ON FITTING OF MATHEMATICAL MODELS OF CELL SIGNALING PATHWAYS USING ADJOINT SYSTEMS

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ABSTRACT. This paper concerns the problem of fitting of mathematical models of cell signaling pathways. Such models frequently take the form of a set of nonlinear ordinary differential equations. While the model is continuous-time, the performance index, used in the fitting procedure, involves measurements taken only at discrete-time moments. Adjoint sensitivity analysis is a tool that can be used for finding a gradient of a performance index in the space of the model's parameters. The paper uses a structural formulation of sensitivity analysis, especially dedicated for hybrid, continuous/discrete-time systems. A numerical example of fitting of the mathematical model of the NF-κB regulatory module is presented.

1. **Introduction.** Mathematical models of cell signaling pathways frequently take the form of a set of nonlinear ordinary differential equations [3, 6, 7]. To compare different models and to test their ability to model processes, for which experimental data are given, an effective method of parameter fitting is needed. Unfortunately, although the model is continuous-time, all available measuring techniques, such as Western blot expression analysis, electrophoretic mobility shift assays, or gene expression microarrays, give measurements only at discrete moments. As a consequence, the whole problem has a hybrid, continuous/discrete nature. Until now, no computationally effective algorithms could solve the problem for large nonlinear models; a common approach is to fit the parameters manually [6]. In [9], a similar problem was solved by using Hartley's modulating function, but the approach may be applied only for some simple nonlinear models under the assumption that measurements are relatively dense in time. In this paper, we propose the approach that depends on adjoint sensitivity analysis.

Adjoint sensitivity analysis is a technique frequently used in practical optimization problems, such as identification or optimal control tasks. It calculates the gradient of a performance index very effectively and decreases computational costs when compared to straight (tangent linearized) sensitivity analysis. In a study related to adjoint systems, such systems are defined for continuous-time systems or discrete-time systems and cannot be directly applied to solve the problem of parameter fitting presented above, because of its hybrid, continuous/discrete nature.

There are also methods that give rules for construction of the adjoint system, when the original system is given as a block diagram. In [8], such rules have been formulated for discrete-time neural networks. Using these rules, a non-casual system (containing z operators) is constructed. In [1], similar rules were proposed for construction of a so-called modified adjoint system [4]. The modified adjoint system is more convenient in practical application (simulation), because it is a casual system solved forward in time.

In our previous work [2], rules for creating the modified adjoint systems for continuous/discrete systems (i.e., systems containing continuous- and discrete-time parts, pulsers, and samplers) have been presented and used to extend the backpropagation through time algorithm, well known in neural-networks theory. As a result, a generalized backpropagation through time (GBPTT) algorithm for training continuous-time neural networks based on discrete-time measurements has been formulated. In the present paper, it is used for the first time for a biological model. The approach is tested on a mathematical model of NF-κB regulatory module recently proposed in literature by Tomasz Lipniacki et al. [6]. As mentioned above, the parameters of the model have been fitted manually based on measurements—images of blots. Here, we treat the model with fitted parameters as a plant, and we choose discrete-time values of the outputs for the fitting procedure. The numerical computations show that the sum-quadratic performance index is minimized while continuous-time signals obtained in the model are convergent with signals obtained in the plant.

2. **Adjoint systems.** Let a given nonlinear dynamical system be denoted in the state space using equations

$$\begin{cases} \dot{x}(t) = f\left(x(t), u(t)\right) \\ y(t) = g\left(x(t)\right) \end{cases} , \quad t \in [0, T], \tag{1}$$

where $x(t)$, $u(t)$, and $y(t)$ are state, input, and output signals having appropriate dimensions. Functions $f(\cdot)$ and $g(\cdot)$ are multidimensional nonlinear functions that are differentiable with respect to their arguments, and T is a final time.

