Impulse Parametric Sensitivity Analysis

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Abstract: Complexity often limits human intuition in understanding system behavior, motivating the creation and analysis of mathematical models to understand these systems. One of the most commonly used analyses is the classical parametric sensitivity analysis (PSA), which maps out the parametric dependence of system behavior. In this article, we present a novel sensitivity analysis, called impulse parametric sensitivity analyses (iPSA), which is based on impulse perturbations to model parameters. Hence, the iPSA gives a step-by-step mechanistic insight on how a particular output behavior is accomplished and complementarily how (an impulse) perturbation propagates through the network. More specifically, iPSA coefficients can reveal which parameters are essential and when they become important. The efficacy of this analysis is demonstrated on examples drawn from biology: the Fas-induced cell death model of human Jurkat T-cells.

Keywords: Sensitivity Analysis, Robustness, Model, Systems Biology.

1. INTRODUCTION

Many problems of current relevance in engineering and science involve complex systems, from biology (e.g. signal transduction, metabolic, and gene regulatory networks) to energy-related chemical processes (e.g. combustion, pyrolysis). Complex systems are typically characterized by a large number of interacting chemical or biochemical species, often giving rise to non-intuitive behavior, such as multi-stability, ultra-sensitivity and oscillations. To this end, mathematical models of these systems have been built, typically based on balance equations, on which quantitative analysis can be applied to gain mechanistic understanding and subsequently to guide process optimization, design and control. Here, transient or dynamic behaviour of the systems is often of great interest.

Various modelling paradigms have been used to model complex systems, of which ordinary differential equations (ODE) are the most commonly used and of particular interest in this work. The ODE formulation considered in this article is general enough to describe most complex systems of interest in biology and chemical kinetics. Different modelling paradigms necessarily require different sets of analysis tools. Among existing quantitative analyses tools, the classical parametric sensitivity analysis (PSA) has been frequently used because of its ease in computation and interpretation of the results (Varma, Morbidelli, & Wu, 1999).

In this analysis, sensitivity coefficients are computed as the ratio between the changes in the system states caused by perturbing model parameters. These coefficients are typically used to investigate the impact of parameter/input changes on model outputs. As model parameters include physicochemical constants (such as those related to reaction kinetics, transport properties, and initial concentrations), a large output sensitivity magnitude thus signifies high importance of a process associated with the particular parameter perturbation in governing that system output. There are generally two types of PSA: local and global. Local analysis concerns with the changes in system behaviour due to an infinitesimal change in a parameter from its nominal value. On the other hand, global sensitivities describe the effect of simultaneous or large variations of parameters on system behaviour (Varma, et al., 1999).

Importantly, in systems biology, the PSA has become a powerful tool in investigating how system behaviour depends on model parameterization (Ingalls, 2008) and has been included in the majority of off-the-shelf numerical tools (Hoare, Regan, & Wilson, 2008; Klipp, Liebermeister, Helbig, Kowald, & Schaber, 2007; Maiwald & Timmer, 2008; Zi, Zheng, Rundell, & Klipp, 2008). In this area, the PSA has find many applications, such as for model calibration and model identifiability, model validation and reduction, and finding bottlenecks of processes of the system (Ingalls, 2008). Some examples of the application of PSA in biological models include programmed cell death (Shoemaker & Doyle III, 2008), budding yeast cell cycle control (Lovrics.A. et al., 2008), IL-6 signaling pathway (Chu, Jayaraman, & Hahn, 2007) and circadian rhythm model in Neurospora (Jin, Peng, Liang, & Ma, 2008). The interpretations of the resulting time varying parametric sensitivities in these examples vary depending on the applications.

In most applications, consolidated sensitivity metrics, e.g. using integral or average of sensitivity magnitudes or using the Fisher Information Matrix (Chu, et al., 2007), are used to indicate parametric importance and to generate parameter ranking. In doing so, the dynamical aspect of cellular regulation is not immediately apparent from these metrics due to the persistent nature of perturbations (Perumal & Gunawan,
More importantly, they can even mislead the modellers in understanding system dynamics and controlling mechanisms. Briefly, the reason stems from the fact that the perturbations are essentially introduced on system parameters, which are usually constants and do not have dynamics, and at a single time point, typically the initial time. Therefore, the parametric sensitivity coefficients already reflect an integrated effect of parameter changes at initial time on the system behaviour (Perumal & Gunawan, 2011).

