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*—Bolous 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]. For instance, Fontes and Pereira [6] prescribed stability conditions for the design of MPC for nonlinear impulsive systems using Nagumo-like invariance conditions, but without the guarantee that the inter-sample trajectory of the system satisfies the state constraints. Impulsive systems can also be cast as hybrid dynamical systems for which considerable developments have recently emerged [7], however, this plethora of theoretical developments has not lead to an applicable control methodology for impulsive systems providing stability properties for the closed-loop system and constraint satisfaction in continuous time.

Except for trivial cases (e.g., the system $\dot{x}=0$), it is impossible to stabilize the state of an impulsive system at any given desired state – a fact that renders the wealth of results in this field not applicable to a great load of scenarios of significant practical interest such as drug administration control. This calls for weaker stability qualifications such as stability with respect to a given *target-set* as opposed to the traditional approach that makes use of equilibrium points. This necessary generalization paves the way for the formulation and solution of MPC problems with linear impulsive models.

This technical note lays the foundations for a rigorous approach to model predictive control of impulsive systems introducing new definitions of invariance and stability. Preliminary results of this work were presented in [8], while in this technical note we provide an alternative methodology for the determination of impulsive controlled invariant sets (see Section IV-C), we state a criterion for local uniform boundedness in the context of impulsive systems (see Proposition 8) and we show how all these novel theoretical tools can be used for the control of intravenous bolous administration of medicines with a particular application on the administration of Lithium.

II. Notation

Let $\mathbb{N}$, $\mathbb{R}^n$, $\mathbb{R}_+$, $\mathbb{R}^{m\times n}$ 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 $f(t^+) := \lim_{\tau\to t^+} f(\tau)$. Hereinafter, we shall use the notation $\mathrm{co}\{\Gamma\}$ to denote the convex hull of a set $\Gamma\subseteq\mathbb{R}^n$.

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 $\mathcal{F}:X\rightrightarrows Y$ and its *domain* is defined to be $\mathrm{dom}\mathcal{F}=\{x\in X \mid \mathcal{F}(x)\neq\varnothing\}$. For a set C, we denote by $\mathrm{cl}\, C$ its topological closure and by $\mathrm{int}\, C$ its interior. For a nonempty set $Y\subseteq\mathbb{R}^n$ we define the point-to-set distance $\mathrm{dist}_Y(x) := \inf_{y\in Y}\|x-y\|$. An ε-neighborhood of Y is defined as the set $\mathcal{B}_\varepsilon^Y := \{z\in\mathbb{R}^n \mid \mathrm{dist}_Y(z)<\varepsilon\}$. 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 $M\in\mathbb{R}^{m\times n}$ we define $MY := \{My \mid y\in Y\}$ and $y_0+Y := \{y+y_0 \mid y\in Y\}$.

A function $\alpha:\mathbb{R}_+\to\mathbb{R}_+$ is called a $\mathcal{K}$-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 $\mathcal{KL}$-class function if for every fixed $s\in\mathbb{R}_+$ the mapping $\beta(\cdot,s)$ is a $\mathcal{K}$-class function, and for every fixed $r\in\mathbb{R}_+$, $\beta(r,\cdot)$ is decreasing and $\lim_{s\to\infty}\beta(r,s)=0$.

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III. Linear Impulsive Systems

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

$$\dot{x}(t) = Ax(t), t \in \mathbb{R} \setminus \mathfrak{T} \tag{1a}$$
$$\Delta x(\tau_k) = Bu_k, k \in \mathbb{N} \tag{1b}$$

where $x \in \mathbb{R}^n$, $u \in \mathbb{R}^m$ and A and B are matrices of proper dimensions and $\tau_k := kT$ 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:

$$x(t) \in X, \forall t \geq 0 \tag{2a}$$

$$u_k \in U, \forall k \in \mathbb{N} \tag{2b}$$

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 Pierce and Schumitzky 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 π 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 $\varphi(t; \tau_0, x_0, \pi)$. Let $t > 0$ and τ_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

$$\varphi(t; x_0, \pi) = e^{A(t-\tau_j)}(e^{jAT}x_0 + \sum_{i=0}^{j} e^{(j-i)AT}Bu_i). \tag{3}$$

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

IV. Invariance for Impulsive Systems

A. Impulsively Controlled Invariant Sets

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

Definition 1 (Impulsively Controlled Invariant): Given a non-empty set $Z \subset \mathbb{R}^n$, 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. $\mathcal{W}(x, u) := \mathrm{cl}\,\{\varphi(r; x, u); r \in (0, T]\} \subseteq Z$,

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

Definition 2 (Impulsively Invariant): Consider the closed-loop impulsive system Σ^g. 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 Σ^g 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 $\mathcal{S}(x, u)$ such that $\mathcal{S}(x, u) \supseteq \mathcal{W}(x, u)$. Thus, introducing some conservatism, we may replace A2 by:

A3. For all $x \in Y$, there is a $u \in U$ so that $\mathcal{S}(x, u) \subseteq Z$,

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 a the observation that ICI sets can be written as the fixed point of an operator.

