An Oscillating Reaction Network With an Exact Closed-Form Time-Domain Solution: Solution Derivation

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1 Preliminaries

This write-up provides details on the derivation of the time domain solution for the reaction network depicted in Fig. 1. Recall that the reaction network is constructed to be a system of linear ODEs. As such, the time domain solution is an initial value problem (IVP).

The reaction network has 8 parameters. There are 6 kinetic constants, $k_i,\ i \in \{1, 2, 3, 4, 5, 6\}$. And there are two initial concentrations, $x_n(0),\ n \in \{1, 2\}$, where $x_n(0)$ is the initial concentration for S_n.

Because the reaction network can be described as a system of linear system (by construction), we know that oscillations are sinusoids. Let $x_n(t)$ be the concentration of species S_n at time t. Then, an oscillating solution has the form

$$x_n(t) = \alpha_n sin(\theta_n t + \phi_n) + \omega_n,$$

where α_n is the amplitude of the sinusoid for S_n, θ_n is its frequency, ϕ_n is its phase, and ω_n is the DC offset (the mean value of the sinusoid over time). It turns out that both species have the same frequency, as we show shortly. So, $\theta_n = \theta$, and there are just 7 parameters. We refer to $\alpha_n, \theta, \phi_n, \omega_n$ as the **oscillation characteristics (OC)** of the reaction network.

We use the following notation:

- $\mathbf{A}$ - Jacobian matrix
- α_n - amplitude of oscillation for species n
- $\mathbf{c} = \begin{pmatrix} c_1 \\ c_2 \end{pmatrix}$ - constants associated with the homogeneous solution
- Δ - $det\mathbf{A})$
- $\mathbf{F}(t)$ - fundamental matrix
- i - indexes constants
- k_i, k_d - positive constant
- K - number of constants
- λ - eigenvalue
- n - indexes species
- N - number of species
- ω_n - offset of species n
- ϕ_n - phase in radians
- t - time
- τ - $tr(\mathbf{A})$
- θ - frequency in radians
- $\mathbf{u}$ - forced input (kinetic constants for zeroth order rates) $\mathbf{x}$ $(N \times 1)$ is the state vector

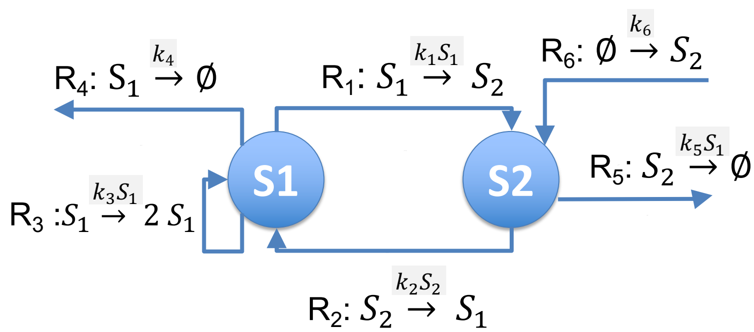

Figure 1 Reaction network that creates oscillations in the chemical species S_1, S_2. The reaction network is designed so that its time domain solution is a system of linear differential equations. The text describes constraints on the kinetic constants (k_i) and initial conditions of the chemical species to create an oscillator such that species concentrations are non-negative, a requirement for biological feasibility.

- $\dot{\mathbf{x}}(t)$ - derivative w.r.t. time of $\mathbf{x}$
- x_n (t) - time varying concentration of species n

Since we have constructed the reaction network so that the dynamics can be described as a system of linear ODEs, it can be described using the vector differential equation:

$$\dot{\mathbf{x}} = \mathbf{A}\mathbf{x} + \mathbf{u}$$

where the Jacobian matrix is $\mathbf{A} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}$

2 Jacobian and Eigenvalues

Here, we calculate the eigenvalues for the reaction network described in the text. If there is an oscillating solution for this system, then the eigenvalues of $\mathbf{A}$ must be pure imaginary. Since this is a two state system, this means that if θi is an eigenvalue, then $-\theta i$ must also be an eigenvalue. This means that $\theta_1 = \theta = \theta_2$, which justifies our previous claim.

