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An assessment of methods of moments for the simulation of population dynamics in large-scale bioreactors

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HIGHLIGHTS

- A biological population balance model is solved using class and moment methods.
- Homogeneous chemostat and heterogeneous fedbatch cultures are simulated.
- Methods are compared through accuracy, stability and computation time.
- The Maximum Entropy method is found to be unstable in the present test-cases.
- QMOM and EQMOM are well suited and have major advantages against class method.

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ABSTRACT

A predictive modelling for the simulation of bioreactors must account for both the biological and hydrodynamics complexities. Population balance models (PBM) are the best approach to conjointly describe these complexities, by accounting for the adaptation of inner metabolism for microorganisms that travel in a large-scale heterogeneous bioreactor. While being accurate for solving the PBM, the Class and Monte-Carlo methods are expensive in terms of calculation and memory use. Here, we apply Methods of Moments to solve a population balance equation describing the dynamic adaptation of a biological population to its environment. The use of quadrature methods (Maximum Entropy, QMOM or EQMOM) is required for a good integration of the metabolic behavior over the population. We then compare the accuracy provided by these methods against the class method which serves as a reference. We found that the use of 5 moments to describe a distribution of growth-rate over the population gives satisfactory accuracy against a simulation with a hundred classes. Thus, all methods of moments allow a significant decrease of memory usage in simulations. In terms of stability, QMOM and EQMOM performed far better than the Maximum Entropy method. The much lower memory impact of the methods of moments offers promising perspectives for the coupling of biological models with a fine hydrodynamics depiction.

1. Introduction

The large-scale simulation of bioreactors is currently a challenging issue. Such simulations must account for both (i) the (multiphase) hydrodynamics and (ii) the metabolic behaviour of the biological population carried by the fluid. The first can be achieved through the use of widespread CFD softwares which require significant computational power. The second can be addressed with advanced cell models which result from community efforts to integrate genome-scale reconstructions of a strain metabolic network and depict thousands of intracellular reactions and metabolite concentrations. Examples are the iJO1366 model for *Escherichia coli* (Orth et al., 2011) and the consensus YEAST model for *Saccharomyces cerevisiae* (Heavner et al., 2012; Heavner et al., 2013). These models describe state of the art knowledge of a cell metabolism, however their implementations require to solve either cumbersome optimization problems to access a steady-state cell-functioning, or to solve dynamically the metabolite concentrations in a cell that experiences exogeneous perturbations.

Even though the computational power increased significantly over the past few decades, it is still not possible to couple the CFD approach with a biological modelling that fully embraces the biological complexity. Such an approach is numerically untractable as it requires to solve dynamically the intracellular concentrations for each cell in a bioreactor with an Euler-Lagrange framework.

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Notation

Roman

C	concentration ($kg.m^{-3}$)
H	Shannon entropy
K	biological affinity constant ($kg.m^{-3}$)
L	quadrature node abscissae (h^{-1})
m	moment of distribution n ($kg.m^{-3}.h^{-k}$)
n	number density function ($h.kg_X.m^{-3}$)
N	number of resolved moments
NC	number of classes
N_c	number of compartments
P	order of moment methods
q	specific reaction rate ($mol.kg_X^{-1}.h^{-1}$)
Q	flow rate ($m^3.h^{-1}$)
R	reaction rate ($kg.m^{-3}.h^{-1}$)
T	time constant of adaptation (h)
V	compartment volume (m^{-3})
w	quadrature node weight ($kg_X.m^{-3}$)
Y	stoichiometric molar coefficient ($mol.mol^{-1}$)

Subscript and superscript

$\tilde{x}$	population mean value
x^*	equilibrium value
x_a	achieved value
x_A	acetate
x_G	glucose
x_i	inhibition
x_k	moment order
x_m	compartment index
x_n	compartment index
x_O	oxygen
x_T	threshold value

Greek symbols

ε	turbulent energy dissipation rate ($W.kg^{-1}$)
κ	PDF kernel
μ	growth rate ($g_X.g_X^{-1}.h^{-1}$)
ν	kinematic viscosity ($m^2.s^{-1}$)
φ	polynomial coefficient
Φ	specific uptake rate ($g.g_X^{-1}.h^{-1}$)
Ψ	environmental limitation coefficient
σ	standard deviation (h^{-1})
ζ	rate of change of specific growth rate (h^{-2})

