

Robust Synthetic Biology Design: Stochastic Game

Theory Approach

Supplementary materials

APPENDIXES

Appendix A: Proof of Proposition 1

Let us consider a Lyapunov energy function $V(\tilde{x}) > 0$, then the cost function in equation (8) is equivalent to

$$J(k, \gamma, v) = E \left[V(\tilde{x}(0)) - V(\tilde{x}(t_f)) + \int_0^{t_f} \left(\tilde{x}^T Q \tilde{x} - g^2 v^T v + \frac{dV(\tilde{x})}{dt} \right) dt \right] \quad (\text{A1})$$

By the chain rule, we get

$$\frac{dV(\tilde{x}(t))}{dt} = \left(\frac{\partial V(\tilde{x}(t))}{\partial \tilde{x}(t)} \right)^T \cdot \frac{d\tilde{x}(t)}{dt} = \left(\frac{\partial V(\tilde{x}(t))}{\partial \tilde{x}(t)} \right)^T \cdot (f(\tilde{x}(t) + x_d(t), k, \gamma) + v(t)) \quad (\text{A2})$$

Substituting (A2) into (A1), we maximize $J(k, \gamma, v)$ by the uncertain disturbance v

$$\begin{aligned} & \max_v J(k, \gamma, v) \\ &= \max_v E \left[V(\tilde{x}(0)) - V(\tilde{x}(t_f)) + \int_0^{t_f} \left(\tilde{x}^T Q \tilde{x} - g^2 v^T v + \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T f(\tilde{x} + x_d, k, \gamma) + \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T v \right) dt \right] \\ &= \max_v E \left[V(\tilde{x}(0)) - V(\tilde{x}(t_f)) + \int_0^{t_f} \left(\tilde{x}^T Q \tilde{x} + \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T f(\tilde{x} + x_d, k, \gamma) \right. \right. \\ & \quad \left. \left. - \left(gv - \frac{1}{2g} \frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T \left(gv - \frac{1}{2g} \frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right) + \frac{1}{4g^2} \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right) \right) dt \right] \\ &= E \left[V(\tilde{x}(0)) - V(\tilde{x}(t_f)) + \int_0^{t_f} \left(\tilde{x}^T Q \tilde{x} + \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T f(\tilde{x} + x_d, k, \gamma) + \frac{1}{4g^2} \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right) \right) dt \right] \end{aligned} \quad (\text{A3})$$

with the worst-case disturbance $v^* = \frac{1}{2g^2} \frac{\partial V(\tilde{x})}{\partial \tilde{x}}$.

By the inequality in (12), it is seen that $V(\tilde{x}(0))$ is the upper bound of (A3) i.e., the sub-minimax problem becomes how to solve the following constrained optimization problem

$$\min_{\substack{k \in [k_1, k_2] \\ \gamma \in [\gamma_1, \gamma_2]}} \max_v J(k, \gamma, v) \leq \min_{\substack{k \in [k_1, k_2] \\ \gamma \in [\gamma_1, \gamma_2]}} E[V(\tilde{x}(0))] \quad (\text{A4})$$

subject to (12) and $V(\tilde{x}) > 0$.

By the fact in (9), $g^2 E[\tilde{x}^T(0)\tilde{x}(0)]$ is the upper bound of $\min_{\substack{k \in [k_1, k_2] \\ \gamma \in [\gamma_1, \gamma_2]}} \max_v J(k, \gamma, v)$.

Therefore $E[V(\tilde{x}(0))]$ in (A4) should be bounded by $g^2 E[\tilde{x}^T(0)\tilde{x}(0)]$, i.e.

