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H_∞–METHODS IN POPULATION MODELLING AND CONTROL

SEBASTIAN ANITA*, GHEORGHE ANICULAESEI*

This paper deals with an H_∞–problem with control constraints for the population dynamics. The biological significance of such a problem is discussed. The necessary and sufficient conditions for the existence of a solution to the suboptimal H_∞ problem for input-output linear population dynamics with control constraints are established. The last part of this paper contains some considerations about possible applications of H_∞ methods to cancer cell population modelling and control.

1. Introduction

Consider the following linear model for the population dynamics:

$$\begin{cases} y_t + y_a + \mu(a)y - \Delta_x y = u(a,x,t) & \text{in } (0,A)\times\Omega\times(0,+\infty) \\ \dfrac{\partial y}{\partial \nu} = 0 & \text{on } (0,A)\times\partial\Omega\times(0,+\infty) \\ y(0,x,t) = \displaystyle\int_0^A b(a)y(a,x,t)\,\mathrm{d}a & \text{in } \Omega\times(0,+\infty) \\ y(a,x,0) = y_0(a,x) & \text{in } (0,A)\times\Omega \end{cases} \tag{1}$$

This model describes the dynamics of a population which is free to move in a region $\Omega \subset \mathbb{R}^n$. Here $y(a,x,t)$ represents the density of population at age a, at position x and at time t, $b(t)$ is the rate of birth and μ – the mortality rate, y_0 – the initial density of population, $u(a,x,t)$ represents a possible infusion or harvest of population, which is used to determine a desired behaviour of the population (u is the control in system (1)). For biological significances of the terms in (1) see (Anita, 1990).

Model (1) takes into account only a few parameters. For this reason it is obvious that a much more appropriate model which describes the population dynamics is as follows:

$$\begin{cases} y_t + y_a + \mu(a)y - \Delta_x y = u(a,x,t) + w(a,x,t) & \text{in } (0,A)\times\Omega\times(0,+\infty) \\ \dfrac{\partial y}{\partial \nu} = 0 & \text{on } (0,A)\times\partial\Omega\times(0,+\infty) \\ y(0,x,t) = \displaystyle\int_0^A b(a)y(a,x,t)\,\mathrm{d}a & \text{in } \Omega\times(0,+\infty) \\ y(a,x,0) = y_0(a,x) & \text{in } (0,A)\times\Omega \end{cases} \tag{2}$$

where w is an unknown term (called disturbance).

* Department of Mathematics, University of Iasi, Iasi 6600, Romania

Suppose that we would like the population density $y(a,x,t)$ to be close to a given $\tilde{y}(a,x,t)$ in a certain way (here $\tilde{y}$ is the solution of (1), where $u(a,x,t)$ is replaced by $\tilde{u}(a,x,t)$).

If we introduce new variables defined by $\bar{y} = y - \tilde{y}$, $\bar{u} = u - \tilde{u}$ and $\bar{y_0} = y_0 - \tilde{y_0}$, it is easy to see that $\bar{y}$ is the solution of (2) with u replaced by $\bar{u}$ and y_0 replaced by $\bar{y_0}$, i.e.

$$\begin{cases} \bar{y}_t + \bar{y}_a + \mu(a)\bar{y} - \Delta_x \bar{y} = \bar{u}(a,x,t) + w(a,x,t) & \text{in } (0,A)\times\Omega\times(0,+\infty) \\ \dfrac{\partial \bar{y}}{\partial \nu} = 0 & \text{on } (0,A)\times\partial\Omega\times(0,+\infty) \\ \bar{y}(0,x,t) = \displaystyle\int_0^A b(a)\bar{y}(a,x,t)\,\mathrm{d}a & \text{in } \Omega\times(0,+\infty) \\ \bar{y}(a,x,0) = \bar{y}_0(a,x) & \text{in } (0,A)\times\Omega \end{cases} \tag{3}$$

Our goal is to find a feedback control $\bar{u} = F\bar{y}$ such that the influence of the unknown disturbance w on $\bar{y}$ (and on $\bar{u}$) is small (in a certain sense).