We first define the mapping $F_{x,u} : \mathbb{R}^{n\times n} \ni L \mapsto F_{x,u}(L) := L(x + Bu) \in \mathbb{R}^n$ and we note that $\mathcal{W}(x, u) = \mathrm{cl}\, F_{x,u}(D)$, where $D := \{e^{A\tau} \mid \tau \in (0, T]\}$. 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 $\mathcal{S}(x, u) := \mathrm{cl}\, F_{x,u}(C)$ 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 $\mathcal{S}(x, u) \supseteq \mathcal{W}(x, u)$. We then define the mapping $\mathrm{Pre}_{Z,\mathcal{S}} : 2^X \to 2^X$ for $Z \subseteq X$ as follows:

$$\mathrm{Pre}_{Z,\mathcal{S}}(Y) := \left\{ x \in X \,\middle|\, \begin{array}{l} \exists u \in U \text{ s.t. } \mathcal{S}(x, u) \subseteq Z \\ \text{and } e^{AT}(x + Bu) \in Y \end{array} \right\}. \tag{4}$$

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

$$Y \subseteq \mathrm{Pre}_{Z,\mathcal{W}}(Y). \tag{5}$$

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

For some $x \in X$ and $u \in U$, $\mathcal{S}(x, u)$, 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 $\{e^{At}; t \in [0, T]\} \subseteq \mathrm{co}\{A_i\}_{i=1}^K$. Such a collection can be determined using methods of polytopic overapproximation of functions in the form $\gamma(x) = e^{Ax}$, where $A \in \mathbb{R}^{n\times n}$ as in [9]. Then, $\mathcal{S}$ can be fully determined by the set of matrices $\{A_i\}_{i=1}^K$ and

$$\mathcal{S}(x, u) = \mathrm{co}\{A_i\}_{i\in\mathbb{N}_{[1,K]}} \cdot (x + Bu). \tag{6}$$

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

$$Y_0^{\mathcal{S}} = Z, \quad Y_{k+1}^{\mathcal{S}} = \mathrm{Pre}_{Z,\mathcal{S}}(Y_k^{\mathcal{S}}) \cap Y_k^{\mathcal{S}}. \tag{7}$$

If (7) converges in a finite number of steps to a nonempty set, then the resulting set $Y^{\mathcal{S}}$ 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 procedure with which we may determine convex, compact ICI sets. To this end, let us first define the polytope

$$M_{\mathcal{S}} := \{x \in Z \mid \exists u \in U, \text{ such that } \mathcal{S}(x,u) \subseteq Z\} \tag{8}$$

assume $M_{\mathcal{S}} \neq \varnothing$ and define the set-valued mapping $\mathcal{H} : M_{\mathcal{S}} \rightrightarrows Z$ by

$$\mathcal{H} : M_{\mathcal{S}} \ni x \mapsto \mathcal{H}(x) := e^{AT}(x + BU) \cap Z. \tag{9}$$

The mapping $\mathcal{H}$ associates every $x \in M_{\mathcal{S}}$ at time τ_k to the set of its reachable states at time τ_{k+1} that are in Z. The following proposition is instrumental to establish the existence of compact ICI sets; it states that if a nonempty compact convex ICI set exists at all, there also exists a singleton ICI set which can be easily determined.

Proposition 3: Let $Z \subseteq X$ be nonempty, $M_{\mathcal{S}} \neq \varnothing$ and $Y \neq \varnothing$ be a convex, compact ICI set with respect to Z. Then, there is a $\bar{x} \in Y$ such that $\mathcal{H}(\bar{x}) \ni \bar{x}$.

Proof: Let us define the multi-valued mapping $\tilde{\mathcal{H}} : Y \rightrightarrows Y$ as $\tilde{\mathcal{H}}(x) := \mathcal{H}(x) \cap Y$. Note that since Y is an ICI set, it follows that $\varnothing \neq Y \subseteq M_{\mathcal{S}}$, therefore the domain of $\tilde{\mathcal{H}}$ is nonempty. For $x \in Y$, there is a u_x such that $e^{AT}(x + Bu_x) \in Y$, so $\tilde{\mathcal{H}}(x) \neq \varnothing$ and $\tilde{\mathcal{H}}(x)$ is convex as an intersection of convex sets. Since Y is closed, the graph of $\tilde{\mathcal{H}}$, i.e., the set $\{(x,y) \in Y \times Y \mid y \in \tilde{\mathcal{H}}(x)\}$ can be written as $\mathrm{proj}_{(x,y)}\{(x,y,v) \in Y \times Y \times U \mid y = e^{AT}(x + Bv)\} \cap (Y \times Y)$, where $\mathrm{proj}_{(x,y)}(x,y,v) = (x,y)$, which is closed because it is polyhedral. Hence, $\tilde{\mathcal{H}}$ satisfies the requirements of the Kakutani fixed-point Theorem [13] which proves the assertion. ■