$E[V(\tilde{x}(0))] \leq g^2 E[\tilde{x}^T(0)\tilde{x}(0)]$. Therefore the suboptimal solution is to minimize its

upper bound. Hence, the sub-minimax problem in (A4) could be replaced by

$$\min_{\substack{k \in [k_1, k_2] \\ \gamma \in [\gamma_1, \gamma_2]}} \max_v J(k, \gamma, v) \leq \min_{\substack{k \in [k_1, k_2] \\ \gamma \in [\gamma_1, \gamma_2]}} E[V(\tilde{x}(0))] \leq \min_{\substack{k \in [k_1, k_2] \\ \gamma \in [\gamma_1, \gamma_2]}} E[g^2 \tilde{x}^T(0)\tilde{x}(0)] = \min_{\substack{k \in [k_1, k_2] \\ \gamma \in [\gamma_1, \gamma_2]}} g^2 \text{Tr}(R_0) \quad (\text{A5})$$

where $\text{Tr}(R_0)$ denotes the trace of R_0 and R_0 denotes the covariance of the initial condition $\tilde{x}(0)$ i.e., $R_0 = E[\tilde{x}(0)\tilde{x}^T(0)]$, which is independent of the choice of k and γ . Therefore, the sub-minimax design problem is equivalent to solving the following constrained optimization

$$\min_{\substack{k \in [k_1, k_2] \\ \gamma \in [\gamma_1, \gamma_2]}} g^2$$

subject to (12) and $V(\tilde{x}) > 0$.

Appendix B: Proof of Proposition 2

We replace error dynamic system in (4) by its fuzzy interpolation system in (15).

Then HJI in (12) can be represented by

$$\left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T \left(\sum_{i=1}^L h_i(\tilde{x}) \mathbf{A}_i(k, \gamma) \tilde{x} \right) + \tilde{x}^T Q \tilde{x} + \frac{1}{4g^2} \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right) < 0 \quad (\text{B1})$$

Let us choose the Lyapunov function $V(\tilde{x})$ as $V(\tilde{x}) = \tilde{x}^T P \tilde{x}$ for some positive definite symmetric matrix P and substitute it into (B1). Then we get

$$\sum_{i=1}^L h_i(\tilde{x}) \left\{ \tilde{x}^T \left(P \mathbf{A}_i(k, r) + \mathbf{A}_i^T(k, r) P + Q + \frac{1}{g^2} P P \right) \tilde{x} \right\} \leq 0 \quad (\text{B2})$$

$$P \leq g^2 I$$

where the property in (17) is used.

It is seen that the inequalities in (19) implies (B2). Therefore, the sub-minimax design for the fuzzy equivalent system becomes how we solve the constrained optimization in (18) and (19). By substituting $V(\tilde{x}) = \tilde{x}^T P \tilde{x}$ into (13), we get the worst-case disturbances v^* in (20).

Appendix C: Proof of Proposition 3

Again, let us consider a Lyapunov energy function $V(\tilde{x}) > 0$, then the equation (23) is equivalent to

$$\begin{aligned} & \min_{\substack{k \in \{k_1, k_2\} \\ \gamma \in \{\gamma_1, \gamma_2\}}} E \left[\int_0^{t_f} \tilde{x}^T Q \tilde{x} dt \right] \\ &= \min_{\substack{k \in \{k_1, k_2\} \\ \gamma \in \{\gamma_1, \gamma_2\}}} E \left[V(\tilde{x}(0)) - V(\tilde{x}(t_f)) + \int_0^{t_f} \left(\tilde{x}^T Q \tilde{x} + \frac{dV(\tilde{x})}{dt} \right) dt \right] \\ &= \min_{\substack{k \in \{k_1, k_2\} \\ \gamma \in \{\gamma_1, \gamma_2\}}} E \left[V(\tilde{x}(0)) - V(\tilde{x}(t_f)) + \int_0^{t_f} \left(\tilde{x}^T Q \tilde{x} + \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T f(\tilde{x} + x_d, k, \gamma) + \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T v \right) dt \right] \end{aligned}$$

