Adaptive Backstepping Control for a Simplified Model of Acute Lymphoblastic Leukemia

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Simplified Jost Model

Consider a simplified Friberg model (last 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 $\mathrm{Base}, \mathrm{slope}$, and k_{tr} are unknown. The system can be written

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

where x_1 represents the circulating mature neutrophils and x_2 represents the proliferating cells in the bone marrow. The input u represents the blood concentration of 6-TGN (the state x_{6tgn} in the original model), which can be viewed as the output of a controllable linear system with known dynamics and known initial condition. We can reparameterize the system as:

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

where

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

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:

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

Under this transformation, the dynamics become:

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

where we define the regressor

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

Setup for Control Design

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

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

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

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

where we $\hat{\theta}_3$ is an estimate of the true parameter θ_3. To ensure convergence while maintaining $\alpha > 0$, we must have $0 < c_1 < k_{ma}$. 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:

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

Adaptive Laws and Stability

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

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

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:

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

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

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

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

$$\begin{aligned}\dot{V} = z_1 &\left[\hat{\theta}_3 z_2 + \frac{\hat{\theta}_3}{\hat{\theta}_3}(-c_1 z_1 + k_{\mathrm{ma}}\xi_1) - k_{\mathrm{ma}}\xi_1\right] \\ &+ z_2\left[e^{\xi_2}\hat{\theta}^\top\varphi(\xi_1, u) - \frac{\partial\alpha}{\partial\xi_1}\left(\hat{\theta}_3 e^{\xi_2} - k_{\mathrm{ma}}\xi_1\right) - \frac{\partial\alpha}{\partial\hat{\theta}_3}\dot{\hat{\theta}}_3\right] \\ &+ \tilde{\theta}^\top\left[z_2 e^{\xi_2}\varphi(\xi_1, u) - \Gamma^{-1}\,\dot{\hat{\theta}}\right] \\ &+ \tilde{\theta}_3\left[z_1 z_2 + \frac{z_1}{\hat{\theta}_3}(-c_1 z_1 + k_{\mathrm{ma}}\xi_1) - z_2\frac{\partial\alpha}{\partial\xi_1}e^{\xi_2}\right] \\ = -c_1 &z_1^2 + \hat{\theta}_3 z_1 z_2 \\ &+ z_2\left[e^{\xi_2}\hat{\theta}^\top\varphi(\xi_1, u) - \frac{\partial\alpha}{\partial\xi_1}\left(\hat{\theta}_3 e^{\xi_2} - k_{\mathrm{ma}}\xi_1\right) - \frac{\partial\alpha}{\partial\hat{\theta}_3}\dot{\hat{\theta}}_3\right] \\ &+ \tilde{\theta}^\top\left[z_2 e^{\xi_2}\varphi(\xi_1, u) - \Gamma^{-1}\,\dot{\hat{\theta}} + \boldsymbol{e}_3\left(z_1 z_2 + \frac{z_1}{\hat{\theta}_3}(-c_1 z_1 + k_{\mathrm{ma}}\xi_1) - z_2\frac{\partial\alpha}{\partial\xi_1}e^{\xi_2}\right)\right],\end{aligned} \tag{13}$$

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 $-c_2 z_2$. This is possible because of 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 select a Γ which allows us to design $\dot{\hat{\theta}}_3$ independently of u. For simplicity, choose $\Gamma = \mathrm{diag}(\gamma_1, \gamma_2, \gamma_3) \succ 0$. In this case, we can select:

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

or more explicitly:

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

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 law $u(z, \xi, \hat{\theta}, \dot{\hat{\theta}}_3)$ to make (13) negative definite:

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

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

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,

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

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

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 Simulation of Maintenance Therapy of Childhood Acute Lymphoblastic Leukemia". In: *Frontiers in Physiology* 11 (2020). ISSN: 1664-042X. DOI: 10.3389/fphys.2020.00217. URL: https://www.frontiersin.org/articles/10.3389/fphys.2020.00217.

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

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