Conversely, it is obvious that if there is a $\bar{x}$ as in Proposition 3, then the set $Y = \{\bar{x}\}$ is an ICI singleton. This leads to the formulation of the following feasibility problem:

$$\mathbb{P}_{\mathrm{ICI}}^{\mathcal{S}} : \quad e^{AT}(x + Bu) = x, \tag{10a}$$
$$x \in Z, u \in U \tag{10b}$$
$$\mathcal{S}(x,u) \subseteq Z. \tag{10c}$$

The set of solutions of $\mathbb{P}_{\mathrm{ICI}}^{\mathcal{S}}$ is a convex and compact ICI set.

Remark: Let $\bar{x}$ solve (10) and $Y_0 = \{\bar{x}\}$. Consider the following iterative procedure starting from Y_0:

$$Y_{k+1} = \mathrm{Pre}_{Z,\mathcal{S}}(Y_k). \tag{11}$$

Every Y_k in (11) is an ICI set with respect to Z and for all $k \in \mathbb{N}$, $Y_{k+1} \supseteq Y_k$; we have, therefore, constructed an increasing sequence of ICI sets.

V. Stability of Sets

In this section, we introduce new stability definitions for impulsive systems with respect to target sets making use of the control invariant set theory we presented in the previous section. Similarly to the case of invariance, stability is also studied with respect to a target-set Z towards which we need to steer the state of the system. The main result in this section is Theorem 10 in which, roughly speaking, we prove that continuous-time stability is implied by stability at impulse times and some notion of boundedness of the trajectories in the interim between impulse times.

Definition 4 (Stable Sets): A nonempty set $Z \subseteq X$ is said to be *stable* for an impulsive system Σ^g—subject to the constraints (2)—with respect to a nonempty set Y if for every $\varepsilon > 0$, there is a $\delta > 0$ so that

$$\varphi_{\mathrm{cl}}(t; x_0, g(\cdot)) \in \mathcal{B}_\varepsilon^Z \cap X, \ \forall t \geq 0 \tag{12}$$

whenever $x_0 \in \mathcal{B}_\delta^Y \cap X$. The set Z is said to be an *(locally) asymptotically stable set* for Σ^g with respect to Y if additionally there is an $\varepsilon_0 > 0$ such that for all $x_0 \in \mathcal{B}_{\varepsilon_0}^Y$, $\lim_{t\to\infty} \mathrm{dist}_Z(\varphi_{\mathrm{cl}}(t; x_0, g(\cdot))) = 0$.

Definition 5 (Domain of Attraction): If Z is asymptotically stable for Σ^g with respect to Y and there is a set $D \subseteq X$ so that for all $x_0 \in D$ it is $\lim_{t\to\infty} \mathrm{dist}_Z(\varphi_{\mathrm{cl}}(t; x_0, g(\cdot))) = 0$ then we say that D is a *domain of attraction* of Z for Σ^g.

This definition of stability is weaker than the classical one introduced by Bainov and Stamova in [14] in the sense that if a set Z is stable with respect to a given set Y, it need not be a stable set. Moreover, the use of the two distances dist_Y and dist_Z in Definition 4 makes the proposed approach more flexible compared to the hybrid systems framework of Goebel *et al.* [7].

We now introduce the definition of weakly stable sets which corresponds to stability at impulsive time instants exclusively. As we shall see in the sequel, if the control law satisfies some conditions which are not very conservative, then weak asymptotic stability entails asymptotic stability.

Definition 6 (Weakly Stable Sets): A set Z is said to be *weakly stable* for the impulsive system Σ^g with respect to Y if for all $\varepsilon > 0$ there is a $\delta > 0$ so that

$$\varphi_{\mathrm{cl}}(\tau_k; x_0, g(\cdot)) \in \mathcal{B}_\varepsilon^Z \cap X, \forall k \in \mathbb{N} \tag{13}$$

whenever $x_0 \in \mathcal{B}_\delta^Y \cap X$. Set Z is said to be *weakly asymptotically stable* if it is weakly stable and there is an $\varepsilon_0 > 0$ so that $\lim_{k\to\infty} \mathrm{dist}_Z(\varphi_{\mathrm{cl}}(\tau_k; x_0, g(\cdot))) = 0$ whenever $x_0 \in \mathcal{B}_{\varepsilon_0}^Y \cap X$.