A sensitivity model (tangent linearized) for the given initial state $x(0)$ and nominal trajectories of the input $u_{nom}(t)$ and the for state $x_{nom}(t)$ is defined for variations $\bar{x}(t)$, $\bar{u}(t)$ and $\bar{y}(t)$ as follows:

$$\begin{cases} \dot{\bar{x}}(t) = A(t)\bar{x}(t) + B(t)\bar{u}(t) \\ \bar{y}(t) = C(t)\bar{x}(t) \end{cases} , \quad t \in [0, T], \tag{2}$$

where matrices $A(t)$, $B(t)$, and $C(t)$ have been created by the differentiation of functions $f(\cdot)$ and $g(\cdot)$ with respect to $x(t)$ and $u(t)$ along nominal trajectories

$$A(t) = \left.\frac{\partial f}{\partial x}\right|_{\substack{x_{nom}(t) \\ u_{nom}(t)}} , B(t) = \left.\frac{\partial f}{\partial u}\right|_{\substack{x_{nom}(t) \\ u_{nom}(t)}} , C(t) = \left.\frac{\partial g}{\partial x}\right|_{\substack{x_{nom}(t) \\ u_{nom}(t)}} , t \in [0, T]. \tag{3}$$

The adjoint system for systems (1) and (2) is denoted as

$$\begin{cases} \dot{\tilde{x}}(t) = -A^T(t)\tilde{x}(t) + C^T(t)\tilde{u}(t) \\ \tilde{y}(t) = B^T(t)\tilde{x}(t) \end{cases} , \quad t \in [0, T], \tag{4}$$

and in practice is simulated backward in time for given final condition.

A time-reversed representation, the so-called modified adjoint system [4], is defined as follows:

$$\begin{cases} \dot{\hat{x}}(t) = A^T(T - t)\hat{x}(t) + C^T(T - t)\hat{u}(t) \\ \hat{y}(t) = B^T(T - t)\hat{x}(t) \end{cases} , \quad t \in [0, T]. \tag{5}$$

It is more convenient from the computational point of view, because it is solved forward in time, unlike the adjoint system (4), for which a final condition usually is given.

In the case of discrete-time systems, the sensitivity model and the adjoint systems can be defined in a similar way.

Under zero initial conditions, systems (2) and (5) may be denoted using integral operators:

$$\bar{y}(t) = \int\limits_0^t \bar{K}(t, \tau)\bar{u}(\tau)\mathrm{d}\tau \tag{6}$$

$$\hat{y}(t) = \int\limits_0^t \hat{K}(t, \tau)\hat{u}(\tau)\mathrm{d}\tau, \tag{7}$$

where $\bar{K}(t, \tau)$ and $\hat{K}(t, \tau)$ are their kernels.

The fundamental property that allows us to use the modified adjoint system (5) instead of the sensitivity model (2) is as follows:

$$\bar{K}(t_2, t_1) = \hat{K}(T - t_1, T - t_2). \tag{8}$$

For example, when systems (2) and (5) are single-input-single-output (SISO) and they are stimulated by Dirac pulses $\bar{u}(t) = \delta(t - t_1)$, $\hat{u}(t) = \delta(t - T + t_2)$ then outputs satisfy the relation $\bar{y}(t_2) = \hat{y}(T - t_1)$.

An alternate approach to obtaining the adjoints is a structural one, where the adjoint system is constructed based on a structural representation of the original system. Both approaches, analytical and structural, are fully equivalent. The latter is particularly convenient if the original system is already given in a block-diagram form, or if the obtained adjoint system is modeled in a simulation software that uses structural representation, for example, in the Matlab-Simulink.

A diagrammatic description is most often used in the case of continuous/discrete systems, because in such a case, an analytical description using a set of differential and difference equations combined with an additional set of equations describing jumps of state variables in sampling time is complicated and illegible.

Recently we proposed a special formulation of structural sensitivity analysis, suitable for hybrid, continuous/discrete-time systems [2]. The method, called GBPTT, specifies the set of rules for creating the modified sensitivity model and describes how to stimulate it to obtain a so-called input-output sensitivity function.

