iScience, Volume *23*

Supplemental Information

An Adaptive Control Scheme for Interleukin-2 Therapy

Sahamoddin Khailaie, Ghazal Montaseri, and Michael Meyer-Hermann

Transparent Methods

Algorithm of adaptive IL-2 dose calculation

In the following, the steps toward calculation of adaptive doses of IL-2 using iZMPC are explained.

Consider the nonlinear system

$$\frac{dx(t)}{dt} = f\left(x(t)\right), \tag{S1}$$

where $x \in \mathbb{R}^n$ is the vector of system dynamics (here, $x = [T, R, I]$). Suppose $u \in \mathbb{R}$ is the drug dose (here, $d_{\mathrm{IL}-2}$) which affects the system at the discrete time intervals τ_i, $i = 1, 2$, by sudden changes in the state variables

$$\Delta x(\tau_i) = x(\tau_i^+) - x(\tau_i) = Bu, \tag{S2}$$

where τ_i^+ denotes the time instant after τ_i. $B \in \mathbb{R}^n$ models the impact of u on the states, and the amplitude of the sudden pulses at τ_i is equal to Bu. We assume equidistant pulses, i.e., $\tau_{i+1} - \tau_i = \delta$, $i = 1, 2, \ldots$. Thus the full system is modeled in the template of nonlinear impulsive systems (Yang, 2001) as an augmentation of equations (S1) and (S2).

Depending on the considered biological framework, different constraints may arise; e.g., drug doses are constrained within the physiologically approved limits and also states should be kept within their functional regions. With

$$\mathcal{U} = \{u : \ \underline{u} \leqslant u \leqslant \bar{u}\},$$
$$\mathcal{X} = \{x : \underline{x} \leqslant x \leqslant \bar{x}\},$$

and an arbitrary target set $\mathcal{X}^{Tar} \subset \mathcal{X}$ (therapeutic target window), the aim is to compute $u \in \mathcal{U}$ to force x moving from its initial value $x(0)$ to a point in $\mathcal{X}^{Tar}$. Calculation of u is based on the iZMPC (Sopasakis et al., 2015). In what follows, we delineate the preliminary steps toward using iZMPC. A detailed description, the mathematical basis of the steps and some other biological application of iZMPC can be found in (Rivadeneira et al., 2015, 2016; González et al., 2017; Rivadeneira et al., 2017).

Step 1: finding equilibrium points (x_s, u_{eq})

Augmented system of (S1) and (S2) can be reformulated as $\dot{x} = f(x) + Bu\delta_d(t - \tau_i)$ where $\delta_d(t - \tau_i)$ is the Dirac delta function

$$\delta_d(t - \tau_i) = \begin{cases} +\infty, & t = \tau_i \\ 0, & t \neq \tau_i \end{cases}$$

Assume continuous delivery of the drug and calculate $u = u_{eq} \in \mathcal{U}$ and x_s satisfying the steady state condition $f(x_s) + Bu_{eq} = 0$.

Step 2: finding equilibrium levels (x_s, u_s)

Find $u = u_s$ such that the impulsive system (augmented equations (S1) and (S2)) with $\Delta x = Bu_s$ and impulse frequency δ reaches almost the same equilibrium level as x_s. Note that, different δ result in different u_s.

Step 3: linearization

Calculate $A = \frac{\partial f(x)}{\partial x}$ at $x = x_s$.

Step 4: shift constraints

Calculate shifted sets $\mathcal{U}_o = \mathcal{U} - u_s$, $\mathcal{X}_o = \mathcal{X} - x_s$ and $\mathcal{X}_o^{Tar} = \mathcal{X}^{Tar} - x_s$.

Step 5: feasible generalized control equilibrium zone (set)

Compute two new sets $\mathcal{X}_s^\circ$ and $\mathcal{X}_s^\bullet$ such that

$$\mathcal{X}_s^\circ \triangleq \{x \in \mathcal{X}_o : \ x = G^\circ u \quad \text{for some} \quad u \in \mathcal{U}_o\},$$
$$\mathcal{X}_s^\bullet \triangleq \{x \in \mathcal{X}_o : \ x = G^\bullet u \quad \text{for some} \quad u \in \mathcal{U}_o\},$$

where

$$G^\circ = (I_n - A_e)^{-1}B^\circ, \quad A_e = e^{\delta A}, \quad B^\circ = B,$$
$$G^\bullet = (I_n - A_e)^{-1}B^\bullet, \quad B^\bullet = e^{\delta A}B,$$

and I_n is the identity matrix of dimension n. $\mathcal{X}_s^\circ$ and $\mathcal{X}_s^\bullet$ implicitly generate the input equilibrium set

$$\mathcal{U}_s \triangleq \{u \in \mathcal{U}_o : (G^\circ u, G^\bullet u) \in (\mathcal{X}_s^\circ, \mathcal{X}_s^\bullet)\}.$$

