

Deterministic model derivation and model reduction of an activator-repressor genetic oscillator

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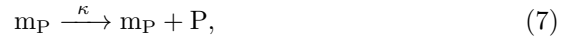
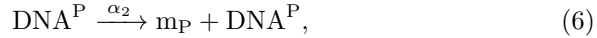
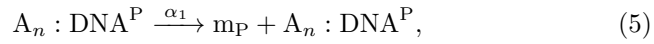
Introduction

This note contains the derivation of the deterministic model and model reduction using singular perturbation used in the submission “Loading as a design parameter for genetic circuits” to the 2016 American Control Conference by the same authors.

Derivation of model

A deterministic ODE model of an activator-repressor (A-R) genetic oscillator is derived considering the biochemical reactions of activation, repression, multimerization, transcription, and translation of a generic protein (P) which, due to the symmetry of the model (both proteins are activated by A and repressed by R) can be used to describe the evolution of the concentration of both A and

R. These reactions are given by:



Let A and R multimerize with cooperativity n and m, with forward rates of β_A, β_R and reverse rates of β'_A, β'_R , respectively, leading to reactions (1)-(2). Since activation and repression are assumed to take place at the transcriptional level, the complex formed by the reversible reaction (with forward rate a^* and reverse rate d^*) between R_m and DNA promoter (DNA^P), denoted $R_m:\text{DNA}^P$, does not contribute to transcription and effectively sequesters free DNA^P , as given in (3). Conversely, $A_n:\text{DNA}^P$ is the complex formed by the reversible reaction (with forward rate a' and reverse rate d') between A_n and DNA^P , as shown in (4). This complex undergoes translation at rate α_1 to produce an mRNA molecule, leading to (5). The model also assumes that some transcription can occur without A bound to DNA^P (i.e., transcriptional leakiness), described by (6). Translation occurs at a rate κ , given in (7), and mRNA and protein decay at a rate δ and γ , respectively, given in (8)-(9). The ODE model for the mRNA and protein dynamics is given by:

$$\begin{aligned} \dot{m}_P &= \alpha_1[A_n : \text{DNA}^P] + \alpha_2[\text{DNA}^P] - \delta m_P, \\ \dot{P} &= \kappa m_P - \gamma P. \end{aligned} \quad (10)$$

Assuming the total concentration of DNA is constant, the following conservation law holds:

$$\text{DNA}_{tot} = \text{DNA}^P + [R_m : \text{DNA}^P] + [A_n : \text{DNA}^P].$$

Assuming complex formation occurs significantly faster than mRNA and protein dynamics [1], setting their respective rate equations at quasi-steady state (i.e., $\dot{A}_n, \dot{R}_m, [A_n : \text{DNA}^P], [R_m : \text{DNA}^P] = 0$) and solving for $[A_n:\text{DNA}^P]$ and $[\text{DNA}^P]$

in terms of A, R yields:

$$[A_n : \text{DNA}^P] = \frac{\frac{\alpha' \beta_A}{d' \beta_{A'}} \text{DNA}_{tot} A^n}{1 + \frac{\alpha' \beta_A}{d' \beta_{A'}} A^n + \frac{\alpha^* \beta_R}{d^* \beta_{R'}} R^m}, \quad (11)$$

$$[\text{DNA}^P] = \frac{\text{DNA}_{tot}}{1 + \frac{\alpha' \beta_A}{d' \beta_{A'}} A^n + \frac{\alpha^* \beta_R}{d^* \beta_{R'}} R^m}. \quad (12)$$

Equation (10) represents the dynamics of a general mRNA and protein system with transcriptional activation and repression by A and R, respectively. Substituting (11)-(12) in (10) and then using the subscripts ‘‘R’’ or ‘‘A’’ to denote parameters corresponding to R or A production and decay, respectively yields the final model equations:

$$\begin{aligned} \dot{m}_A &= \frac{\alpha(A/k_A)^n + \alpha_0}{1 + (A/k_A)^n + (R/k_R)^m} - \delta_A m_A, \\ \dot{m}_R &= \frac{\alpha(A/k_A)^n + \alpha_0}{1 + (A/k_A)^n + (R/k_R)^m} - \delta_R m_R, \\ \dot{A} &= \kappa_A m_A - \gamma_A A, \\ \dot{R} &= \kappa_R m_R - \gamma_R R. \end{aligned} \quad (13)$$

