Thank you for your good work. Please see my feedback below.

A sentence like this can be added to justify the use of the simplified model.

Adaptive Backstepping Control for a Simplified Model of Acute Lymphoblastic Leukemia

While the simplified model is unrealistic as it neglects delay and pharmacokinetics, it does include a key challenging aspect of the original 8(?)-state model, which is the nonlinear drug feedback aspect. Therefore, it is a natural model to study.

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Simplified Jost Model

Consider a simplified Friberg model (last ~~four~~ five ? states of the model from [1]), where we have removed the transitional compartments $x_{tr1}, x_{tr2}, x_{tr3}$. We assume the parameters k_{ma} and γ are known, but Base, slope, and k_{tr} are unknown. The system can be written as

please specify that we set $u := x_{6tgn}$. and describe in words what x_{6tgn} represents.

not sure why we need parentheses

$$\begin{cases} \dot{x}_1 &= k_{\text{tr}} x_2 - k_{\text{ma}} x_1 \\ \dot{x}_2 &= k_{\text{tr}} \left((1 - \text{slope}\, u)\text{Base}^{\gamma} x_1^{-\gamma}\right) x_2 - k_{\text{tr}} x_2 \end{cases}, \tag{1}$$

where x_1 represents the circulating mature neutrophils and x_2 represents the proliferating ~~cells~~ neutrophils in the bone marrow. We can reparameterize the system as:

$$\begin{cases} \dot{x}_1 &= \theta_3 x_2 - k_{\text{ma}} x_1 \\ \dot{x}_2 &= \theta_1 x_1^{-\gamma} x_2 - \theta_2 x_1^{-\gamma} x_2 u - \theta_3 x_2 \end{cases}, \tag{2}$$

where

$$\theta = \begin{bmatrix} k_{\text{tr}} \text{Base}^{\gamma} \\ k_{\text{tr}} \text{Base}^{\gamma} \text{slope} \\ k_{\text{tr}} \end{bmatrix}. \tag{3}$$

We now proceed to analyze and control the system following an approach similar to [3, Example 3.4.2]. Because x_1 and x_2 should always be positive (for a living person), the following co-ordinate transformation is invertible:

Do simulation results agree with this assumption, i.e., for some plausible selection of u, do we see in simulation whether $x_1 > 0$ and $x_2 > 0$ for all t? Doing this simulation may help us see whether the assumption $x_1 > 0$ and $x_2 > 0$ is reasonable.

$$\xi_1 = x_1, \quad \xi_2 = \ln(x_2).$$

Under this transformation, the dynamics become:

$$\begin{cases} \dot{\xi}_1 &= \theta_3 e^{\xi_2} - k_{\text{ma}} \xi_1 \\ \dot{\xi}_2 &= \theta_1 \xi_1^{-\gamma} - \theta_2 \xi_1^{-\gamma} u - \theta_3 \ , \\ &= \theta^{\top} \varphi(\xi_1, u) \end{cases} \tag{4}$$

should go to the previous line for clarity

where we define the regressor

$$\varphi(\xi_1, u) = \begin{bmatrix} \xi_1^{-\gamma} \\ -\xi_1^{-\gamma} u \\ -1 \end{bmatrix}. \tag{5}$$

Let's do this analysis in the special case of x_{1d} (reference) being constant for simplicity.

good to specify that this is constant so the reader knows that $\dot{z}_1 = \dot{\xi}_1$.

Setup for Control Design

circulating mature neutrophils

$\downarrow = \xi_1$ $\in \mathbb{R}$

Our goal for the system is to steer the state x_1 to a desired reference x_{1d}. To this end, we define the reference tracking error z_1:

$$z_1 = \xi_1 - \xi_{1d} = x_1 - x_{1d} \tag{6}$$

and proceed to design an adaptive backstepping controller using state feedback. To stabilize the ξ_1 dynamics, we can choose e^{ξ_2} as virtual control. We want e^{ξ_2} to follow

$=x_1$

$$\alpha(\xi_1, \hat{\theta}_3) = \frac{1}{\hat{\theta}_3}\left(-c_1 z_1 + k_{\mathrm{ma}}\xi_1\right), \tag{7}$$

We should specify a feasibility region where $\hat{\Theta}_3 \neq 0$, $\hat{\Theta}_2 \neq 0$.

This choice makes sense to obtain $\dot{z}_1 \approx -c_1 z_1$ if $x_{1d} \in \mathbb{R}$ (i.e., is constant).
I don't know whether (7) makes if x_{1d} is not constant. However, in our work, we only care about the case when x_{1d} is constant, which simplifies our math.