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

Definition 7 (Uniform Boundedness): The trajectories of Σ^g are called (Z,Y)-*locally uniformly bounded* over an interval $I \subseteq [0,\infty)$ if there is an $\eta > 0$ and a $\mathcal{K}$-class function α such that it is $\mathrm{dist}_Z(\varphi_{\mathrm{cl}}(t; x_0, g(\cdot))) \leq \alpha(\mathrm{dist}_Y(x_0))$ for all $t \in I$ whenever $x_0 \in \mathcal{B}_\eta^Y \cap X$.

Note that if Y is impulsively invariant with respect to Z, then if $x_0 \in Y$, i.e., $\mathrm{dist}_Y(x_0) = 0$, then $\varphi_{\mathrm{cl}}(t; x_0, g(\cdot)) \in Z$, i.e., $\mathrm{dist}_Z(\varphi_{\mathrm{cl}}(t; x_0, g(\cdot))) = 0$ 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 Σ^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 $\mathrm{dist}_Z(\varphi_{\mathrm{cl}}(t; x_0, g(\cdot))) < \varepsilon$ whenever $x_0 \in \mathcal{B}_{\delta(\varepsilon)}^Y \cap X$ 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 Σ^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 impulsively invariant set for Σ^g with respect to Z. Assume that there is an $\eta > 0$ and a $\mathcal{K}$-class function $\gamma : \mathbb{R}_+ \to \mathbb{R}_+$ so that for every $y \in \mathcal{B}_\eta^Y \cap X$ there is a $\rho_y > 0$ so that

$$\|g(x) - g(y)\| \leq \gamma(\|x - y\|) \tag{14}$$

whenever $x \in \mathcal{B}_\eta^Y \cap X$ and $\|x - y\| < \rho_y$. Then the trajectories of Σ^g are (Z,Y)-locally uniformly bounded over the interval $(0,T]$.

Proof: Define $h_g(x) := x + Bg(x)$ and $\alpha(s) := s + \|B\|\gamma(s)$. It can be easily seen that for $x, y \in \mathcal{B}_\eta^Y \cap X$ and $\|x - y\| \leq \rho_y$, it is $\|h_g(x) - h_g(y)\| \leq \alpha(\|x - y\|)$, and it can be verified that α is a $\mathcal{K}$-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 $\rho := \inf_{y\in\mathcal{B}_\eta^Y \cap X} \rho_y$; it is $\rho > 0$ because of the compactness of Y. Take $x \in \mathcal{B}_{\delta(\varepsilon)}^Y \cap X$ and notice that $x \in \mathcal{B}_\eta^Y$; then we may find a $y_x \in Y$ so that $\|y_x - x\| \leq \delta(\varepsilon) \leq \min\{\rho, \eta\}$. Since $y_x \in Y$ and Y is an impulsively invariant set for Σ^g, it is $e^{At}h_g(y_x) \in Z$ for all $t \in (0,T]$, and since $\varphi_{\mathrm{cl}}(t; x, g(\cdot)) = e^{At}h_g(x)$, we have

$$\begin{aligned}
\mathrm{dist}_Z(e^{At}h_g(x)) &= \inf_{z\in Z} \|e^{At}h_g(x) - z\| \\
&\leq \|e^{At}h_g(x) - e^{At}h_g(y_x)\| \\
&\leq \|e^{At}\| \cdot \|h_g(x) - h_g(y_x)\| \leq M\alpha(\|x - y_x\|) \\
&\leq M\alpha(\delta(\varepsilon)) \leq M\alpha\left(\alpha^{-1}\left(\frac{\varepsilon}{2M}\right)\right) < \varepsilon
\end{aligned}$$

for all $t \in (0,T]$. ■

Note also that condition (14) is weaker than the locally Lipschitz continuity of g in $\mathcal{B}_\eta^Y \cap X$. If the compactness requirement in Proposition 8 is dropped, then (14) has to be satisfied for all $x, y \in \mathcal{B}_\eta^Y \cap X$ 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 $\varnothing \neq Y \subseteq Z$, Y is impulsively invariant with respect to Z and there is a constant $\eta > 0$ and a $\mathcal{K}$-class function ω such that for all $k \in \mathbb{N}$

$$\operatorname{dist}_Y\left(\varphi_{\mathrm{cl}}\left(\tau_k; x_0, g(\cdot)\right)\right) \leq \omega\left(\operatorname{dist}_Y\left(x_0\right)\right)$$

whenever $x_0 \in \mathcal{B}_\eta^Y \cap X$. That is, Y is weakly stable with respect to itself.

