Model Predictive Control for Linear Impulsive Systems
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Abstract—Linear impulsive control systems have been extensively studied with respect to their equilibrium points which, in most cases, are no other than the origin. However, the trajectory of an impulsive system cannot be stabilized to arbitrary desired points hindering their utilization in a great many applications. In this technical note, we study the equilibrium of linear impulsive systems with respect to target-sets. We properly extend the notion of invariance and design stabilizing model predictive controllers (MPC). Finally, we apply the proposed methodology to control the intravenous bolus administration of Lithium.

Index Terms—Bolus drug administration, impulsive systems, invariance, model predictive control, stability.

I. INTRODUCTION

The motivation for this work comes mainly from the field of pharmacokinetics and the need for prescribing optimal and individualized drug administration policies. Physiologically-Based Pharmacokinetic (PBPK) models have been found to provide a reliable modeling framework for drug absorption, distribution, metabolism, and elimination and there are already a lot of relevant experimental data available in the literature [1]. When a drug is administered intravenously or in any other way not continuously, instantaneous jumps are observed in the concentration of the drug in some organs; this is mathematically conceptualized as a discontinuity of the first kind and gives rise to the so-called impulsive systems [2].

Impulsive systems have attracted a lot of attention also in the context of industrial, telecommunications and other applications. For instance, in [3] a model of a spacecraft is formulated as a linear impulsive system. Shen et al. use impulsive differential equations to describe the dynamics of a fed-batch fermentator [4]. However, there is a notable scantiness in bibliographical references to applications of impulsive systems mainly due to the shortcomings of the current theoretical tools for the design of feedback controllers under constraints.

Linear impulsive systems have been studied to a great extent regarding existence and uniqueness of solutions, stability and other qualitative properties [2]. The existing theory addresses stability in light of the equilibrium points of the system and in most cases boils down to the study of the properties of the zero solution exclusively [5].

II. NOTATION

Let \( N, \mathbb{R}^n, \mathbb{R}_+, \mathbb{R}^{m \times n} \) denote the set of non-negative integers, the set of column real vectors of length \( n \), the set of non-negative numbers and the set of \( m \)-by-\( n \) real matrices, respectively. For any nonnegative integers \( k_1 \leq k_2 \) the finite set \( \{k_1, \ldots, k_2\} \) is denoted by \( \mathbb{N}_{[k_1, k_2]} \).

For a function \( f : \mathbb{R} \to \mathbb{R}^n \) and \( t_0 \in \mathbb{R} \), we denote \( \Delta f(t_0) := \lim_{t \to t_0^+} f(t) - f(t_0) \); we also make use of the notation \( f(t^-) := \lim_{t \to t_-} f(t) \).

For a set \( Y \), we denote its powerset by \( 2^Y \). A set-valued function \( \mathcal{F} : X \to 2^Y \) will be denoted as \( F : X \to Y \) and its domain is defined to be \( \text{dom} \mathcal{F} = \{ x \in X \mid F(x) \neq \emptyset \} \).

A function \( f \) is \( \mathcal{C} \)-continuous at \( x_0 \) if \( f \) is continuous at \( x_0 \) and \( \lim_{x \to x_0} f(x) = f(x_0) \).

For a nonempty set \( Y \subseteq \mathbb{R}^n \) we define the point-to-set distance \( d_{\mathcal{J}}(x) := \inf_{y \in Y} \| x - y \| \).

A set \( B^V \) is defined as the set of all \( z \in \mathbb{R}^n \) such that \( d_{\mathcal{J}}(z) < \varepsilon \).

For any matrix \( B \in \mathbb{R}^{m \times n} \), \( \| B \| \) denotes its induced norm (by the Euclidean vector norm \( \| \cdot \| \)), i.e., \( \| B \| := \sup_{\| x \| = 1} \| Bx \| \).

For \( Y \subseteq \mathbb{R}^n \), \( y_0 \in \mathbb{R}^n \) and \( M \subseteq \mathbb{R}^{m \times n} \) we define \( MY := \{ My \mid y \in Y \} \).

A function \( \alpha : \mathbb{R}_+ \to \mathbb{R}_+ \) is called a \( K \)-class function if it is continuous, \( \alpha(0) = 0 \) and strictly increasing. A function \( \beta : \mathbb{R}_+ \times \mathbb{R}_+ \to \mathbb{R}_+ \) is said to be a \( K \)-class function if for every fixed \( s \in \mathbb{R}_+ \) the mapping \( \beta(\cdot, s) \) is a \( K \)-class function, and for every fixed \( r \in \mathbb{R}_+ \), \( \beta(r, \cdot) \) is decreasing and \( \lim_{s \to \infty} \beta(r, s) = 0 \).