I will assume that x_{1d} is constant in my review.

where $\hat{\theta}_3$ is an estimate of the true parameter θ_3 and $c_1 > 0$. Now define a tracking error state z_2:

$$z_2 = e^{\xi_2} - \alpha(\xi_1, \hat{\theta}_3) \tag{8}$$

In all, we have the following error dynamics:

$$\begin{cases} \dot{z}_1 = \theta_3 z_2 + \dfrac{\theta_3}{\hat{\theta}_3}\left(-c_1 z_1 + k_{\mathrm{ma}}\xi_1\right) - k_{\mathrm{ma}}\xi_1 - \cancel{\dot{\xi}_{1d}} \\ \dot{z}_2 = e^{\xi_2}\theta^\top \varphi(\xi_1, u) - \dfrac{\partial \alpha}{\partial \xi_1}\dot{\xi}_1 - \dfrac{\partial \alpha}{\partial \hat{\theta}_3}\dot{\hat{\theta}}_3 \end{cases} \tag{9}$$

I believe this should be written in terms of z_i's rather than both z_i's and ξ_i's (if the math is not too messy)

Adaptive Laws and Stability

We want the error states to converge to zero, so it is natural to consider the Lyapunov function candidate

$$V(z_1, z_2, \hat{\theta}) = \frac{1}{2}z_1^2 + \frac{1}{2}z_2^2 + \frac{1}{2}\tilde{\theta}^\top \Gamma \tilde{\theta}, \tag{10}$$

where $\tilde{\theta} = \theta - \hat{\theta} \in \mathbb{R}^3$ is the parameter estimation error vector, and $\Gamma \succ 0$. This function has the total time derivative:

$$\begin{aligned} \dot{V} &= z_1\dot{z}_1 + z_2\dot{z}_2 - \tilde{\theta}^\top \Gamma \dot{\hat{\theta}} \\ &= z_1\left[\theta_3 z_2 + \frac{\theta_3}{\hat{\theta}_3}(-c_1 z_1 + k_{\mathrm{ma}}\xi_1) - k_{\mathrm{ma}}\xi_1 \cancel{- \dot{\xi}_{1d}}\right] \\ &\quad + z_2\left[e^{\xi_2}\theta^\top\varphi(\xi_1, u) - \frac{\partial\alpha}{\partial\xi_1}\dot{\xi}_1 - \frac{\partial\alpha}{\partial\hat{\theta}_3}\dot{\hat{\theta}}_3\right] - \tilde{\theta}^\top \Gamma \dot{\hat{\theta}} \end{aligned} \tag{11}$$

We can substitute $\theta = \tilde{\theta} + \hat{\theta}$ to remove explicit dependence on the unknown parameter:

$$\begin{aligned} \dot{V} = z_1&\left[(\tilde{\theta}_3 + \hat{\theta}_3)z_2 + \frac{(\tilde{\theta}_3 + \hat{\theta}_3)}{\hat{\theta}_3}(-c_1 z_1 + k_{\mathrm{ma}}\xi_1) - k_{\mathrm{ma}}\xi_1 \cancel{- \dot{\xi}_{1d}}\right] \\ &+ z_2\left[e^{\xi_2}(\tilde{\theta}^\top + \hat{\theta}^\top)\varphi(\xi_1, u) - \frac{\partial\alpha}{\partial\xi_1}\dot{\xi}_1 - \frac{\partial\alpha}{\partial\hat{\theta}_3}\dot{\hat{\theta}}_3\right] - \tilde{\theta}^\top\Gamma\dot{\hat{\theta}} \end{aligned} \tag{12}$$

Potential logic issue:

We must substitute $\theta = \tilde{\theta} + \hat{\theta}$ to remove explicit dependence on θ, but in (13) and in subsequent steps, we keep $\dot{\xi}_1 = \theta_3 e^{\xi_2} - k_{ma}\xi_1$, which still depends on θ_3. Hence, I believe that the explicit form of $\dot{\xi}_1$ should be substituted in earlier so that the θ_3 parameter in $\dot{\xi}_1$ can be dealt with appropriately.

