Robust Feedback Design For Combined Therapy of Cancer

Mazen Alamir*

CNRS-University of Grenoble. Control Systems Department of Gipsa-Lab. 11 rue des mathmatiques, 38402, Saint-Martin d’Hres, France. Email: mazen.alamir@grenoble-inp.fr

SUMMARY

In this paper, a mathematical model for the scheduling of angiogenic inhibitors with a killing agent is used to derive a robust state feedback control of the combined cancer therapy. Robustness is considered against parameter uncertainties through the solution of the associated Hamilton-Jacobi-Isaacs (HJI) partial differential equation. Unlike open-loop optimal control, solving the HJI equation provides a guaranteed-cost feedback control and a whole visibility of the achievable performance for any possible initial state within the region of interest and for any predefined level of parameter uncertainties. Numerical investigation is proposed using an existing model that has been validated using human data. Copyright © 0000 John Wiley & Sons, Ltd.

KEY WORDS: Combined therapy of cancer, nonlinear robust control, Hamilton-Jacobi-Isaacs PDE’s, parameters uncertainty

1. INTRODUCTION

The use of applied mathematics in the analysis and the rationalization of actions on biological systems is a long tradition that showed many success stories [8]. In particular, the recent decades witnessed an increasing interest in applying optimal control theory to the problem of cancer treatment using chemotherapy [10] or, more recently, combined approaches including immunotherapy [6, 5, 4] or angiogenic inhibition [7, 9] to cite but few examples.

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It is a fact however that the acceptance by the practitioners of the rather simple models generally used in such studies remains hopelessly limited. The main argument lies in the fact that these models involve too many unknown, non measured and dynamically varying set of parameters. These include death rates, transfer rates between population subsets, drug efficiency rate and so on. This drawback strongly affects the relevance of classical optimal control like solutions which may be very sensitive to model discrepancies.

Based on the above fact, it may be argued that a wider acceptance of applied mathematic models may rely on the use of robust control approaches that enable a guaranteed achievement in a large domain of parameter sets to be assessed. This paper goes in this direction by applying the nonlinear robust control design to the problem of combined therapy of cancer. More precisely, it is shown that the Hamilton-Jacobi-Isaacs (HJI) equations describing the optimal solution to the robust min/max formulation of the combined therapy problem can be solved using the algorithms proposed in [1]. This results in a priori guaranteed tumor contraction map as a function of the initial state (represented by the tumor volume and the carrying capacity of the vasculature) and the quantity of already used drugs.

This paper is organized as follows: First, the model proposed in [7] to capture the combined therapy of cancer using chemotherapy and angiogenic inhibition is first recalled in section 3. Then the general robust control formalism involving the HJI equations is recalled in section 4 and then applied to the specific context of combined chemotherapy/angiogenic therapy in section 5. Several examples of computation are proposed for two different available quantities and worst case uncertainty levels of 15%, 30% and 35% on all the model parameters. Resulting guaranteed contraction maps are provided together with a typical form of the resulting state feedback.
Finally, it is important to note that while the experimentally validated model of [7] is used in the present paper to illustrate the proposed approach, the relevance of the latter does not heavily rely on the specific model that, like any other model, can be amended or questioned.

2. MATHEMATICAL MODEL FOR ANTI-ANGIOGENIC TREATMENT WITH A KILLING TERM

Let us consider the following mathematical model that has been developed in [7] in order to describe the dynamical behavior of the primary tumor population $p$ and the carrying capacity of vasculature $q$:

\[
\begin{align}
\dot{p} & = -w_1 p \ln \left( \frac{p}{q} \right) - w_2 p v_2 \\
\dot{q} & = w_3 p - (w_4 + w_5 p^{\frac{2}{3}}) q - w_6 v_1 q \\
\dot{y}_1 & = v_1 \\
\dot{y}_2 & = v_2
\end{align}
\]

where the $w_i$’s ($i \in \{1, \ldots, 6\}$) represent the model parameters, $v_1 \in [0, v_1^{max}]$ stands for the concentration of inhibitor and $v_2 \in [0, v_2^{max}]$ refers to the concentration of the killing agent. Regarding the dynamic model (1)-(2), it can be shown that for all admissible control profile and any initial positive conditions $p(0) = p_0$ and $q(0) = q_0$, there is a well defined positive solution to the system equations.