III. LINEAR IMPULSIVE SYSTEMS

Let $T > 0$ be a constant referred to as the impulsive period. Consider the set of impulse time instants $\mathcal{T} = \{kT; \ k \in \mathbb{N}\}$ and the following linear impulsive system $\Sigma$:

$$\dot{x}(t) = Ax(t), \ t \in \mathbb{R} \setminus \mathcal{T}$$

$$\Delta x(t_k) = Bu_k, \ k \in \mathbb{N}$$

where $x \in \mathbb{R}^n$, $u \in \mathbb{R}^m$ and $A$ and $B$ are matrices of proper dimensions and $t_k := kT$ are the impulsive time instants. Equation (1b) describes the discontinuous jumps that happen on the continuous-time trajectory of the system which follows the linear dynamics given in (1a).

The system is subject to the following state and input constraints:

$$x(t) \in X, \forall t \geq 0$$

$$u_k \in U, \forall k \in \mathbb{N}$$

where $X$ and $U$ are assumed to be polyhedral sets.

The constraints in (2) render any optimization problem formulated thereupon (such as finite-horizon optimal control problems which arise in MPC) semi-infinite since it employs an infinite number of constraints. Such a problem would be particularly difficult to cope with per se, so, we propose a methodology to replace these constraints by a finite set of affine inequalities. Such a reduction was proposed by Pereira and Schmitzky for a planar linear impulsive system of the Kruger-Thiemer form wherein $A$ has only real eigenvalues and the state and input constraints are assumed to be rectangular. To overcome this limitation, we employ polytopic inclusions of the continuous-time trajectory of the system as in our previous work on sampled-data systems with random time delay [9], [10].

Let $\pi$ denote a sequence of inputs $\pi = \{u_0, u_1, \ldots, u_{N-1}\}$ drawn from $U$ and $\varphi(t; x_0, \pi)$, for $t \in [0, (N-1)T]$ be a solution of (1) satisfying $\varphi(0; x_0, \pi) = x_0$. Whenever we need to explicitly note that the initial time instant is other than 0, we use the notation $\varphi(t; x_0, \pi)$. Let $t > 0$ and $\tau_j$ be the largest impulse time not exceeding $t$ and $j \leq N - 1$. Then, for $\tau_j < t < \tau_{j+1}$ it is $\varphi(t; x_0, \pi) = e^{A(t-\tau_j)} \varphi(\tau_j^-; x_0, \pi)$, or, what is the same

$$\varphi(t; x_0, \pi) = e^{A(t-\tau_j)} (e^{AT_{\tau_j}} x_0 + \sum_{i=0}^{j} e^{(t-i)AT} Bu_i).$$

We denote by $\Sigma^p$ the closed-loop impulsive system with the application of the control law $\Delta x(t_k) = Bg(x(t_k))$, where $g : X \to U$ is a feedback function and $\varphi(t; x_0, g(\cdot))$ denotes the closed-loop trajectory of the above system satisfying the initial condition $\varphi(0; x_0, g(\cdot)) = x_0$.

IV. INVARIANCE FOR IMPULSIVE SYSTEMS

A. Impulsively Controlled Invariant Sets

In this section, we introduce generalized notions of invariance for impulsively systems with respect to a given target-set.

Definition 1 (Impulsively Controlled Invariant): Given a non-empty set $Z \subseteq \mathbb{R}^n$, a set $Y \subseteq Z$ such that for every $x \in Y$ there is a $u \in U$ so that the following conditions hold true for the system (1):

A1. $\varphi(T; x, u) \in Y$, where $\varphi(T; x, u) = e^{AT} (x + Bu)$,
A2. $W(x, u) := \{\varphi(r; x, u); r \in [0, T]\} \subseteq Z$

is an impulsively controlled invariant (ICI) set with respect to $Z$.

Definition 2 (Impulsively Invariant): Consider the closed-loop impulsive system $\Sigma^p$. Given a nonempty set $Z \subseteq \mathbb{R}^n$, a set $Y \subseteq Z$ such that for every $x \in Y$, A1 and A2 hold for $u = g(x)$ is called an impulsively invariant set for $\Sigma^p$ with respect to $Z$.

These definitions of invariance are more flexible than the conventional ones employed by Pereira et al. [11] for impulsive control systems and harmonize with control practice where the target-set is a given design requirement as in drug administration [12].

