Construction and evaluation of "global" Micahelis-Menten reduced models

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Objectives

A detailed analysis of the Michaelis-Menten (MM) biological mechanism [1] is reported. Reduced models of the MM mechanism are widely used in the fields of biology, pharmacokinetics and ecology to eliminate the multiscale behavior of the mechanism. The present analysis is based on the algorithmic *Geometric Singular Perturbation Theory* (GSPT) and aims on:

a) the construction of stable and accurate reduced models with "global" validity and

b) acquiring better understanding about the physical processes under investigation

Methods

The analysis is carried out with the use of the *Computational Singular Perturbation* (CSP) iterative algorithm [2], which provides:

i) approximation of the relations emerging from the constrains of the system (emanating equilibria),

ii) stable and accurate slow system, which governs the constrained solution on the above relations,

iii) diagnostic tools for the physical understanding of the processes [3], by identifying:

- the reactions contributing in the generation of the fast timescales,
- the reactions generating the emanating equilibria and
- the variables related the most with the fast timescales

iv) algebraic criteria for the evaluation of the validity of the traditional *Partial Equilibrium* (PEA) and *Quasi Steady-State* (QSSA) approximations [4].

CSP is employed for the derivation of new reduced models, which are validated for both stability and accuracy. Algebraic criteria are derived for the validity of traditional PEA and QSSA approximations.

Mathematical Model
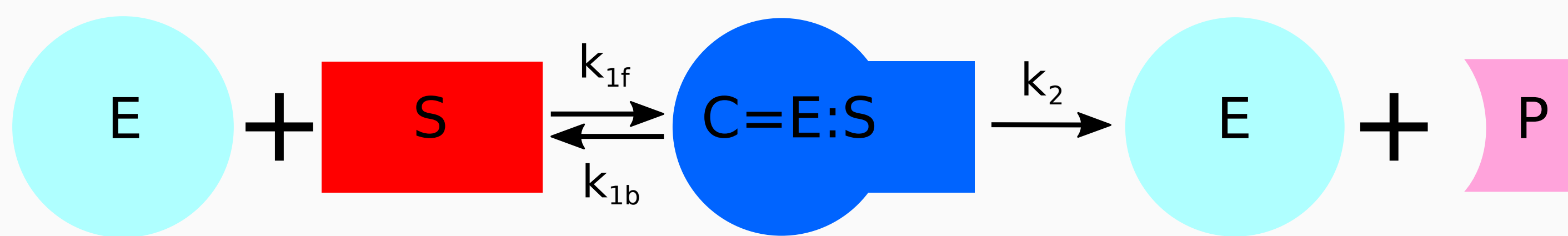
Chemical Kinetics and conservation laws for the MM system:

$$\frac{ds}{dt} = -k_{1f}(e_0 - c)s + k_{1b}c$$
$$\frac{dc}{dt} = k_{1f}(e_0 - c)s - k_{1b}c - k_2c$$