Step 6: generalized equilibrium zone (set)
Compute $\mathcal{X}_s^{\circ Tar} \triangleq \mathcal{X}_s^\circ \cap \mathcal{X}_o^{Tar}$ and $\mathcal{X}_s^{\bullet Tar} \triangleq \mathcal{X}_s^\bullet \cap \mathcal{X}_o^{Tar}$. Correspondingly, we can obtain $\mathcal{U}_s^{Tar} \triangleq \{u \in \mathcal{U}_o : (G^\circ u, G^\bullet u) \in (\mathcal{X}_s^{\circ Tar}, \mathcal{X}_s^{\bullet Tar})\}$. If $\mathcal{X}_s^{\circ Tar}$ or $\mathcal{X}_s^\bullet$ is empty, the control problem is not properly formulated and $\mathcal{X}^{Tar}$ must be increased or δ should be decreased. There is a free set computation toolbox "mpt3" in MATLAB which can be downloaded at http://people.ee.ethz.ch/mpt/3/.

Step 7: MPC input
At each $t = \tau_i$, we use the current state of the system of augmented equations (S1) and (S2) x and provide $x - x_s$ as input to the iZMPC algorithm (see Step 8) which determines u.

Step 8: iZMPC problem
MPC is a finite time-horizon optimization problem which receives the current state of the system and returns $\mathbf{U} = \{\mathbf{u}(0), \mathbf{u}(1), ..., \mathbf{u}(N-1)\}$ (with N the control horizon). It predicts the next N states of the system using the sampled current state and calculates the next N control actions (here, IL-2 doses). Only the first calculated input, i.e. $\mathbf{u}(0)$ is applied to the system and this process is repeated at every sampling time.

iZMPC is an MPC which at each impulse τ_i, $i = 1, 2, ...$ (i.e., the sampling times) takes $x(\tau_i)$ and calculates $\mathbf{U}$ for the impulsive system. Note that, iZMPC is mainly developed for linear impulsive systems. Using the method of linearization around equilibrium levels makes it possible to apply iZMPC to linearized impulsive systems which are originally nonlinear. In the case that errors due to linearization are not acceptable, one may have to stretch out for nonlinear impulsive MPC (Rivadeneira et al., 2017).

The optimization problem to be solved at each τ_i by iZMPC is given by

$$\begin{aligned}
\min_{\mathbf{U}, x_a, u_a} \quad & V_N\left(x - x_s, \mathcal{X}_o, \mathcal{U}_o, \mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{\bullet Tar}; \mathbf{U}, x_a, u_a\right) \\
\text{subject to} \quad & \\
& x^\bullet(0) = x - x_s, \\
& x^\bullet(j+1) = A_e x^\bullet(j) + B^\bullet \mathbf{u}(j), \ j = 1, 2, ..., N-1 \\
& x^\bullet(j) \in \mathcal{X}_o, \ \mathbf{u}(j) \in \mathcal{U}_o, \qquad j = 1, 2, ..., N-1 \\
& x^\bullet(N) = x_a, \\
& x_a = A_e x_a + B^\bullet u_a, \quad \text{or} \quad ((x_a, u_a) \in (\mathcal{X}_s^\bullet, \mathcal{U}_s))\,,
\end{aligned} \tag{S3}$$

where

$$\begin{aligned}
& V_N\left(x - x_s, \mathcal{X}_o, \mathcal{U}_o, \mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{\bullet Tar}; \mathbf{U}, x_a, u_a\right) \\
& = \sum_{j=0}^{N-1} \left(x^\bullet(j) - x_a\right)^T \mathscr{Q} \left(x^\bullet(j) - x_a\right) + \left(\mathbf{u}(j) - u_a\right)^T \mathscr{R} \left(\mathbf{u}(j) - u_a\right) \\
& \qquad + \mathscr{P}\left(\mathrm{dist}_{\mathcal{X}_s^\bullet}^{Tar}(x_a) + \mathrm{dist}_{\mathcal{U}_s^{Tar}}(u_a)\right),
\end{aligned}$$

and $\mathscr{Q}$, $\mathscr{R}$ and $\mathscr{P}$ are positive definite matrices and positive numbers respectively. The transit behavior of the system under iZMPC can be tuned using these weighting matrices and parameters. In addition, $\mathrm{dist}_{\mathcal{Y}}(x) = \min_{y \in \mathcal{Y}} \|x - y\|$.

Note that, $x - x_s, \mathcal{X}_o, \mathcal{U}_o, \mathcal{X}_s^{\bullet Tar}, \mathcal{U}_s^{\bullet Tar}$ are given parameters in the optimization problem, whereas $\mathbf{U} = \{\mathbf{u}(0), \mathbf{u}(1), ..., \mathbf{u}(N-1)\}$, x_a and u_a are the optimization variables. When the iZMPC problem (S3) is solved, the optimal drug dose u in the system of augmented equations (S1) and (S2) (or $d_{\mathrm{IL}-2}$ in (3)) is obtained by $u = \mathbf{u}(0) + u_s$.