In what follows, the set $Z$ is assumed to be polyhedral. For a given state $x$ and input $u$, we construct a polytope-valued mapping $S(x, u)$ such that $S(x, u) \supseteq W(x, u)$. Thus, introducing some conservatism, we may replace A2 by:

A3. For all $x \in Y$, there is a $u \in U$ so that $S(x, u) \subseteq Z$, and notice that condition A3 implies condition A2, therefore a set $Y$ satisfying both conditions A1 and A3 is an ICI set with respect to $Z$. The use of A3 will, however, be preferred for reasons of computational tractability as explained in the previous section.

B. Determination of ICI Sets

In this section, we elaborate on the properties of ICI sets and we describe a methodology for the algorithmic determination of ICI sets based on the observation that ICI sets can be written as the fixed point of an operator.

We first define the mapping $F_{x,u} : \mathbb{R}^{n \times n} \ni L \rightarrow F_{x,u}(L) := L(x + Bu) \in \mathbb{R}^n$ and we note that $W(x, u) = cl F_{x,u}(D)$, where $D := \{e^{AT} \mid \tau \in [0, T]\}$. Given a polytope $C = \{\Phi = \sum_{i=1}^{K} \lambda_i A_i \mid \lambda_i \geq 0, \sum_{i=1}^{K} \lambda_i = 1\} \supseteq D$ define $S(x, u) := cl F_{x,u}(C)$ and observe that since $C \supseteq D$, it follows that for all $x$ and $u$, $F_{x,u}(C) \supseteq F_{x,u}(D)$, which proves that $S(x, u) \subseteq W(x, u)$. We then define the mapping $Pre_{Z,S} : 2^X \rightarrow 2^X$ for $Z \subseteq X$ as follows:

$$Pre_{Z,S}(Y) := \{x \in X \mid \exists u \in U \text{ s.t. } S(x, u) \subseteq Z \text{ and } e^{AT}(x + Bu) \in Y\}.$$ (4)

A set $Y$ which satisfies both A1 and A2 is impulsively control invariant with respect to $Z$ and satisfies:

$$Y \subseteq Pre_{Z,W}(Y).$$ (5)

In general, a set $Y$ is ICI with respect to $Z$ if and only if $Y \subseteq Pre_{Z,S}(Y)$ for some $S$ such that $S(x, u) \supseteq W(x, u)$ for all $x$ and for all $u$. Indeed, assume that set $Y$ satisfies $Y \subseteq Pre_{Z,S}(Y)$, then, for every $x \in Y$, $x \in Pre_{Z,S}(Y)$, i.e., there is a $u \in U$ such that $S(x, u) \subseteq Z$ (Condition A3) and $e^{AT}(x + Bu) \in Y$ (Condition A1), consequently $Y$ is an ICI set with respect to $Z$.

For some $x \in X$ and $u \in U$, $(x, u)$, being a polytope, can be represented as the convex hull of its extreme points (by virtue of the Krein-Milman Theorem). In particular, let $\{A_i\}_{i=1}^K$ be a collection of matrices such that $\{e^{AT} ; t \in [0, T]\} \subseteq co\{A_i\}_{i=1}^K$. Such a collection can be determined using methods of polytope overapproximation of functions in the form $\sigma(x) = e^{Ax}$, where $A \in \mathbb{R}^{n \times n}$ as in [9]. Then, $S$ can be fully determined by the set of matrices $\{A_i\}_{i=1}^K$ and

$$S(x, u) = co\{A_i\}_{i=1}^K \cdot (x + Bu).$$ (6)

Let us now present a way to calculate a polytopic ICI set $Y^S$. Any of the fixed points of the operator $\Omega \rightarrow Pre_{Z,S}(\Omega) \cap \Omega$, for $\Omega \subseteq X$, is an ICI set because of (5) and can be calculated by the iterative procedure

$$Y_0^S = Z, \hspace{1cm} Y_{k+1}^S = Pre_{Z,S}(Y_k^S) \cap Y_k^S.$$ (7)

If (7) converges in a finite number of steps to a nonempty set, then the resulting set $Y^S$ is impulsively controlled invariant and polyhedral.