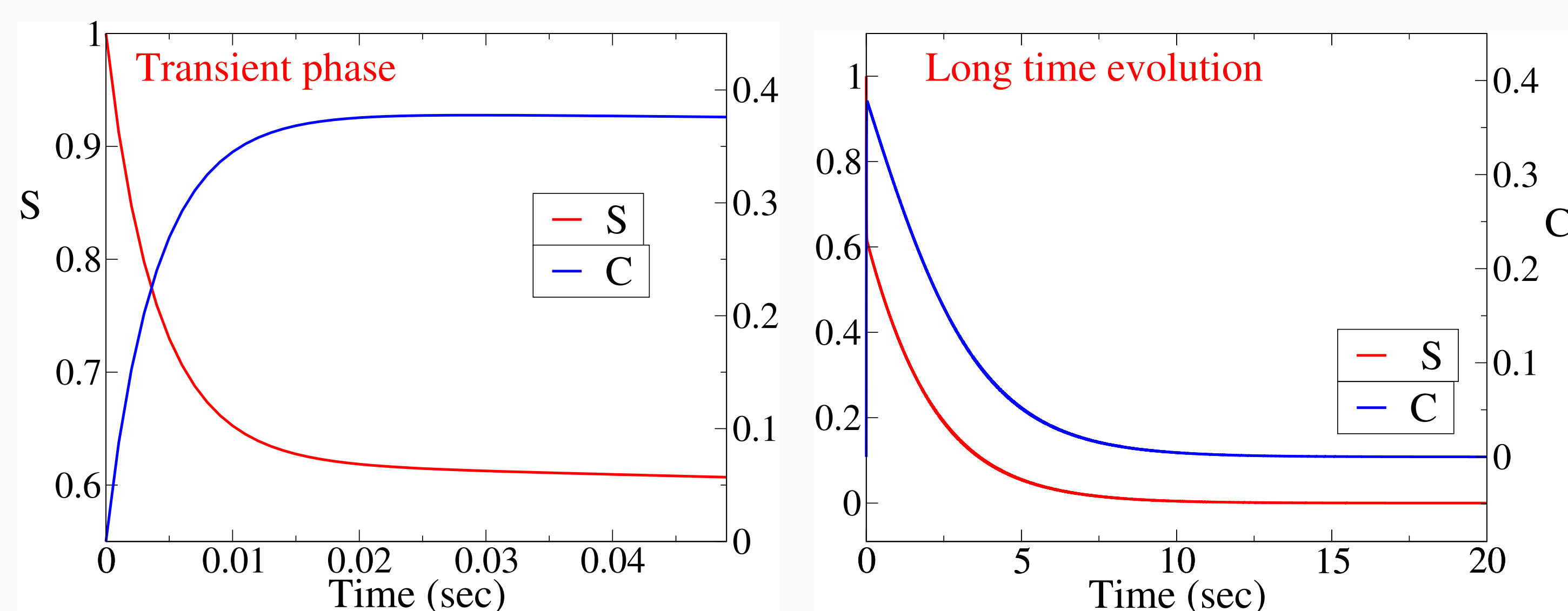| Concentrations		Kinetic Parameters	
c	Complex	k_{1f}	Forward rate constant
s	Substrate	k_{1b}	Backward rate constant
e_0	Initial Enzyme	k_2	Catalysis constant

Fig. 1: Solution of the system for $k_{1f} = k_{1b} = 100$, $k_2 = 1$ and $e_0 = s(0) = 1$, $c(0) = 0$.

CSP reduced models

The CSP algorithm identifies the variable and the reaction related the most with the fast processes of the MM mechanism and constructs the CSP reduced models, which consist of:

i) the algebraic equation, emanating from the equilibrations of the physical processes

$$f_1(s, c) \approx 0$$

ii) the slow system that drives the system under these equilibrations

$$\frac{d}{dt}\begin{bmatrix} s \\ c \end{bmatrix} \approx \begin{bmatrix} a_1 \\ a_2 \end{bmatrix} f_2(s, c)$$

The CSP-generated reduced models are free of the fast processes.

Validation

Depending on which variable (c or s) relates the most to the fast timescale, the CSP algorithm constructs the CSP_c or CSP_s reduced models.

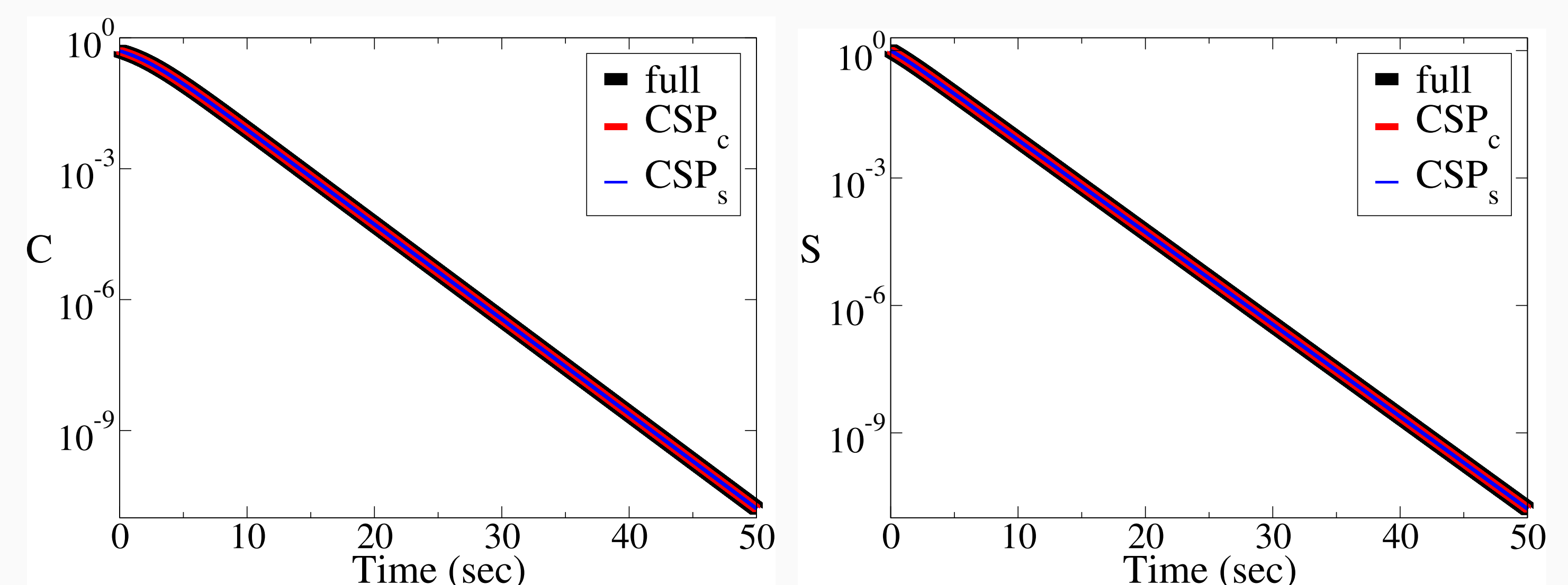**$k_{1f} = k_{1b} = 1000$, $k_2 = 1$ and $e_0 = 1$ (PEA valid)**