Theorem 10 (Criterion for Asymptotic Stability): Let Z and Y be given nonempty sets and Assumption 9 be satisfied. Assume that Z is weakly asymptotically stable for Σ^g with respect to Y and the trajectories of Σ^g are (Z, Y)-locally uniformly bounded over $(0, T]$. Then Z is asymptotically stable with respect to Y.

Proof: The proof can be found in [8]. ■

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 continuous-time asymptotically stable.

We define the set-valued mapping $\mathcal{U}_f : Y \rightrightarrows U$ as follows:

$$\mathcal{U}_f(x) := \{u \in U : e^{AT}(x + Bu) \in Y,\ \mathcal{S}(x, u) \subseteq Z\}. \tag{15}$$

We also define the set D as follows:

$$D = \left\{(x, u) \in \mathbb{R}^{n+m} \middle|\ x \in Y,\ u \in \mathcal{U}_f\left(x\right)\right\}. \tag{16}$$

This set is the graph of the set-valued mapping $\mathcal{U}_f$. We now introduce the following stage cost function:

$$\ell(x, u) = \operatorname{dist}_D^2(x, u) = \min_{(z,v)\in D} \|(x, u) - (z, v)\|^2. \tag{17}$$

Notice that $\ell(x, u) = 0$ if and only if $x \in Y$ and $u \in \mathcal{U}_f(x)$. 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 τ_k the following finite horizon optimal control problem:

$$V_N^\star\left(x\left(\tau_k\right)\right) = \inf_{\pi \in \mathcal{U}_N(x(\tau_k))} V_N\left(x\left(\tau_k\right), \pi\right) \tag{18}$$

where

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

and

$$\mathcal{U}_N(x) = \left\{\pi \,\middle|\, \begin{array}{c} \forall j \in \mathbb{N}_{[0,N-1]} :\ u_j \in U, \\ \mathcal{S}\left(\varphi\left(\tau_j; x, \pi\right), u_j\right) \subseteq X \\ \varphi\left(\tau_N; x, \pi\right) \in Y \end{array}\right\}. \tag{20}$$

The MPC problem (18) can be reformulated as a convex QP

$$V_N^\star\left(x\left(\tau_k\right)\right) = \inf_{\pi,z,v} \bar{V}_N(x(\tau_k), \pi, z, v) \tag{21a}$$

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

subject to the constraints

$$\pi \in \mathcal{U}_N\left(x\left(\tau_k\right)\right),\ (z_j, v_j) \in D,\ \forall j \in \mathbb{N}_{[0,N-1]}. \tag{21c}$$

The feasible domain of this problem is simply the set $X_N = \operatorname{dom}\mathcal{U}_N$, 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 $u \in \mathcal{U}_f(x)$ it holds that $\ell(x, u) = 0$. Let us denote by $\pi^\star(x(\tau_k)) = (\pi_0^\star(x(\tau_k)), \pi_1^\star(x(\tau_k)), \ldots, \pi_{N-1}^\star(x(\tau_k)))$ the (possibly) set-valued optimizer of (18). This gives rise to a family of feedback control laws $\sigma(x(\tau_k)) = \pi_0^\star(x(\tau_k))$ and notice that if $x \in Y$ then $\sigma(x) = \mathcal{U}_f(x)$. Then every $s : X_N \to U$ 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].

B. Stability Properties

In this section, we present the stability properties (in the sense of stability of sets as in Definition 4) for the closed-loop impulsive system in presence of the MPC controller which we introduced in the previous section.

Theorem 11: Given a target-set Z assume that there is a nonempty ICI set Y with respect to Z. Let $s : X_N \to U$ be an optimal control law for (18). Then, Z is weakly asymptotically stable for Σ^s with respect to Y with domain of attraction the set X_N.

Proof: See the Appendix. ■

Remark 1: X_N is not invariant in continuous-time; that is if $x(\tau_k) \in X_N$, then on one hand at impulsive time instants the trajectory of the closed-loop will remain in X_N, but on the other hand, this property is not implied for the intermediate time instants. There may be time instants $\hat{t} \in [\tau_k, \tau_{k+1})$ so that $x(\tau_k) \in X_N$ and $x(\tau_{k+1}) \in X_N$, but $\varphi_{\mathrm{cl}}(\hat{t}; \tau_k, x(\tau_k), s(\cdot)) \in X \setminus X_N$. However, in the interim between impulsive time instants, the state trajectory will be bounded inside X, thus the imposed constraints will not be violated. Overall, any closed-loop trajectory starting from $x_0 \in X_N$ satisfies constraints (2a). At the same time, X_N is a feasible subset of X.

