of E. coli metabolism. PeerJ, 2015, 3, pp.e1128. hal-01269219

HAL Id: hal-01269219

<https://hal.science/hal-01269219>

Submitted on 27 May 2020

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Multi-scale modelling of *E. coli* metabolism

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Abstract

In response to environmental and genetic perturbations, micro-organisms may regulate their metabolism both metabolically – via metabolite–enzyme interactions – and hierarchically – via modulating enzyme capacities. In this report, we develop a combined metabolic and genetic regulatory model of *E. coli* that may be used to test this multi-scale response.

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9 Metabolic module

10 A number of kinetic models of *E. coli* metabolism are available in the literature [1, 2, 3, 4, 5],
11 varying both in their level of detail and in their availability in standardised formats. As a
12 scaffold, we use the metabolic model of Chassagnole *et al.* [1], available from the BioModels
13 database [6] in SBML format [7] with accession number BIOMD0000000051. Some changes
14 are made to this model, to enhance its use:

- 15 • co-metabolites AxP and NAD/P/H are allowed to vary
- 16 • dilution of intracellular pools due to growth, which have a negligible effect on system
17 dynamics, are removed
- 18 • glucose uptake is set to an experimentally-determined initial rate of 1.23 mM s^{-1} , of
19 which 22% enters the pentose phosphate pathway [8]
- 20 • **rMax** values are rescaled to ensure the system starts at steady state, as was done in the
21 original paper
- 22 • biomass-producing branches (that is, those other than GPS, PDH and PPC) are coupled
23 via a single reaction, to simulate growth at an initial rate of $1.67 \times 10^{-4} \text{ s}^{-1}$. This
24 ensures that all the metabolic building blocks are used in stoichiometric proportions
25 dictated by the cell composition, and links metabolism to overall cell physiology.

26 Integration of metabolism with regulation of gene expression

27 The model of Nishio *et al.* [5] contains a detailed description of the glucose phosphotransferase
28 system (PTS) – the mechanism via which *E. coli* uptakes glucose – and its genetic regulation.
29 We encoded their model in SBML format, now available from the BioModels database with
30 accession number MODEL1501300000.

31 We found that the Nishio model shows a non-monotonic response of glucose flux to changes
32 in glucose levels: as glucose concentration increases beyond approximately 0.01 mM, glucose
33 uptake rate decreases. This non-physiological response appears to be due to an imbalance
34 between the “accelerator” and “brake” modules. Since this balance is controlled by the
35 “computer” module, we focused on this module to rebalance the two others. By increasing
36 the affinity of CYA for IIA^P – changing the parameter **kb** in reaction **binding_IIA_P_Cya**
37 from 100 to 5000 mM^{-2} – this non-physiological behaviour is alleviated.

38 We rescale glucose flux, as above, to rate 1.23 mM s^{-1} . This means that Nishio, and the
39 metabolic module set out above, are compatible models: their overlapping elements – the
40 PTS system – have equal fluxes, and the two models may be easily merged by removing the
41 simple PTS reaction from the metabolic model, and appending the entire Nishio model.

42 Expansion of the regulatory module

43 The model is then expanded through inclusion of transcription and translation for all the
44 metabolic enzymes. This is achieved by using the transcriptional and translational reactions
45 of Nishio to guide us as to typical parameter values for these processes. The approach of
46 building models using typical parameter values has been used previously to derive large-scale
47 metabolic models [9, 10]; the justification is that model is largely driven by its structure, and
48 hence approximate parameter values are often sufficient to produce correct overall behaviour.
49 Typical parameter values are set out in Table 1.

50 We finally added transcriptional regulation, in addition to that already in present in Nishio.
51 Included regulatory interactions are set out in Table 2.

52 Evaluation of predictive capabilities

53 The model developed here simulates the steady-state metabolic operation of *E. coli* growing
54 under abundant glucose. To test the predictive capabilities of this model, we simulate both
55 the time-course response of *E. coli* to a sudden decrease of glucose level (from 2 mM to 10 μ M,
56 Figure 1), and the steady-state reached by the system under a large range of glucose levels
57 (from 10 μ M to 10 mM, Figure 2).