Next we develop the conditions for the Jacobian $\mathbf{A}$ to have a pure imaginary eigenvalues. The determinant of $\mathbf{A}$ is $det(\mathbf{A}) = a_{11}a_{22} - a_{12}a_{21} = \Delta$. The trace of $\mathbf{A}$ is $tr(\mathbf{A}) = a_{11} + a_{22} = \tau$. So, the eigenvalues λ are in $\frac{1}{2}\left(-\tau \pm \sqrt{\tau^2 - 4\Delta}\right)$. We get pure imaginary eigenvalues if the following constraints hold:

- $\tau = 0$
- $\Delta > 0$.

Now, we analyze $\mathbf{A}$ for the reaction network.

$$\mathbf{A} = \begin{pmatrix} k_3 - k_1 & k_2 \\ k_1 - k_5 & -k_2 \end{pmatrix}$$

and

$$\mathbf{u} = \begin{pmatrix} -k_4 \\ k_6 \end{pmatrix}$$

So the trace and determinant are:

$$\begin{aligned} \tau &= k_3 - k_1 - k_2 \\ \Delta &= (k_3 - k_1)(-k_2) - k_2(k_1 - k_5) \\ &= k_2(k_5 - k_3) \end{aligned}$$

To obtain purely imaginary solutions, we require that $\tau = 0$ and $\Delta > 0$. The former implies that $k_3 = k_1 + k_2$. The latter implies that that $k_5 > k_3$. We define $k_d = k_5 - k_3 > 0$ Applying the foregoing to the $\mathbf{A}$ matrix, we first note that

$$\begin{aligned} k_1 - k_5 = & \quad k_1 - k_3 - k_d \\ = & \quad k_3 - k_2 - k_3 - k_d \\ = & \quad -k_2 - k_d \end{aligned}$$

Applying the constraints, we see that

$$\mathbf{A} = \begin{pmatrix} k_2 & k_2 \\ -k_2 - k_d & -k_2 \end{pmatrix}$$

Observe that $\Delta = k_2 k_d$. As a result $\theta = \pm\sqrt{\Delta} = \pm\sqrt{k_2 k_d}$. Hereafter, we drop the $\pm$.

3 Eigenvectors and Fundamental Matrix

We find the eigenvectors of $\mathbf{A}$ as an intermediate step to finding the time domain solution.
First, observe that that since $k_d > 0$, $\mathbf{A}$ is nonsingular, and so we can calculate eigenvectors directly.

$$\mathbf{w}_1 = \begin{pmatrix} -\frac{k_2}{k_2+k_d} + \frac{i\theta}{k_2+k_d} \\ 1 \end{pmatrix}$$

for the eigenvalue $\lambda_1 = -\sqrt{k_d k_2}$.

$$\mathbf{w}_2 = \begin{pmatrix} -\frac{k_2}{k_2+k_d} - \frac{i\theta}{k_2+k_d} \\ 1 \end{pmatrix}$$

for the eigenvalue $\lambda_1 = \sqrt{k_d k_2}$.

The solution to the initial value problem is a sum of eigenvectors multiplied by their eigenvalues. The **fundamental matrix F** of a system of linear ODEs has a column for each eigenvector multiplied by its eigenvalue, $\mathbf{w}_n e^{\lambda_n}$.

Rather than writing $\mathbf{F}(t)$ immediately, we first observe that it can be transformed into a real valued matrix. We can use the decomposition of eigenvectors into real and imaginary parts along with Euler formulas to express $\mathbf{F}(t)$ in terms of sin and cos. We do some further simplifications by taking linear combinations of the columns of the fundamental matrix, transformations that change the basis for the solution space but not the solution space itself.

$$\mathbf{F}(t) = \begin{pmatrix} -\frac{k_2 \cos(t\theta)}{k_2+k_d} + \frac{\theta \sin(t\theta)}{k_2+k_d} & -\frac{k_2 \sin(t\theta)}{k_2+k_d} - \frac{\theta \cos(t\theta)}{k_2+k_d} \\ \cos(t\theta) & \sin(t\theta) \end{pmatrix}$$

