Something Cool

1 Motivation

Hello

We assume that we are working with a woman of age 65, height of 161.8 cm, and weight of 75.5 kg.

Our state vector is $\mathbf{x}(t) = \begin{bmatrix} T(t) & N(t) & CD(t) & NK(t) \end{bmatrix}^\intercal$ where $T(t)$ be the IDC burden at time t, measured in days, $N(t)$ be the cell count of normal epithelial cells, $CD(t)$ be the CD8$^+$ cell count, and $NK(t)$ be the count of NK cells. All of these located at the duct where IDC begins. We denote the control vector as $\mathbf{u}(t) = \begin{bmatrix} D_c(t) & D_d(t) \end{bmatrix}^\intercal$ where D_d is the drug concentration of doxorubicin and D_c the drug concentration of cyclophosphamide. We consider the problem of modeling AC treatment for a total of 6 doses administered every 21 days plus an extra 30 days after the end of the treatment (156 days total).

Our functional is

$$J[\mathbf{u}] = \int_0^{156} \mathbf{u}(t)^\intercal Q\mathbf{u}(t) + T^2(t)\,\mathrm{d}t + \xi_{156}T^2(156)$$

where $Q = \begin{bmatrix} \xi_c & 0 \\ 0 & \xi_d \end{bmatrix}$ denotes the positive weights for each of the elements of $\mathbf{u}$ and ξ_{156} the final weight for the final tumor population at the end of 156 days.

The concentration for each drug must meet the following constraints (sum of each max dose)

$$0 \leq D_d \leq 1,700\frac{\mathrm{mg}}{\mathrm{m}^2}$$
$$0 \leq D_c \leq 127.5\frac{\mathrm{mg}}{\mathrm{m}^2}$$

Furthermore, the elements of the state evolve according to

$$\begin{aligned}
\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= g_T T \ln\Big(\frac{T_{\max}}{T}\Big) - a_1 NT - a_2 NKT - a_3 CDT - \Big(E_c D_c + \frac{4}{5} E_d D_d\Big)T, \\
\frac{\mathrm{d}N(t)}{\mathrm{d}t} &= g_N N \ln\Big(\frac{N_{\max}}{N}\Big) - k_N N - a_0 NT, \\
\frac{\mathrm{d}CD(t)}{\mathrm{d}t} &= r_{CD} - k_{CD} CD - \frac{\rho_0 CDT^i}{\alpha_0 + T^i} - a_4 CDT - b_{CD} D_c CD, \\
\frac{\mathrm{d}NK(t)}{\mathrm{d}t} &= r_{NK} - k_{NK} NK - \frac{\rho_1 NKT^i}{\alpha_1 + T^i}. - a_5 NKT
\end{aligned}$$

In order to be able to incorporate these hard constraints, we add in the following equations

$$\begin{aligned}
&\frac{\alpha_1}{1 + (D_d - 1,700)^{\lambda_1}} \\
&\frac{\alpha_2}{1 + D_d^{\lambda_2}} \\
&\frac{\alpha_3}{1 + (D_c - 127.5)^{\lambda_3}} \\
&\frac{\alpha_4}{1 + (D_c)^{\lambda_4}}
\end{aligned}$$

These allow us to transform the hard constraints into hard constraints. The λ_j terms denote exponents that can be used to move the model to lower dosage as increase λ_j would lead to. The α_j terms denote the weights

Thus, our cost functional becomes

$$\begin{aligned}
J[\mathbf{u}] = \int_0^{156} & \mathbf{u}(t)^{\intercal} Q \mathbf{u}(t) + T^2(t) + \frac{\alpha_1}{1 + (D_d - 1,700)^{\lambda_1}} + \frac{\alpha_2}{1 + D_d^{\lambda_2}} \\
&+ \frac{\alpha_3}{1 + (D_c - 127.5)^{\lambda_3}} + \frac{\alpha_4}{1 + D_c^{\lambda_4}} \, \mathrm{d}t + \xi_{156} T^2(156)
\end{aligned}$$

