Toward a quantitative *in silico* model for the *E. coli* ammonium assimilation system

Kazuhiro Maeda[1] Fred C. Boogerd[2], Frank J. Bruggeman[3,4,5],
Hans V. Westerhoff[2,5,6], and Hiroyuki Kurata[1,7]

1 Department of Bioscience and Bioinformatics, Kyushu Instituteof Technology, Iizuka, Fukuoka, Japan

2 Molecular Cell Physiology, Netherlands Institute for Systems Biology, VU University Amsterdam, The Netherlands

3 Regulatory Networks Group, Netherlands Institute for Systems Biology, Amsterdam, The Netherlands

4 Life Sciences, Centre for Mathematics and Computer Science (CWI), Amsterdam, The Netherlands

5 Synthetic Systems Biology, Swammerdam Institute for Life Sciences, University of Amsterdam, The Netherlands

6 Manchester Centre for Integrative Systems Biology, University of Manchester, UK

7 Biomedical Informatics R&D Center, Kyushu Institute of Technology, Iizuka, Fukuoka, Japan

Contact: kurata@bio.kyutech.ac.jp Tel&Fax 81-948-29-7828

Ammonium supports the fastest growth rate and is therefore considered the preferred nitrogen source for *Escherichia coli* [1]. The bacterium adds ammonium to α-ketoglutarate an intermediate of TCA cycle, for synthesizing glutamate and glutamine. ~88% of cellular nitrogen is derived from α-amino group of glutamate whereas the remainder is derived from the amide group of glutamine [2].

We propose a new kinetic model of *E. coli* ammonium assimilation network, centered on the regulation of glutamine synthetase (GS) and an ammonium transporter AmtB. Our model employs realistic kinetic parameter values and can quantitatively reproduce both metabolome dynamics upon ammonium upshift (Yuan et al., Mol Syst Biol, 2009) and experimental data regarding cell growth, ammonium assimilation flux and intracellular ammonium concentration under low ammonium conditions (Kim et al., Mol Syst Biol, 2012). Our modeling is achieved by the following novel ideas. (i) Incorporating the diffusion resistance enables the model to explain both Yuan's and Kim's data, because we found that Yuan's experimental data cannot be explained without taking into account ammonia/ammonium diffusion resistance in media. (ii) The parameter estimation problem is formulated as a constrained optimization problem, which minimizes changes in kinetic parameter values from their literature values and thus greatly enhances development of a realistic model. We revealed rational and integrative regulations of GS and AmtB, which limits futile cycling of ammonium.