2. Hypotheses and Problem Formulation

In what follows $\Omega \subset \mathbb{R}^n$ is an open and bounded subset with a C^1 – class boundary. Denote by $X = L^2((0,A)\times\Omega)$, $Z = X \times X$, by $(\cdot,\cdot)$, $(\cdot,\cdot)_Z$ their usual scalar products and by $|\cdot|$, $|\cdot|_Z$ the corresponding norms. Consider $U_0 = \{u \in L^2(\mathbb{R}^+; X);\ \alpha \le u(a,x,t) \le \beta$ a.e. in $(0,A)\times\Omega\times(0,+\infty)\}$.

We shall use the following hypotheses :

1. $b \in L^\infty(0,A)$, $\quad b(a) \ge 0$ a.e.
2. $\mu \in C([0,A])$
3. $\bar{y_0} \in X$

By definition, an admissible control is a mapping $F : X \to U_0$ such that every measurable function $y = y(t)$ satisfies the condition that the map $t \to F(y(t))$ is measurable on $\mathbb{R}^+$.

Consider the operator

$$\mathcal{A} = -y_a - \mu(a)y + \Delta_x y \tag{4}$$

where

$$\mathcal{D}(\mathcal{A}) = \Big\{ y \in L^2(0,A;W^{2,2}(\Omega));\quad y_a \in X,\ \frac{\partial y}{\partial \nu} = 0 \quad \text{in} \quad (0,A)\times\partial\Omega$$

$$y(0,x) = \int_0^A b(a)y(a,x)\,da \quad \text{a.e. in} \quad \Omega \Big\} \tag{5}$$

It has been proved in (Anita, 1990) that $\mathcal{A}$ is the generator of a C_0 – semigroup on X (denoted by $e^{\mathcal{A}t}$, $t \ge 0$).

We shall postulate that the feedback control $\bar{u} = F\bar{y} \in U_0$ a.e., $t \in \mathbb{R}^+$ (which is a natural condition).

An admissible feedback control F is said to be stabilizable if for every $x_0 \in X$ and $f \in L^2(\mathbb{R}^+; X)$ the following Cauchy problem :

$$\begin{cases} x' = \mathcal{A}x + Fx + f \quad \text{in} \quad \mathbb{R}^+ \\ x(0) = x_0 \end{cases} \tag{6}$$

has at least one mild solution $x \in C(\mathbb{R}^+; X) \cap L^2(\mathbb{R}^+; X)$ with $u = Fx \in L^2(\mathbb{R}^+, X)$, ($x$ is the mild solution of (6), i.e. $x(t) = e^{\mathcal{A}t}x_0 + \int_0^t e^{\mathcal{A}(t-s)}(Fx(s) + f(s))\,\mathrm{d}s$).

We shall denote by $\mathcal{F}$ the set of all stabilizable feedback controls F. For every $F \in \mathcal{F}$, $w \in L^2(\mathbb{R}^+; X)$, $x_0 \in X$ we set $S_F(x_0, w) = z = (x, 0) + (0, u)$, where x is the mild solution of (6) with $f = w$.

The problem that we shall study can be formulated as follows: given $\gamma > 0$, find $F \in \mathcal{F}$ such that

$$\|S_F(x_0, w))\|^2_{L^2(\mathbb{R}^+;Z)} \le \rho^2 \|w\|^2_{L^2(\mathbb{R}^+;X)} + c|x_0|^2$$
$$\forall\, (x_0, w) \in X \times L^2(\mathbb{R}^+; X) \tag{7}$$

where $0 < \rho < \gamma$ and $c \in \mathbb{R}^+$.
This is an H_∞–suboptimal control problem for system (3) (Barbu, 1992; Keulen *et al.*, 1993).

The main result of this work is that the above problem is solved in terms of a stationary Hamilton-Jacobi equation. This idea was already used in (Barbu, 1992; Ichikawa, 1992; Keulen *et al.*, 1993) and it consists in reducing the problem to a differential game associated with system (3).

3. The Main Result

Theorem 1. *Let $\gamma > 0$. If the H_∞–suboptimal control problem has a solution $F \in \mathcal{F}$, then there exists a continuous, convex and Gâteaux differentiable function $\phi : X \to \mathbb{R}$ such that:*

$$0 \le \phi(x) \le c|x|^2, \quad \forall x \in X \tag{8}$$

$$(\mathcal{A}, \nabla\phi(x)) + \frac{1}{2}|P_{U_0}(-\nabla\phi(x))|^2 + \frac{1}{2\gamma^2}|\nabla\phi(x)|^2$$
$$+(\nabla\phi(x), P_{U_0}(\nabla\phi(x))) + \frac{1}{2}|x|^2 = 0, \quad \forall x \in D(\mathcal{A}) \tag{9}$$

