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A hybrid semiparametric approach to dynamical modeling of biological systems based on delayed differential equations

M. von Stosch[1], R. Oliveira[2], J. Peres[1], S. Feyo de Azevedo[1*]
[1] LEPAE, Departamento de Engenharia Química, Faculdade de Engenharia, Universidade do Porto, Rua Dr. Roberto Frias s/n, 4200-465 Porto, Portugal
[2] REQUIMTE/CQFB, Departamento de Quimica, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal

Time delays play an important role in biological functions. They can be source of instabilities and oscillations, but are also deeply involved in regulatory effects. Time delays are either related to a process that takes an intrinsic discrete delay to be accomplished, e.g. transcriptional reactions, or to the modelling approach used, i.e. lumping a sequence of events. A general mathematical representation for phenomenological modelling is given by Retarded Functional Differential Equations (RFDE). Under simplifications some special cases, i.e. discrete delays or distributed delays, are obtained. However development of phenomenological models based on RFDEs is cost expensive and their application limited to the modelled phenomena. Hybrid modelling represents an inexpensive, rather unlimited alternative, which combines valuable additive mechanistic and statistical knowledge.

The idea of this work is to display better consistency with the nature of biological systems by ascribing the dynamics of observed biological phenomena to the parametric/nonparametric submodel. Such a novel hybrid methodology is presented incorporating discrete time series, namely AutoRegressive (eXegenous), AR(X), models into a serial parametric/nonparametric hybrid modelling framework, which results into a set of Delay Differential Equations describing the time trajectory of the system state. Usage of AR(X) is no limitation for application, as it is mathematically clear that a weighted discrete time series is equivalent to an integration of a time delay weighting function and thus analogous to application of the distributed delay framework. This is confirmed by better values of the Bayesian Information Criteria for independent data validation sets of the proposed hybrid structure in comparison to the so far applied hybrid structure, e.g.

1 -5170 to -5836, respectively, for a simulation case study on the effects of macromolecular transport of protein from the cytosol to the nucleus, which exhibits some “staircase” state transition function of the transcriptional factor in mammalian cells due to a discrete delay.

2 -4564 to -5127, respectively, for a simulation case study on a fed-batch bioprocess wherein a distributed time delay between the substrate uptake, biomass growth and product formation is considered as observed e.g. for fed-batch fermentations of *Saccharomyces cerevisiae* or *Pichia pastoris.*

3 -13545 to -13755, respectively, for fed-batch experimental data of the antibody expression by recombinant *Pichia Pastoris.*

As such it is concluded that the structure is equally applicable to discrete and distributed delays and that the consistency of the model with the biologic nature is the better the larger the delay in the system.

* Corresponding author. Tel + 351-225-081694. E-mail: sfeyo@fe.up.pt (S.F. de Azevedo)