C. Alternative Procedure

Algorithm (7) may not converge in a finite number of steps or may return an empty set. In such a case no conclusions may be drawn about the existence of an ICI set. In this section we present an alternative
The set of solutions of the impulsive system $\Sigma^g$ with respect to $Y$ if for all $\varepsilon > 0$ there is a $\delta > 0$ so that
\[
\varphi_{\varepsilon}(\tau_k; x_0, g(\cdot)) \in \mathcal{B}_\varepsilon^Z \cap X, \forall k \in \mathbb{N}
\]
whenever $x_0 \in \mathcal{B}_\varepsilon^Y \cap X$. Set $Z$ is said to be weakly asymptotically stable if it is weakly stable and there is an $\varepsilon > 0$ so that $\lim_{k \to \infty} \text{dist}_Z(\varphi_{\varepsilon}(\tau_k; x_0, g(\cdot))) = 0$ whenever $x_0 \in \mathcal{B}_\varepsilon^Y \cap X$.

The domain of attraction for weakly asymptotically stable systems is defined analogously.

**Definition 7 (Uniform Boundedness):** The trajectories of $\Sigma^g$ are called $(Z, Y)$-locally uniformly bounded over an interval $I \subseteq [0, \infty)$ if there is an $\eta > 0$ and a $K$-class function $\gamma : \mathbb{R} \to \mathbb{R}_+$ so that $\gamma(x) \leq \gamma(\text{dist}_Z(\varphi_{\varepsilon}(t; x_0, g(\cdot))))$ for all $t \in I$ whenever $x_0 \in \mathcal{B}_\varepsilon^Y \cap X$.

Note that if $Y$ is impulsive invariant with respect to $Z$, then if $x_0 \in Y$, i.e., $\text{dist}_Y(x_0) = 0$, then $\varphi_{\varepsilon}(t; x_0, g(\cdot)) \subseteq Y$, i.e., $\text{dist}_Z(\varphi_{\varepsilon}(t; x_0, g(\cdot))) = 0$ and the aforementioned condition is trivially satisfied. This condition demands that the escape from $Z$ is controlled by the distance of the initial condition from $Y$. The trajectories of $\Sigma^g$ are $(Z, Y)$-locally uniformly bounded over $I$ if and only if for every $\varepsilon > 0$ there is a $\delta = \delta(\varepsilon) > 0$ so that $\text{dist}_Z(\varphi_{\varepsilon}(t; x_0, g(\cdot))) < \varepsilon$ whenever $x_0 \in \mathcal{B}_\varepsilon^Y \cap X$ for all $t \in I$ as it can be proven along the lines of [15, Lemma 4.5].

It is natural to ask under what conditions (imposed on $g$) the trajectories of $\Sigma^g$ are $(Z, Y)$-locally uniformly bounded. Proposition 8 provides such a sufficient condition on $g$.

**Proposition 8 (Uniform Boundedness):** Assume that $Y$ is a nonempty compact impulsive invariant set for $\Sigma^g$ with respect to $Z$. Assume that there is an $\eta > 0$ and a $K$-class function $\gamma : \mathbb{R}_+ \to \mathbb{R}_+$ so that for every $y \in \mathcal{B}_\varepsilon^Y \cap X$ there is a $\rho_Y > 0$ so that
\[
\|g(x) - g(y)\| \leq \gamma(\|x - y\|)
\]
whenever $x \in \mathcal{B}_\varepsilon^Y \cap X$ and $\|x - y\| < \rho_Y$. Then the trajectories of $\Sigma^g$ are $(Z, Y)$-locally uniformly bounded over the interval $(0, T]$.

**Proof:** Define $h_{\varepsilon}(x) := x + B\gamma(x)$ and $\alpha(s) := s + \|B\|\gamma(s)$. It can be easily seen that for $x, y \in \mathcal{B}_\varepsilon^Y \cap X$ and $\|x - y\| < \rho_Y$, it is $\|h_{\varepsilon}(x) - h_{\varepsilon}(y)\| \leq \alpha(\|x - y\|)$, and it can be verified that $\alpha$ is a $K$-class function. Let $\varepsilon > 0$ and define
\[
\delta(\varepsilon) := \min\left\{\rho, \eta, \alpha^{-1}\left(\frac{\varepsilon}{2M}\right)\right\}
\]
where $M := \sup_{t \in (0, T]} \|e^{At}\|$ and $\rho := \inf_{y \in \mathcal{B}_\varepsilon^Y \cap X} \rho_Y$; it is $\rho > 0$ because of the compactness of $Y$. Take $x_0 \in \mathcal{B}_\varepsilon^Y \cap X \cap X$; then we may find a $y_0 \in Y$ so that $\|y_0 - x_0\| \leq \delta(\varepsilon) \leq \min(\rho, \eta)$. Since $y_0 \in Y$ and $Y$ is an impulsive invariant set for $\Sigma^g$, it is $e^{At}h_{\varepsilon}(y_0) \in Z$ for all $t \in (0, T]$, and since $\varphi_{\varepsilon}(t; x_0, g(\cdot))$, we have
\[
\text{dist}_Z(e^{At}h_{\varepsilon}(y_0)) = \inf_{x \in Z} \|e^{At}h_{\varepsilon}(y_0) - x\| \\
\leq \|e^{At}h_{\varepsilon}(x) - e^{At}h_{\varepsilon}(y_0)\| \\
\leq \|e^{At}\| \cdot \|h_{\varepsilon}(x) - h_{\varepsilon}(y_0)\| \leq M\alpha(\|x - y_0\|) \\
\leq M\alpha(\delta(\varepsilon)) \leq M\alpha\left(\alpha^{-1}\left(\frac{\varepsilon}{2M}\right)\right) < \varepsilon
\]
for all $t \in (0, T]$.\]
Note also that condition (14) is weaker than the locally Lipschitz continuity of \( g \) in \( B^g_X \cap X \). If the compactness requirement in Proposition 8 is dropped, then (14) has to be satisfied for all \( x, y \in B^g_X \cap X \) with \( ||x - y|| \leq \rho \) for some \( \rho > 0 \).

