Asymptotic Analysis on a TMDD model: Control of the process

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Objectives

A detailed multi-scale analysis of an one compartment PKPD target mediated drug disposition model (TMDD) is performed. This TMDD model incorporates the interaction of a drug with its target, the binding of the compounds (generation of the complex) and the outcome of their interaction.

The purpose of this analysis is to identify methodologies for the control of the process by acquiring a full system-level understanding.

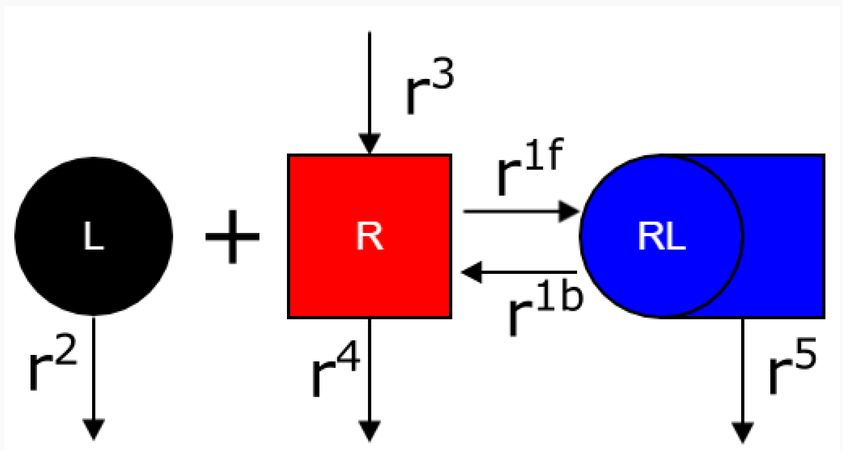
Methods

The analysis is based on the Computational Singular Perturbation (CSP) algorithm [1]. CSP provides a number of diagnostic tools that can identify:

i. the reactions that generate the fast timescales, through the *CSP Timescale Participation Index (TPI)*,
ii. the reactions that generate the equilibria in which the system evolves, through the *CSP Amplitude Participation Index (API)*,
iii. the variables that are related the most with the timescales (fast or slow), through the *CSP Pointer (PO)*.

CSP can identify numerically the stages in the evolution of the process where Quasi Steady State (QSS) or Partial Equilibrium (PE) approximations are valid [2].

Evolution of the Process

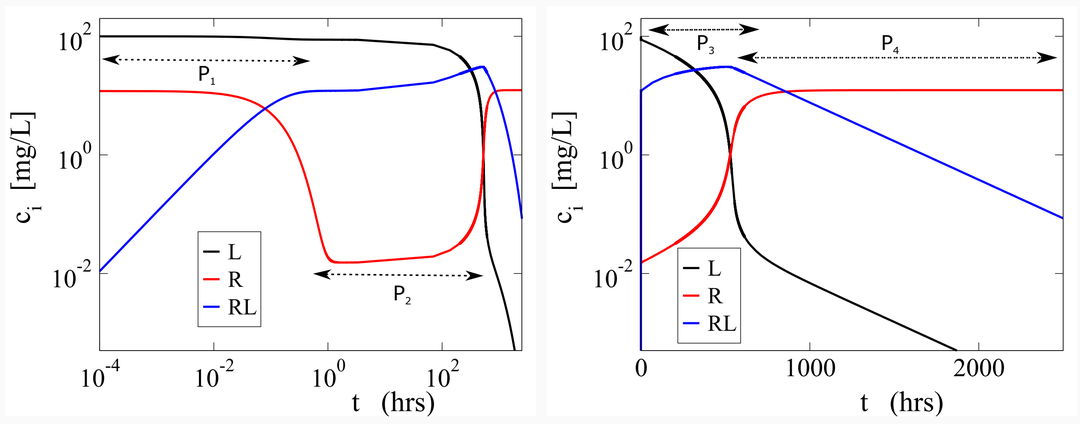


$$\frac{d}{dt}\begin{bmatrix} L \\ R \\ RL \end{bmatrix} = \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix} r^1 + \begin{bmatrix} -1 \\ 0 \\ 0 \end{bmatrix} r^2 + \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} r^3 + \begin{bmatrix} 0 \\ -1 \\ 0 \end{bmatrix} r^4 + \begin{bmatrix} 0 \\ 0 \\ -1 \end{bmatrix} r^5$$

$$r^1 = r^{1f} - r^{1b} = k_{on} L\ R - k_{off}\ R\ L, \quad r^2 = k_{el}\ L$$
$$r^3 = k_{syn}, \quad r^4 = k_{deg}\ R, \quad r^5 = k_{int}\ R\ L$$

The TMDD process evolves in four periods, which are characterized by fast or slow dynamics [1,3-5]:

- The first fast period P_1 relates to the generation of the complex,
- the second slow period P_2 relates to the attainment of a constant concentration of the complex,
- the third fast period P_3 relates to the depletion of the drug and
- the final slow period P_4 relates to the depletion of the complex.



Response of the system using $L_0 = 100$, $R_0 = 12$ and $RL_0 = 0$.

