Abstract: - In this paper we consider the bilinear model in the cell cycle specific cancer chemotherapy. The realistic control schemes have to deal with parametric uncertainties, hence, we apply the robust control to maximize both the bone marrow mass and the dose over the treatment interval. The robust control for bilinear system requires a solution to the state dependent algebraic Riccati equation. The bilinear system is described as polytopic parameter varying systems where state vector as parameter varying. The formulation of controller synthesis is done with reformulated the bilinear matrix inequalities in linear matrix inequalities for each subsystem on a polytope. Feasible solution which satisfies the linear matrix inequalities for design the controller is found. From the numerical calculations, we obtain the optimal treatment that prevent excessive destruction of the bone marrow based on the specific weights in our objective functional.

Key-Words: - Robust control, bilinear system, cell-cycle-specific, LPV system

1 Introduction

Many problems in science and engineering can be modeled in the bilinear model such as population models, nuclear fission, transmission and power system, and so on. Bilinear systems have been considered since the early 1960s as a gateway between the linear and nonlinear systems.

Designing control for the bilinear systems have developed with several approaches such as sliding mode control, quadratic feedback, linear state feedback, and model reference control.

In this paper we consider the bilinear model for the dynamic of the cell-cycle of the bone-marrow cell transition between the proliferating phase and the rest phase. To maximize the quantity of drug injected over the treatment period T, we utilize the robust control. By using this control, the parametric uncertainties can be considered in designing control.

The robust control for bilinear system requires a solution to the state dependent algebraic Riccati equation [1]. One approach to solve the Riccati equation can be found in [7]. In this paper we use that the bilinear system is approached as polytopic parameter varying systems where state vector as parameter varying. The formulation of controller synthesis is done with reformulated the bilinear matrix inequalities in linear matrix inequalities for each subsystem on a polytope. Feasible solution which satisfies the linear matrix inequalities for design the controller is found. From the numerical calculations, we obtain the optimal treatment that prevent excessive destruction of the bone marrow based on the specific weights in our objective functional.

2 Bilinear System Model

Consider the bilinear system as follow:
\[
\begin{align*}
\dot{x}(t) &= Ax(t) + B(x(t))u(t) \\
y(t) &= Cx(t) + Du(t)
\end{align*}
\] (1)

where \( x \in \mathbb{R}^n \) is the state vector, \( u \in \mathbb{R}^m \) is the input vector, \( y \in \mathbb{R}^p \) is the output vector, \( A \in \mathbb{R}^{n \times n}, C \in \mathbb{R}^{p \times n}, D \in \mathbb{R}^{p \times m}, \) \( B(x) = B + \sum_{i=1}^n N_i x_i, B, N_i \in \mathbb{R}^{n \times m}, i = 1, 2, ..., n \) is the continuous matrix-valued functions. Assume that system (1-2) is stabilizable. Furthermore, the cost function is defined by
\[
V(x) := \sup_{u \in L_2[0, \infty]} \int_0^\infty \gamma^2 \|u(t)\|^2 - \|y(t)\|^2 dt.
\]

In [8], the bilinear system (1-2) asymptotically stable and have gain-\( L_2 \leq \gamma \), where \( R = \gamma^2 I - D^T D > 0 \). If \( V \) differentiable to \( x \in \mathbb{R}^n \) where \( \frac{\partial V}{\partial x}(x) = 2x^TP^T(x) \), then
\[ H(P, x) = x^T (A^TP + PA + C^TC + B(x)^TP + D^TC) \]
\[ R^{-1}(B(x)^TP + D^TC)x \leq 0. \] 
(3)

The optimal control is obtained as 
\[ u^* = R^{-1}D^T(Cx)^T + \frac{1}{2} R^{-1}B(x)^T \frac{\partial H}{\partial x}. \]

Hence, we must find \( P \) to obtain the optimal controller \( u^* \). Furthermore, we will derive the last condition into another form that is matrix inequality as follow

\[ H(P, x) \leq 0, R = y^2I - D^TD > 0 \]

\[ \Rightarrow x^T(A^TP + PA + C^TC + B(x)^TP + D^TC)R^{-1} \]
\[ (B(x)^TP + D^TC)x \leq 0, R > 0 \]

\[ \Rightarrow x^T(A^TP + PA + C^TC + B(x)^TP + D^TC)^T \]
\[ (y^2I - D^TD)^{-1}(B(x)^TP + D^TC)x \leq 0 \]

\[ \Rightarrow \left[ \begin{array}{cc} A^TP + PA & PB(x) \\ B(x)^TP & -y^2I \end{array} \right] + \left[ \begin{array}{cc} C^T \\ D^T \end{array} \right] I[C \quad D] \leq 0. \] 
(4)