Moreover, the Cauchy problem

$$\begin{cases} x' = \mathcal{A}x + P_{U_0}(-\nabla\phi(x)) + \gamma^{-2}\nabla\phi(x) \\ x(0) = x_0 \end{cases} \tag{10}$$

has for every $x_0 \in X$ *at least one mild solution* $x^* \in C(\mathbb{R}^+; X) \cap L^2(\mathbb{R}^+; X)$ *which satisfies*

$$\lim_{t \to +\infty} x^*(t) = 0$$

Conversely, if equation (9) has a solution ϕ *with the above properties, then the feedback* $F = P_{U_0}(-\nabla\phi)$ *is stabilizable and guarantees ineqality (7) with* $\rho = \gamma$.

(Here $P_{U_0} : X \to U_0$ is the projection operator on the set U_0 and $\nabla\phi$ is the gradient of ϕ).

Remark. In the case of unconstrained H_∞ – control problem, i.e. $U_0 = X$, equation (9) reduces to the Riccati equation corresponding to the regular H_∞-problem (see Keulen *et al.*, 1993; Kimmel and Świerniak, 1983) while the closed loop inequality (7) becomes

$$||S_F(0, w)||^2_{L^2(\mathbb{R}^+;Z)} \leq \rho^2 ||w||^2_{L^2(\mathbb{R}^+;X)}$$

4. Proof of Theorem 1

In what follows we shall give the main steps in the proof of Theorem 1.

Assume that $F \in \mathcal{F}$ is such that inequality (7) is satisfied. Define on the space $L^2(\mathbb{R}^+; X) \times L^2(\mathbb{R}^+, X)$ the function

$$K(u, w) = \frac{1}{2} \int_0^\infty (|z(t)|^2_Z + I_{U_0}(u(t)) - \gamma^2 |w(t)|^2)\, dt$$
$$= \frac{1}{2} \int_0^\infty (|x(t)|^2 + |u(t)|^2 + I_{U_0}(u(t)) - \gamma^2 |w(t)|^2)\, dt \qquad (11)$$

where x is the mild solution of (6), with $f = w$ and $I_{U_0} : X \to (-\infty, +\infty]$ is the indicator function of U_0, i.e. $I_{U_0}(u) = 0$ for $u \in X$, $I_{U_0}(u) = +\infty$ elsewhere. Denote $\mathcal{U} = L^2(\mathbb{R}^+; L^2(\mathbb{R}^+; X))$, $\mathcal{W} = \mathcal{U}$ and consider the problem

$$\sup_{w \in \mathcal{W}} \inf_{u \in \mathcal{U}} K(u, w) \qquad (12)$$

The following result is proved first of all.

Lemma 1. *Problem (12) has a unique solution* $(u^*, w^*) \in \mathcal{U} \times \mathcal{W}$.

In order to obtain the Euler-Lagrange optimality conditions corresponding to problem (12), we consider a family of approximating sup inf problems on the finite intervals $[0, n]$, namely

$$\sup_{w \in \mathcal{W}_n} \inf_{u \in \mathcal{U}_n} K(u, w) \qquad (13)$$

where

$$K_n(u, w) = \frac{1}{2} \int_0^n (|x(t)|^2 + |u(t)|^2 + I_{U_0}(u(t)) - \gamma^2 |w(t)|^2)\, dt \qquad (14)$$

x being the corresponding solution to (6) with $f = w$ on $[0,n]$ and $\mathcal{U}_n = L^2(0,n;X)$, $\mathcal{W}_n = L^2(0,n;X)$.

Lemma 2. *Problem (13) has a unique solution (u_n, w_n) which is expressed as*

$$u_n(t) = P_{U_0}(p_n(t));\ \ w_n(t) = -\gamma^{-2} p_n(t) \quad a.e., \quad t \in (0,n) \tag{15}$$

where

$$p_n' = -\mathcal{A}^* p_n + x_n \quad in \quad [0,n], \ \ p_n(n) = 0 \tag{16}$$

Moreover we have

$$\lim_{n\to+\infty} \int_0^n (|x_n(t) - x^*(t)|^2 + |u_n(t) - u^*|^2 + |w_n(t) - w^*(t)|_W^2)\,\mathrm{d}t = 0 \tag{17}$$

Define the functions $\phi : X \to \mathbb{R}$, $\phi_n : X \to \mathbb{R}$, $\phi(x_0) = \sup\inf K(u,w) = K(u^*,w^*)$, $\phi_n(x_0) = \sup\inf K_n(u_n,w_n)$, $n = 1,2,\ldots$ It follows immediately that ϕ, ϕ_n are convex, continuous functions.