To gain dynamical insights, we have developed a method based on perturbations on initial conditions at different times, called as the Green’s function matrix (GFM)-based sensitivity analyses (Perumal, Wu, & Gunawan, 2009). Complementary to the GFM analysis, we present here an impulse parametric sensitivity analysis (iPSA). The fundamental difference between GFM and iPSA is in the manner of which perturbations are introduced. The iPSA makes impulse perturbations to model parameters, which may include initial conditions. While both analyses can give a step-by-step mechanistic insight on how particular system behaviour is accomplished and how (an impulse) perturbation propagates through the network, the choice of using one over the other depends on the end application. The efficacy of this analysis is demonstrated on example drawn from biology: a Fas-induced programmed cell death model (Hua, Hautaniemi, Yokoo, & Lauffenburger, 2006).

2. METHOD

2.1. Mathematical Models:

Ordinary differential equation models of dynamic systems can generally be written as:

$$\frac{dx(t, \hat{p})}{dt} = f(x, \hat{p})$$

$$x(t_0, \hat{p}) = x_0$$

(1)

where $x \in \mathbb{R}^n$ typically represents the concentration vector of (bio)molecular species and the function $f$ is a vector valued nonlinear rate equations. The right hand side of the ODE captures the generation and consumption of (bio)molecules due to a variety of processes (e.g. in cell, these can include transcription, translation, phosphorylation and dephosphorylation), the rates of which depend on a set of kinetic parameters that are consolidated in the vector $\hat{p} \in \mathbb{R}^m$. Since the initial conditions $x_0$ can be treated in the same way as model parameters, the aggregate vector $p \in \mathbb{R}^{m+n}$ is used here to denote the combined parameters and initial conditions, i.e.

$$p = [\hat{p}^T \ x_0^T]^T$$

2.2. Impulse parametric sensitivity analysis (iPSA):

As mentioned earlier, the iPSA introduces impulse perturbations to model parameters and quantifies the resulting change in system states, as illustrated in Fig. 1(a-b). Hence the corresponding impulse sensitivity coefficient $iS_{ij}(t, \tau)$ reflects the change in the $i$-th state at time $t$ due to an impulse perturbation of $j$-th parameter at time $\tau$. Since impulse perturbations on system parameters can cause an immediate and localized effect on system states at the time of perturbation, the dynamical inference of parametric importance can be obtained from these time varying impulse perturbations. Hence, the iPSA can give not only the important parameters, but also the time of importance on the state dynamics.

The derivation of the iPSA coefficients follows the illustration in Fig. 1(c-d). Analogous to the PSA, the sensitivity coefficients of the iPSA are derived by quantifying the ratio between the change in the state $x_i$ at time $t$ and the causative pulse perturbation of size $\Delta p_j/\Delta \tau$ at time $\tau$. The perturbation is exerted on the parameter $p_j$ for a duration of $\Delta \tau$. The derivation starts by quantifying the change in the states $x$ at time $t+\Delta \tau$ using a Taylor series expansion:

$$\Delta x(t + \Delta \tau) = S_{I,j}(\tau + \Delta \tau) \frac{\Delta p_j}{\Delta \tau} + O(\Delta p_j^2)$$

(2)

Subsequently, this change $\Delta x(t + \Delta \tau)$ is propagated to the change in the state $x_i$ at time $t$ using the Green’s function matrix (GFM) $S^I(t, \tau + \Delta \tau)$ (Perumal, et al., 2009). The $(ij)$-th element of the GFM represents the sensitivity of the state $x_i$ at time $t$ to alteration in the state $x_j$ at some previous time $\tau$, i.e.

$$S_{ij}^I(t, \tau) = \frac{\partial x_i(t)}{\partial x_j(\tau)}$$

(3)

Thus, the change $\Delta x_i(t)$ due to the pulse perturbation is given by

$$\Delta x_i(t) = S_{I,j}^I(t, \tau + \Delta \tau) \Delta x(t + \Delta \tau).$$

(4)

Substitution of eqn. (2) in eqn. (4) then gives:

![Fig. 1. Impulse Parametric Sensitivity Analysis. (a-b) Impulse perturbations on parameters cause an immediate and localized effect on the states. (c-d) Derivation of iPSA uses a pulse perturbation to approximate the impulse, in the limit $\Delta p_j, \Delta \tau \rightarrow 0$.](image-url)
Taking Taylor series expansion of the parametric sensitivities around the time $\tau$ and dividing both sides by $\Delta p_j$, one will arrive with:

$$
\Delta x_i(t) = S_{i[t]}(t, \tau + \Delta \tau) S_{[t]}(\tau + \Delta \tau, \tau) \frac{\Delta p_j}{\Delta \tau} + O(\Delta \tau^2).
$$

For constant FasL ($=2$ nM) stimulus, caspase-3 activation occurs by means of a direct mitochondria independent pathway (type-I) and an indirect mitochondria dependent pathway (type-II). (b) Switch-like caspase-3 activation for a constant stimulus of FasL.