It turns out that weak asymptotic stability and uniform boundedness entail asymptotic stability for a set \( Z \) under certain additional conditions establishing this way a clear analogy between the following result and [16, Theorem 2.27] for sampled-data systems.

**Assumption 9:** We assume that \( \emptyset \neq Y \subseteq Z \), \( Y \) is impulsively invariant with respect to \( Z \) and there is a constant \( \eta > 0 \) and a \( K \)-class function \( \omega \) such that for all \( k \in \mathbb{N} \)

\[
\text{dist}_Y (\varphi^j(\tau_k; x_0, g(\cdot))) \leq \omega (\text{dist}_Y (x_0))
\]

whenever \( x_0 \in B^g_X \cap X \). That is, \( Y \) is weakly asymptotically stable with respect to \( Z \) and, under certain conditions, also continuously-time asymptotically stable.

We define the set-valued mapping \( U_f : Y \rightrightarrows U \) as follows:

\[
U_f (x) := \{ u \in U : e^{AT} (x + Bu) \in Y, S(x, u) \subseteq Z \}.
\] (15)

We also define the set \( D \) as follows:

\[
D = \{ (x, u) \in \mathbb{R}^{n+m} | x \in Y, u \in U_f (x) \}.
\] (16)

This set is the graph of the set-valued mapping \( U_f \). We now introduce the following stage cost function:

\[
\ell(x, u) = \text{dist}_D^2 (x, u, \min_{(x, v) \in D} \| (x, u) - (x, v) \|^2.
\] (17)

Notice that \( \ell(x, u) = 0 \) if and only if \( x \in Y \) and \( u \in U_f (x) \). This stage cost will allow to automatically perform dual-mode MPC without actually having computed an auxiliary, local controller beforehand.

The proposed MPC scheme amounts in solving at every impulse time \( \tau_k \) the following finite horizon optimal control problem:

\[
V^*_N (x(\tau_k)) = \inf_{\pi \in U_N (x(\tau_k))} V_N (x(\tau_k), \pi)
\] (18)

where

\[
V_N (x(\tau_k), \pi) = \sum_{j=0}^{N-1} \ell (\varphi (\tau_{k+j}; x(\tau_k), \pi), u_j)
\] (19)

and

\[
U_N (x) = \left\{ \pi \mid \forall j \in \{0, N-1\} : u_j \in U, S (\varphi (\tau_j; x, \pi), u_j) \subseteq X, \varphi (\tau_j; x, \pi) \in Y \right\}.
\] (20)

The MPC problem can be reformulated as a convexQP

\[
V^*_N (x(\tau_k)) = \inf_{\pi, x, v} \bar{V}_N (x(\tau_k), \pi, x, v)
\] (21a)

\[
\bar{V}_N (x(\tau_k), \pi, x, v) := \sum_{j=0}^{N-1} \left\| \varphi (\tau_{k+j}; x, \pi) - z_j \right\|_{u_j - v_j}^2
\] (21b)

subject to the constraints

\[
\pi \in U_N (x(\tau_k)) \ , \ (z_j, v_j) \in D, \forall j \in \{0, N-1\}.
\] (21c)