4 Solving the Initial Value Problem

We proceed in the usual way to solve an IVP:

1 Find the solution to the homogeneous system $\dot{\mathbf{x}}^H(t) = \mathbf{A}\mathbf{x}^H(t)$.

2 Find a particular solution such that $\dot{x}^P(t) = \mathbf{A}\mathbf{x}^P(t) + \mathbf{u}$

3 $\mathbf{x}(t) = \begin{pmatrix} c_1 x_1^H(t) \\ c_2 x_2^H(t) \end{pmatrix} + \mathbf{x}^P(t)$, where $\mathbf{c}$ is determined by the initial conditions.

$\mathbf{x}^H(t) = \mathbf{F}(t)\mathbf{c}$, where $\mathbf{c}$ is a vector of unknown constants that are determined based on initial conditions, intitial conditions are the initial concentrations of S_1, S_2.

We assume that $\mathbf{x}^P(t) = \mathbf{F}(t)\mathbf{v}$. This means that

$$\begin{aligned} \dot{\mathbf{x}}^P(t) &= \dot{\mathbf{F}}(t)\mathbf{v} + \mathbf{F}(t)\dot{\mathbf{v}} \\ \dot{\mathbf{F}}(t)\mathbf{v} + \mathbf{F}(t)\dot{\mathbf{v}} &= \mathbf{A}\mathbf{F}(t)\mathbf{v} + \mathbf{u} \\ \mathbf{A}\mathbf{F}(t)\mathbf{v} + \mathbf{F}(t)\dot{\mathbf{v}} &= \mathbf{A}\mathbf{F}(t)\mathbf{v} + \mathbf{u} \\ \mathbf{F}(t)\dot{\mathbf{v}} &= \mathbf{u} \end{aligned}$$

$$\mathbf{v} = \int \left(\mathbf{F}^{-1}(t)\mathbf{u}\right) dt$$

Calculating this integral (with help from the python package `sympy`), we have

$$\begin{aligned} \mathbf{x}^P(t) &= \mathbf{F}(t)\mathbf{v} \\ &= \begin{pmatrix} \frac{-k_2^2 k_4 \cos(t\theta) - k_2^2 k_4 + k_2^2 k_6 \cos(t\theta) + k_2^2 k_6 - k_2 k_4 k_d \cos(t\theta) - k_2 k_4 k_d + k_2 k_4 \theta \sin(t\theta) - k_2 k_6 \theta \sin(t\theta) + k_4 k_d \theta \sin(t\theta) + k_6 \theta^2}{\theta^2 (k_2+k_d)} \\ \frac{k_2 k_4 \cos(t\theta) + k_2 k_4 - k_2 k_6 \cos(t\theta) - k_2 k_6 + k_4 k_d \cos(t\theta) + k_4 k_d}{\theta^2} \end{pmatrix} \end{aligned}$$

$$\begin{aligned}
\mathbf{x}(t) &= \mathbf{x}^H(t) + \mathbf{x}^P(t) \\
&= \begin{pmatrix} -\frac{k_2 \cos(t\theta)}{k_2+k_d} + \frac{\theta \sin(t\theta)}{k_2+k_d} & -\frac{k_2 \sin(t\theta)}{k_2+k_d} - \frac{\theta \cos(t\theta)}{k_2+k_d} \\ \cos(t\theta) & \sin(t\theta) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \end{pmatrix} \\
&\quad + \begin{pmatrix} \frac{-k_2^2 k_4 \cos(t\theta) - k_2^2 k_4 + k_2^2 k_6 \cos(t\theta) + k_2^2 k_6 - k_2 k_4 k_d \cos(t\theta) - k_2 k_4 k_d + k_2 k_4 \theta \sin(t\theta) - k_2 k_6 \theta \sin(t\theta) + k_4 k_d \theta \sin(t\theta) + k_6 \theta^2}{\theta^2 (k_2+k_d)} \\ \frac{k_2 k_4 \cos(t\theta) + k_2 k_4 - k_2 k_6 \cos(t\theta) - k_2 k_6 + k_4 k_d \cos(t\theta) + k_4 k_d}{\theta^2} \end{pmatrix}
\end{aligned}$$

