Computational costs related to *Bohl-Marek decomposition* applied to a class of biochemical networks

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This study presents an application of one special method, further called as Bohl-Marek decomposition, related to the mathematical modeling of biochemical networks with mass conservation properties. Erich Bohl and Ivo Marek used this method in series of papers, e.g. [1, 2, 3], to transform systems of nonlinear ODEs arising in biochemical networks into a set of smaller, quasi-linear subsystems. The smaller subsystems can be expressed as linear ODEs with matrices that are negative M-matrices, i.e. $\dot{x}_M(t) = M(x(t))\, x_M(t)$. While Erich Bohl and Ivo Marek used this method to prove existence and uniqueness results, here we show computational advantages when compared with solving the original system of nonlinear ODEs in form $\dot{x}(t) = Ax(t) + b(t)$. Although our ultimate goal is to propose an efficient and reliable procedure for fitting model parameters to experimental data of a corresponding biochemical process, i.e., to solve an inverse problem, here, we study specific numerical issues within the framework of the forward initial value problem for ODEs. More precisely, for the two model formulations, (i) the classical formulation and (ii) the 'quasi-linear' Bohl-Marek formulation, we determine and compare the computational costs related to both.

ODE system governing the wide class of biochemical systems (non-autonomous due to the input $u(t) = d_{dose}(t)$) has the form of

$$\frac{\mathrm{d}\, x(t)}{\mathrm{d}\, t} = Ax(t) + b(x(t)) + u(t), \tag{1}$$

where the state variables $x(t) \in \mathcal{R}^n$. Given initial conditions $x(0) = x_0$, an IVP is well defined. The matrix of constant coefficient A represents the linear part of the system, while the vector b represents nonlinear (bilinear) parts $(x_i\, x_j)$, $i \neq j$.

Example The ODE system (1) describing the processes under study, see Fig. 1 and the table below, can be systematically derived as a linear transformation (imposed by the matrix S, the so-called stoichiometric matrix $S \in \mathcal{R}^{n\times q}$, q is the number of reactions including the transport of species X) of the vector of reaction rates $\nu \in \mathcal{R}^q$, which depends on corresponding states $x = (X_{ext}, X_{int}, E, C, P)^T$ and model parameter vector $p = (k_0, k_1, k_{-1}, k_2)^T$. I. e., $\dot{x}(t) = S\, \nu(x, p)$.
Reaction networks frequently possess subsets of reactants that remain constant at all times. Generally, there exists a conservation matrix Γ (with dimension $h \times n$), where the rows represent the linear combination of conserved species, which are constant in time. It can be solved explicitly for large systems ($0 = \Gamma\, S$). For our case, the conservation property reads

$$x_3 + x_4 = e_0, \quad x_1 + x_2 + x_4 + x_5 = u_0, \quad \Gamma = \begin{pmatrix} 0 & 0 & 1 & 1 & 0 \\ 1 & 1 & 0 & 1 & 1 \end{pmatrix}. \tag{2}$$

Description of the related process	Chem. notation	Param.
R_0: Substrate X_{ext} dosing (model input)	$\emptyset \to X_{ext}$	$u(t)$
R_1: Substrate transport between compartments	$X_{ext} \rightleftharpoons X_{int}$	k_0
$R_{2,3}$: Enzyme E binds to substrate, reversibly	$X_{int} + E \rightleftharpoons C$	$k_1,\ k_{-1}$
R_4: Complex breaks down into E plus Product	$C \to E + P$	k_2

The existence of relations (2) signifies not only the possibility to reduce the number of state variables, but also induces the reformulation of the governing equations for species concentration using negative M-matrices, see (3).

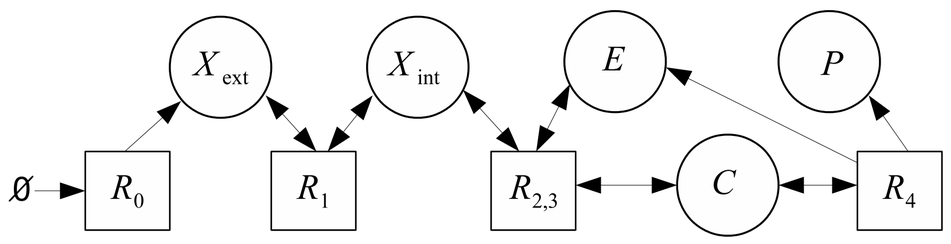

Figure 1: *Graph representation of the biochemical process. Reaction nodes identified by squares represent reactions between species nodes (circles).*

M-Matrix In our case study, the state variables can be listed in two subsets $\{x_3, x_4\}$ and $\{x_1, x_2, x_4, x_5\}$, and thus the non-linear ODEs (1) can be represented as a linear system with the system matrix of a special form, a negative M-matrix. These two subsets of state variables can be assembled and merged together as follows: $\tilde{x}(t)^T = \left(x^{1^T}(t),\ x^{2^T}(t)\right)$. Then the ODE system for modified state variable vector $\tilde{x}(t)$ is

$$\frac{\mathrm{d}\tilde{x}(t)}{\mathrm{d}t} = M\tilde{x}(t), \qquad M = \begin{pmatrix} M_1 & 0 \\ 0 & M_2 \end{pmatrix}, \tag{3}$$

$$M_1 = \begin{pmatrix} -k_1 \cdot x_2 & k_{-1} + k_2 \\ k_1 \cdot x_2 & -(k_{-1} + k_2) \end{pmatrix}, \quad M_2 = \begin{pmatrix} -k_0 & k_0 & 0 & 0 \\ k_0 & -k_0 - k_1 \cdot x_3 & k_{-1} & 0 \\ 0 & k_1 \cdot x_3 & -(k_{-1} + k_2) & 0 \\ 0 & 0 & k_2 & 0 \end{pmatrix}.$$

Results Numerical experiments consist of comparison of three methods: (i) ODE system (1), 5 equations; (ii) simplified ODEs (1) using Conservation Property (2), 3 equations; and (iii) Bohl-Marek decomposition (3), 6 equations. The first two systems contain nonlinear terms (so the Newton method as an inner iteration must be used) while the third one not. Stopping criteria for the inner Newton method are 10^{-6} and max number of extra inner Newton iterations is set to 1. **NWT** is the total number of extra Newton iterations, while **Relative error** and **Time** mean the total relative difference of the solutions and time speedup, both related to the full system (1), respectively.

Model	NWT	Relative error	Time (speed up)
Full ODE (1)	88	-	1.00
Simplified (1) using CP	381	2.20E-3	0.86
Bohl-Marek (3)	-	8.14E-2	0.61

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