Model reduction via singular perturbation of system with load to A

We consider A transcriptionally regulating downstream promoter sites. Let the free promoter sites be denoted as C_{10} and the sites bound to A be denoted as C_{11} . Since DNA does not decay, the total concentration of promoter sites is conserved, that is $C_{10} + C_{11} = C_{t1}$, where C_{t1} represents the total concentration of the free and bound promoter sites. The complex formation reaction is given by: $C_{10} + A \xrightleftharpoons[d]{a} C_{11}$, leading to the three-state system:

$$\begin{aligned} \dot{A} &= \frac{\kappa_A}{\delta_A} \frac{\alpha(A/k_A)^n + \alpha_0}{1 + (A/k_A)^n + (R/k_R)^m} - \gamma_A A - \dot{C}_{11}, \\ \dot{R} &= \frac{\kappa_R}{\delta_R} \frac{\alpha(A/k_A)^n + \alpha_0}{1 + (A/k_A)^n + (R/k_R)^m} - \gamma_R R, \\ \dot{C}_{11} &= a(C_{t1} - C_{11})A - dC_{11}. \end{aligned} \quad (14)$$

In order to analyze how the eigenvalues of the linearized system change due to the addition of C_{t1} , we consider a reduced order model. Using the assumption that complex formation (C_{11}) occurs relatively faster than protein dynamics (A,R) [1], the three-state system can be reduced to two states. To this end, we employ singular perturbation and introduce the new (slow) variable Z , defined as $Z = A + C_{11}$. Rewrite the system by defining $\epsilon = \frac{\gamma_A}{d}$, $K_{d1} = \frac{d}{a}$, and $a = \frac{\gamma_A}{\epsilon K_{d1}}$.

Substituting these expressions into (14) yields the system in standard singular perturbation form given by:

$$\begin{aligned}\dot{Z} &= \frac{\kappa_A}{\delta_A} \frac{\alpha \left(\frac{Z-C_{11}}{k_A}\right)^n + \alpha_0}{1 + \left(\frac{Z-C_{11}}{k_A}\right)^n + (R/k_R)^m} - \gamma_A(Z - C_{11}), \\ \dot{R} &= \frac{\kappa_R}{\delta_R} \frac{\alpha \left(\frac{Z-C_{11}}{k_A}\right)^n + \alpha_0}{1 + \left(\frac{Z-C_{11}}{k_A}\right)^n + (R/k_R)^m} - \gamma_R R, \\ \epsilon \dot{C}_{11} &= \frac{\gamma_A}{K_{d1}} (C_{t1} - C_{11})(Z - C_{11}) - \gamma_A C_{11}.\end{aligned}\quad (15)$$

Setting $\epsilon = 0$ and solving for C_{11} in terms of A yields the slow manifold:

$$C_{11} = \frac{C_{t1}A/K_{d1}}{1 + A/K_{d1}} = g_1(A),$$

which can be shown to be locally exponentially stable [2]. Since $Z = A + C_{11}$, we have $\dot{Z} = \dot{A} + \dot{C}_{11}$, and so:

$$\dot{Z} = \dot{A} + \frac{dg_1(A)}{dA} \dot{A}.$$

Solving for \dot{A} yields:

$$\begin{aligned}\dot{A} &= \frac{\dot{Z}}{1 + \frac{dg_1(A)}{dA}}, \\ &= \left(\frac{\kappa_A}{\delta_A} \frac{\alpha \left(\frac{A}{k_A}\right)^n + \alpha_0}{1 + \left(\frac{A}{k_A}\right)^n + \left(\frac{R}{k_R}\right)^m} - \gamma_A A \right) \frac{\left(1 + \frac{A}{K_{d1}}\right)^2}{\left(1 + \frac{A}{K_{d1}}\right)^2 + \frac{C_{t1}}{K_{d1}}}.\end{aligned}$$