We find c_1, c_2 by solving

$$\begin{aligned}
\mathbf{x}(0) &= \begin{pmatrix} x_1(0) \\ x_2(0) \end{pmatrix} \\
&= \begin{pmatrix} -\frac{k_2 \cos(t\theta)}{k_2+k_d} + \frac{\theta \sin(t\theta)}{k_2+k_d} & -\frac{k_2 \sin(t\theta)}{k_2+k_d} - \frac{\theta \cos(t\theta)}{k_2+k_d} \\ \cos(t\theta) & \sin(t\theta) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \end{pmatrix} \\
&\quad + \begin{pmatrix} \frac{-k_2^2 k_4 \cos(t\theta) - k_2^2 k_4 + k_2^2 k_6 \cos(t\theta) + k_2^2 k_6 - k_2 k_4 k_d \cos(t\theta) - k_2 k_4 k_d + k_2 k_4 \theta \sin(t\theta) - k_2 k_6 \theta \sin(t\theta) + k_4 k_d \theta \sin(t\theta) + k_6 \theta^2}{\theta^2 (k_2+k_d)} \\ \frac{k_2 k_4 \cos(t\theta) + k_2 k_4 - k_2 k_6 \cos(t\theta) - k_2 k_6 + k_4 k_d \cos(t\theta) + k_4 k_d}{\theta^2} \end{pmatrix}
\end{aligned}$$

The result is

$$\begin{aligned}
x_1(t) &= \frac{1}{\theta} \left(-\frac{k_2 \sin(t\theta)}{k_2 + k_d} - \frac{\theta \cos(t\theta)}{k_2 + k_d} \right) (-k_2 x_1(0) - k_2 x_2(0) + k_6 - k_d x_1(0)) \\
&\quad + \frac{1}{\theta^2} \left(-\frac{k_2 \cos(t\theta)}{k_2 + k_d} + \frac{\theta \sin(t\theta)}{k_2 + k_d} \right) \left(-2k_2 k_4 + 2k_2 k_6 - 2k_4 k_d + \theta^2 x_2(0) \right) \\
&\quad + \frac{1}{\theta^2 (k_2 + k_d)} \left(-k_2^2 k_4 \cos(t\theta) - k_2^2 k_4 + k_2^2 k_6 \cos(t\theta) + k_2^2 k_6 + k_6 \theta^2 - k_2 k_4 k_d \right) \\
&\quad + \frac{1}{\theta^2 (k_2 + k_d)} (-k_2 k_4 k_d \cos(t\theta) + k_2 k_4 \theta \sin(t\theta) - k_2 k_6 \theta \sin(t\theta) + k_4 k_d \theta \sin(t\theta))
\end{aligned} \tag{1}$$

$$\begin{aligned}
x_2(t) &= \frac{1}{\theta} (-k_2 x_1(0) - k_2 x_2(0) + k_6 - k_d x_1(0)) \sin(t\theta) \\
&\quad + \frac{1}{\theta^2} \left(-2k_2 k_4 + 2k_2 k_6 - 2k_4 k_d + \theta^2 x_2(0) \right) \cos(t\theta) \\
&\quad + \frac{1}{\theta^2} (k_2 k_4 \cos(t\theta) + k_2 k_4 - k_2 k_6 \cos(t\theta) - k_2 k_6 + k_4 k_d \cos(t\theta) + k_4 k_d)
\end{aligned} \tag{2}$$