Remark 2: The set Y in Theorem 11 is impulsively invariant for the closed-loop system with respect to Z. Indeed, if $x(\tau_k) \in Y$, the MPC feedback law possesses the property $s(x) \in \mathcal{U}_f(x)$ and by definition of $\mathcal{U}_f$ and since $Y = \operatorname{dom}\mathcal{U}_f$, impulsive invariance follows.

According to Theorem 11, all trajectories of the MPC-controlled system Σ^s starting from an initial state inside X_N can approach Y arbitrarily close at the impulsive time instants. Under some additional conditions on Y, Z becomes asymptotically stable with respect to Y in continuous time.

Proposition 12: Let Z be a nonempty convex target set and $Y \subseteq Z$ be a nonempty ICI set with respect to Z such that either of the following holds:

1) Let $Y \subseteq \operatorname{int}\operatorname{Pre}_{X,\mathcal{S}}(Y)$. Choose $\eta > 0$ so that $\mathcal{B}_\eta^Y \subseteq \operatorname{Pre}_{X,\mathcal{S}}(Y)$ and introduce a local control law $\kappa_{\mathrm{loc}} : \mathcal{B}_\eta^Y \to U$ so that $e^{AT}(x + B\kappa_{\mathrm{loc}}(x)) \in Y$ and $\mathcal{S}(x, \kappa_{\mathrm{loc}}(x)) \subseteq X$ for all $x \in \mathcal{B}_\eta^Y$.
2) $Y = \{\bar{x}\}$ is a singleton ICI, and $D = \{(\bar{x}, \bar{u})\}$ where $\bar{u} \in \mathcal{U}_f(\bar{x})$.

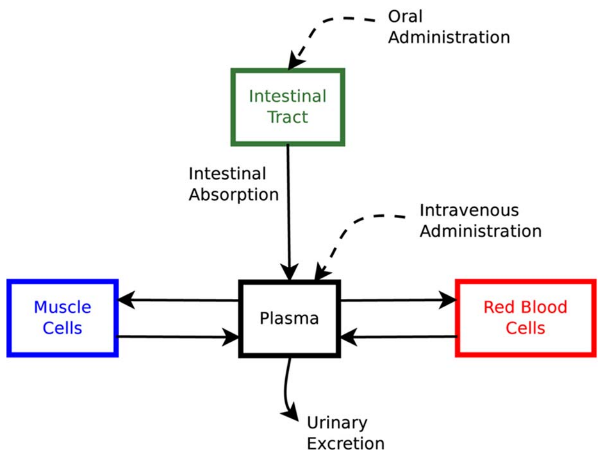

Fig. 1. Topology of the interconnected compartments of the PBPK model.

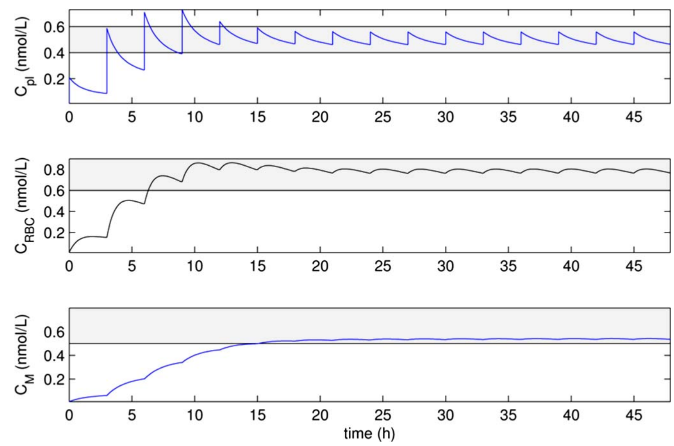

Fig. 2. Controlled trajectory using the proposed controller.

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 $\mathcal{B}_\eta^Y \subseteq \mathrm{Pre}_{X,\mathcal{S}}(Y)$. Because of Theorem 11, for every $x \in X_N$ there is a $k_x \in \mathbb{N}$ so that $\varphi_{\mathrm{cl}}(t; x, s(\cdot)) \in \mathcal{B}_\eta^Y$ for all $t \geq \tau_{k_x}$. As a result, $\varphi_{\mathrm{cl}}(t; x, s(\cdot)) \in \mathrm{Pre}_{X,\mathcal{S}}(Y)$ for all $t \geq \tau_{k_x}$. Once the state enters $\mathcal{B}_\eta^Y$ at an impulsive time τ_k, the local control law κ_{loc} will lead it inside Y at time τ_{k+1} without violating the constraints in continuous time (since $\mathcal{S}(x, \kappa_{\mathrm{loc}}(x)) \subseteq X$), 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 κ_{loc} as in Proposition 12 is easy to obtain by solving for each $x \in \mathcal{B}_\eta^Y$ 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), $\sigma : X_N \rightrightarrows U$, 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 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 $x(t) := [C_P(t) C_{RBC}(t) C_M(t)]'$. The exact topology of the model is illustrated in Fig. 1.