By multiplying on each side of inequality (4) by \( y^{-1} \) and let \( P_1 = y^{-1}P \) then we obtain

\[ \left[ \begin{array}{cc} P_1A + A^TP_1 & P_1B(x) \\ B(x)^TP_1 & -yI \end{array} \right] + \left[ \begin{array}{cc} C^T \\ D^T \end{array} \right] y^{-1}I[C \quad D] \leq 0. \]
(5)

By Schur complement, inequality (5) can be written as

\[ \left[ \begin{array}{cc} A^TP + PA & PB(x) \\ B(x)^TP & -yI \end{array} \right] - \left[ \begin{array}{cc} C^T \\ D^T \end{array} \right] I[C \quad D] \leq 0. \] 
(6)

If \( B(x) \) is fixed then inequality in (6) becomes a sufficient and necessary for bounded real lemma on linear system as on [6].

**Lemma [8]:** If system (1-2) satisfy
1. there is matrix valued function \( P(x) > 0 \) such that \( \forall x \in \mathbb{R}^n \) satisfy the inequality (6),
2. there is a function \( V(x) > 0, V \in \mathcal{C}^1 \) such that
\[ \frac{\partial V(x)}{\partial x} = 2x^TP(x)^T, \]
then system (1-2) have \( L_2 \)-gain \( \gamma, \gamma \geq 0 \) and asymptotically stable.

For designing control system, we consider the bilinear model as the linear time varying (LPV). The designing control for the LPV with minimum order can be found in [5]. Consider \( \mathcal{F}_\rho = \{ \rho(t) | \rho : \mathbb{R} \rightarrow \mathcal{P} \subset \mathbb{R}^n \} \) denotes the set of all piecewise continuous mapping from \( \mathbb{R} \) to \( \mathcal{P} \) where \( \mathcal{P} \) is compact set, \( \rho_{\text{hmin}} \leq \rho_h \leq \rho_{\text{hmax}}, h = 1,2,...,n \) and there is a finite number of discontinuity in any interval. The linear parameter varying systems can be presented by state space \( \mathcal{P}(\rho) \) as follow

\[ \dot{x}(t) = A(\rho(t))x(t) + B(\rho(t))u(t), \rho \in \mathcal{F}_\rho, \] 
(7)
\[ y(t) = Cx(t) + Du(t). \] 
(8)

The dependence of \( A(\rho), B(\rho), C, D \) on \( \rho \) is affine. The matrix polytopes are defined as convex hull of a finite number of matrices, that is

\[ \mathcal{C}_\rho \{ S_i, i = 1,2,...,p \} \]
\[ = \{ \sum_{i=1}^{p} \alpha_i S_i | \alpha_i \geq 0, \sum_{i=1}^{p} \alpha_i = 1 \}. \]

Suppose polytope \( \mathcal{P} \subset \mathbb{R}^n \),
\[ \mathcal{P} = \text{conv}\{ \rho_1, \rho_2,...,\rho_p \} \]
\[ = \text{conv}\{ x_{(1)}, x_{(2)},...,x_{(p)} \}, p = 2^n, \] 
(9)
where \( p \) are integer number, \( x_{(i)} \) is \( i \)-th vertex of \( \mathcal{P} \) polytope, \( \text{conv}\{ \} \) is convex hull of argument.

### 3 Design Control Via LPV

Suppose the generalized LPV system \( G(\rho) \) is described as follows
\[ \dot{x}(t) = A(\rho(t))x(t) + B_1w(t) + B_2(\rho(t))u(t), \]
(10)
\[ x(t) = C_1x(t) + D_{11}w(t) + D_{12}u(t), \]
\[ y(t) = C_2x(t) + D_{21}w(t) + D_{22}u(t), \rho \in \mathcal{F}_\rho, \]
(11)
(12)
where \( w \in \mathbb{R}^q \) is the exogenous inputs, \( u \in \mathbb{R}^m \) is the control inputs, \( y \in \mathbb{R}^p \) is the measured outputs and \( z \in \mathbb{R}^r \) is the controlled outputs also \( A, B_1, B_2, C_1, C_2, D_{11}, D_{12}, D_{21} \) are matrices of suitable dimensions. We assume the system is strictly proper from \( u \) to \( y \), i.e. \( D_{22} = 0 \). The generalized plant \( G(\rho) \) in polytopic form as follow

