Stability Analysis of Impulsive Nonlinear Quadratic Systems

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Outline

Impulsive Quadratic Systems and Biological Processes

- Quadratic systems can describe several biological phenomena
- Beside continuous–time evolutions of the concentrations of species, in biological systems discrete events arise from abrupt state transitions, hence. . .
- *Impulsive* quadratic dynamical systems (IDS) are likely to improve the understanding and the prediction of cellular interactions, pharmacodynamics and drug scheduling in cancer therapy
- IDS are systems that exhibit jumps in the state trajectory, which can be either time–driven (*time–dependent* IDS), or driven by specific state values (*state–dependent* IDS)

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Estimation of the Domain of Attraction of IDS

- An important issue is that of estimating the Domain of Attraction (DA) of stable equilibria
- From the practical viewpoint it is satisfactory to determine whether an assigned polytope containing the origin of the state space belongs to the DA of the zero equilibrium point

Contribution of the paper

- Motivated by biological applications, in this work we present sufficient conditions to determine whether a polytope belongs to the DA of the zero equilibrium point both for time-dependent and state-dependent Impulsive Quadratic Dynamical Systems
- The proposed results are stated in terms of Linear Matrix Inequalities (LMIs) problems
- The proposed approach is applied to the analysis of a biological model for tumor progression

Impulsive Quadratic Dynamical Systems

We consider IDS having the form

$$\dot{x}(t) = Ax(t) + B(x)\,, \quad x(t_0) = x_0\,, \quad \big(t, x(t)\big) \notin \mathcal{S} \tag{1a}$$
$$x^+(t) = Jx(t)\,, \quad \big(t, x(t)\big) \in \mathcal{S}\,, \tag{1b}$$

where $A \in \mathbb{R}^{n\times n}$, $J \in \mathbb{R}^{n\times n}$ and

$$B(x) = \begin{pmatrix} x^T B_1 x \\ x^T B_2 x \\ \vdots \\ x^T B_n x \end{pmatrix}\,, \quad B_i \in \mathbb{R}^{n\times n}\,, \quad i = 1, 2 \ldots n \tag{2}$$

- (1a) is a nonlinear quadratic dynamical system describing the *continuous–time* dynamics
- (1b) describes the *resetting law* of the system over the *resetting set* $\mathcal{S} \subset \mathbb{R}_0^+ \times \mathbb{R}^n$

Resetting times and resetting states

If $x(\cdot)$ is a solution of (1) from an initial condition $x_0 = x(t_0)$, it is then possible to define the correspondent *resetting times* and *resetting states* sets associated to the solution $x(\cdot)$ as follows:

$$\mathcal{T} = \left\{ t \in \mathbb{R}_0^+ \mid \left(t , x(t) \right) \in \mathcal{S} \right\},$$

$$\mathcal{D} = \left\{ x \in \mathbb{R}^n \mid \left(t , x(t) \right) \in \mathcal{S} \right\}.$$

Time–dependent and state–dependent IDS

Depending on the definition of the resetting set $\mathcal{S}$, IDS can be classified as follows:

i) *Time–dependent IDS (TD–IDS)* when the resetting set is defined by a prescribed sequence of time instants, which are independent of the state $x(\cdot)$

ii) *State–dependent IDS (SD–IDS)* when the resetting set is defined by a region in the state space, which does not depend on the time.

Basic assumptions

In order to assure well-posedness of the resetting times and to prevent Zeno behavior, the following assumption are made

Assumption 1

For all $t \in \big[0, +\infty\big[$ such that $\big(t, x(t)\big) \in \mathcal{S}$,

$$\exists\ \varepsilon > 0 : \big(t + \delta\,, x(t + \delta)\big) \notin \mathcal{S}, \quad \forall \delta \in \,]0, \varepsilon]$$

Assumption 2

Given a compact interval $[t_0\,, t_0 + T]$, it includes only a finite number of resetting times. It follows that the resetting set to be considered in the time interval $[t_0\,, t_0 + T]$ is given by

$$\mathcal{S} = \mathcal{T} \times \mathcal{X} \subset [t_0\,, t_0 + T] \times \mathbb{R}^n\,,$$

with $\mathcal{T} = \big\{t_1\,, t_2\,, \ldots\,, t_r\big\}$

Problem statement

The problem we consider can be formalized as follows

Problem

Given system (1) and a polytope $\mathcal{P}$, $0 \in \mathcal{P}$, verify that $\mathcal{P}$ belongs to the DA of the zero equilibrium point

We propose two sufficient conditions to solve the problem above, one for SD–IDS and the other for TD–IDS

Polytopes

A polytope $\mathcal{P} \subset \mathbb{R}^n$ can be described as follows:

$$\begin{aligned} \mathcal{P} &= \mathrm{conv}\left\{x_{(1)}, x_{(2)}, \dots, x_{(p)}\right\} \\ &= \left\{x \in \mathbb{R}^n \,:\, a_k^T x \leq 1\,,\; k = 1, 2, \dots, q\right\}\,, \end{aligned} \tag{3}$$

where:

