Supplement to
Parameter Estimation for Dynamical Systems with Discrete Events and Logical Operations

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1 Objective Function Gradient

For the objective function $J(\theta)$ the derivative with respect to a parameter θ_k is given by

$$\frac{\partial J(\theta)}{\partial \theta_k} = \frac{\partial J_y(\theta)}{\partial \theta_k} + \frac{\partial J_z(\theta)}{\partial \theta_k},$$

where

$$\frac{\partial J_y(\theta)}{\partial \theta_k} = \sum_{i=1}^{n_y} \sum_{m=1}^{n_t} \left. \frac{\bar{y}_{i,m} - y}{\sigma_{i,m}^{(y)\,2}} s_{i,k}^{y} \right|_{t_m} + \frac{1}{\sigma_{i,m}^{(y)}} \left(\frac{1}{2} - \left(\frac{\bar{y}_{i,m} - y}{\sigma_{i,m}^{(y)}} \right)^2 \right) \left. \frac{\partial \sigma_{i,m}^{(y)}}{\partial \theta_k} \right|_{t_m}$$

and

$$\frac{\partial J_z(\theta)}{\partial \theta_k} = \sum_{j=1}^{n_e} \sum_{q=1}^{n_z(j)} \sum_{l=1}^{n_\tau(j)} \frac{\mathcal{J}_{l,q}^{z^{(j)}}}{\partial \theta_k}.$$

The derivative of the objective function for the individual events is given by

$$\frac{\mathcal{J}_{l,q}^{z^{(j)}}}{\partial \theta_k} = \frac{1}{2\omega_{l,q}^{(j)\,2}} + \begin{cases} \frac{\bar{z}_{l,q}^{(j)} - z_{l,q}^{(j)}}{\omega_{l,q}^{(j)\,2}} s_k^{z_{l,q}^{(j)}} + \frac{(\bar{z}_{l,q}^{(j)} - z_{l,q}^{(j)})^2}{\omega_{l,q}^{(j)\,3}} \frac{\partial \omega_{l,q}^{(j)}}{\partial \theta_k} & \text{if } \tau_l^{(j)} \leq t_f \\ \left. \frac{g_j}{\omega_{l,q}^{(j)\,2}} \frac{\partial g_j}{\partial \theta_k} \right|_{t_f} + \left. \frac{g_j^2}{\omega_{l,q}^{(j)\,3}} \frac{\partial \omega_{l,q}^{(z)}}{\partial \theta_k} \right|_{t_f} & \text{if } \tau_l^{(j)} > t_f \end{cases}.$$

2 Supported Logical Operators

AMICI allows the user to specify models in a native format (see `AMICI_guide.pdf` shipped with AMICI for further details). In this native format it is possible to specify events through the `amievent(trigger,update,z)`

Table 1: Discontinuous functions supported by AMICI.

function	AMICI function	symbolic function
heaviside(a)	`heaviside(a)`	$H(a)$
$\begin{cases} a \text{ if } c \\ b \text{ else} \end{cases}$	`am_if(c,a,b)`	$b + H(c) \cdot (a - b)$
$\delta(a)$	`dirac(a)`	$\delta(a)$

Table 2: Logical operators supported by AMICI.

operator	AMICI function	trigger function
$a \vee b$	`am_or(a,b)`	$\max(a, b)$
$a \wedge b$	`am_and(a,b)`	$a \cdot b$
$a \geq b$	`am_ge(a,b)`	$a - b$
$a > b$	`am_gt(a,b)`	$a - b$
$a \leq b$	`am_le(a,b)`	$b - a$
$a < b$	`am_lt(a,b)`	$b - a$

function. Additionally, events are automatically introduced for discontinuous functions at the points discontinuities (see Table 1). All of these functions result in an event with empty z and for all but `dirac(a)` the update function is set to 0. For `dirac(g(t))` the update function is set to $v = (\frac{\partial g}{\partial t})^{-1} w$.

Piecewise defined functions can be specified via the `am_if(c,a,b)` function, where the condition c may contain basic logical operators (see Table 2). These logical operators can also serve as trigger functions, which makes the respective event fire upon every change in the boolean value of the operator.