58 Firstly, the metabolic and regulatory modules show different dynamics in response to a sudden
59 decrease of glucose concentration. While the metabolic module responds rapidly (in the
60 second to minute range), the regulatory module shows a slower response (in the minute to
61 hour range), as expected.

62 Secondly, both the steady-state glucose uptake and growth rates monotonically increase with
63 the glucose level. This is qualitatively consistent with observations, although the predicted
64 growth rate is higher than measured at low glucose levels. Expanding the model with addi-
65 tional metabolic pathways and/or regulatory interactions, as well as performing a new round
66 of calibration, may improve these predictions. Regarding intracellular fluxes, the partition
67 of carbon at the glycolysis-pentose phosphate pathway node is stable for all glucose levels,
68 which is in excellent agreement with experimental data [11].

69 Conclusion

70 We present a combined metabolic and genetic regulatory model of *E. coli*. Simulation results
71 indicate that, while the model is developed and calibrated using experimental data collected
72 under a unique metabolic steady-state, the predicted flux responses to perturbations are
73 consistent with current knowledge. Its predictive capabilities will be improved by refining
74 parameters and expanding it with additional metabolic and regulatory processes (e.g. post-
75 transcriptional regulation).

76 This model may be useful in the field of systems biology, to investigate the specific roles of
77 metabolic and hierarchical regulation in the long-term response of *E. coli* to environmental

78 and genetic perturbations. It may also assist the design of more efficient and robust cell
79 factories in biotechnology.

80 The model outlined here is available from the BioModels database with accession number
81 MODEL1503050000.

82 **Acknowledgements** KS was funded by the EU FP7 (KBBE) grant 289434 “BioPreDyn:
83 New Bioinformatics Methods and Tools for Data-Driven Predictive Dynamic Modelling in
84 Biotechnological Applications”. PM acknowledges the support of INRA.

Table 1: Typical parameter values, derived from Nishio *et al.*.

parameter	value	units
[gene]	2.43×10^{-7}	mM
[mRNA]	10^{-4}	mM
[protein]	10^{-2}	mM
[regulator:metabolite]	10^{-4}	mM
transcription	1	s^{-1}
translation	0.183	s^{-1}
mRNA degradation	2.43×10^{-3}	s^{-1}
protein degradation	1.83×10^{-3}	s^{-1}
effector:site binding	10^5	mM^{-1}

Table 2: Transcriptional regulatory interactions included in the model. Those in the top half are taken from Nishio *et al.*.

regulator	gene target	effect
Mlc	<i>ptsG</i>	–
	<i>ptsH</i>	–
	<i>ptsI</i>	–
Crp:cAMP	<i>crp</i>	+
	<i>cyaA</i>	–
	<i>mlc</i>	+/-
	<i>ptsG</i>	+
	<i>ptsH</i>	+
	<i>ptsI</i>	+
Crp:cAMP	<i>pdh</i>	–
Cra	<i>pfk</i>	–
	<i>ppc</i>	–
	<i>ptsH</i>	–
	<i>pyk</i>	–
	<i>tpi</i>	–
	<i>zwf</i>	–
PdhR:PYR	<i>pdh</i>	–

Figure 1: A sudden decrease of glucose levels (from 2 mM to 10 μ M) is applied to the model at $t = 100$ s. The glucose uptake flux immediately decreases after the decrease of glucose concentration (A). This results in an increase of cAMP production (B) and of its concentration (C). In turn, the concentration of Crp:cAMP complex increases (D) and regulates the transcription of genes encoding metabolic enzymes (e.g. *cyaA*, E) and global regulators (e.g. *crp*, G). The dynamics of mRNA levels (e.g. *cyaA*, F, and *crp*, H) are slower.

Figure 2: Steady-state response of the glucose uptake rate (solid, mM s^{-1}) and growth rate (dashed, s^{-1}) (A), and of the partition of carbon at the glycolytic (solid) – PPP (dashed) node (B) when glucose concentration is varied between $10 \mu\text{M}$ and 10mM .

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