The use of equations (3)-(4) enables the constraints on the total amount of available drugs to be expressed according to:

\[
\int_0^T v_i(\tau)d\tau = y_i(T) \leq y_i^{max} \quad ; \quad (i \in \{1, 2\})
\]

where $T$ is the treatment duration.
3. PROBLEM STATEMENT

In a recent work [9], the analysis of the open-loop optimal control problem consisting in finding the optimal control profile $v(\cdot)$ over $[0, T]$ for a given pair of initial values $p(0) = p_0$ and $q(0) = q_0$ has been addressed. More precisely, optimality has been defined with respect to the terminal value $p(T)$ of the primary tumor volume that has to be minimized under the saturation constraints (5) on the control inputs.

This viewpoint suffers from the following drawbacks:

- First, it gives the solution for a given initial pair $(p_0, q_0)$ but does not give an overview on the achievable performance as a function of the initial states.

- More importantly, the approach is based on a set of nominal values of the model parameters which unfortunately neglects the high level of uncertainties (including potential unmodeled dynamics) that affects these parameters when the patient changes or even for the same patient during the treatment duration.

To address these issues, the following optimization problem is considered in this contribution:

**Definition 1**

Find a close approximation of the optimal value function $J^{opt}(x)$ (depending on the initial state) and the corresponding state feedback $v^{opt}(t) = K(t, x(t))$ defined on $\mathbb{R}_+^2 \times [0, T]$ that solves the following dynamic game:

$$
\min_{v \in [0, v^{max}] [0, \tau]} \max_{w \in [\mathbb{R}^n w] [0, \tau]} J(x_0, v(\cdot), w(\cdot)) :=
$$

$$
p(T) + \int_0^T \left[ \|v(\tau)\|^2_R - \|w(\tau) - w^{nom}\|^2_W \right] d\tau
$$

under the constraints (5)

(6)
in which \( p(T) \) is the solution of the dynamic system (1)-(2) at instant \( T \) starting from the initial state \( x(0) = x_0 := (p_0, q_0) \). \( R \) and

\[
W^\frac{1}{2} := \gamma^\frac{1}{2} \cdot \text{diag}(\frac{1}{w_{1,nom}}, \ldots, \frac{1}{w_{n,nom}})
\]

are weighting matrices. \( \diamond \)

The rationale behind the above formulation lies in the following straightforward proposition [3]:

**Proposition 3.1**

If the problem stated in Definition 1 admits a feedback solution leading to the optimal cost function \( J^{opt}(\cdot) \) and the optimal trajectory \( p^{opt}(\cdot, \cdot) \) then the following inequality

\[
p^{opt}(T, x_0) \leq J^{opt}(x_0) + \int_0^T ||w(\tau) - w^{nom}||_W^2 d\tau
\]

holds for all uncertainty profile \( w(\cdot) \) and all initial conditions \( x_0 = (p_0, q_0) \). \( \diamond \)

Based on Proposition 3.1 the following corollary can be inferred:

**Corollary 3.1**

Under the conditions of Proposition 3.1 for any uncertainty profile that remains in the following subset \( \mathcal{W} \in \mathbb{R}^{n_w} \) centered at the nominal value \( w^{nom} \) such that:

\[
\mathcal{W} := \left\{ w \in \mathbb{R}^{n_w} \mid w_i = w_{i,nom} (1 + \eta_i) \right\}
\]

where \( \eta_i \in [-\bar{\eta}_i, +\bar{\eta}_i] \), the use of the time varying robust state-feedback strategy \( K(\cdot, \cdot) \) invoked in Definition 1 leads to the following guaranteed contraction factor on the primary tumor volume:

\[
\theta^{opt}(x(0)) := \frac{p^{opt}(T, x(0))}{p(0)} \leq \frac{J^{opt}(x(0)) + \gamma \cdot T \cdot \sum_{i=1}^{n_w} \bar{\eta}_i}{p(0)}
\]

for all initial condition \( x(0) \) and all uncertainty (even time varying) scenario that belong to the admissible set defined by (10). \( \diamond \)
In order to solve the above dynamic game, the computational framework proposed in [1] is used. This framework is recalled in the following section.