5 Formulas for Oscillation Characteristics

Our final task is to restructure $\mathbf{x}(t)$ to isolate the oscillation characteristics $\theta, \alpha_n, \phi_n, \omega_n$. From this The first step is to factor Eq. (1) and Eq. (2) so that

$$x_n(t) = a_n \cos(\theta t) + b_n \sin(\theta t) + \omega_n \tag{3}$$

That is, the sum of terms that are not multiplied by $\cos, \sin$ will constitute the DC offset. From Eq. (3), we calculate α_n, ϕ_n using the the trigonometric equality $a_n cos(t\theta) + b_n sin(t\theta) = \sqrt{a_n^2 + b_n^2} sin(t\theta + tan^{-1} \frac{a_n}{b_n})$. Thus, $\alpha_n = \sqrt{a_n^2 + b_n^2}$, and $\phi_n = tan^{-1} \frac{a_n}{b_n}$.
The results are:

- $\theta = \sqrt{k_2 k_d}$
- $\alpha_1 = \frac{\sqrt{\nu_1}}{\theta^2(k_2+k_d)}$

$$\begin{aligned}\nu_1 &= \theta^2\left(k_2^2x_1(0)+k_2^2x_2(0)-k_2k_4+k_2k_dx_1(0)-k_4k_d+\theta^2x_2(0)\right)^2 \\ &\quad+\left(k_2^2k_4-k_2^2k_6+k_2k_4k_d+k_2\theta^2x_1(0)-k_6\theta^2+k_d\theta^2x_1(0)\right)^2\end{aligned}$$

- $\alpha_2 = \frac{\sqrt{\theta^2(k_2x_1(0)+k_2x_2(0)-k_6+k_dx_1(0))^2+(k_2k_4-k_2k_6+k_4k_d-\theta^2x_2(0))^2}}{\theta^2}$
- $\phi_1 = \tan^{-1}\left(\frac{k_2^2k_4-k_2^2k_6+k_2k_4k_d+k_2\theta^2x_1(0)-k_6\theta^2+k_d\theta^2x_1(0)}{\theta\left(k_2^2x_1(0)+k_2^2x_2(0)-k_2k_4+k_2k_dx_1(0)-k_4k_d+\theta^2x_2(0)\right)}\right)+\pi_1$
- $\phi_2 = \tan^{-1}\left(\frac{k_2k_4-k_2k_6+k_4k_d-\theta^2x_2(0)}{\theta(k_2x_1(0)+k_2x_2(0)-k_6+k_dx_1(0))}\right)+\pi_2$
- $\omega_1 = \frac{-k_2^2k_4+k_2^2k_6-k_2k_4k_d+k_6\theta^2}{k_2\theta^2+k_d\theta^2}$
- $\omega_2 = \frac{k_2k_4-k_2k_6+k_4k_d}{\theta^2}$

π_1, π_2 arise from techical conditions related to taking the inverse of the tangent function. Tangent is only defined over a range of π since it is calculated from the ration of a_n to b_n. Hence we cannot distinguish between to positive values of these number, and two negative values of these numbers.

$$\begin{aligned}cond_1 &= \frac{k_2^2x_1(0)}{k_2\theta+k_d\theta}+\frac{k_2^2x_2(0)}{k_2\theta+k_d\theta}+\frac{k_2k_4\theta}{k_2\theta^2+k_d\theta^2}-\frac{2k_2k_4}{k_2\theta+k_d\theta}-\frac{k_2k_6\theta}{k_2\theta^2+k_d\theta^2} \\ &\quad+\frac{k_2k_6}{k_2\theta+k_d\theta}+\frac{k_2k_dx_1(0)}{k_2\theta+k_d\theta}+\frac{k_4k_d\theta}{k_2\theta^2+k_d\theta^2}-\frac{2k_4k_d}{k_2\theta+k_d\theta}+\frac{\theta x_2(0)}{k_2+k_d}\end{aligned}$$

$$\begin{aligned}\pi_1 &= \pi \text{ if } cond_1 < 0 \\ &= 0 \text{ otherwise}\end{aligned}$$

$$cond_2 = \frac{k_2x_1(0)}{\theta}+\frac{k_2x_2(0)}{\theta}-\frac{k_6}{\theta}+\frac{k_dx_1(0)}{\theta}$$

$$\begin{aligned}\pi_2 &= \pi \text{ if } cond_2 > 0 \\ &= 0 \text{ otherwise}\end{aligned}$$