\[
\begin{bmatrix}
A(\rho(t)) & B_1(t) & B_2(\rho(t)) \\
C_1 & D_{11} & D_{12} \\
C_2 & D_{21} & D_{22}
\end{bmatrix} \in \mathcal{P},
\]

where \( \mathcal{P} \) is a compact open set which contain the origin point. If \( k = n \) then it is called a full order controller. From (10-12) and (14-15) will be obtained closed loop system as follow

\[
\dot{x}_c(t) = A_c(\rho(t))x_c(t) + B_c(\rho(t))w(t),
\]

\[
x(t) = C_c(\rho(t))x_c(t) + D_c(\rho(t))w(t), \rho \in \mathbb{F}_p,
\]

where \( \mathbb{F}_p \) is a compact open set which contain the origin point. If \( k = n \) then it is called a full order controller.

Furthermore, we present the definition of strong robust \( H_\infty \)-performance of a system. System (9-10) is said to have strong robust \( H_\infty \)-performance if there exists \( P \) such that

\[
\forall x \in \mathbb{R}^n, \quad \begin{bmatrix} A_c^T P_c + P_c A_c & P_c B_c & C_c^T \\ B_c^T P_c & -\gamma I & D_c^T \\ C_c & D_c & -\gamma I \end{bmatrix} \leq 0,
\]

and

\[
\frac{\partial V_c(x, \xi)}{\partial x} = 2x^T P_c \forall x \in \mathbb{R}^n \times \mathbb{R}^k,
\]

for some definite positive function \( V_c \in \mathcal{C}_1 \).

Let Lyapunov function for closed loop system as follow

\[
V_c(x_c) = x_c^TP_c x_c
\]

\[
= [x^T \xi^T] \begin{bmatrix} P(x) & P_1^T(x) \\ P_1(x) & P_0(x) \end{bmatrix} [x \xi]
\]

\[
= x^T P(x) x + \xi^T P_1(x) x + x^T P_1^T(x) \xi + \xi^T P_0(x) \xi
\]

\[
= V(x) + U(\xi - \phi(x))
\]

where \( V \) is Lyapunov function for state feedback, \( \frac{\partial V_c(x, \xi)}{\partial x} = 2x^T P(x) \) and \( U \) is Lyapunov function for observer. We assume that there exist function \( \phi : x \to \xi, \phi(0) = 0, e = \xi - \phi(x) \) such that

\[
\frac{\partial V_c(x, \xi)}{\partial e} \bigg|_{\xi = \phi(x)} = \frac{\partial V_c}{\partial e}(e) \bigg|_{e = 0} = 0
\]

Hence

\[
\frac{\partial V_c(x_c)}{\partial x_c} = \begin{bmatrix} \frac{\partial V_c}{\partial x}(x, \xi) & \frac{\partial V_c}{\partial \xi}(x, \xi) \end{bmatrix}
\]

\[
= [2x^T P(x) + 2\xi^T P_1(x) x + 2x^T P_1^T(x) \xi + 2\xi^T P_0(x) \xi]
\]

\[
= 2[x^T \xi^T] \begin{bmatrix} P(x) & P_1^T(x) \\ P_1(x) & P_0(x) \end{bmatrix}
\]

\[
= 2x_c^T P_c.
\]

Synthesis problem:

Given the generalized plant (13). The problem of control design is find \( \mathcal{K}(\rho) \) such that closed loop system (16-17) asymptotically stable and minimizes \( \gamma \).
Formulation (18) is a bilinear matrix inequality of the variables $P_c$ and $K(\rho)$. The condition $H_\infty$-norm of closed loop system less than $\gamma$ is robustness problem of bilinear system. Therefore, robust control synthesis problem is minimizing $\gamma$ such that (18-19). Because (18) is bilinear matrix inequality form then it is a difficult problem to solved. Furthermore, we will derive an LMI condition equivalent to (18). BMI (18) equivalent to following BMI:

$$\begin{bmatrix}
-A_c^TP_c - P_cA_c & P_cB_c & C_c^T \\
B_c^TP_c & \gamma I & -D_c^T \\
C_c & -D_c & \gamma I
\end{bmatrix} \succeq 0. \quad (20)$$

The formulation of full order controller for bilinear system is presented on Theorem 1. It will be derived the basic characterization of the full order parameter varying controller.