4. COMPUTATIONAL FRAMEWORK

Consider a nonlinear dynamical system that is governed by the following Ordinary Differential Equations (ODE’s):

\[
\dot{x} = f(x, u, w) \quad (x, u, w) \in \mathbb{R}^n \times \mathbb{R}^n \times \mathbb{R}^n\]

(12)

where the control \( u \) and the exogenous input \( w \) are subject to the following constraints for all \( t \geq 0 \):

\[
u(t) \in U(x(t)) \quad ; \quad w(t) \in W(x(t))
\]

(13)

Most of the control engineering problems can be reduced to the problem of finding a feedback strategy:

\[
u(t, x(t)) := \arg \min_{u(\cdot)} \max_{w(\cdot)} J_T(x(t), u(\cdot), w(\cdot), t)
\]

(14)

under the constraint (13) where the cost function \( J_T \) is given by:

\[
J_T := \Psi(x(T)) + \int_t^T L(x(\tau), u(\tau), w(\tau))d\tau
\]

(15)

in which \( L(\cdot) \) is some penalty function expressing the control objective while \( \Psi(\cdot) \) penalizes the terminal value of the state. The Hamiltonian \( H \) is defined for all \( \lambda \in \mathbb{R}^n \) by:

\[
H(x, \lambda, u, w) := \lambda^T f(x, u, w) + L(x, u, w)
\]

(16)

The computational framework proposed in [1] relies on the following assumption:

**Assumption 4.1**

[Saddle points of \( H \)]

For all \((x, \lambda) \in \mathbb{R}^n \times \mathbb{R}^n\), there are solutions \( \hat{u}(x, \lambda) \) and \( \hat{w}(x, \lambda) \) of the following static game:

\[
\hat{H}(x, \lambda) := \min_{u \in U(x)} \max_{w \in W(x)} H(x, \lambda, u, w)
\]

(17)
The relevance of Assumption 4.1 lies in the fact that it underlines the Isaacs verification theorem that can be stated as follows [3]:

**Theorem 4.1**

[Isaacs verification theorem]

If a $C^1$ function $V(t, x)$ satisfies the following PDE:

$$V_t + \hat{H}(x, V_x) = 0 \quad ; \quad V(T, x) = \Psi(x)$$

(18)

where $\hat{H}$ is given by (17) then the feedback control strategy given by:

$$u(\tau, x) := \hat{u}(x, V_x(\tau, x))$$

(19)

is an optimal solution for the dynamic game (14). Furthermore, the corresponding optimal value is precisely $V(t, x(t))$. ◊

The computational framework proposed in [1] aims at finding a $C^1$ approximate solution to (18) which takes the form:

$$V_N(t, x) = \Phi_N^T(x) \cdot M^\dagger \cdot \bar{V}(t)$$

(20)

where $\Phi_N(x) := (\phi_1(x), \ldots, \phi_N(x))^T$ is a functional basis of dimension $N$, $M$ is the matrix defined by:

$$M := \begin{pmatrix}
\Phi^T_N(x^1) \\
\vdots \\
\Phi^T_N(x^{n_p})
\end{pmatrix} \in \mathbb{R}^{n_p \times N}$$

(21)

in which $\{x^i\}_{i=1}^{n_p}$ is a regular subset of interpolation points defined in the state space. $\bar{V}(t) \in \mathbb{R}^{n_p}$ is the vector of values of the solution at the interpolation points $\{x^i\}_{i=1}^{n_p}$. Based on the above notation, the gradient of $V_N(t, x)$ is given by:

$$\frac{\partial V_N}{\partial x}(t, x) := \left[ \frac{\partial \Phi_N}{\partial x}(x) \right]^T [M^\dagger] \bar{V}(t)$$

(22)
it has been shown in [1] that the evolution of $\tilde{V}(\cdot)$ can be obtained by integrating an $n_p$ dimensional ODE of the form:

$$\frac{d\tilde{V}}{dt} = \Gamma(\tilde{V}) ; \quad \tilde{V}(T) = \Psi := \begin{pmatrix} \Psi(x^1) \\ \vdots \\ \Psi(x^{n_p}) \end{pmatrix}$$  \hspace{1cm} (23)

where $\Psi(\cdot)$ is the terminal penalty function involved in the definition (15) of the cost function and $\Gamma(\cdot)$ is given by [according to (18) and (22)]:

$$\Gamma(\tilde{V}) := \begin{pmatrix} -\dot{H}\left(x^1, \left[ \frac{\partial \Phi_N}{\partial x}(x^1) \right]^T [M^T] \tilde{V} \right) \\ \vdots \\ -\dot{H}\left(x^{n_p}, \left[ \frac{\partial \Phi_N}{\partial x}(x^{n_p}) \right]^T [M^T] \tilde{V} \right) \end{pmatrix}$$  \hspace{1cm} (24)

By doing so, the ODE (23) is nothing but an approximate version of the HJI equation (18).

