

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 Base, slope, and k_{tr} are unknown. The system can be written

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

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:

$$\begin{cases} \dot{x}_1 = \theta_3x_2 - k_{ma}x_1 \\ \dot{x}_2 = \theta_1x_1^{-\gamma}x_2 - \theta_2x_1^{-\gamma}x_2u - \theta_3x_2 \end{cases}, \quad (2)$$

where

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

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:

$$\begin{cases} \dot{\xi}_1 = \theta_3e^{\xi_2} - k_{ma}\xi_1 \\ \dot{\xi}_2 = \theta_1\xi_1^{-\gamma} - \theta_2\xi_1^{-\gamma}u - \theta_3 = \theta^\top \varphi(\xi_1, u) \end{cases}, \quad (4)$$

where we define the regressor

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

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

$$z_1 = \xi_1 - \xi_{1d} = x_1 - x_{1d} \quad (6)$$

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

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

where $\hat{\theta}_3$ 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 :

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

In all, we have the following error dynamics:

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

Adaptive Laws and Stability

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

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

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

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

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

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

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

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

where \mathbf{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 $\Gamma = \text{diag}(\gamma_1, \gamma_2, \gamma_3) \succ 0$. In this case, we can select:

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

or more explicitly:

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

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:

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

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

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

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

which ensures, by LaSalle's Invariance Principle,

$$z_1, z_2 \rightarrow 0 \text{ as } t \rightarrow \infty \quad (20)$$

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

1 Appendix

Consider the autonomous system

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

where $f : D \rightarrow \mathbb{R}^n$ 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 $V : D \rightarrow \mathbb{R}$ 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 $t \rightarrow \infty$.

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.