Beyond its native model format, AMICI also supports the import of SBML models via the `SBML2AMICI` command. `SBML2AMICI` supports SBML events and `AssignmentsRule` attributes and automatically translates them into user-defined events.

3 Model for mRNA Transfection

For the model of mRNA transfection it is possible to analytically compute the model output. This enables a more precise analysis of the integration error and allows for an easy identification of structural non-identifiabilities. In the following we will provide analytical formulas for the model output and respective sensitivities. Furthermore, we introduce a reparametrisation that renders all parameters structurally identifiable.

3.1 Analytical Solution

For the model of mRNA transfection, the analytical solution can be derived using e.g. the Laplace transformation. For $\beta \neq \gamma$ we find that

$$y = \log\left(k_2 m_0 s \frac{e^{-\beta(t-t_r)} - e^{-\gamma(t-t_r)}}{\gamma - \beta} H(t - t_r) + b\right) . \tag{1}$$

Accordingly, we can also compute output sensitivities analytically by computing the partial derivatives of (1):

$$\begin{aligned}
\frac{\partial y}{\partial k_2} &= \frac{m_0 s \mathbb{Y}}{k_2 m_0 s \mathbb{Y} + b} & \frac{\partial y}{\partial \beta} &= \frac{-k_2 m_0 s \frac{e^{-\beta(t-t_r)} - e^{-\gamma(t-t_r)} + (\gamma-\beta)(t-t_r)e^{-\beta(t-t_r)}}{(\gamma-\beta)^2} H(t-t_r)}{k_2 m_0 s \mathbb{Y} + b} \\
\frac{\partial y}{\partial m_0} &= \frac{k_2 s \mathbb{Y}}{k_2 m_0 s \mathbb{Y} + b} & \frac{\partial y}{\partial \gamma} &= \frac{k_2 m_0 s \frac{e^{-\beta(t-t_r)} - e^{-\gamma(t-t_r)} + (\gamma-\beta)(t-t_r)e^{-\gamma(t-t_r)}}{(\gamma-\beta)^2} H(t-t_r)}{k_2 m_0 s \mathbb{Y} + b} \\
\frac{\partial y}{\partial s} &= \frac{k_2 m_0 \mathbb{Y}}{k_2 m_0 s \mathbb{Y} + b} & \frac{\partial y}{\partial t_r} &= \frac{k_2 m_0 s \frac{\beta e^{-\beta(t-t_r)} - \gamma e^{-\gamma(t-t_r)}}{\gamma-\beta} H(t-t_r)}{k_2 m_0 s \mathbb{Y} + b} \\
\frac{\partial y}{\partial b} &= \frac{1}{k_2 m_0 s \mathbb{Y} + b} ,
\end{aligned}$$

where

$$\mathbb{Y} = \frac{e^{-\beta(t-t_r)} - e^{-\gamma(t-t_r)}}{\gamma - \beta} H(t - t_r)\,.$$

3.2 Reparametrisation

From (1) it is evident that parameters k_2, m_0 and s are structurally non-identifiable as they only occur as factors in the product $k_2 m_0 s$. To circumvent the structural non-identifiability, we introduce the transformed state

$$\begin{aligned}\xi_1 &= \frac{x_1}{m_0}\\ \xi_2 &= s x_2\,.\end{aligned}$$

This transformation yields the following ordinary differential equation:

$$\begin{aligned}\frac{d\xi_1}{dt} &= -\beta\xi_1, && \xi_1(0) = 0\\ \frac{d\xi_2}{dt} &= k_2 m_0 s \xi_1 - \gamma\xi_2, && \xi_2(0) = 0\\ g &= t - t_r, \qquad v = [1, 0]^T\\ y &= \log(\xi_2 + b)\,.\end{aligned} \tag{2}$$

In (2) the parameters k_2, m_0 and s also appear as product and can thus be merged into a single parameter k_3, which yields the following ordinary differential equation:

$$\begin{aligned}\frac{d\xi_1}{dt} &= -\beta\xi_1, && \xi_1(0) = 0\\ \frac{d\xi_2}{dt} &= k_3 \xi_1 - \gamma\xi_2, && \xi_2(0) = 0\\ g &= t - t_r, \qquad v = [1, 0]^T\\ y &= \log(\xi_2 + b)\,.\end{aligned}$$