Identifiability and sensitivity analysis of a Photodynamic Therapy model

Simona Dobre, Thierry Bastogne, Muriel Barberi-Heyob, Alain Richard

Identifiability and sensitivity analysis of a Photodynamic Therapy model

Simona Dobre[a]*, Thierry Bastogne[a], Muriel Barberi-Heyob[b], Alain Richard[a]

[a]*Centre de Recherche en Automatique de Nancy (CRAN), Nancy Université, CNRS 7039, Campus Science, BP 70239, 54506, Vandoeuvre-lès-Nancy Cedex, France*

[b]*Centre de Recherche en Automatique de Nancy (CRAN), Nancy Université, CNRS 7039, Centre Alexis Vautrin, 54511, Vandoeuvre-lès-Nancy Cedex, France*

Abstract

Photodynamic therapy (PDT) is an alternative treatment for cancer that involves the administration of a photosensitizing agent, which is activated by light at a specific wavelength. The photo-toxic phase of this therapy can be described by a dynamic model composed of six nonlinear differential equations. The model parameters can be used to compare photosensitizing agents in their capability to produce cytotoxic species. The practical issue is their estimation from *in vivo* experimental data. In this paper, a new approach is proposed to analyze the photophysical parameters estimability through a local practical identifiability study combined with a global sensitivity analysis. Results show that only three parameters can reasonably be estimated in a given and realistic experimental framework. Input design (light signal) and model reduction are currently in progress.

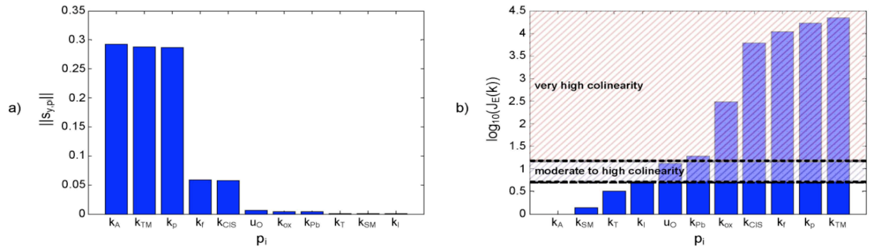
Identifiability, sensitivity analysis, nonlinear systems, biomedical systems

* Corresponding author. Tel.: +33-(0)38-368-4495; fax:+33-(0)38-368-4462.
E-mail address:Simona.Dobre@cran.uhp-nancy.fr.

1. Problem statement and motivation

Based on the kinetics equations of the photoreactions induced by PDT, a state-space model composed of six nonlinear differential equations was introduced [Dobre2008] to describe the photo-toxic phase of this therapy. This model has one output variable (y): the fluorescence intensity associated with the intratumoral concentration of the photosensitizing agent; one input variable: the irradiation signal, six state variables corresponding to the concentrations of intermediate species, and eleven model parameters gathered in the vector **p**. These parameters usually correspond to reaction rate constants. The comparison of photosensitizing agents in their capability to produce cytotoxic species is a crucial step in their development. Unfortunately, up to now it was impossible to carry out such a comparative study in an *in vivo* framework, except if we can solve the estimation problem of the model parameters from *in vivo* data. In this paper we analyze the estimability of model parameters in a realistic experimental context by considering two complementary studies: a local practical identifiability study and a global sensitivity analysis (through a variance based method, known in the literature also as Sobol' method).

A practical identifiability analysis is locally carried out through the evaluation of the sensitivity matrix **S**, composed by the output sensitivity functions, $\mathbf{s}_{y,p_i} = \partial \ln(y)/\partial \ln(p_i)$, and the corresponding Fisher Information Matrix, $\mathbf{F} = \mathbf{S}^T \cdot \mathbf{S}$ [Dochain2001]. Herein, the output sensitivity functions were computed by the software Diffedge© which enables the sensitivity analysis of Simulink© block diagrams. The practically identifiable parameters are selected according to numerical properties of the Fisher Information Matrix [Brun2001]. Results are presented in Fig.1. Only four parameters are locally identifiable. Except k_A, all the other parameters seem to be non identifiable



either because they are not output sensitizing enough or because their sensitivity functions are too correlated.

Figure 1. Parameter selections according: (a) to L2-norm of sensitivity functions, $||s_{y,pi}||$, and (b) colinearity indices, $J_E(k)=\min_{pk}(EV(\Sigma_k^T \cdot \Sigma_k))^{-2}$ where $\mathbf{p}_k$ represents a subvector of **p**, Σ_k its corresponding sensitivity matrix and EV(.) the operator calculating the eigenvalues of the argument

Global sensitivity analysis: in a second step, a global sensitivity analysis [Saltelli2008] was carried out to corroborate the local conclusions, based on Sobol' method adapted to dynamical systems. For an empirical threshold of significance fixed at 0.1, only six parameters appear to be significantly influent. It is known that the local study depends on the parameters values. Nonetheless, we found some similarities between the classification according to a local sensitivity measure (k_A, k_{TM}, k_p k_f, k_{CIS}) and the global results (k_p, k_A,k_{TM}, k_l, k_f, k_{CIS}). After a colinearity study, this subset is finally reduced to two parameters that remains candidate to practical identifiability.

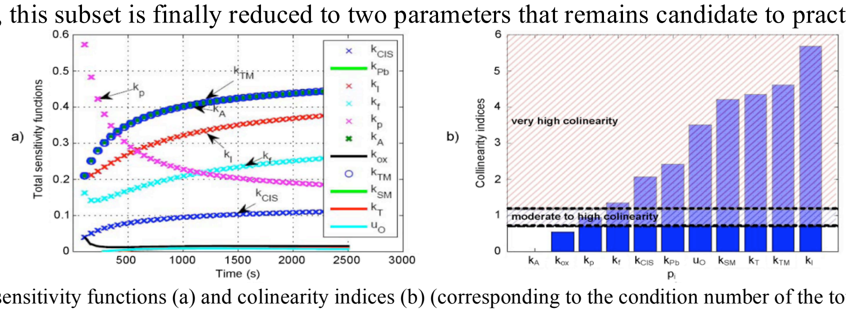


Figure 2. Total sensitivity functions (a) and colinearity indices (b) (corresponding to the condition number of the total sensitivity matrix)

Conclusion: In this paper, we point out that the non-estimability of model parameters in a given experimental framework can be due not only to non-sensitive parameters (indicated by a non-significant total sensitivity function, i.e. inferior to an empirical threshold), but, as it is illustrated for the PDT case, also to colinearity of sensitivity functions w.r.t. time. Current works are in progress to improve parameter estimability accuracy by input signal design and the implementation of new sensors.

2. References

Brun R., Reichert P., and Kunsch H. R., 2001: "Practical identifiability analysis of large environmental simulation model", Water Resource Research, 37, pp. 1015-1030.

Dochain D. and Vanrolleghem P., 2001: "Dynamical modeling and estimation in wastewater treatment processes", IWA Publishing.

Dobre S., Bastogne T., Barberi-Heyob M., Bechet D, Didelon J. and Richard A., 2008: "System identification of the intracellular photoreaction process induced by photodynamic therapy", *16th Mediterranean Conference on Control and Automation, 2008*, pp. 1729-1734.

Saltelli, A., Ratto M., Andres T., Campolongo F., Cariboni J., Gatelli D., Saisana M. and Tarantola S., 2008: "Global sensitivity analysis: The primer", *Wiley*.