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

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = \begin{bmatrix} -0.6137 & 0.1835 & 0.2406 \\ 1.2644 & -0.8 & 0 \\ 0.2054 & 0 & -0.19 \end{bmatrix} x(t) \tag{22a}$$

$$\Delta x(t) = [10.9 \quad 0 \quad 0]' \, u. \tag{22b}$$

The administration period is fixed to $3\mathrm{hr}$. The constraints $0 \leq x(t) \leq x_{\max}$ are imposed on the state variables in continuous time where $x_{\max} = (2, 1.2, 1.2)' \mathrm{nmol} \cdot \mathrm{L}^{-1}$. The input variable u corresponds to the amount of administered dose and it should not exceed $5.95\mathrm{nmol}$, i.e., $0 \leq u_k \leq 5.95\ \mathrm{nmol}$. The target-set Z is circumscribed by the set of inequalities $x_L \leq x(t) \leq x_H$ where $x_L = (0.4, 0.6, 0.5)'\ \mathrm{nmol} \cdot \mathrm{L}^{-1}$ and $x_H = (0.6, 0.9, 0.8)'\ \mathrm{nmol} \cdot \mathrm{L}^{-1}$. 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 $i \in \mathbb{N}_{[1,10]}$ 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 $\mathrm{Pre}_{Z,\mathcal{S}}(Y)$, 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 $x(\tau_k) \in X_N$, it holds true that

$$V_N^\star\left(x\left(\tau_{k+1}\right)\right) - V_N^\star\left(x\left(\tau_k\right)\right) \leq -\ell\left(x\left(\tau_k\right), s\left(x\left(\tau_k\right)\right)\right) \tag{23}$$

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

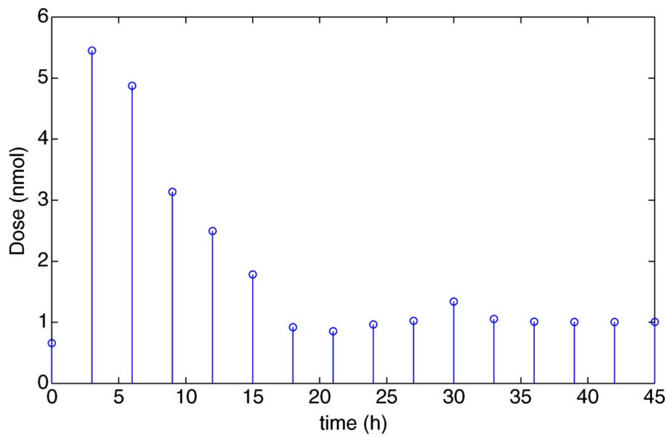

Fig. 3. Amount of administered dose as it was computed by the impulsive MPC controller.

Let $x(\tau_k) \in X_N$ and $\pi^\star(x(\tau_k)) := \{u_i^\star(x(\tau_k))\}_{i=0}^{N-1}$ be an optimal control sequence, i.e., $V_N^\star(x(\tau_k)) = V_N(x(\tau_k), \pi^\star(x(\tau_k)))$. If we apply $\pi^\star(x(\tau_k))$ to the impulsive system, the following sequence of states will occur: $\mathbf{x}^\star(x(\tau_k)) = \{x_{k+i}^\star(x(\tau_k))\}_{i=0}^{N}$, with $x_{k+i}^\star(x(\tau_k)) = \varphi(\tau_{k+i}; \tau_k, x(\tau_k), \pi^\star(x(\tau_k)))$ for $i = 0, \ldots, N$, and $x_{k+N}^\star(x(\tau_k)) \in Y$. At the next time instant, τ_{k+1}, the state of the system will be $x_{k+1}^\star(x(\tau_k))$ for which we choose the (sub-optimal) control sequence $\tilde{\pi}(x(\tau_k)) = \left\{u_{k+1}^\star(x(\tau_k)), \ldots, u_{k+N-1}^\star(x(\tau_k)), u\right\}$ where the last element $u \in U$ is to be determined. Then, the resulting state sequence is $\tilde{\mathbf{x}}(x(\tau_k)) = \{x_{k+1}^\star(x(\tau_k)), \ldots, x_{k+N+1}^\star(x(\tau_k))\}$, where $x_{k+N+1}^\star(x(\tau_k)) := \varphi(\tau_{k+N+1}; \tau_{k+N}, x_{k+N}^\star(x(\tau_k)), u)$. Provided that the last element of $\tilde{\mathbf{x}}(x(\tau_k))$ is in Y, the sequence of inputs $\tilde{\pi}(x(\tau_k))$ is admissible since $u \in \mathcal{U}_f(x_{k+N}^\star(x(\tau_k))) \neq \varnothing$. Then $V_N^\star(x(\tau_k)) = V_N(x(\tau_k), \pi^\star(x(\tau_k)))$ is