Now, we can collect terms involving $\tilde{\theta}$:

$$
\begin{aligned}
\dot{V} &= z_1\left[\hat{\theta}_3 z_2 + \frac{\theta_3}{\hat{\theta}_3}(-c_1 z_1 + k_{\mathrm{ma}}\xi_1) - k_{\mathrm{ma}}\xi_1\right] \\
&\quad + z_2\left[e^{\xi_2}\hat{\theta}^\top\varphi(\xi_1,u) - \frac{\partial\alpha}{\partial\xi_1}\dot{\xi}_1 - \frac{\partial\alpha}{\partial\hat{\theta}_3}\dot{\hat{\theta}}_3\right] \\
&\quad + \tilde{\theta}^\top\left[z_2 e^{\xi_2}\varphi(\xi_1,u) - \Gamma\,\dot{\hat{\theta}}\right] + \tilde{\theta}_3\left[z_1 z_2 + \frac{z_1}{\hat{\theta}_3}(-c_1 z_1 + k_{\mathrm{ma}}\xi_1)\right] \\
&= -c_1 z_1^2 + \hat{\theta}_3 z_1 z_2 \\
&\quad + z_2\left[e^{\xi_2}\hat{\theta}^\top\varphi(\xi_1,u) - \frac{\partial\alpha}{\partial\xi_1}\dot{\xi}_1 - \frac{\partial\alpha}{\partial\hat{\theta}_3}\dot{\hat{\theta}}_3\right] \\
&\quad + \tilde{\theta}^\top\left[z_2 e^{\xi_2}\varphi(\xi_1,u) - \Gamma\,\dot{\hat{\theta}} + \boldsymbol{e}_3\left(z_1 z_2 + \frac{z_1}{\hat{\theta}_3}(-c_1 z_1 + k_{\mathrm{ma}}\xi_1)\right)\right],
\end{aligned}
\tag{13}
$$

This is correct (as long as we delete e_3^T)

$\tilde{\theta}^T e_3 = \tilde{\theta}_3$

where $\boldsymbol{e}_3$ is the third standard basis vector.

Finally, we can begin selecting our adaptation and control laws to cancel terms and ensure $\dot{V} \leq 0$. We can make the second bracketed term in (13) vanish by selecting $\dot{\hat{\theta}}$. Then, we can design u such that the first square bracketed term in (13) becomes $-c_2 z_2$. At first glance, it might appear we have a circular argument. However, recall the structure of $\varphi(\xi_1, u)$:

$$
\varphi(\xi_1,u) = \begin{bmatrix} \xi_1^{-\gamma} \\ -\xi_1^{-\gamma}u \\ -1 \end{bmatrix}. \tag{14}
$$

Because u does not appear in all components of $\varphi(\xi_1, u)$, we can choose a Γ which allows us to design $\dot{\hat{\theta}}_3$ independently. For simplicity, assume $\Gamma = \mathrm{diag}(\gamma_1, \gamma_2, \gamma_3)$. with $\gamma_i > 0$.
In this case, we can select:

$$
\dot{\hat{\theta}} = \Gamma^{-1}\left[z_2 e^{\xi_2}\varphi(\xi_1,u) + \boldsymbol{e}_3\left(z_1 z_2 + \frac{z_1}{\hat{\theta}_3}(-c_1 z_1 + k_{\mathrm{ma}}\xi_1)\right)\right], \tag{15}
$$

$\begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}$

or more explicitly:

$$
\begin{cases}
\dot{\hat{\theta}}_1 = \frac{1}{\gamma_1} z_2 e^{\xi_2}\xi_1^{-\gamma}, \\
\dot{\hat{\theta}}_2 = -\frac{1}{\gamma_2} z_2 e^{\xi_2}\xi_1^{-\gamma}u, \\
\dot{\hat{\theta}}_3 = \frac{1}{\gamma_3}\left(-z_2 e^{\xi_2} + z_1 z_2 + \frac{z_1}{\hat{\theta}_3}(-c_1 z_1 + k_{\mathrm{ma}}\xi_1)\right).
\end{cases}
\tag{16}
$$

Notice $\dot{\hat{\theta}}_3$ is independent of u. With these choices of adaptation laws, we ensure the last square bracketed term in (13) vanishes. Now, we can choose our control

Aren't we really trying to choose u so that

$$\hat{\theta}_3 z_1 z_2 + z_2 \left[e^{\xi_2} \hat{\theta}^\top \varphi(\xi_1, u) - \frac{\partial \alpha}{\partial \xi_1} \dot{\xi}_1 - \frac{\partial \alpha}{\partial \hat{\theta}_3} \dot{\hat{\theta}}_3 \right] = -c_2 z_2^2,$$

that is, we are doing more than just dealing with the term in the square brackets?

law $u(z, \xi, \hat{\theta}, \dot{\hat{\theta}}_3)$ to cancel the first term enclosed in square brackets in (13):

Do we know that $\hat{\theta}_2 \neq 0$?