The feasible domain of this problem is simply the set \( X_N = \text{dom} \ell_f \), i.e., states that can be steered inside \( Y \) in \( N \) steps while the continuous-time trajectory remains inside \( X \). This problem is merely convex, therefore the optimizer is in general set-valued. This is evident since for every \( x \in Y \) and every \( u \in U_f (x) \) it holds that \( \ell(x, u) = 0 \). Let us denote by \( \pi^*(x(\tau_k)) = (\pi^0 (x(\tau_k)), \pi^1 (x(\tau_k)), \ldots, \pi^{N-1} (x(\tau_k))) \) the (possibly) set-valued optimizer of (18). This gives rise to a family of feedback control laws \( \sigma (x(\tau_k)) = \pi^0 (x(\tau_k)) \) and notice that if \( x \in Y \) then \( \sigma (x) = U_f (x) \). Then every \( s : X_N \rightarrow U \) such that \( s(x) \in \sigma (x) \) for all \( x \in X_N \) is called an optimal control law. As we prove in the following section, every such optimal control law deems \( Z \) weakly stable with respect to \( Y \) while all controlled trajectories of the system satisfy the constraints in continuous-time.

It should be noted that the minimum of (18) is attainable if \( D \) is bounded according to [17, Thm. 1.9].

### VI. Model Predictive Control

#### A. Formulation

In this section, we use the above theoretical developments to design a MPC which leads the system’s state to a specified target set \( Z \) by involving an ICI set \( Y \) (with respect to \( Z \)) in the formulation of the MPC problem. We prove that the MPC controller leads to the satisfaction of the state and input constraints in continuous-time, it renders \( Z \) weakly asymptotically stable with respect to \( Y \) and, under certain conditions, also continuously-time asymptotically stable.

We define the set-valued mapping \( U_f : Y \rightrightarrows U \) as follows:

\[
U_f (x) := \{ u \in U : e^{AT} (x + Bu) \in Y, S(x, u) \subseteq Z \}.
\]

We also define the set \( D \) as follows:

\[
D = \{ (x, u) \in \mathbb{R}^{n+m} | x \in Y, u \in U_f (x) \}.
\]

This set is the graph of the set-valued mapping \( U_f \). We now introduce the following stage cost function:

\[
\ell(x, u) = \text{dist}_D^2 (x, u, \min_{(x, v) \in D} \| (x, u) - (x, v) \|^2.
\]

Notice that \( \ell(x, u) = 0 \) if and only if \( x \in Y \) and \( u \in U_f (x) \). This stage cost will allow to automatically perform dual-mode MPC without actually having computed an auxiliary, local controller beforehand.

The proposed MPC scheme amounts in solving at every impulse time \( \tau_k \) the following finite horizon optimal control problem:

\[
V^*_N (x(\tau_k)) = \inf_{\pi \in U_N (x(\tau_k))} V_N (x(\tau_k), \pi)
\]

where

\[
V_N (x(\tau_k), \pi) = \sum_{j=0}^{N-1} \ell (\varphi (\tau_{k+j}; x(\tau_k), \pi), u_j)
\]

and

\[
U_N (x) = \left\{ \pi \mid \forall j \in \{0, N-1\} : u_j \in U, S (\varphi (\tau_j; x, \pi), u_j) \subseteq X, \varphi (\tau_j; x, \pi) \in Y \right\}.
\]
Then, $Y$ is asymptotically stable for the MPC-controlled system with respect to $Z$.

**Proof:** If the first condition is satisfied, then there is an $\eta > 0$ so that $\mathcal{B}_Y^\eta \subseteq \text{Pre}_{\mathcal{X},S}(Y)$. Because of Theorem 11, for every $x \in \mathcal{X}_N$ there is a $k_x \in \mathbb{N}$ so that $\varphi_{cl}(t; x, s(\cdot)) \in \mathcal{B}_Y^\eta$ for all $t \geq \tau_{k_x}$. As a result, $\varphi_{cl}(t; x, s(\cdot)) \in \text{Pre}_{\mathcal{X},S}(Y)$ for all $t \geq \tau_{k_x}$. Once the state enters $\mathcal{B}_Y^\eta$ at an impulsive time $\tau_k$, the local control law $\kappa_{loc}$ will lead it inside $Y$ at time $\tau_{k+1}$ without violating the constraints in continuous time (since $S(x, \kappa_{loc}(x)) \subseteq X$), from which the assertion follows.

In the second case, the optimizer of (18) becomes single-valued and Lipschitz-continuous because of [18], so the requirements of Proposition 8 are satisfied and the assertion follows.