Therefore, two simplified approaches are usually applied. On the one hand, one can neglect the spatial heterogeneity and solve a complex metabolic model in homogeneous batch or chemostat cultures (Meadows et al., 2010; Matsuoka and Shimizu, 2013). On the other hand, one will describe the hydrodynamic complexity jointly with a simplified biological approach such as either structured or unstructured kinetic models (Bezzo et al., 2003; Elqotbi et al., 2013; Lu et al., 2015).

Concentration gradients are known to be responsible for metabolic dysfunctions in large-scale reactors (Enfors et al., 2001), therefore we should avoid the first approach and describe the spatial heterogeneities. However, the use of kinetic models should be discarded too. Indeed, from the point of view of a cell travelling in these heterogeneous concentrations fields, the concentration signal is fluctuating (Linkès et al., 2014; Haringa et al., 2016). This make kinetic models inappropriate as they are usually based on the Monod kinetics law which reflects a steady-state equilibrium between a population and its environment. By making use of a Monod law, the kinetic models have "been over simplified by allowing instantaneous adaptation of the cell to the abiotic environment" (Silveston et al., 2008).

In previous work (Pigou and Morchain, 2015), we stepped back in both the hydrodynamic description by using a Compartment Model Approach (Cui et al., 1996; Mayr et al., 1993; Vrábel et al., 2000; Vrábel et al., 2001) and in the metabolic description of *E. coli* by simplifying the key reactions of the central carbon metabolism into a 6 reactions model inspired by the model proposed by Xu et al. (1999). More importantly, we introduced the use of a Population Balance Model (PBM) as a key modelling tool that allows describing simultaneously both (i) the concentration gradients, (ii) a dynamic adaptation of cells to the fluctuating conditions they experience along their trajectories and (iii) the metabolic impact of a disequilibrium between a cell and its local environment. This approach has been successfully challenged against experimental data in lab-scale batch culture and industrial-scale heterogeneous fedbatch culture. More recently, we improved the PBM to account for an experimentally observed stochastic diversity related to cell-division (Morchain et al., in press).

Until now, we solved the PBM using a class method (also known as fixed pivot method, Kumar and Ramkrishna (1996a, 2001)) with at least 60 classes to span the entire range of possible values for the chosen variable (i.e. the maximum growth-rate achievable by a cell provided enough nutrients are available). Each class represents a scalar that must be transported by the hydrodynamic framework. While transporting a hundred classes within a 70 compartments model (Pigou and Morchain, 2015) was perfectly feasible, doing the same in a CFD simulation would be prohibitively expensive.

The current paper thus makes the focus on improving the numerical tractability of the PBM, through the use of the Method of Moments (MOM), in order to increase the allowed level of spatial accuracy. Instead of performing a direct resolution of the population balance equation, the MOM describes the evolution of the first moments of a Number Density Function (NDF). However, it will be of interest to perform a reverse operation and to recover an approximation of the NDF from a finite set of its moments; this is known as a truncated moment problem (Abramov, 2007).

Many methods are available to tackle this problem. A review of such methods is available (John et al., 2007) though new methods or improvements are available since its publication. More recently, Lebaz et al. (2016) compared the most common approaches which are Kernel Density Element Method (KDEM), Spline-based method, and the Maximum Entropy (MaxEnt) method applied to the case of a depolymerization process. The KDEM approximates the unknown NDF as the sum of weighted Kernel Density Functions (KDF). The identification of the weights is performed through a constrained minimization procedure, which requires a high number of moments to prevent an underdetermined problem and the multiplicity of solutions. The spline method (John et al., 2007) leads to a piece-wise polynomial reconstruction, but the resulting reconstruction is highly dependent on numerical parameters, and can lead to negative values of the reconstructed NDF. For these reasons, the KDEM and spline methods will be discarded in the current work.

The MaxEnt method (Mead and Papanicolaou, 1984; Tagliani, 1999) was point out as efficient and accurate, even with a low number of moments, by Lebaz et al. (2016). It is however