3. **Mathematical model of the NF-κB regulatory module.** The transcription factor NF-κB regulates many genes that play important roles in intra- and extracellular signaling. It governs many cell processes, such as cellular stress responses and cell growth, survival, and apoptosis. This section presents a model proposed in [6], which is presented schematically in Figure 1. Upon TNF stimula-
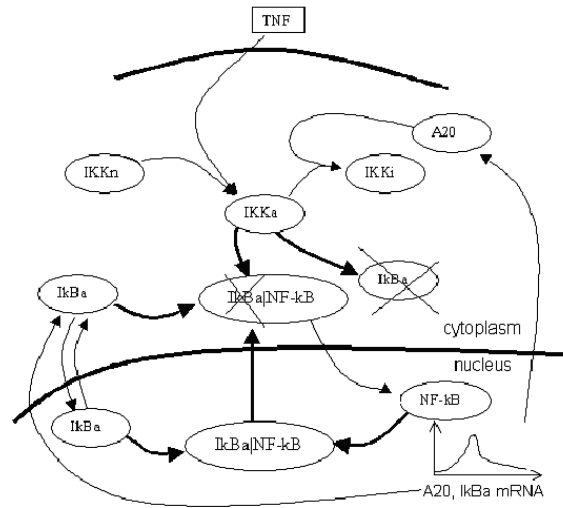

FIGURE 1. Schematic depiction of the the model of NF-κB regulatory module.

tion, neutral IKKn is transformed into its active form, IKKa. Active IKKa forms complexes with IκBα and (IκBα|NF-κB) and strongly catalyses IκBα degradation. Liberated NF-κB enters the nucleus, where it binds to κB motifs in A20, IκBα, or other gene promoters. The newly synthetized IκBα enters the nucleus and leads NF-κB again to cytoplasm, while newly synthetized A20 triggers transformation of IKKa into inactive IKKi. Readers interested in biological details are referred to articles [3, 5, 6].

The model takes the form of 15 first-order nonlinear differential equations:

$$\dot{x}_1 = k_{prod} - k_{deg}x_1 - k_1 u x_1$$
$$\dot{x}_2 = k_1 u x_1 - k_3 x_2 - k_2 u x_2 x_8 - k_{deg}x_2 - a_2 x_2 x_{10} + t_1 x_4 - a_3 x_2 x_{13} + t_2 x_5$$
$$\dot{x}_3 = k_3 x_3 + k_2 u x_2 x_8$$
$$\dot{x}_4 = a_2 x_2 x_{10} - t_1 x_4$$
$$\dot{x}_5 = a_3 x_2 x_{13} - t_2 x_5$$
$$\dot{x}_6 = c_{6a} x_{13} - a_1 x_6 x_{10} + t_2 x_5 - i_1 x_6$$
$$\dot{x}_7 = i_1 k_v x_6 - a_1 x_7 x_{11}$$
$$\dot{x}_8 = c_4 x_9 - c_5 x_8 \tag{9}$$
$$\dot{x}_9 = c_2 + c_1 x_7 - c_3 x_9$$
$$\dot{x}_{10} = -a_2 x_2 x_{10} - a_1 x_6 x_{10} + c_{4a} x_{12} - c_{5a} x_{10} - i_{1a} x_{10} + e_{1a} x_{11}$$
$$\dot{x}_{11} = -a_1 x_7 x_{11} + i_{1a} k_v x_{10} - e_{1a} k_v x_{11}$$
$$\dot{x}_{12} = c_{2a} + c_{1a} x_7 - c_{3a} x_{12}$$
$$\dot{x}_{13} = a_1 x_6 x_{10} - c_{6a} x_{13} - a_3 x_2 x_{13} + e_{2a} x_{14}$$
$$\dot{x}_{14} = a_1 x_7 x_{11} - e_{2a} k_v x_{14}$$
$$\dot{x}_{15} = c_{2c} + c_{1c} x_7 - c_{3c} x_{15}.$$