Note that a local controller $\kappa_{loc}$ as in Proposition 12 is easy to obtain by solving for each $x \in \mathcal{B}_Y^\eta$ a feasibility problem. According to Proposition 12, unless $D$ is a singleton, a local controller in a neighborhood of $Y$ is necessary to guarantee asymptotic stability in continuous time.

Notice that if neither of the conditions of Proposition 12 are satisfied, the optimizer of (18), $\sigma : \mathcal{X}_N \Rightarrow U$, is multi-valued, outer-semicontinuous, but not necessarily inner-semicontinuous [18], consequently, a locally Lipschitz (or even locally continuous in a neighborhood of $Y$) selection $s$ may not exist. In such a case, $Z$ will still be weakly asymptotically stable for the controlled system with respect to $Y$ and all constraints will be satisfied in continuous time for all initial states in $\mathcal{X}_N$, however, continuous-time stability will not be guaranteed.

**VII. APPLICATION**

Ehrlich et al. [1] provide a physiological pharmacokinetic model based on experimental data which describes the distribution of Lithium ions in the human body upon oral administration. However, the compartmental nature of the model enables us to study the scenario of intravenous administration. The compartments taken into account correspond to the plasma (P), the red blood cells (RBC) and the muscle cells (M). The respective concentrations are denoted by $C_P$, $C_{RBC}$ and $C_M$ and they define the system’s state vector $x(t) := [C_P(t) C_{RBC}(t) C_M(t)]^T$. The exact topology of the model is illustrated in Fig. 1.

The dynamics of the drug distribution is described by the following impulsive system:

$$\frac{dx(t)}{dt} = \begin{bmatrix} -0.6137 & 0.1835 & 0.2406 \\ 1.2644 & -0.8 & 0 \\ 0.2054 & 0 & -0.19 \end{bmatrix} x(t)$$

(22a)

$$\Delta x(t) = \begin{bmatrix} -1.9 \\ 0 \\ 0 \end{bmatrix} u.$$  

(22b)

The administration period is fixed to 3hr. The constraints $0 \leq x(t) \leq x_{\text{max}}$ are imposed on the state variables in continuous time where $x_{\text{max}} = (2, 1.2, 1.2) \text{nmol} \cdot \text{L}^{-1}$. The input variable $u$ corresponds to the amount of administered dose and it should not exceed 5.95 nmol, i.e., $0 \leq u_k \leq 5.95 \text{ nmol}$. The target-set $Z$ is circumscribed by the set of inequalities $x_L \leq x(t) \leq x_H$ where $x_L = (0.4, 0.6, 0.5)' \text{nmol} \cdot \text{L}^{-1}$ and $x_H = (0.6, 0.9, 0.8)' \text{nmol} \cdot \text{L}^{-1}$. Such a set is determined by the treating doctor and is known as the therapeutic window [12]. The stay of the drug’s concentration within the boundaries of $Z$ guarantees the effectiveness of the therapy. The aim of the proposed MPC methodology is to eventually lead the trajectories of the system towards set $Z$. The set $Y$ is a polytope in $\mathbb{R}^3$ and was calculated in 5 iterations of (7) in 4.3s and its minimal representation comprised 15 inequalities. The set $\{A_i\}_{i=1}^{10}$ with $A_i \in \mathbb{R}^{3 \times 3}$ for $i \in [\mathbb{N} \in [1, 10]]$ in (6) was computed using the methodology of gridding and norm bounding as in [9] in 4.4s. All reported computation times were measured on a Mac OS X v10.8.2 machine, 2.2GHz Intel Core i7, 8GB RAM.

The MPC control problem is formulated according to (21a) and the prediction horizon was set to $N = 15$. The controlled trajectory in presence of the proposed impulsive model predictive controller is presented in Fig. 2 and one may notice that the state constraints are satisfied at all (impulsive and continuous) time instants while the trajectory of the system ends up inside the prescribed target-set. It is guaranteed that once the system’s state enters $Y$ it will remain inside the therapeutic window $Z$ at all continuous-time instants. The sequence of control actions produced by the MPC controller is presented in Fig. 3. One may also notice that the state and input constraints are satisfied at all times. Because of Theorem 11, $Z$ is weakly asymptotically stable with respect to $Y$. Additionally, set $Y$ is contained in the interior of $\text{Pre}_{\mathcal{X},S}(Y)$, so the controlled system is asymptotically stable with the use of a local controller as in Proposition 12 with $\eta = 10^{-5}$.

The MPC problem was solved online using Gurobi [19] and the average computation time on 100 iterations was 22.0 ms (st.dev.: 20.95 ms, max: 80 ms).