Once an approximate solution (20) is obtained by integrating (23) backward in time over $[0, T]$, the expression of the corresponding state feedback law is obtained according to (19), namely:

$$u(\tau, x) := \hat{u}\left(x, \left[ \frac{\partial \Phi_N}{\partial x}(x) \right]^T [M^T] \tilde{V}(\tau) \right)$$  \hspace{1cm} (25)

The reader may refer to [1] for some additional details concerning the implementation of the integration algorithms that involves some stabilization techniques which greatly improve the numerical stability of the process. Moreover, several theoretical results concerning the convergence analysis are proposed in [1] that are skipped here to concentrate on the underlying case study.

5. ROBUST FEEDBACK DESIGN FOR COMBINED THERAPY OF CANCER

In order to use the general framework invoked in section 4, the integral constraints (5) has to be handled through a change in the control variable. Namely:

$$v_i(t) = S(y_i(t)/y_i^{max}) \cdot u_i(t)$$  \hspace{1cm} (26)
Figure 1. Evolution of $S(r)$ used in (26) to address the saturation constraint (5) on the available quantities of drugs

in which, the function $S(\cdot)$ is defined by (see Figure 1):

$$S(r) = \max\{-\tanh(\beta_s(r - 1)), 0\} \in [0, 1]$$

The constraints on the new control variable $u$ becomes $u \in [0, v_1^{\text{max}}] \times [0, v_2^{\text{max}}]$ since this, together with (26) and (27) guarantee the fulfillment of the saturation constraints as well as the integral constraints on the original control variables.

The general framework of section 4 can now be applied to the 4-dimensional system (1)-(4) with the normalized state given by:

$$x = \left( \frac{p}{p_1^{\text{max}}} \quad \frac{q}{q_1^{\text{max}}} \quad \frac{y_1}{y_1^{\text{max}}} \quad \frac{y_2}{y_2^{\text{max}}} \right)^T \in \mathbb{R}^4$$

and in which the model parameter vector $w$ plays the role of the uncertainty vector. This leads to the following expression of the function $f$ involved in (12):

$$f(x, u, w) :=
\begin{pmatrix}
-w_1 x_1 \ln(\alpha x_1/x_2) - w_2 x_1 S(x_4) u_2 \\
\alpha w_3 x_1 - (w_4 + \beta w_5 x_1^{2/3}) x_2 - w_6 x_2 S(x_3) u_1 \\
g_1 \cdot S(x_3) u_1 \\
g_2 \cdot S(x_4) u_2
\end{pmatrix}$$
Table I. Nominal values of the model parameters and the constraints/normalization related values that are used to illustrate the computational framework

<table>
<thead>
<tr>
<th>$w_{1\text{nom}}$</th>
<th>0.084 day$^{-1}$</th>
<th>$v_{1\text{max}}$</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>$w_{2\text{nom}}$</td>
<td>0.5 kg/day/mg</td>
<td>$v_{2\text{max}}$</td>
<td>1</td>
</tr>
<tr>
<td>$w_{3\text{nom}}$</td>
<td>5.85 day$^{-1}$</td>
<td>$y_{1\text{max}}$</td>
<td>${0.5, 1}$</td>
</tr>
<tr>
<td>$w_{4\text{nom}}$</td>
<td>0.02 day$^{-1}$</td>
<td>$y_{2\text{max}}$</td>
<td>${0.5, 1}$</td>
</tr>
<tr>
<td>$w_{5\text{nom}}$</td>
<td>0.00875 day$^{-1}$/mm$^2$</td>
<td>$p_{\text{max}}$</td>
<td>$2 \times 10^4$</td>
</tr>
<tr>
<td>$w_{6\text{nom}}$</td>
<td>0.15 kg/day/mm$^2$</td>
<td>$q_{\text{max}}$</td>
<td>$2 \times 10^4$</td>
</tr>
</tbody>
</table>

where $\alpha$, $\beta$, $\sigma$ and $\varrho_i$ are positive constant given by:

$$
\alpha := \frac{p_{\text{max}}}{q_{\text{max}}} ; \quad \beta := \left(\frac{p_{\text{max}}}{q_{\text{max}}}\right)^2 ; \quad \sigma := \frac{1}{q_{\text{max}}} ; \quad \varrho_i := \frac{1}{y_{i\text{max}}}
$$

The nominal value $w_{\text{nom}}$ of the model parameter vector $w$ as well as $p_{\text{max}}$ and $q_{\text{max}}$ are given on Table I.

