**Llaneras, F.**; **Picó, J.**

**An interval approach for dealing with flux distributions and elementary modes activity patterns.** (English) Zbl 1451.92150

J. Theor. Biol. 246, No. 2, 290-308 (2007).

Summary: This work introduces the use of an interval representation of fluxes. This representation can be useful in two common situations: (a) when fluxes are uncertain due to the lack of accurate measurements and (b) when the flux distribution is partially unknown. In addition, the interval representation can be used for other purposes such as dealing with inconsistency or representing a range of behaviour.

Two main problems are addressed. On the one hand, the translation of a metabolic flux distribution into an elementary modes or extreme pathways activity pattern is analysed. In general, there is not a unique solution for this problem but a range of solutions. To represent the whole solution region in an easy way, it is possible to compute the $\alpha$-spectrum (i.e., the range of possible values for each elementary mode or extreme pathway activity). Herein, a method is proposed which, based on the interval representation of fluxes, makes it possible to compute the $\alpha$-spectrum from an uncertain or even partially unknown flux distribution.

On the other hand, the concept of the flux-spectrum is introduced as a variant of the metabolic flux analysis methodology that presents some advantages: applicable when measurements are insufficient (underdetermined case), integration of uncertain measurements, inclusion of irreversibility constraints and an alternative procedure to deal with inconsistency. Frequently, when applying metabolic flux analysis the available measurements are insufficient and/or uncertain and the complete flux distribution cannot be uniquely calculated. The method proposed here allows the determination of the ranges of possible values for each non-calculable flux, resulting in a flux region called flux-spectrum.

In order to illustrate the proposed methods, the example of the metabolic network of CHO cells cultivated in stirred flasks is used.

**MSC:**

92C42 Systems biology, networks
92C37 Cell biology



**Keywords:**

$\alpha$-spectrum; elementary modes; extreme pathways; metabolic flux analysis

**Software:**

Metatool; YANA

**Full Text:** DOI

**References:**

[1] Bonarius, H.P.J., Hatzimanikatis, V., Meesters, K.P.H., de Gooijer, C.D., Schmid, G., Tramper, J., 1996. Biotechnol. Bioeng. 50(3), 299–318.

[2] Bonarius, H. P.J.; Schmid, G.; Tramper, J., Flux analysis of underdetermined metabolic networks: the quest for the missing constraints, Tibtech, 15, 308-314 (1997)

[3] Cornish-Bowden, A.; Cárdenas, M. L., From genome to cellular phenotype—a role for metabolic flux analysis?, Nature Biotechnology, 18, 3, 267-268 (2000)

[4] Gambhir, A.; Korke, R.; Lee, J.; Fu, P. C.; Europa, A.; Hu, W. S., Analysis of cellular metabolism of hybridoma cells at distinct physiological states, J. Biosci. Bioeng., 95, 4, 317-327 (2003)

[5] Kitano, H., Computational systems biology, Nature, 420, 6912, 206-210 (2002)

[6] Klamt, S.; Schuster, S.; Gilles, E. D., Calculability analysis in underdetermined metabolic networks illustrated by a model of the central metabolism in purple nonsulfur bacteria, Biotechnol. Bioeng., 77, 7, 734-751 (2002)

[7] Klapa, M. I.; Park, S. M.; Sinskey, A. J.; Stephanopoulos, G., Metabolite and isotopomer balancing in the analysis of metabolic cycles: I. theory, Biotechnol. Bioeng., 62, 4, 375-391 (1999), 10.1002/(SICI)1097-0290(19990220)62:4&☒60;375::AID-

BIT1&⊠62;3.0.CO;2-O

[8] Palsson, B., The challenges of in silico biology, Nat. Biotechnol., 18, 11, 1147-1150 (2000)

[9] Papin, J. A.; Price, N. D.; Wiback, S. J.; Fell, D. A.; Palsson, B. O., Metabolic pathways in the post-genome era, Trends Biochem. Sci., 28, 5, 250-258 (2003)

[10] Papin, J. A.; Stelling, J.; Price, N. D.; Klamt, S.; Schuster, S.; Palsson, B. O., Comparison of network-based pathway analysis methods, Trends Biotechnol., 22, 8, 400-405 (2004)