In model (9), state variables are concentrations of proteins, complexes of proteins, or their transcripts: x_1, IKK kinase in the neutral state; x_2, IKK kinase in the active state; x_3, IKK kinase in the inactive state; x_4, complexes of proteins (IKKa|IκBα); x_5, complexes of proteins (IKKa|IκBα|NFκB); x_6, protein NFκB; x_7, protein NFκB in the nucleus; x_8, protein A20; x_9, protein A20 transcript; x_{10}, free IκBα protein; x_{11}, free nuclear IκBα protein; x_{12}, IκBα transcript; x_{13}, complexes of proteins (IκBα|NFκB); x_{14}, nuclear complexes of proteins (IκBα|NFκB); x_{15}, control gene transcript. All concentrations are specified for cell cytoplasm, except those indicated as nuclear. The input signal u is a logical variable 1 or 0 and is equal to 1 when the signaling pathway is stimulated by an extracellular signal (TNF or IL-1). State variables and input signals are time-dependent; thus to simplify the notation it is not indicated in the model. The rest of the variables in the model (9) are parameters. In [6] some of these parameters have been assumed to be known and 10 parameters have been fitted manually on the basis of the data from [3] and [5].

4. **Adjoint system and fitting of the parameters.** To test the approach, we used the model with parameters taken from [6] as a plant. We simulated this model for a period of seven hours (25,200 seconds), with step stimulation by TNF starting at one-hour moment. The "measurements" were taken at $t_1 = 5,000$, $t_2 = 7,500$, $t_3 = 10,000$, $t_4 = 15,000$ and $t_5 = 20,000$ time moments (in seconds). It was assumed that all 15 state variables (9) are measured, so we obtained 75 scalar discrete-time measurements: $m_i(t_n); i = 1, 2, \ldots, I; n = 1, 2, \ldots, N; I = 15; N = 5$. The performance index was defined as follows:

$$J = \frac{1}{2} \sum_{i=1}^{I} q_i \sum_{n=1}^{N} [x_i(t_n) - m_i(t_n)]^2, \tag{10}$$

where q_i are weights that take into account different scales for different state variables. We fitted 10 parameters (the same that were fitted in [6]), assuming the same values of remaining parameters. The mathematical model (9) is presented in block-diagram form in Figure 2.
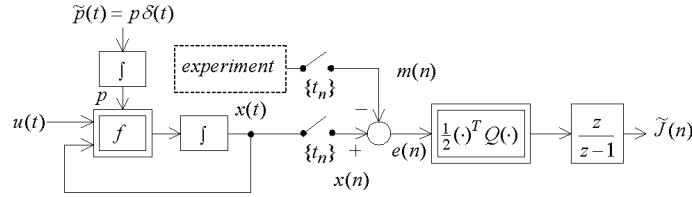
FIGURE 2. The block diagram of the mathematical model of an
NF-κB regulatory module, with additional elements concerning the
performance index.

The block diagram contains several additional elements. There is a discrete-time
part where we use notation $x(n)$ instead of $x(t_n)$. One may see on the output the
signal $\tilde{J}(N)$, which at final discrete time N is equal to the performance index (10).
The matrix Q is a diagonal matrix composed of weights q_i: $Q = diag(q_1, q_2, \ldots, q_{15})$.
The constant signal p is generated by passing the signal $\tilde{p}(t) = p\delta(t)$ (where $\delta(t)$
is a Dirac pulse) through the integrator. As a result, the problem of finding the
gradient of the performance index (10) may be treated as a problem of finding the
so called input-output sensitivity function [1, 2],

$$S_{\tilde{p}(0)}^{\tilde{J}(N)}. \tag{11}$$

We used the gradient of the performance index obtained with the modified adjoint system which block diagram is presented in Fig. 3.
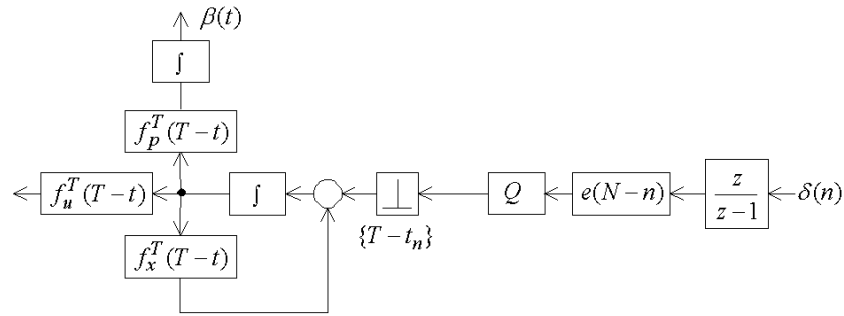

FIGURE 3. The modified adjoint system generating the gradient
of the performance index.