**Theorem:** Consider a subsystem of bilinear system that

$$G_i = \{A_i, B_1, B_2, C_1, D_{11}, D_{12}, D_{21}, D_{22}\}$$

and a local controller $K_i = \{A_i, B_i, C_i, D_i\}$. The inequality (20) hold for some $(P_{ci}, K_i)$, if only if LMI (21-22) hold for some

$$P_i = \{V_i, W_i, F_i, G_i, H_i, L_i\},$$

where

$$\begin{bmatrix}
V_i & I \\
I & W_i
\end{bmatrix} > 0, V_i, W_i > 0 \quad (21)$$

$$\begin{bmatrix}
\varphi_{11} & * & * & * \\
\varphi_{21} & \varphi_{22} & * & * \\
\varphi_{31} & \varphi_{32} & \gamma I & * \\
\varphi_{41} & \varphi_{42} & \varphi_{43} & \gamma I
\end{bmatrix} \succeq 0, \quad (22)$$

where * present this matrix is symmetric,

$$\varphi_{11} = -(A_iV_i + B_2F_i) - (A_iV_i + B_2F_i)^T,$$

$$\varphi_{21} = -L_i - (A_i + B_2H_iC_2)^T,$$

$$\varphi_{22} = -(W_iA_i + G_2C_2) - (W_iA_i + G_2C_2)^T,$$

$$\varphi_{31} = (B_1i + B_2iH_iD_{21})^T,$$

$$\varphi_{32} = (W_iB_1i + G_1iD_{21})^T,$$

$$\varphi_{41} = C_1iV_i + D_{12i}F_i,$$

$$\varphi_{42} = C_1i + D_{12i}H_iC_2i.$$

and

$$\varphi_{43} = -(D_{11}i + D_{12i}H_iD_{21i}).$$

If the LMI (14-15) has a solution $P_i$, one of the solutions to the LMI is given by

$$\begin{align*}
\hat{A}_i &= W_i^{-1}G_iC_2iV_iS_i^{-1} - B_2iH_iC_2iV_iS_i^{-1} + B_2iF_iS_i^{-1} - W_i^{-1}L_iS_i^{-1} + A_iV_iS_i^{-1}, \\
\hat{B}_i &= B_2iH_i - W_i^{-1}G_i, \\
\hat{C}_i &= F_iS_i^{-1} - H_iC_2iV_iS_i^{-1}, \\
\hat{D}_i &= H_i.
\end{align*}$$

**Corollary:** Consider the generalized LPV system $G(\rho)$ where polytopic form (13). There exists a polytopic LPV controller $K = \{\hat{A}, \hat{B}, \hat{C}, \hat{D}\}$ such that polytopic of closed loop system will asymptotically stable and have $L_2$- gain $\leq \gamma, \gamma > 0$, where

$$\begin{bmatrix}
\hat{A} & \hat{B} \\
\hat{C} & \hat{D}
\end{bmatrix} = \sum_{i=1}^{\rho} \alpha_i(t) \begin{bmatrix}
\hat{A}_i & \hat{B}_i \\
\hat{C}_i & \hat{D}_i
\end{bmatrix}, \alpha_i(t) \geq 0, \sum_{i=1}^{\rho} \alpha_i = 1,$$

$K_i = \{\hat{A}_i, \hat{B}_i, \hat{C}_i, \hat{D}_i\}, i = 1, 2, \ldots, \rho$ are suboptimal solution of Theorem.

Furthermore, we propose the algorithms to obtain the robust $H_\infty$ controller for bilinear system.

**Input:** Generalized bilinear system consist of $A_i, B_1, B_2(\lambda), C_1, D_{11}, D_{12}, D_{21}, D_{22}$, polytope $P \subset \mathbb{R}^n$ where vertices $x_{(1)}, x_{(2)}, x_{(3)}, \ldots, x_{(\rho)}$ and $\alpha_1, \alpha_2, \alpha_3, \ldots, \alpha_\rho, \alpha_i(t) \geq 0, \sum_{i=1}^{\rho} \alpha_i = 1.$

**Process:**

1. Determine a subsystem of bilinear system by using the vertices $x_{(1)}, x_{(2)}, x_{(3)}, \ldots, x_{(\rho)}$.
2. Design the local controller on each subsystem by using the above Theorem.