By the fact that $2a^T b \leq a^T a + b^T b$ for any two-vectors a and b , we get

$$\begin{aligned} \min_{\substack{k \in \{k_1, k_2\} \\ \gamma \in \{\gamma_1, \gamma_2\}}} E \left[\int_0^{t_f} \tilde{x}^T Q \tilde{x} dt \right] &= \min_{\substack{k \in \{k_1, k_2\} \\ \gamma \in \{\gamma_1, \gamma_2\}}} E \left[V(\tilde{x}(0)) - V(\tilde{x}(t_f)) + \int_0^{t_f} \left(\tilde{x}^T Q \tilde{x} + \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T f(\tilde{x} + x_d, k, \gamma) \right. \right. \\ & \left. \left. + \frac{1}{2} \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right)^T \left(\frac{\partial V(\tilde{x})}{\partial \tilde{x}} \right) + \frac{1}{2} v^T v \right) dt \right] \end{aligned}$$

By the inequality in (25), we get the sub-optimal regulation problem as follows

$$\min_{\substack{k \in [k_1, k_2] \\ \gamma \in [\gamma_1, \gamma_2]}} E \left[\int_0^{t_f} \tilde{x}^T Q \tilde{x} dt \right] \leq \min_{\substack{k \in [k_1, k_2] \\ \gamma \in [\gamma_1, \gamma_2]}} E \left[V(\tilde{x}(0)) + \frac{1}{2} \int_0^{t_f} v^T v dt \right]$$

Since disturbance v is independent of the choice of parameters k and γ , and only the choice of $V(\tilde{x})$ will influence the above minimization, the sub-optimal design becomes how to solve the constrained optimization problem in (24) and (25).

Appendix D: *Parameters of the T-S fuzzy model with the specified kinetic parameters*

k^* and decay rates γ^*

$$\mathbf{A}_1 = \begin{bmatrix} -1.6879 & -0.060601 & 0.11879 & -0.0092833 \\ 0.38914 & -0.093297 & 0.010249 & -0.0065119 \\ 0.10826 & -0.02841 & -1.4996 & -0.0060343 \\ 0.00097167 & -0.0025457 & 0.0053402 & -0.066832 \end{bmatrix}$$

$$\mathbf{A}_2 = \begin{bmatrix} -3.5629 & -0.12704 & 0.25074 & -0.0092833 \\ 0.20138 & -0.193 & 0.021476 & -0.0065109 \\ 0.22906 & -0.11458 & -3.1644 & -0.0060447 \\ 0.0014069 & -0.00054073 & 0.0071284 & -0.066833 \end{bmatrix}$$

$$\mathbf{A}_3 = \begin{bmatrix} -1.5351 & -0.060529 & 0.11879 & -0.0092832 \\ 0.40408 & -0.092851 & 0.010249 & -0.0065573 \\ -0.18285 & 0.0322 & -1.4996 & 0.0041303 \\ 0.0012516 & -0.0027325 & -0.0017594 & -0.066801 \end{bmatrix}$$

$$\mathbf{A}_4 = \begin{bmatrix} -3.2403 & -0.12689 & 0.25074 & -0.0092832 \\ 0.23298 & -0.19466 & 0.021741 & -0.0065573 \\ -0.38598 & 0.039126 & -3.1671 & 0.0041304 \\ 0.0019632 & 0.00067731 & -0.00013562 & -0.066801 \end{bmatrix}$$

$$\mathbf{A}_5 = \begin{bmatrix} -3.5287 & -0.060601 & 0.24784 & -0.0093278 \\ 0.19497 & -0.093286 & 0.017006 & 0.0019312 \\ 0.22212 & -0.080273 & -3.1614 & -0.0042428 \\ 0.001744 & -0.0025529 & 0.0072707 & -0.067233 \end{bmatrix}$$

$$\mathbf{A}_6 = \begin{bmatrix} -7.4489 & -0.12704 & 0.52318 & -0.0093278 \\ -0.18351 & -0.1982 & 0.095548 & 0.0014778 \\ 0.21344 & -0.11298 & -7.2861 & 0.00040939 \\ -0.012439 & 0.0026832 & -0.025864 & -0.066952 \end{bmatrix}$$