This block diagram has been constructed using the GBPTT method presented
in [2]. In the modified adjoint system, there is an ideal pulser that gives Dirac
pulses proportional to the discrete-time signal $e(N - n)$. The system from Figure
3, stimulated at discrete time $N = 0$ by the Kronecker pulse, generates on its
output the signal $\beta(t)$. This signal at final time T is equal to the input-output
sensitivity function (11), and at the same time it is equal to the searched gradient
of the performance index:

$$\nabla_p J = \beta(T). \tag{12}$$

The model and the adjoint system were modeled in Matlab-Simulink. Results of
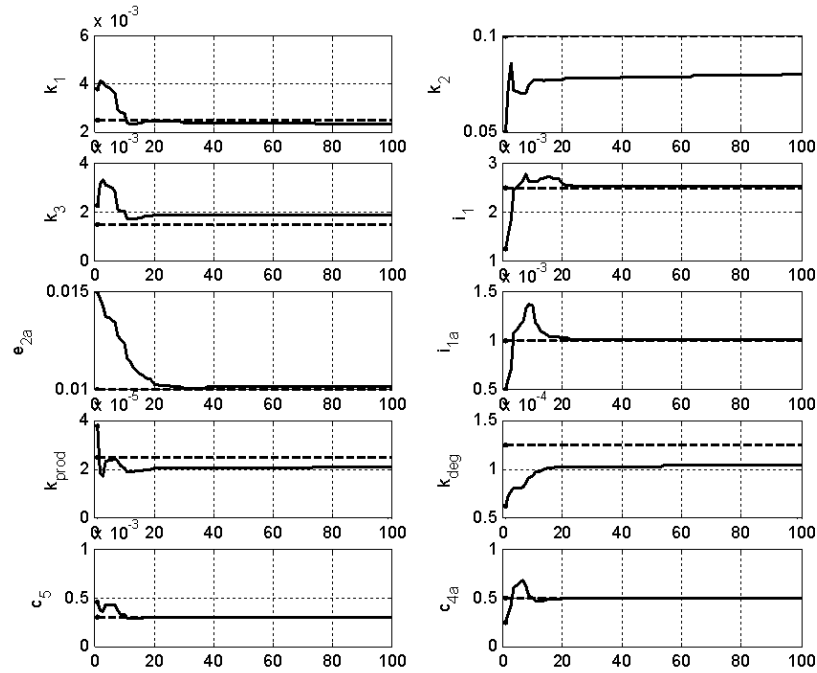fitting of 10 parameters for 100 iterations are presented in Figure 4.

FIGURE 4. Values of 10 fitted parameters during 100 iterations of the algorithm. Dashed lines indicate values used for generation the data.

Dashed lines indicate proper (known to us) values used during generation of the data. The performance index, starting from a value of about 2000, reached a value of 0.042 in the 100th iteration. Moreover, all 15 trajectories fitted the "real" trajectories, obtained as well during generation of the data. Nevertheless, one may observe that not all parameters reached values used during generation of the data. At least two reasons may explain this phenomenon. The solution in the space of fitted parameters may not be unique, or the performance index may be much less sensitive to a part of the parameters, and this sensitivity is comparable to the sensitivity with respect to numerical errors. This phenomenon needs further investigation.

5. **Conclusion.** In this paper the application of the adjoint systems to fitting of parameters of the mathematical models of cell signaling pathways is proposed. The model of the biological system takes the form of a set of nonlinear ordinary equations. The data coming from experiments are given only at discrete-time moments. To construct an adjoint system, the structural formulation on sensitivity analysis for hybrid, continuous/discrete-time systems is utilized. The adjoint system gives the gradient of a quadratic performance index and is used for fitting of parameters of the model. The approach proposed in this article needs further investigation concerning convergence properties, and it will be tested on real noisy experimental data. The algorithm can also give the gradient of the performance index in a space of input signals, which can be used for optimization of signals that stimulate the biological system.

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