**Output:** The total controller is stated in above Corollary.

The process is repeated until the total controller will resulting the closed-loop system (16-17) which is asymptotically stable. While the $L_2$-gain of closed-loop system (16-17) is maximum of $L_2$-gains at local closed-loop systems.

**4 Simulation Results**

The dynamic model of cell-cycle-specific cancer
chemotherapy in the bilinear model as follows [4]:

\[
\frac{dP(t)}{dt} = (\gamma - \delta - \alpha - s f(t))P(t) + \beta Q(t)
\]

\[
\frac{dQ(t)}{dt} = \alpha P(t) - (\lambda + \beta)Q(t)
\]

where \( P(0) = P_0 \) and \( Q(0) = Q_0 \). \( P \) is the proliferating cell mass and \( Q \) is the quiescent cell mass in the bone marrow. The parameters are all considered constant, positive, and are defined as follows: \( \gamma \), cycling cells’ growth rate; \( \alpha \), transition rate from proliferating to resting; \( \delta \), natural cell death; \( \beta \), transition rate from resting to proliferating; \( \lambda \), cell differentiation—mature bone marrow cell leaving the bone marrow and entering the blood stream as various types of blood cells; and \( s \), the strength or effectiveness of the treatment. The function \( f(t) \) is the control describing the effects of the chemotherapeutic treatment only on the proliferating cells.

Table 1 Bone marrow parameters

<table>
<thead>
<tr>
<th>Mean (Range)</th>
<th>Units = days(^{-1})</th>
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<tbody>
<tr>
<td>( \gamma = 1.47, (0.6667 - 2) )</td>
<td>( \delta = 0 )</td>
</tr>
<tr>
<td>( \alpha = 5.643, (4.92 - 6.12) )</td>
<td>( \beta = 0.48 )</td>
</tr>
<tr>
<td>( \lambda = 0.164 )</td>
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</table>

We can see from the Figure 1, without chemotherapy, the \( P(t), Q(t), P(t) + Q(t) \) will converge to the equilibrium point: \( P(T) = 0.1206, Q(T) = 1.0493, P(T) + Q(T) = 1.1699 \). It means that in the normal tissue that the proliferating cells fewer than the quiescent cells.

Figure 1. Bone Marrow without control

Meanwhile, if the chemotherapy is given, as shown in Figure 2, the bone marrow is decreased. Amount of the \( P(t) + Q(t) = 0.7376 \) in the final period \( T \). The optimal results is obtained if the drug is given at \( t = 14 \).

Figure 2. Bone marrow with chemotherapy

For interval \( T = 7 \), it is obtained that the cost function is minimum comparing to the other interval period, but having shortest waiting time and decreasing bone marrow is fewest. Hence, if we want to maximize the dose drug, it is better that the chemotherapy is given in the short period, as shown in Figure 3.
Figure 3. Bone Marrow with the variation of $T$

Figure 4. Bone Marrow with the variation of weighting

We can alter the optimal treatment by changing the weighting function. By increasing the weight $b$ while fixing $a$ we obtain the maximum dose and more drug is used. In a similar result, increasing $a$ with $b$ fixed signifies that to maximize the bone marrow mass rather than the dose. We can also see from the Figure 4, 5, 6, and 7 the effects variation of $s$. If we fix all the parameters except $s$ we can observe how changes in the drug strength affects the optimal treatment.

Figure 5. The variation of weighting function

Figure 6. The variation of weighting function

Figure 7. The variation of the weighting function
4 Conclusions

In this paper, we proposed design control system for the bilinear model via LPV. The LPV approach may provide complementary and profit in control design because LPV systems may describe nonlinear phenomena. The formulation of robust $H_\infty$ control design based on LMIs to solve the Riccati equations. The robust $H_\infty$ controller for bilinear system can be obtained by designing the local controllers for each subsystems. The local controllers are obtained by solving the set of LMIs. Furthermore, the robust $H_\infty$ controller for bilinear system is a convex linear combination of local controllers. A numerical example is given to verify the proposed method for design the robust $H_\infty$ controller of bilinear system.

References: