

Reverse Engineering of Network Models of Bioartificial Liver Cell Systems

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ABSTRACT: Reverse engineering methods play an important role to elucidate network structures and parameters that exist in natural and bioartificial systems of life. Man-made bioartificial cell systems designed to be used in medical therapy take their key characteristics from nature. Analysing such bioartificial cell systems by reverse engineering methods can not only contribute to their advanced design, operation and control with respect to therapy but can in turn also substantially improve understanding of natural cell systems. This in particular applies when such systems are used for bioartificially inspired elucidation of information processing structures and parameters that are immanent in them as a necessary precondition of their functioning. This paper reports on the network model based analysis of a bioartificial liver cell system consisting of primary human liver cells cultured in the artificial environment of a specially designed bioreactor. This multi-compartment capillary membrane bioreactor closely mimics conditions existing in the natural liver organ. The bioartificial system serves to recover and maintain human liver cells for use in liver support therapy. Different network reconstruction methods were employed in order to elucidate interrelations between various variables based on their bioreactor input/output measurements and the bioreactor performance. Methods applied focused on the reconstruction of correlation networks as non-directed models, of rule based networks and Bayesian networks as directed probabilistic models and of differential equation systems as directed deterministic models. Prior to application of most of these methods, cluster analysis of the time courses (kinetics) of the variables was carried out to typify their dynamics. Data analysed originated from up to 86 bioreactor runs with primary human liver cells. Using the network models with respect to the prediction of the long-term performance of the liver cells inside the bioreactor, the analysis yielded that no single kinetic variable of the 33 investigated (15 biochemical ones and 18 amino acids) is better suited to predict all bioreactor performance levels (low, medium, high) than galactose, followed second by urea. Of the amino acids at least two, methionine and leucine, are jointly required to reliably predict all three performance levels. These findings were supported by an additional analysis of data that describe donor organ properties and preservation as well as cell isolation and inoculation prior to bioreactor operation (25 non-kinetic variables) where no single or joint variables could be found that would better predict all bioreactor performance levels than the variables named above. A major result obtained by the network analysis was that for high performance bioreactor runs many strong correlations exist between the various variables' kinetics, while for medium and low performance runs this is not the case, i.e. it was quantitatively shown that there is a substantial breakdown in the network interconnections when the bioartificial system is not functioning at high performance level. Based on the specific quantitative results obtained applying the network reconstruction methods described, a number of more general issues related to nature-inspired information systems will also be addressed, such as predictability of complexity, robustness of behaviour and order in highly complex systems. The results altogether demonstrate the high potential of the applied reverse engineering methods to elucidate network structures and parameters of bioartificial systems and potentially of other systems of life and nature, too.

KEYWORDS: Reverse Engineering, Network Model Reconstruction, Nature-inspired Systems, Bioartificial Systems, Liver Support Therapy, Systems Biology