The Hamiltonian becomes

$$
\begin{aligned}
H &= H(t,\mathbf{x}(t),\mathbf{u}(t),\mathbf{p}(t)) = \mathbf{p}(t)\cdot\mathbf{x}'(t) - L(t,\mathbf{x}(t),\mathbf{u}(t))\\
&= g_T p_1 T \ln\left(\frac{T_{\max}}{T}\right) - a_1 p_1 NT - a_2 p_1 NKT - a_3 p_1 CDT - p_1\left(E_c D_c + \frac{4}{5}E_d D_d\right)T\\
&+ g_N p_2 N \ln\left(\frac{N_{\max}}{N}\right) - k_N p_2 N - a_0 p_2 NT\\
&+ r_{CD} p_3 - k_{CD} p_3 CD - p_3 \frac{\rho_0 CDT^i}{\alpha_0 + T^i} - a_4 p_3 CDT - b_{CD} p_3 D_c CD\\
&+ r_{NK} p_4 - k_{NK} p_4 NK - p_4 \frac{\rho_1 NKT^i}{\alpha_1 + T^i} - a_5 p_4 NKT\\
&- \xi_c D_c^2 - \xi_d D_d^2 - T^2 - \gamma_1 D_c - \gamma_2 D_d - \frac{\alpha_1}{1+(D_d - 1,700)^{\lambda_1}} - \frac{\alpha_2}{1+D_d^{\lambda_2}}\\
&- \frac{\alpha_3}{1+(D_c - 127.5)^{\lambda_3}} - \frac{\alpha_4}{1+D_c^{\lambda_4}}
\end{aligned}
$$

By Pontryagin's principle, we have

$$
\frac{DH}{D\mathbf{u}} = \left[\tfrac{\partial H}{\partial D_c}\,\tfrac{\partial H}{\partial D_d}\right] = \mathbf{0}
$$

Hence,

$$
\begin{aligned}
0 &= \frac{\partial H}{\partial D_c} = -p_1 E_c T - p_3 b_{CD} CD - 2\xi_c D_c + \frac{\alpha_3\lambda_3 (D_c - 127.5)^{\lambda_3 - 1}}{(1+(D_c - 127.5)^{\lambda_3})^2} + \frac{\alpha_4 \lambda_4 D_c^{\lambda_4 - 1}}{(1+D_c^{\lambda_4})^2}\\
0 &= \frac{\partial H}{\partial D_d} = -\left(\frac{4E_d}{5}\right)p_1 T - 2\xi_d D_d + \frac{\alpha_1\lambda_1 (D_d - 1,700)^{\lambda_1 - 1}}{(1+(D_d - 1,700)^{\lambda_1})^2} + \frac{\alpha_2\lambda_2 D_d^{\lambda_2 - 1}}{(1+D_c^{\lambda_2})^2}
\end{aligned}
$$

Moreover, we also know that $\mathbf{p}' = -\frac{DH}{D\mathbf{x}}$ and that $\mathbf{p}(156) = -\frac{D\phi}{D\mathbf{x}(156)}$, where $\phi(\mathbf{x}(156)) = \xi_{156}T^2(156)$. We have

$$
\begin{aligned}
p_1' = &-\Bigg(- g_T p_1 + g_T p_1 \ln\left(\frac{T_{max}}{T}\right) - a_1 p_1 N - a_2 p_1 N K - a_3 p_1 C D - p_1 \left(E_c D_c + \frac{4}{5} E_d D_d\right) \\
&- a_0 p_2 N + \frac{-(\alpha_0 + T^i)(i\rho_0 p_3 C D T^{i-1}) + (\rho_0 p_3 C D T^i)(i T^{i-1})}{(\alpha_0 + T^i)^2} - a_4 p_3 C D \\
&+ \frac{-(\alpha_1 + T^i)(i\rho_1 p_4 N K T^{i-1}) + (\rho_1 p_4 N K T^i)(i T^{i-1})}{(\alpha_1 + T^i)^2} - a_5 p_4 N K - 2T \Bigg) \\
p_2' = &-(-a_1 p_1 T + g_N p_2 \ln\left(\frac{N_{max}}{N}\right) - g_N p_2 - k_N p_2 - a_0 p_2 T) \\
p_3' = &-(-a_3 p_1 T - k_{CD} p_3 - p_3 \frac{\rho_0 T^i}{\alpha_0 + T^i} - a_4 p_3 T - b_{CD} p_3 D_c) \\
p_4' = &-(-a_2 p_1 T - k_{NK} p_4 - p_4 \frac{\rho_1 T^i}{\alpha_1 + T^i} - a_5 p_4 T)
\end{aligned}
$$

with $p_1(156) = -2\xi_{156}T(156)$ and $p_2(156) = p_3(156) = p_4(156) = 0$

A Definitions

- Invasive Ductal Carcinoma: invasive breast cancer that starts in the milk ducts, the tubes that carry milk from the lobules to the nipple. [?] Hello

References