The cost function is obtained by identifying (15) to (6) leading to the following expressions:

$$
\Psi(x) = x_1
$$

$$
L(x, u, w) := u^T R u - \| w - w_{\text{nom}} \|^2_W
$$

Straightforward computations show that the resulting Hamiltonian can be written in the following form:

$$
H(x, u, w) = u^T R u - \| w - w_{\text{nom}} \|^2_W + \lambda^T (F_0(x) + F_1(x)u_1 + F_2(x)u_2)^T w + \lambda^T F_3(x)u
$$

(28)

with appropriate definitions of the matrices $F_0(x)$, $F_1(x)$, $F_2(x)$ and $F_3(x)$ (See Appendix A).

Examination of (28) clearly shows that Assumption 4.1 is satisfied since the Hamiltonian is a strictly quadratic function of both $u$ and $w$. More precisely, straightforward computations
show that the following expressions hold for $\hat{u}(x,\lambda)$ and $\hat{w}(x,\lambda)$ involved in Assumption 4.1:

$$\hat{u}(x,\lambda) := \min_{u \in [0,u_{\text{max}}]} \frac{1}{2} u^T [R(x,\lambda)] u + [f(x,\lambda)] u$$

$$\hat{w}(x,\lambda) := w_{\text{nom}} + \frac{1}{2} W^{-1} [\Theta_0(x,\lambda) + \Theta_1(x,\lambda) \hat{u}(x,\lambda)]$$

where

$$R(x,\lambda) := 2R + \frac{1}{2} \Theta_1^T(x,\lambda) W^{-1} \Theta_1(x,\lambda)$$

$$f(x,\lambda) := \frac{1}{2} \Theta_0^T(x,\lambda) W^{-1} \Theta_1(x,\lambda) +$$

$$+ \frac{1}{2} (w_{\text{nom}})^T \Theta_1(x,\lambda) + \lambda^T F_3(x)$$

$$\Theta_0(x,\lambda) := F_0(x)\lambda$$

$$\Theta_1(x,\lambda) := [F_1(x)\lambda, F_2(x)\lambda]$$

Two treatment durations $T = 1$ and $T = 2$ are used hereafter for illustration purpose while $\gamma = 0.05$ is adopted in the definition of the weighting matrix (8). A four dimensional quadratic polynomial has been used to define $\Phi_N(x)$ which leads to $N = 15$ dimensional functional basis while $n_p = 5^4 = 625$ interpolation points have been used through a uniform grid to define the set of interpolation points $\{x^i\}_{i=1}^{n_p}$.

Numerical investigation are conducted for two level sets $y_{1\text{max}} = y_{2\text{max}} = 1$ and $y_{1\text{max}} = y_{2\text{max}} = 0.5$ leading to situations where the integral constraints (5) is not active or active respectively. The corresponding results are shown in Figures 2 and 3. On each of these figures, three different uncertainty levels are used, namely $\eta_i = 15\%$ (top), $\eta_i = 30\%$ (Middle) and $\eta_i = 35\%$ (bottom). For each uncertainty level, three functions of the state $x = (p,q,0,0)$ are plotted, namely the optimal cost $J_{\text{opt}}$ (Left), the contraction rate $\theta_{\text{opt}}$ defined by (33) (Center) as well as the contour plot of $\Theta_{\text{opt}}$ (Right).