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

Because of the terminal-state constraints, $x_{k+N+1}^\star(x(\tau_k)) \in Y$, and also $u \in \mathcal{U}_f(x_{k+N+1}^\star(x(\tau_k)))$, so $\ell(x_{k+N+1}^\star(x(\tau_k)), u) = 0$, and we have

$$\begin{aligned} V_N(x_{k+1}^\star(x(\tau_k)), \tilde{\pi}) =& V_N^\star(x(\tau_k)) - \ell(x(\tau_k), u_k^\star(x(\tau_k))) \\ &+ \ell(x_{k+N+1}^\star(x(\tau_k)), u) \\ =& V_N^\star(x(\tau_k)) - \ell(x(\tau_k), s(x(\tau_k))). \end{aligned}$$

Due to the suboptimality of $\tilde{\pi}(x(\tau_k))$, we have

$$\begin{aligned} V_N^\star(x_{k+1}^\star(x(\tau_k))) &\leq V_N(x_{k+1}^\star(x(\tau_k)), \tilde{\pi}) \\ &= V_N^\star(x(\tau_k)) - \ell(x(\tau_k), s(x(\tau_k))) \end{aligned}$$

for all $x(\tau_k) \in X_N$, which proves (23).

Step 2. Weak Stability of Y. Let $\varepsilon > 0$ and $\Omega_\beta := \{x \in \mathcal{B}_\varepsilon^Y \cap X_N, V_N^\star(x) \leq \beta\}$ and take $x(\tau_k) \in \Omega_\beta$. By (23), one has that $V_N^\star(\varphi_{\mathrm{cl}}(\tau_{k+1}; \tau_k, x(\tau_k), s(\cdot))) \leq V_N^\star(x(\tau_k)) \leq \beta$, hence $\varphi_{\mathrm{cl}}(\tau_{k+1}; \tau_k, x(\tau_k), s(\cdot)) \in \Omega_\beta$. Since $V_N^\star$ admits the value 0 on Y and $\Omega_\beta \supseteq Y$ and $V_N^\star$ is continuous, there is a $\eta > 0$ such that $\mathcal{B}_\eta^Y \cap X_N \subseteq \Omega_\beta$. So, if we choose $x(\tau_k) \in \mathcal{B}_\eta^Y \cap X_N$, we have that $\varphi_{\mathrm{cl}}(\tau_{k+1}; \tau_k, x(\tau_k), s(\cdot)) \in \mathcal{B}_\varepsilon^Y \cap X_N$ so Y is weakly stable with respect to itself.

Step 3. Asymptotic Stability and Attractivity of Y over X_N. $V_N^\star$ is strictly decreasing and nonnegative outside Y, so there is a $c \geq 0$ so that $\lim_{j\to\infty} V_N^\star(\varphi_{\mathrm{cl}}(\tau_{k+j}; \tau_k, x(\tau_k), s(\cdot))) = c$.

Let $\tilde{\Omega}_c = \{x \in X_N | V_N^\star(x) \leq c\}$, assume that $c > 0$ and let $0 < \zeta < c$ such that $\mathcal{B}_\zeta^Y \cap X_N \subseteq \tilde{\Omega}_c$. Then, for all $j \in \mathbb{N}$, $V_N^\star(\varphi_{\mathrm{cl}}(\tau_{k+j}; \tau_k, x(\tau_k), s(\cdot))) > \zeta$. Define $\gamma_r := -\max\{\ell(x, s(x)); \zeta \leq \mathrm{dist}_Y(x) \leq r,\ x \in X_N\}$ for $r > \zeta$ (Evidently $\gamma_r < 0$ for all $r > \zeta$). Then, by (23) it is:

$$\begin{aligned} V_N^\star\left(x\left(\tau_{k+j}\right)\right) &\leq V_N^\star\left(x\left(\tau_k\right)\right) - \sum_{i=0}^{j-1} \ell\left(x\left(\tau_{k+i}\right), s\left(x\left(\tau_{k+1}\right)\right)\right) \\ &< V_N^\star\left(x\left(\tau_k\right)\right) - j\gamma_r. \end{aligned}$$

Eventually, for $j \geq {\gamma_r}^{-1} V_N^\star(x(\tau_k))$ we have that $V_N^\star(x(\tau_{k+j})) < 0$ 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. ■

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