[11] Pfeiffer, T.; Sanchez-Valdenebro, I.; Nuno, J. C.; Montero, F.; Schuster, S., METATOOL: for studying metabolic networks, Bioinformatics (Oxford, England), 15, 3, 251-257 (1999)

[12] Poolman, M. G.; Venkatesh, K. V.; Pidcock, M. K.; Fell, D. A., A method for the determination of flux in elementary modes, and its application to lactobacillus rhamnosus, Biotechnol. Bioeng., 88, 5, 601-612 (2004)

[13] Price, N. D.; Papin, J. A.; Schilling, C. H.; Palsson, B. O., Genome-scale microbial in silico models: the constraints-based approach, Trends Biotechnol., 21, 4, 162-169 (2003)

[14] Provost, A., Bastin, G., Agathos, S.N., Schneider, Y.J., 2005. Metabolic design of macroscopic models: application to CHO cells. Decision and Control, 2005 and 2005 European Control Conference.CDC-ECC'05.44th IEEE Conference on: pp. 2982-2989.

[15] Provost, A.; Bastin, G., Dynamic metabolic modelling under the balanced growth condition, J. Process Control, 14, 7, 717-728 (2004)

[16] Sauer, U., High-throughput phenomics: experimental methods for mapping fluxomes, Curr. Opin. Biotechnol., 15, 1, 58-63 (2004)

[17] Schilling, C. H.; Letscher, D.; Palsson, B. O., Theory for the systemic definition of metabolic pathways and their use in interpreting metabolic function from a pathway-oriented perspective, J. Theor. Biol., 203, 3, 229-248 (2000)

[18] Schilling, C. H.; Schuster, S.; Palsson, B. O.; Heinrich, R., Metabolic pathway analysis: basic concepts and scientific applications in the post-genomic era, Biotechnol. Progr., 15, 3, 296-303 (1999)

[19] Schmidt, K.; Nielsen, J.; Villadsen, J., Quantitative analysis of metabolic fluxes in Escherichia coli, using two-dimensional NMR spectroscopy and complete isotopomer models, J. Biotechnol., 71, 1-3, 175-189 (1999)

[20] Schuster, S.; Dandekar, T.; Fell, D. A., Detection of elementary flux modes in biochemical networks: a promising tool for pathway analysis and metabolic engineering, Trends Biotechnol., 17, 2, 53-60 (1999)

[21] Schuster, S.; Fell, D. A.; Dandekar, T., A general definition of metabolic pathways useful for systematic organization and analysis of complex metabolic networks, Nat. Biotechnol., 18, 3, 326-332 (2000)

[22] Schwartz, J. M.; Kanehisa, M., Quantitative elementary mode analysis of metabolic pathways: the example of yeast glycolysis, BMC Bioinformat., 7, 186 (2006)

[23] Schwarz, R.; Musch, P.; von Kamp, A.; Engels, B.; Schirmer, H.; Schuster, S.; Dandekar, T., YANA—a software tool for analyzing flux modes, gene-expression and enzyme activities, BMC Bioinformat., 6, 1, 135 (2005)

[24] Stelling, J.; Klamt, S.; Bettenbrock, K.; Schuster, S.; Gilles, E. D., Metabolic network structure determines key aspects of functionality and regulation, Nature, 420, 6912, 190-193 (2002)

[25] Stephanopoulos, G. N.; Aristidou, A. A.; Nielsen, J., Metabolic Engineering: Principles and Methodologies (1998), Academic Press: Academic Press San Diego

[26] Wagner, A.; Fell, D. A., The small world inside large metabolic networks, Biological Sciences, 268, 1478, 1803-1810 (2001)

[27] Wiback, S. J.; Mahadevan, R.; Palsson, B. O., Reconstructing metabolic flux vectors from extreme pathways: defining the alpha-spectrum, J. Theor. Biol., 224, 3, 313-324 (2003)

[28] Wiechert, W.; Mollney, M.; Petersen, S.; de Graaf, A. A., A universal framework for 13C metabolic flux analysis, Metab. Eng., 3, 3, 265-283 (2001)

[29] Zupke, C.; Stephanopoulos, G., Intracellular flux analysis in hybridomas using mass balances and in vitro 13C NMR, Biotechnol. Bioeng., 45, 4, 292-303 (1995)