**APPENDIX**

**PROOF OF THEOREM 11**

Step 1. We prove a Lyapunov-type inequality. First, we show that for all $x(\tau_k) \in \mathcal{X}_N$, it holds true that

$$V_N'(x(\tau_{k+1})) - V_N'(x(\tau_k)) \leq -\ell(x(\tau_k), s(x(\tau_k)))$$

(23)

where $x(\tau_{k+1}) = \varphi_{cl}(\tau_{k+1}; \tau_k, x(\tau_k), s(\cdot))$. 

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**Fig. 1.** Topology of the interconnected compartments of the PBPK model.

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**Fig. 2.** Controlled trajectory using the proposed controller.
Let \( x(\tau_k) \in X_N \) and \( \pi^* (x(\tau_k)) := \{ u_k^*(x(\tau_k)) \}_{k=0}^{N-1} \) be an optimal control sequence, i.e., \( V_N^*(x(\tau_k)) = V_N(x(\tau_k), \pi^*(x(\tau_k))) \). If we apply \( \pi^*(x(\tau_k)) \) to the impulsive system, the following sequence of states will occur: \( x_{k+1}^*(x(\tau_k)) = \varphi(\tau_{k+1}; \tau_k, x(\tau_k), \pi^*(x(\tau_k))) \) for \( i = 0, \ldots, N \), and \( x_{N+1}^*(x(\tau_k)) \in Y \). At the next time instant, \( \tau_{k+1} \), the state of the system will be \( x_{k+1}^*(x(\tau_k)) \) for which we choose the (sub-optimal) control sequence \( \tilde{\pi}(x(\tau_k)) = \{ u_{k+1}^*(x(\tau_k)), \ldots, u_{k+N-1}^*(x(\tau_k)) \} \) where the last element \( u \in U \) is to be determined. Then, the resulting state sequence is \( \tilde{x}(x(\tau_k)) = \{ x_{k+1}^*(x(\tau_k)), \ldots, x_{k+N-1}^*(x(\tau_k)) \} \), where \( x_{k+N}^*(x(\tau_k)) := \varphi(\tau_{k+N}; \tau_k, x_{k+N-1}^*(x(\tau_k)), u) \). Provided that the last element of \( \tilde{x}(x(\tau_k)) \) is in \( Y \), the sequence of inputs \( \tilde{\pi}(x(\tau_k)) \) is admissible since \( u \in U \). Then \( V_N^*(x(\tau_k)) = V_N(x(\tau_k), \pi^*(x(\tau_k))) \) is

\[
V_N^*(x(\tau_k)) = \sum_{j=0}^{N-1} \ell(x_{k+j}^*(x(\tau_k)), u_{k+j}^*(x(\tau_k))).
\]

Because of the terminal-state constraints, \( x_{k+N}^*(x(\tau_k)) \in Y \), and also \( u \in U \), \( x_{k+N}^*(x(\tau_k)) = \varphi(\tau_{k+N}; \tau_k, x_{k+N-1}^*(x(\tau_k)), u) \).

Let \( \tilde{\Omega}_c := \{ x \in X_N | V_N^*(x) \leq c \} \), assume that \( c > 0 \) and let \( 0 < \zeta < c \) such that \( B_c^v \cap X_N \subseteq \tilde{\Omega}_c \). Then, for all \( j \in \mathbb{N} \), \( V_N(\varphi_j(\tau_{k+j}; \tau_k, x(\tau_k), s(\cdot))) \geq c \). Define \( \gamma_r := -\max(\ell(x, s(x)), \zeta) \leq \text{dist}y(x, r, X_N) \) for \( r > \zeta \). Evidently \( \gamma_r < 0 \) for all \( r > \zeta \). Then, by (23) it is

\[
V_N^*(x(\tau_{k+j})) \leq V_N^*(x(\tau_k)) - \sum_{i=0}^{j-1} \ell(x(\tau_{k+i+1}), s(x(\tau_{k+i+1}))).
\]

Eventually, for \( j \geq \tau_k^{-1} V_N^*(x(\tau_k)) \) we have that \( V_N^*(x(\tau_{k+j})) < 0 \) which is a contradiction and as a result \( c = 0 \). The set \( Y \) is, therefore, weakly asymptotically stable with respect to itself with domain of attraction the set \( X_N \). As a result, since \( Z \supseteq Y \), \( Z \) is weakly asymptotically stable with respect to \( Y \) with domain of attraction \( X_N \).

REFERENCES