Fig. 2: Solution of the CSP_c and CSP_s reduced models (red and blue) in comparison with the full MM mechanism (black), with initial conditions satisfying the $f_1(s(0), c(0)) = 0$ algebraic equation.
Left figure: Complex c on time, Right figure: Substrate s on time

Property	Behavior	Evaluation
Stability	Smooth evolution of the CSP reduced models	$\checkmark$
Accuracy	Small relative error of $O(10^{-6})$ arising from the solutions	$\checkmark$

Both c and s are identified to be equally related with the fast timescale, therefore both CSP_c and CSP_s reduced models are stable and accurate.

PEA/QSSA validity criteria

New conditions under which the traditional PEA/QSSA are valid.

	Stability	Accuracy	Bibliography
PEA	$\dfrac{K}{K_M + s} \ll 1$	$\dfrac{K(e_0 - c)}{(K_M + s)(K_R + s)} \ll 1$	-
QSSA$_{s1}$	Always	$\dfrac{K_R + s}{e_0 - c} \ll 1$	$\dfrac{K}{e_0} \ll 1$, $\dfrac{s_0}{e_0} \ll 1$
QSSA$_{c1}$	$\dfrac{K}{K_M + s} \ll 1$	$\dfrac{K(e_0 - c)}{(K_M + s)(K_R + s)} \ll 1$, $\dfrac{e_0 - c}{K_R + s} \ll 1$	-
QSSA$_{c2}$	$\dfrac{K_R + s}{K_M + s} \ll 1$	$\dfrac{e_0 - c}{K_M + s} \ll 1$	$\dfrac{e_0}{K_M + s_0} \ll 1$

$$K_R = k_{1b}/k_{1f} \qquad K = k_2/k_{1f} \qquad K_M = K_R + K = (k_{1b} + k_2)/k_{1f}$$

Conclusions

The CSP iterative algorithm provides:

- **Stable** and **accurate** MM reduced models. Important for **parameter estimation** purposes
- **Robust** reduced models, under any set of kinetic parameters
- **Qualitative** understanding of the process
- **Systematization** of the literature on MM mechanism
- New **validity criteria** of the traditional PEA/QSSA approximations

References

[1] Michaelis, L., and Menten, M. L. "Die kinetik der invertinwirkung." Biochem. z, 49.333-369 (1913): 352.
[2] Lam, S. H., and Goussis D. A. "The CSP method for simplifying kinetics." International Journal of Chemical Kinetics, 26.4 (1994): 461-486.
[3] Lam, S. H., and Goussis D. A. "Understanding complex chemical kinetics with computational singular perturbation." Symposium (International) on Combustion. Vol. 22. No. 1. Elsevier, 1989.
[4] Goussis, D. A. "Quasi steady state and partial equilibrium approximations: their relation and their validity." Combustion Theory and Modelling, 16.5 (2012): 869-926.

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