- p and q are suitable integers
- $x_{(i)}$ denotes the i-th vertex of the polytope $\mathcal{P}$
- $a_k \in \mathbb{R}^n$

Theorem 1 – SD case

A polytope $\mathcal{P}$ defined by (3) belongs to the DA of a given SD–IDS (1) if there exist a scalar γ and a **positive definite** matrix $P \in \mathbb{R}^{n\times n}$ such that the following conditions are satisfied

$$0 < \gamma < 1 \tag{4a}$$

$$\begin{pmatrix} 1 & \gamma a_k^T \\ \gamma a_k & P \end{pmatrix} \geq 0\,, \quad k = 1, 2, \ldots, q \tag{4b}$$

$$x_{(i)}^T P x_{(i)} \leq 1\,, \quad i = 1, 2, \ldots, p \tag{4c}$$

$$\gamma\left(A^T P + PA\right) + P \begin{pmatrix} x_{(i)}^T B_1 \\ x_{(i)}^T B_2 \\ \vdots \\ x_{(i)}^T B_n \end{pmatrix} + \begin{pmatrix} B_1^T x_{(i)} & B_2^T x_{(i)} & \ldots & B_n^T x_{(i)} \end{pmatrix} P < 0$$

$$i = 1, 2, \ldots, p \tag{4d}$$

$$J^T P J - P - \sum_{h=1}^{r_j} c_{j,h} Q_{j,h} < 0\,, \quad j = 1, \ldots, N \tag{4e}$$

with $c_{j,h} \geq 0$, $j = 1, \ldots, N$, $h = 1, \ldots, r_j$, and $Q_{j,h}$ are a set of symmetric matrices satisfying

$$x^T Q_{j,h} x \leq 0\,, \quad x \in \mathcal{D}_j \cap \frac{\mathcal{P}}{\gamma}\,. \tag{5}$$

Main arguments of the proof - 1

- The proof is based on the well known condition for a set $E \subset \mathbb{R}^n$ to be contained in the DA of system (1) (see Khalil, 2001).

Theorem

A given closed set $E \subset \mathbb{R}^n$, $0 \in E$, is contained in the DA of the impulsive dynamical system (1) if

i) *E is an invariant set for system (1)*
ii) *there exists a Lyapunov function $v(x)$ such that*
  a) *$v(x)$ is positive definite on E*
  b) *$\dot{v}(x)$ computed along the solution of system (1) is negative definite on E (at the discontinuity points, $\dot{v}(x)$ has to be replaced by the difference $v\left(x^+(t_k)\right) - v\left(x(t_k)\right)$)*

- It exploits Lyapunov-based arguments

Main arguments of the proof - 2

- Without loss of generality it is assumed that that the resetting states set is given by the union of a finite number of regions, i.e.

$$\mathcal{D} = \bigcup_{j=1}^{N} \mathcal{D}_j \, .$$

- S-procedure arguments are exploited (conditions (4e) and (5))

Time–dependent case

We have assumed that system (1) does not exhibit Zeno behavior, hence it is possible to define the minimum time interval between two resetting times as

$$\Delta T^* := \min_{t_k, t_{k+1} \in \mathcal{T} \cup \{t_0\}} \left(t_{k+1} - t_k \right), \tag{6}$$

Theorem 2 – TD case

Given a TD–IDS (1) and a polytope $\mathcal{P}$ defined by (3), assume that there exist two scalars α, γ and a symmetric matrix $P \in \mathbb{R}^{n\times n}$ such that conditions (4a)–(4c) are satisfied. Furthermore, if

$$\alpha > 0 \tag{7a}$$

$$\gamma(A^T P + PA) + P\begin{pmatrix} x_{(i)}^T B_1 \\ x_{(i)}^T B_2 \\ \vdots \\ x_{(i)}^T B_n \end{pmatrix} + \begin{pmatrix} B_1^T x_{(i)} & B_2^T x_{(i)} & \dots & B_n^T x_{(i)} \end{pmatrix} P < -\alpha P$$

$$i = 1, 2, \dots, p \tag{7b}$$

$$\|J\|^2 \operatorname{cond}(P) e^{-\alpha \Delta T^*} \leq 1 \tag{7c}$$

where ΔT^* is given by (6) and $\operatorname{cond}(P)$ denotes the condition number of P, then the polytope $\mathcal{P}$ belongs to the domain of attraction of the TD–IDS (1).