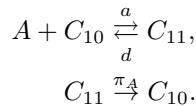
The resulting reduced model of the clock with load on A is thus given by:

$$\begin{aligned}\dot{A} &= \frac{\left(1 + \frac{A}{K_{d1}}\right)^2}{\left(1 + \frac{A}{K_{d1}}\right)^2 + \frac{C_{t1}}{K_{d1}}} \left(\frac{\kappa_A}{\delta_A} \frac{\alpha \left(\frac{A}{k_A}\right)^n + \alpha_0}{1 + \left(\frac{A}{k_A}\right)^n + \left(\frac{R}{k_R}\right)^m} - \gamma_A A \right), \\ \dot{R} &= \frac{\kappa_R}{\delta_R} \frac{\alpha (A/k_A)^n + \alpha_0}{1 + (A/k_A)^n + (R/k_R)^m} - \gamma_R R.\end{aligned}$$

Model reduction of the system with load on R can be similarly derived.

Model reduction via singular perturbation of system with load and complex decay

We consider load to A transcriptionally regulating downstream promoter sites that decay at a constant rate when bound with A. The modified load reactions to A are given by:



The dynamics of the three-state system have changed to ($f_1(A, R) = \frac{\kappa_A}{\delta_A} \frac{\alpha(A/k_A)^n + \alpha_0}{1+(A/k_A)^n+(R/k_R)^m}$, $f_2(A, R) = \frac{\kappa_R}{\delta_R} \frac{\alpha(A/k_A)^n + \alpha_0}{1+(A/k_A)^n+(R/k_R)^m}$):

$$\begin{aligned}\dot{A} &= f_1(A, R) - \gamma_A A + dC_{11} - aA(C_{t1} - C_{11}), \\ \dot{R} &= f_2(A, R) - \gamma_R R, \\ \dot{C}_{11} &= aA(C_{t1} - C_{11}) - (d + \pi_A)C_{11}.\end{aligned}$$

Introduce a slow (X) and fast (Y) variable, given by:

$$\begin{aligned}X &= A + C_{11}, \\ Y &= \frac{d}{d + \pi_A} C_{11}.\end{aligned}$$

The three-state system is thus now given by ($p_A = \frac{d}{d + \pi_A}$):

$$\begin{aligned}\dot{X} &= f_1(X - \frac{Y}{p_A}, R) - \gamma_A(X - \frac{Y}{p_A}) - \frac{\pi_A Y}{p_A}, \\ \dot{Y} &= p_A a(X - \frac{Y}{p_A})(C_{t1} - \frac{Y}{p_A}) - d \frac{Y}{p_A}, \\ \dot{R} &= f_2(X - \frac{Y}{p_A}, R) - \gamma_R R.\end{aligned}$$

Define $\epsilon = \frac{\gamma_A}{d}$, $K_{d1} = \frac{d}{a}$. This leads to $d = \frac{\gamma_A}{\epsilon}$, $a = \frac{\gamma_A}{\epsilon K_{d1}}$, and:

$$\epsilon \dot{Y} = \frac{\gamma_A p_A}{K_{d1}} A(C_{t1} - \frac{Y}{p_A}) - \frac{\gamma_A Y}{K_{d1}}.$$

Set $\epsilon = 0$ to find the slow manifold:

$$\begin{aligned}Y &= \frac{p_A^2}{K_{d1}} A(C_{t1} - \frac{Y}{p_A}), \\ &= \frac{p_A^2 C_{t1} A}{K_{d1} + p_A A} = h_1(A).\end{aligned}$$

Solving for \dot{A} :

$$\begin{aligned}X &= A + \frac{Y}{p_A}, \\ \dot{X} &= \dot{A} + \frac{1}{p_A} \frac{\partial h_1}{\partial A} \dot{A} \implies \dot{A} = \frac{\dot{X}}{1 + \frac{1}{p_A} \frac{\partial h_1}{\partial A}}, \\ \dot{A} &= \frac{f_1(A, R) - \gamma_A A - \frac{\pi_A p_A C_{t1} A}{K_{d1} + p_A A}}{1 + \frac{p_A K_{d1} C_{t1}}{(K_{d1} + p_A A)^2}}.\end{aligned}$$

Model reduction of the system with load on R and complex decay can be similarly derived.

References

- [1] U. Alon, “An Introduction to Systems Biology: Design Principles of Biological Circuits,” *Chapman & Hall/CRC*, 2007.
- [2] D. del Vecchio and R. Murray, “Biomolecular Feedback Systems,” *Princeton University Press*, 2014.