A Modular Elementary Flux Mode Reduction Procedure for Dynamic Metabolic Modelling

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1 Abstract

Elementary flux modes (EFMs) are a powerful concept in metabolic engineering for the derivation of macroscopic dynamic models, which are useful for the design of bioprocess monitoring and control strategies. However, for detailed metabolic networks, the number of modes increases significantly leading to an intractable initial set of EFMs. In that context, systematic procedures for the generation or selection of subsets of EFMs are required. In a preliminary study [1], the authors proposed such a procedure, which is improved in the current study by including additional features, including the computation of the initial set of elementary vectors, the differentiate consideration of positivity constraints on the fluxes and the prediction error of reduced macroscopic reaction sets (reduced below the number of measured components). The procedure proceeds in several steps including minimal generation algorithms and geometric and optimization-based criteria for the reduction while ensuring a biological interpretation of the reduced set of modes. This work makes use of experimental data of CHO-cells in batch cultures on the basis of a detailed network and proposes different measurement configurations to highlight the performance of the procedure. Finally, a simple dynamic model including the prediction of the biomass is built on the basis of the resulting macroscopic bioreaction scheme.

2 Methods and results

Fig.1 illustrates the reduction procedure aimed at systematically reducing the number of elementary flux modes up to a number Λ chosen below the number of measured extracellular species. It starts from an initial set of modes generated by complete enumeration or subset selection and is made of several steps which can all be activated or bypassed as necessary. The reduction ensures (i) the removal of modes leading to macroreactions without a biological interpretation, (ii) the elimination of collinear modes based on a cosine-criterion and (iii) the respect of positivity constraints and the satisfaction of a least-squares deviation from experimental data by means of a series of optimization problems.

This study relies on a detailed metabolic network leading to

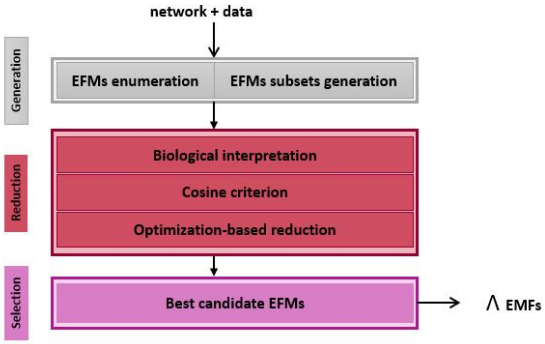

Figure 1: The reduction procedure

almost one billion EFMs, giving to the reduction procedure all its significance. In this case, a fast generation algorithm is used to identify an initial subset of modes and the reduction is executed to select a number of elementary flux vectors below the number of measured components. Different case studies are addressed, i.e., either 6 or 20 extracellular measurements. Validations are provided and show very satisfactory results. Fig.2 depicts the evolution of the measured concentrations as compared to the prediction of a dynamic simulator built on the basis of the bioreaction scheme obtained with the EFM reduction procedure.

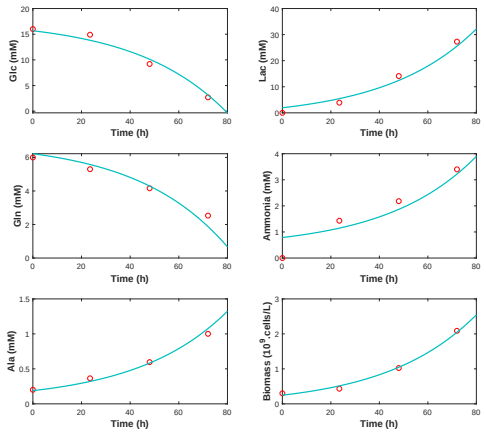

Figure 2: Time evolution of measured concentrations

References

[1] M. Maton, Ph. Bogaerts, and A. Vande Wouwer, "Selection of a suboptimal minimal set of EFMs for dynamic metabolic modelling," IFAC-PapersOnLine, 2021. Vol.54(3) 667-672