Lemma 3. *The functions ϕ_n are Gâteaux differentiable and $\nabla\phi_n(x_0) = -p_n(0)$, $\forall x_0 \in X$ where p_n is the solution to (16).*

Lemma 4. *There exists $c > 0$ independent of N such that*

$$|p_n(t)| \le c, \qquad \forall t \in [0,n]$$

Lemma 5. *The solution (u^*, w^*) to problem (12) is given by*

$$u^* = P_{U_0}(p(t)), \qquad w^*(t) = -\gamma^{-2}p(t), \qquad \forall t \ge 0$$

where $p \in C(\mathbb{R}^+; X)$ is a mild solution to

$$p' = -\mathcal{A}^* p + x^* \qquad in \quad \mathbb{R}^+, \qquad \lim_{t\to+\infty} p(t) = 0$$

i.e.

$$p(t) = e^{\mathcal{A}^*(T-t)}p(T) - \int_t^T e^{\mathcal{A}^*(s-t)}x^*(s)\,\mathrm{d}s, \tag{18}$$

for all $0 \le t \le T \le +\infty$.

Lemma 6. *The function ϕ is Gâteaux differentiable on X and*

$$\nabla\phi(x_0) = -p(0)$$

where p is the solution to (18).

As is readily seen, (u^*, w^*) is the solution to the problem

$$\sup_{w\in L^2(t,+\infty;x)} \inf_{u\in L^2(t,+\infty;x)} \left\{ \int_t^\infty (|x(s)|^2 + |u(s)|^2 + I_{U_0}(u(s)) \right.$$

$$\left. -\gamma^2|w(s)|^2)\,\mathrm{d}s, \quad x' = \mathcal{A}x + u + w \quad \text{in} \quad (t,+\infty); x(t) = x^*(t) \right\}$$

and therefore

$$\phi(x^*(t)) = \frac{1}{2}\int_t^{\infty} (|x^*(s)|^2 + |u^*(s)|^2 + I_{U_0}(u^*(s)) - \gamma^2 |w^*(s)|^2)\, \mathrm{d}s, \ t \geq 0$$

It is proved that ϕ satisfies the Hamilton-Jacobi equation (9). For the proof of "only if" part, using the hypotheses it is shown that the equation

$$\begin{cases} x' = Ax + P_{U_0}(-\nabla\phi(x)) + w, & t \in \mathbb{R}^+ \\ x(0) = x_0 \end{cases}$$

has a differentiable solution on some interval $[0, T_0)$. Some calculations involving this solution shows that inequality (7) holds, thus proving Theorem 1.

6. Final Remarks

In (Kimmel and Świerniak, 1983) the following model of cancer cell proliferation was proposed

$$\begin{cases} \dfrac{dN}{\mathrm{d}t} = -aN(t) + 2(1 - u(t))N(t), & t \geq 0 \\ N(0) = N_0 \end{cases} \tag{19}$$

where $N(t)$ is the size of a cancer cell population, $1-u(t)$ represents probability of cell survival after a citostatic dosage, a is a constant and is an inverse of average length of cell cycle time, 2 represents a mother cell symmetric division into two daughter cells. A performance index is of the form

$$J = rN(t) + \int_0^T u(t)\, \mathrm{d}t$$

where r is a weighting coefficient ; the second term represents a negative cummulative cytostatic effect, T – the length of chemotherapy time.

Taking into account the possible disturbances we are lead to the following model

$$\begin{cases} \dfrac{dN}{\mathrm{d}t} = -aN(t) + 2(1 - u(t))N(t) + w(t), & t \geq 0 \\ N(0) = N_0 \end{cases} \tag{20}$$

It would be interesting to find a feedback control $u(t) = FN(t)$ such that the influence of the disturbance on the system is "small" (in a certain sense).

This problem can be treated by analogy with the H_∞ – control problem with constraints (we shall consider a certain related max–min problem). Here we have a problem with finite horizon (which is easier), but with a bilinear term (which is a serious problem).

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