$$\mathbf{A}_7 = \begin{bmatrix} -3.2061 & -0.060529 & 0.24784 & -0.0093277 \\ 0.22649 & -0.092851 & 0.01727 & 0.0018016 \\ -0.38483 & -0.019544 & -3.1642 & 0.0068314 \\ 0.0023517 & -0.0027325 & 6.7334e-006 & -0.067149 \end{bmatrix}$$

$$\mathbf{A}_8 = \begin{bmatrix} -6.768 & -0.12689 & 0.52318 & -0.0093277 \\ -0.14191 & -0.19465 & -0.023172 & 0.0018026 \\ -0.81178 & -0.012738 & -6.0679 & 0.0068211 \\ 0.0043172 & 0.00067013 & 0.040657 & -0.06715 \end{bmatrix}$$

$$\mathbf{A}_9 = \begin{bmatrix} -1.6879 & 0.12793 & -0.25078 & 0.019598 \\ -0.727 & -0.07319 & -0.026022 & -0.003619 \\ 0.10826 & -0.031432 & -0.80806 & -0.005567 \\ 0.00097182 & -0.0027504 & 0.0047284 & -0.066801 \end{bmatrix}$$

$$\mathbf{A}_{10} = \begin{bmatrix} -3.5629 & 0.26819 & -0.52934 & 0.019598 \\ -0.91465 & -0.15344 & -0.05495 & -0.003619 \\ 0.22793 & -0.094274 & -1.7058 & -0.005567 \\ 0.0013385 & 0.00063963 & 0.0057541 & -0.066801 \end{bmatrix}$$

$$\mathbf{A}_{11} = \begin{bmatrix} -1.5351 & 0.12778 & -0.25078 & 0.019598 \\ -0.71206 & -0.073303 & -0.026022 & -0.0036189 \\ -0.18285 & 0.034225 & -0.80806 & 0.0041294 \\ 0.0012516 & -0.0026058 & -0.0023716 & -0.066797 \end{bmatrix}$$

$$\mathbf{A}_{12} = \begin{bmatrix} -3.2403 & 0.26787 & -0.52934 & 0.019598 \\ -0.88316 & -0.15367 & -0.054951 & -0.0036189 \\ -0.38597 & 0.043382 & -1.7058 & 0.0041294 \\ 0.0019634 & 0.00094337 & -0.0013455 & -0.066797 \end{bmatrix}$$

$$\mathbf{A}_{13} = \begin{bmatrix} -3.5287 & 0.12793 & -0.52322 & 0.019692 \\ -0.92106 & -0.07319 & -0.058507 & 0.0047537 \\ 0.22099 & -0.083177 & -1.7026 & -0.0029125 \\ 0.0016756 & -0.0027503 & 0.0059171 & -0.067149 \end{bmatrix}$$

$$\mathbf{A}_{14} = \begin{bmatrix} -7.4489 & 0.26819 & -1.1045 & 0.019692 \\ -1.3492 & -0.15343 & -0.12363 & 0.0047547 \\ 0.72194 & -0.14614 & -3.593 & -0.0029229 \\ 0.018292 & 0.00063245 & 0.0083449 & -0.06715 \end{bmatrix}$$

$$\mathbf{A}_{15} = \begin{bmatrix} -3.2061 & 0.12778 & -0.52322 & 0.019692 \\ -0.88965 & -0.073303 & -0.058507 & 0.0047076 \\ -0.38483 & -0.01752 & -1.7026 & 0.0073033 \\ 0.0023519 & -0.0026058 & -0.0011826 & -0.067117 \end{bmatrix}$$

$$\mathbf{A}_{16} = \begin{bmatrix} -6.768 & 0.26787 & -1.1045 & 0.019692 \\ -1.2579 & -0.15367 & -0.12336 & 0.0047076 \\ -0.81291 & -0.0083629 & -3.5957 & 0.0073033 \\ 0.0042487 & 0.00094338 & 0.0010809 & -0.067117 \end{bmatrix}$$