Analysis of branched-chain amino acid biosynthesis by a Thomas network approach

Aurélie Urbain, Pierre Renault, S.Dusko Ehrlich, Jean-Michel Batto

INRA - Institut National de la Recherche Agronomique

Jean-Michel Batto, UR895 – Domaine de Vilvert 78352 Jouy-en-Josas, FRANCE
Email : jean-michel.batto@jouy.inra.fr

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Cellular growth depends upon the ability of the cell to synthesize new molecules from nutrients present in the environment. It includes a lot of different processes such as increase in cell mass, catabolism and anabolism of various components, duplication of the bacterial chromosome as well as transcription and translation of genes. During the phase of exponential growth, cells divide at a constant rate depending on availability of nutrients and on their ability to form new membrane and proteins. Because of the complexity of biology encompassing all these interactions by a holistic approach is a difficult task. For example, *Bacillus subtilis* biosynthesis of amino acids requires 120 genes [1].
Our goal is to better understand biological mechanisms involved in cell growth by building a predictive computational model. So we prefer to adopt a step-by-step approach and work on targeted mechanisms. We focused on the prediction of one biological mechanism in one species, hoping to achieve a general understanding of the mechanism (holding true for many, and ideally all, species). Thus, we are working on a local/transversal approach with the aim of combining genetic and enzymatic levels of regulation in order to describe production of essential aminoacid. Our model aims to describe the production of Isoleucine Leucine and Valine (ILV) during growth of the widely studied bacteria *B.subtilis*, *L.lactis* and *E.coli*.
We are attempting to draw a first draft of a common regulation pattern in the absence of the requested wet lab data, using a regulation network modeling. In fact, we can build a topological view of interaction for the studied regulation, but we lack in-vitro view of the metabolite-protein interactions. As the topological model can only support a set of untested hypotheses, we use the formal logic of René Thomas [2-4] to describe the differential equations governing the studied process. However, the space of possibilities is huge. For example a model with 4 interactants and 12 direct activation and feedback regulations yields to a set of 1022 networks. To reduce this space we use a model checker (NuSMV [5]) associated with SMBioNet [6] to represent the global regulatory network as a graph.
The reduction of the space is based on a systematic validation of each graph. A selected biological regulatory graph would describe a true regulation network as it corresponds to a biological fact. In the prospect of describing the differences between the selected networks, we have designed a protocol that allow the classification of the set of networks. We used the length of the graph, the existence of a dead-end and the number of loops for traveling between René Thomas state's. Preliminary results show a correlation between length of the networks and the growth rate. Our next objective is to test variants of a studied formal model and deduce biological property of the subset we study.
This approach should be relevant to a number of complex systems. As it combines the contribution of different levels of regulation, our *in silico* model will be a fast and easy-to-use tool to test hypothesis for wet lab biologists at the early stage of their research projects.

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