Control of the Process

By applying the CSP method, the diagnostic tools in the P_2 region indicate:

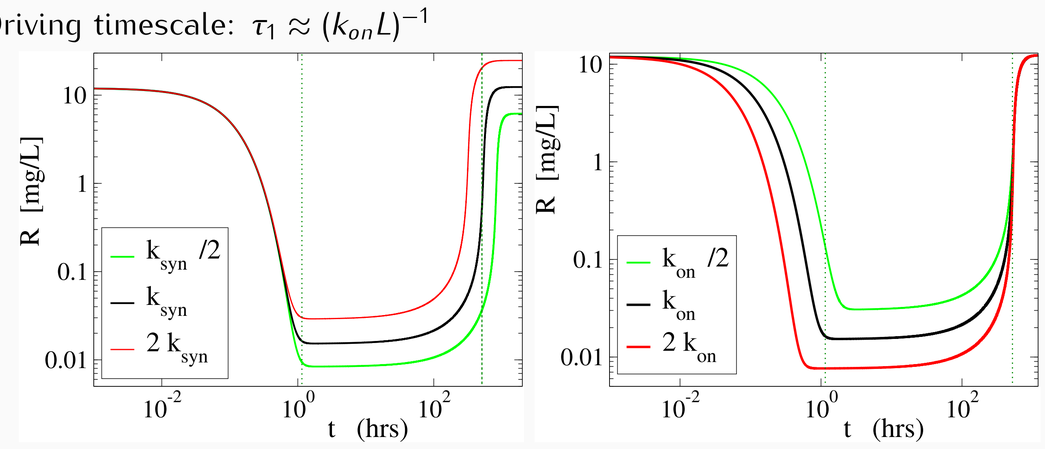
Period	PO	API	TPI
P_2	R	$r^{1f} \approx r^3 + r^{1b}$	r^{1f}
P_4	L	$r^{1f} \approx r^{1b}$	r^{1f}
late P_4	L	$r^{1f} \approx r^{1b}$	r^{1f}
	R	$r^3 \approx r^4$	r^4

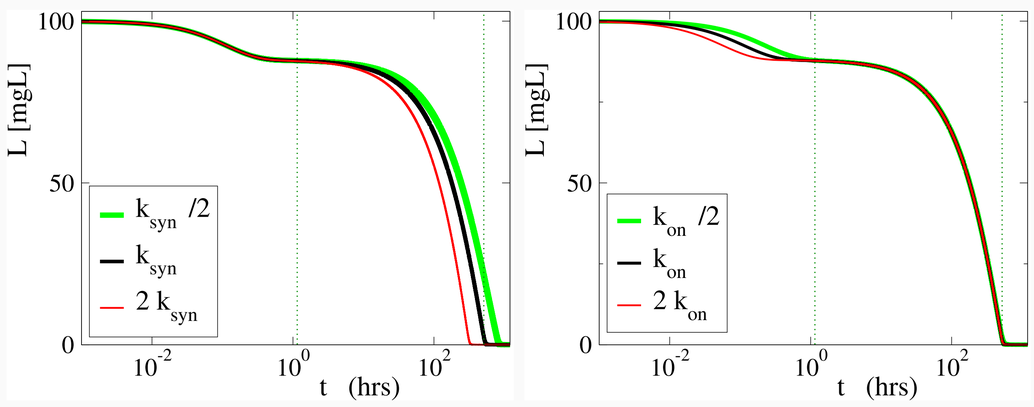
i. **QSSA for R** at P_2 phase, with r^{1f} driving the system to the $r^{1f} \approx r^3 + r^{1b}$ equilibrium
ii. **QSSA for L** at P_4 phase, with r^{1f} driving the system to the $r^{1f} \approx r^{1b}$ equilibrium
iii. **QSSA for L** and for **R** at late stage of P_4 phase, with r^{1f} and r^4 driving the system to the $r^{1f} \approx r^{1b}$ and $r^3 \approx r^4$ equilibria, respectively.

P_2: period of effectiveness of the drug

Constraints: $r^{1f} \approx r^3 + r^{1b} \Rightarrow k_{on} L\ R \approx k_{syn} + k_{off} RL$

Driving timescale: $\tau_1 \approx (k_{on} L)^{-1}$





Altering k_{syn} (left) and k_{on} (right) is shown to alter the position of the equilibrium and the time where the solution is driven on it.

Conclusion

The present analysis systemizes the findings in the literature for the one-compartment TMDD model and provides some new insights about the control of the process. These findings aim to i) propose improvements in the design of new TMDD models and ii) find ways to control the evolution of the process on existing TMDD models by identifying the correct parameters that must be more accurately specified [3].

References

[1] Lam, S.H. and Goussis, D.A., *The CSP Method for Simplifying Kinetics*, Int. J. Chemical Kinetics, 26:461-486, 1994.
[2] Goussis, D. A. *Quasi steady state and partial equilibrium approximations: their relation and their validity*. Combustion Theory and Modelling, 16(5), 869-926, 2012.
[3] Patsatzis, D.G., Maris, D.T. and Goussis, D.A., *Asymptotic analysis of a target-mediated drug disposition model: algorithmic and traditional approaches*. Bulletin of mathematical biology 78(6): 1121-1161, 2016.
[4] Peletier, L.A. and Gabrielsson, J., *Dynamics of target-mediated drug disposition: characteristic profiles and parameter identification*, J. Pharmacokinetics and Pharmacodynamics, 39:429-451, 2012.
[5] Van der Graaf, P.H., Benson, N. and Peletier, L.A., *Topics in Mathematical Pharmacology*, J. Dyn. Differential Equations, 1-20, 2015.