$$u = \frac{1}{\hat{\theta}_2} \Bigg[\hat{\theta}_1 - \hat{\theta}_3 \xi_1^\gamma \left(1 + \frac{\partial \alpha}{\partial \xi_1} \right) \tag{17}$$

does not depend on u

$$+ e^{-\xi_2} \xi_1^\gamma \left(c_2 z_2 + k_{\text{ma}} \frac{\partial \alpha}{\partial \xi_1} \xi_1 - \frac{\partial \alpha}{\partial \hat{\theta}_3} \dot{\hat{\theta}}_3 + \hat{\theta}_3 z_1 \text{[redacted]} \right) \Bigg]. \tag{18}$$

Instead of using $\dot{\xi}_1 = \theta_3 e^{\xi_2} - k_{\text{ma}} \xi_1$, this controller may be using $\dot{\xi}_1 = \hat{\theta}_3 e^{\xi_2} - k_{\text{ma}} \xi_1$, which is not true in general.

I believe the correct expression for $\dot{\xi}_1$ must be substituted in earlier in the analysis

With these choices for the control law and the adaptation laws, we establish

$$\dot{V} = -c_1 z_1^2 - c_2 z_2^2 \leq 0 \tag{19}$$

which ensures, by LaSalle's Invariance Principle,

I'm not convinced that the application of LaSalle's Principle is correct here. (see below)

$$z_1, z_2 \to 0 \text{ as } t \to \infty \tag{20}$$

$$\implies x_1 \to x_{1d},\ x_2 \to \alpha(\xi_1, \hat{\theta}_3) \text{ as } t \to \infty. \tag{21}$$

1 Appendix

Consider the autonomous system

$$\dot{x} = f(x), \tag{22}$$

where $f : D \to \mathbb{R}^n$ is a locally Lipschitz map from a domain $D \subset \mathbb{R}^n$ to $\mathbb{R}^n$.

LaSalle's Invariance Principle [2, Theorem 4.4]: Let $\Omega \subset D$ be a compact set that is positively invariant with respect to (22). Let $V : D \to R$ be a continuously differentiable function such that $\dot{V}(x) \leq 0$ in Ω. Let E be the set of all points in Ω where $\dot{V}(x) = 0$. Let M be the largest invariant set in E. Then every solution starting in Ω approaches M as $t \to \infty$.

References

[1] Felix Jost et al. "Model-based optimal AML consolidation treatment". In: *IEEE Transactions on Biomedical Engineering* 67.12 (2020), pp. 3296–3306.

[2] HK Khalil. *Nonlinear systems*. Prentice Hall, 2002.

[3] M Krstic, Kanellakopoulos I, and P Kokotovic. *Nonlinear and Adaptive Control Design*. John Wiley and Sons, 1995.

Notes about applying LaSalle's Principle to our setting

- We must specify a feasibility region, i.e., a region where our controller and all the dynamics make sense, e.g. perhaps

$$\left\{ \begin{bmatrix} z_1 \\ z_2 \\ \hat{\theta} \end{bmatrix} \in \mathbb{R}^5 \;:\; \hat{\theta}_2 \neq 0,\ \hat{\theta}_3 \neq 0 \right\}.$$

- According to a discussion from Krstic & Kanellakopoulos (pp. 179–180; pages 189–190 of the PDF reader):

> Krstic textbook (pdf page 189–190):
>
> $$\dot{z} = f_1(z, \tilde{\theta})$$
> $$\dot{\tilde{\theta}} = f_2(z).$$
>
> The derivative of $V = \frac{1}{2} z^T z + \frac{1}{2} \tilde{\theta}^T \Gamma^{-1} \tilde{\theta}$ is $\dot{V} = -\sum_{i=1}^{n} c_i z_i^2$
>
> ⋮
>
> "Finally, by applying [81, theorem 4.8] (a local version of the LaSalle-Yoshizawa theorem (Theorem A.8) to $\dot{V} = -\sum_{i=1}^{n} c_i z_i^2$, it follows that $z(t) \to 0$ as $t \to \infty$."
>
> I think they may be applying [81, Theorem 4.9] instead
>
> ↑ Khalil *Nonlinear Systems*. pdf page 549

it appears that we may only have a local result. In particular, I believe that it would be useful for us to apply Theorem 4.9 (p.152) from Khalil, *Nonlinear Systems* (pdf page 169) to help us truly understand whether z_1, z_2 should converge to the origin in our setting.

- Overall, to apply LaSalle appropriately, I believe a closer look at the theory is needed to ensure correctness.