Apoptosis

- Biological systems are inherently robust. Biological robustness refers to the ability to maintain the biological functions despite changing of environmental conditions, genetic variations, etc.
- Among cellular functions, *apoptosis* plays a key role since enables the organism to remove superfluous, damaged and malignant cells
- When considering *apoptosis*, an especially important specification of the biological systems is the robustness to intra–cellular and extra–cellular perturbations which might lead to severe pathological alterations, like as the tumor progression

Prey-predator model of cancer progression

The model equations read

$$\begin{cases} \dot{M} = q + rM\left(1 - \frac{M}{k_1}\right) - \tau MN \\ \dot{N} = \beta NZ - d_1 N \\ \dot{Z} = sZ\left(1 - \frac{Z}{k_2}\right) - \beta NZ - d_2 Z \end{cases} \tag{8}$$

- M – density of tumor cells
- N – density of hunting predator cells
- Z – density of resting predator cells
- r – growth rate of the tumor cells
- q – rate of conversion of the normal cells to the malignant ones
- τ – rate of predation of the tumor cells by the hunting cells
- β – rate of conversion of the resting cells to the hunting cells
- d_1 – natural death of the hunting cells
- s – growth rate of the resting predator cells
- d_2 – natural death of the resting cells
- k_1 – maximum carrying or packing capacity of the tumor cells
- k_2 – maximum carrying capacity of the resting cells.

Modeling perturbations

- We assume that, in response to an external perturbation, the densities of malignant cells and immune cells vary in an impulsive fashion
- This stimulus enhances the density of the malignant cells, whereas the density of immune cells decreases
- The resulting effect should be that the malignant cells can overcome the immune cells, leading the tumor to an unbounded growth

This impulsive perturbation can be modeled as

$$\begin{cases} M^+ = \delta M \\ N^+ = \eta N \\ Z^+ = \vartheta Z \end{cases} , \qquad (9)$$

with $\delta > 1$, $\eta < 1$, $\vartheta < 1$.

Prey-predator model as Impulsive Quadratic Dynamical System

System (8)–(9) represents an IDS with

$$A=\begin{pmatrix} r & 0 & 0\\ 0 & -d_1 & 0\\ 0 & 0 & s-d_2\end{pmatrix},\quad B_1=\begin{pmatrix} -\frac{r}{k_1} & -\frac{\tau}{2} & 0\\ -\frac{\tau}{2} & 0 & 0\\ 0 & 0 & 0\end{pmatrix},$$

$$B_2=\begin{pmatrix} 0 & 0 & 0\\ 0 & 0 & \frac{\beta}{2}\\ 0 & \frac{\beta}{2} & 0\end{pmatrix},\qquad B_3=\begin{pmatrix} 0 & 0 & 0\\ 0 & 0 & -\frac{\beta}{2}\\ 0 & -\frac{\beta}{2} & -\frac{s}{k_2}\end{pmatrix}$$

$$J=\begin{pmatrix} \delta & 0 & 0\\ 0 & \eta & 0\\ 0 & 0 & \vartheta\end{pmatrix}. \qquad (10)$$

Model parameters

Let us assume the following values for the model parameters

$$q = 10\,, \quad r = 0.9\,, \quad \tau = 0.3\,, \quad k_1 = 0.8\,,$$
$$\beta = 0.1\,, \quad d_1 = 0.02\,, \quad s = 0.8\,, \quad k_2 = 0.7\,, \quad d_2 = 0.03\,.$$

Equilibrium point

System (8) exhibits the asymptotically stable equilibrium point

$$E_3 = \begin{bmatrix} 2.67 & 5.41 & 0.2 \end{bmatrix}^T \,,$$

which corresponds to tumor dormancy (see Merola, 2008). Indeed, at equilibrium E_3 the tumor growth is blocked.

Modeling a decreasing of immune function

Assuming that the minimum window of time ΔT^* between two impulsive events is 600 sec and the resetting law parameters are

$$\delta = 1.2\,, \quad \eta = 0.8\,, \quad \vartheta = 0.8\,,$$

The above kind of perturbation might occur when, due to environmental factors the immune function has decreased and, therefore, is unable to successfully control the growth of the tumor cell population.

Exploit the sufficient conditions for TD–IDS we analyze if the box $\mathcal{P} := [1.5, 4] \times [3.5, 7] \times [0.1, 0.3]$, is contained in the DA of E_3. The proposed feasibility has been solved by means of the LMI Toolbox, and an admissible solution is

$$\alpha = 0.01\,, \quad \gamma = 0.433\,,$$
$$P = \begin{pmatrix} 0.167 & 0.054 & 0.0062 \\ 0.054 & 0.092 & -0.0026 \\ 0.0062 & -0.0026 & 18.82 \end{pmatrix}.$$

Therefore, it is possible to conclude that $\mathcal{P}$ belongs to the DA of the tumor dormancy equilibrium.

Biological interpretation of the result

- Translating this result into biological terms, $\mathcal{P}$ represents a safety region where the immunosurveillance is effective, since the convergence to the healthy steady state is guaranteed against perturbations
- If the perturbations do not violate the prescribed bounds, the immune cells are restraining tumor cells to the extents that they are not allowing the malignant cells density to grow unboundedly

Conclusions

- Sufficient conditions to determine whether a polytope belongs to the DA of the zero equilibrium point of a Impulsive Quadratic Dynamical System have been presented for both TD and SD case
- The results are provided in terms of LMIs problems, which can be efficiently solved by using off-the-shelf tools
- A preliminary application of the proposed technique as been presented for the robustness analysis of tumor dormancy
- Less conservative conditions
- Further applications

Thank you!