Note that by definition, the optimal cost $J_{\text{opt}}$ is independent of the relative uncertainty level
$\bar{n}$ so that the three left plots are identical for each figure. Note also that $p$ and $q$ are presented in normalized values with $p^{max} = q^{max} = 2 \times 10^4$. The relevance of the proposed approach can be assessed on the contour plots (at the right of Figures 2 and 3 where the guaranteed achievable contraction can be obtained as a function of the initial state $(p, q)$. Note that the use of $y_i^{max} = 0.5$ reduces the contraction region since less amount of drug is allowed during the treatment duration. In particular, while Figure 2 shows unconditional tumor contraction under the uncertainty level $\bar{n}_i = 30\%$, the constraints on the total amount of injected drug leads to a small region where contraction cannot be achieved (see the subplot (2,3) of Figure 3). Figure 4 shows the results when a longer treatment period is considered while keeping the same amount of drug as the one used in Figure 2, namely $y_1^{max} = y_2^{max} = 1$. One clearly notices that as long as the uncertainties remain lower that 15\% the results are better. However, when the treatment duration increases, the worst case scenario becomes eventually too pessimistic and may negatively affect the map of guaranteed contraction. This is because increasing the treatment duration while keeping unchanged the quantity of available drugs gives the bad player ($w$) longest period to act while the good player ($u$) disposes of the same amount of drug that it can only distribute differently during the treatment. To overcome this difficulty, the computed solution has to be applied in a receding-horizon way which amounts to apply the first part of the solution during a given sampling period before the time is reset to 0. This drastically reduces the level of pessimism of the min-max approach as suggested by [2]. Finally, Figures 5 and 6 shows the resulting state feedbacks to be applied at instant 0 as a function of the normalized state $(p, q)$ under the conditions used for figures 2 and 4 respectively.

6. CONCLUSION AND FUTURE WORK

In this paper, it is shown how the HJI formalism can be used to obtain guaranteed tumor contraction maps as a function of the initial state of tumor and the vasculature capacity. This guaranteed contraction maps are obtained in the presence of high levels of dynamically varying...
Figure 2. Guaranteed achievable performance as a function of the normalized initial state \((p, q, 0, 0)\) with the integral constraints defined by \(y_{1}^{\max} = y_{2}^{\max} = 1\) and a treatment duration \(T = 1\). Left: optimal cost \(J_{\text{opt}}\), Center: guaranteed contraction factor \(\theta_{\text{opt}}\), Right: contour lines for \(\theta_{\text{opt}}\).

uncertainties affecting the model parameter and integral saturation constraints reflecting limited amounted of total drug injection. The author is deeply convinced that such an approach can highly enforce the credibility of even simple models and the associated control tools when viewed by practitioners since it partially removes the criticism of oversimplification that actually faces optimization and control oriented approaches.

REFERENCES


Figure 3. Guaranteed achievable performance as a function of the normalized initial state \((p, q, 0, 0)\) with the integral constraints defined by \(y_1^{\max} = y_2^{\max} = 0.5\) and a treatment duration \(T = 1\). Left: optimal cost \(J^{opt}\), Center: guaranteed contraction factor \(\theta^{opt}\), Right: contour lines for \(\theta^{opt}\).


Figure 4. Guaranteed achievable performance as a function of the normalized initial state \((p, q, 0, 0)\) with the integral constraints defined by \(y_1^{\text{max}} = y_2^{\text{max}} = 1\) and a treatment duration \(T = 2\). Left: optimal cost \(J^{\text{opt}}\), Center: guaranteed contraction factor \(\theta^{\text{opt}}\), Right: contour lines for \(\theta^{\text{opt}}\).

Figure 5. The state feedback map \(u = K(0, x)\) for \(x = (p, q, 0, 0)^T\) obtained when the integral saturations \(y_1^{\text{max}} = y_2^{\text{max}} = 1\) is used together with the treatment duration \(T = 1\)

Figure 6. The state feedback map \(u = K(0, x)\) for \(x = (p, q, 0, 0)^T\) under the parameter choices \(T = 2\), \(y_1^{\text{max}} = y_2^{\text{max}} = 1\) used in Figure 4
### A. Expressions of $F_0(x)$, $F_1(x)$ and $F_2(x)$

\[
F_0(x) := \begin{pmatrix} -x_1 \ln(\alpha x_1/x_2) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & \alpha x_1 & 0 & 0 \\ 0 & -x_2 & 0 & 0 \\ 0 & -\beta x_1^{2/3} x_2 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}
\]

\[
F_1(x), F_2(x) := \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & -x_2 S(x_3) & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}
\]

\[
F_3(x) := \begin{pmatrix} 0 & 0 \\ 0 & 0 \\ \varrho_1 S(x_3) & 0 \\ 0 & \varrho_2 S(x_4) \end{pmatrix}
\]