

Selection of Elementary Flux Modes for the Development of Reduced Macroscopic Models

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1 Abstract

Over the years, mathematical modelling of mammalian cell cultures has received an ever increasing attention for the optimization of the production of biopharmaceuticals, such as monoclonal antibodies, viral vaccines and recombinant proteins. The development of dynamic macroscopic models from the knowledge of detailed metabolic networks relies on the concept of elementary flux modes (EFMs) regarded as the simplest metabolic pathways linking substrates to products. With the complexity and the size of the network, the number of elementary modes explodes and a selection of the most informative modes is required. In this connection, the present study proposes an algorithm called REM, i.e., Reducer of Elementary Modes, to cut the initial set of modes and to pick the most informative ones for the purpose of deriving reduced macroscopic models. The REM algorithm is a two-step procedure. First, the initial set of EFMs is drastically reduced by enlarging the concept of the cosine-similarity algorithm introduced in [1]. Then, the methodology is pursued by extracting the most informative modes from the first reduced set by means of a series of optimisation problems. This work makes use of experimental data of hybridoma cultures in batch and perfusion modes and two metabolic networks of different sizes illustrate the performance of the whole procedure.

2 REM algorithm

Fig.1 depicts the reduction algorithm used to select a minimal set of elementary modes, $K_{reduced}$, from an initial set K , this latter obtained on the basis of the metabolic network knowledge and the measurements of extracellular fluxes. The REM algorithm is an iterative method based on an optimisation problem where SSR_q represents the sum of squared residuals and determines if the observed phenotypes are part of the solution space. The whole procedure is mainly composed of two steps : (i) a pre-filtering exploiting the cosine similarity for collinearity identification and (ii) a further reduction to identify and retain the most informative modes according to a target number fixed beforehand. These steps involve a number of checks where a user-defined tolerance value guides the selection.

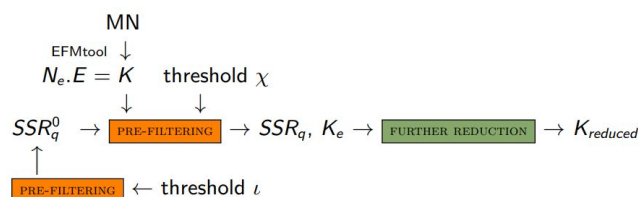


Figure 1: REM algorithm

3 Results

The present study relies on two metabolic networks and different measurements scenarios. The first network includes only 24 reactions leading to 11 EFMs, the second considers 70 reactions and leads to more than 22 thousands modes justifying the use of reduction algorithms. In that respect, when the methodology is applied to the more detailed network, the pre-filtering step allows cutting the initial set of EFMs from 22'563 to 476 and the subsequent steps allow a further reduction to 22 modes or less - depending on the measurements scenario and the fixed target number. Fig.2 shows the evolution of lactate concentration deduced from 476 modes (orange line) and from 22 modes (green line). This figure illustrates the merits of the REM algorithm.

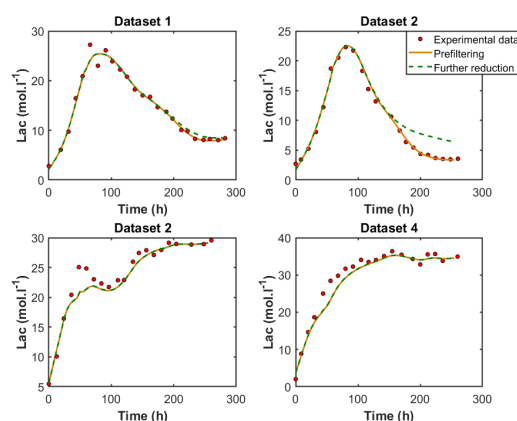


Figure 2: Time evolution of lactate concentration

References

- [1] L. Hebing, T. Neymann, T. Thüte, A. Jockwer, and S. Engell, "Efficient generation of models of fed-batch fermentations for process design and control," IFAC-PapersOnLine, 2016. Vol.49(7) 621-626