By rewriting eqn. (7) as:

$$
iS_{i,j}(t, \tau) = S_{i[t]}(t, \tau) \frac{\partial f}{\partial p_j}(\tau).
$$

Fig. 2. Fas-induced apoptotic pathway of human Jurkat T-cell lines (Hua, et al., 2006) (for detailed rate equations and parameter values readers are kindly referred to the source article). (a) A 28 state and 22 reaction model for caspase-3 activation. (b) Switch-like caspase-3 activation for a constant stimulus of FasL.
one can further see that the impact of this impulse perturbation takes effect only at the perturbation time $\tau$ and that the consequence on the state trajectory is equivalent to perturbing the states themselves, similar to the GFM analysis (Perumal, et al., 2009). Like in the PSA, the iPSA coefficients should be normalized for comparison and parameter ranking purposes, according to:

$$i\overline{S}_{ij}(t, \tau) = iS_{ij}(t, \tau) \frac{p_j}{x_i(t)}$$  \hspace{1cm} \text{(9)}$$

3. APPLICATION OF iPSA

The efficacy of the iPSA is demonstrated in an application to an example from biology: the Fas-induced programmed cell death in human Jurkat T-cell lines (Hua, et al., 2006). Fig. 2 summarises the model which consists of 28 molecular species and 32 reactions. In this system, the output of interest is caspase-3, also known as the executioner caspase, a protease that cleaves many protein substrates (Reed, Doctor, & Godzik, 2004). The activation of caspase-3 followed a switch-like response to a constant cell death stimulus (FasL $= 2nM$) as shown in Fig. 2 (see inset). The model includes two major pathways for caspase-3 activation: a direct caspase-8 or mitochondria-independent (type-I) and a mitochondria-dependent pathway (type-II). The iPSA was performed to assess the dominance of one pathway over the other, as well as to compare the activation dynamics of caspase-3 activation by both the pathways.

The analysis was performed under a constant FasL stimulation (FasL $= 2nM$) over the time range of 10,000 seconds. Fig 3(a-h) shows the iPSA coefficient contours of selected parameters of the system in caspase-3 activation. By focusing on the observation time between 4000 to 7000 seconds (switching duration) in the y-axis of Fig. 3, one can identify the sequence of key parameters that control the observed caspase-3 activation. Fig. 3(a-b) suggests that the upstream reactions $r_1$ and $r_3$ (DISC and caspase-8 formation) were among the early significant contributors before switching. Fig 3(c) illustrates that the initial caspase-3 activation can be mostly attributed to the type-I mitochondria-independent pathway. Fig 3(d-e) suggests that a type-II dominant pathway in the caspase-3 activation. Furthermore, Fig. 3(c) also points to the lack of type-I role during switching. As seen in Fig. 3(f) we can also deduce the insignificance of caspase-6 feedback pathway. Also, looking at the impulse sensitivities of forward rate constants of $r_{11}$ and $r_{5}$ in Fig. 3(g-h), we can conclude that XIAP and Bcl-2 are the strong and weak inhibitors of caspase-3 activation, respectively.

A more detailed understanding can also be obtained by fixing the observation time ($t_i$) of interest. The iPSA coefficients of caspase-3 at the final time ($t = 10000s$) in Fig. 4 confirms the above dynamic regulation of caspase-3 activation, suggesting a type-II dominance in the cell death regulation of human Jurkat T-lymphocyte cell lines (sensitivities to $J_{5,k}$ is larger than that to $J_{14,k}$ only before switching). The same conclusion on caspase-3 activation came from the GFM analysis of this model (Perumal, et al., 2009), which was also in agreement with the previous experimental results (Scaffidi et al., 1998).

Complementarily, the other dynamical information that can be extracted from the iPSA coefficients relates to how an impulse perturbation given to a rate constant propagates through the network. By setting the perturbation time to zero $(t_0=0)$, Fig. 5 elucidates the magnitude of changes in the molecular concentrations as the impulse signal initiates from the first reaction (i.e., sensitivities to $J_{1,f}$) and travels through the network. In this case, the signal starts from the upstream reactions that are common to both the pathways, followed by type-I and caspase-6 feedback, and later traverses through the type-II pathway. This finding is consistent with the above
finding of caspase 3 activation.

4. CONCLUSION
Understanding non-intuitive systems dynamics is of great interest in many fields. To this end, we have presented an impulse parametric sensitivity analysis (iPSA) that offers dynamical insights on the functional regulation and signal propagation in a system. In particular, the iPSA makes use of impulse perturbations introduced at different times on the model parameters to produce the necessary information for understanding system dynamics. In the application to a Fas-induced programmed cell death model for Jurkat cells, the iPSA suggested a type-II regulation in caspase-3 activation in this cell line, which was in agreement with the experimental evidence.

5. REFERENCES


