Modeling a Genetic Clock: ODE Formulation and Simulation

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Problem 1: ODE Model Formulation with (k_b=50)

We consider a genetic clock model in which a gene is transcribed into mRNA, which is then translated into protein. The protein in turn promotes the production of a repressor, which binds to the gene's DNA, thereby inhibiting transcription. In this model we allow for degradation of the repressor in both free and bound states. Let the variables be:

- $M(t)$: Concentration of mRNA,
- $P(t)$: Concentration of protein,
- $F(t)$: Concentration of free repressor,
- $D_R(t)$: Concentration of repressed (bound) DNA,
- $D_A(t)$: Concentration of free (active) DNA.

The total DNA is conserved:

$$D_A(t) + D_R(t) = D_T,$$

with D_T given in nM.

The reaction scheme is modeled as follows:

1. **Transcription:** $D_A \xrightarrow{a_M} D_A + M$.
   ODE: $\dfrac{dM}{dt} = a_M\, D_A - b_M\, M.$
2. **Translation:** $M \xrightarrow{a_P} M + P$.
   ODE: $\dfrac{dP}{dt} = a_P\, M - b_P\, P.$
3. **Repressor Production:** $P \xrightarrow{a_F} P + F$.
   ODE: $\dfrac{dF}{dt} = a_F\, P - b_F\, F + k_b\, D_R - k_f\, D_A\, F.$
4. **DNA Binding/Unbinding:**

- Binding: $D_A + F \xrightarrow{k_f} D_R$.
- Unbinding: $D_R \xrightarrow{k_b} D_A + F$.
- Bound repressor degradation: $D_R \xrightarrow{b_F} D_A$.

ODEs:

$$\frac{dD_R}{dt} = k_f\, D_A\, F - k_b\, D_R - b_F\, D_R,$$
$$\frac{dD_A}{dt} = -k_f\, D_A\, F + k_b\, D_R + b_F\, D_R.$$

Thus, the complete ODE system is:

$$\frac{dM}{dt} = a_M\, D_A - b_M\, M, \tag{1}$$
$$\frac{dP}{dt} = a_P\, M - b_P\, P, \tag{2}$$
$$\frac{dF}{dt} = a_F\, P - b_F\, F + k_b\, D_R - k_f\, D_A\, F, \tag{3}$$
$$\frac{dD_R}{dt} = k_f\, D_A\, F - k_b\, D_R - b_F\, D_R, \tag{4}$$
$$\frac{dD_A}{dt} = -k_f\, D_A\, F + k_b\, D_R + b_F\, D_R, \tag{5}$$

with the conservation constraint:

$$D_A + D_R = D_T.$$

The initial conditions are specified as:

$$M(0) = 0, \quad P(0) = 0, \quad F(0) = 0, \quad D_R(0) = 0, \quad D_A(0) = D_T.$$

Interpretation of Simulation Results

After numerically solving the above system (using `solve_ivp` in Python) over an appropriate time span, the simulation produces oscillatory behavior in $M(t)$ and $P(t)$. The key observations from the resulting plot are:

- **Sustained Oscillations:** Both M (mRNA) and P (protein) exhibit regular oscillations over time. This indicates that the negative feedback loop, which is delayed by the degradation of repressor even in the bound state, is sufficiently strong to produce rhythmic behavior.

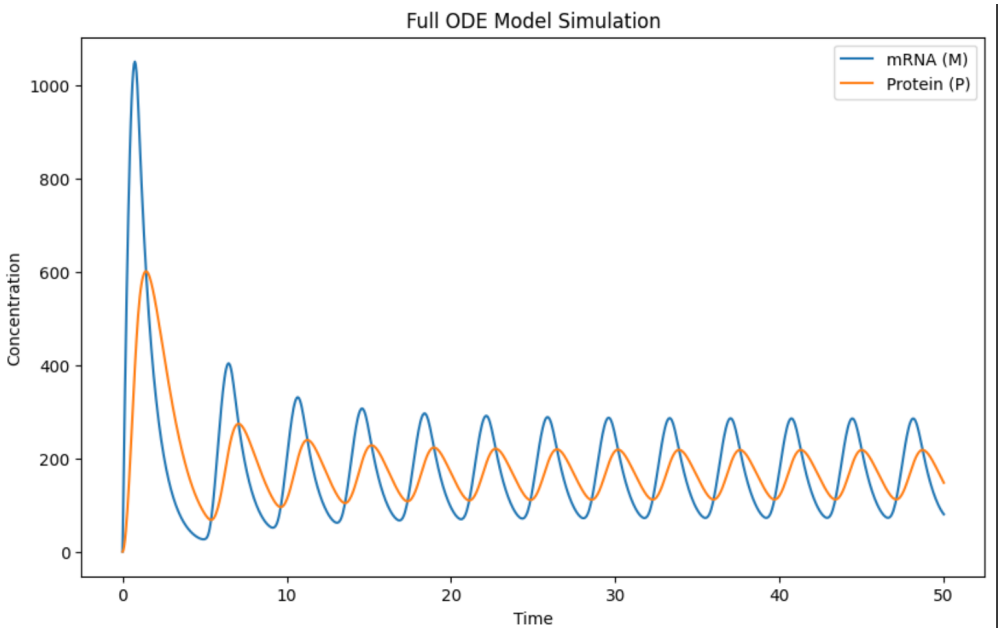

Figure 1: Simulated time courses of mRNA (M) and protein (P). The sustained oscillations, indicating a robust genetic clock behavior.

Problem 2: Effect of Dissociation Constant on Oscillatory Dynamics

To investigate how the stability of the DNA–repressor complex influences the oscillatory behavior of the system, we varied the unbinding rate k_b while keeping the binding rate k_f constant. Recall that the dissociation constant is defined as

$$K_d = \frac{k_b}{k_f}.$$

By increasing k_b from 50 to 200, K_d increases from 0.25 to 1.

Figure 4 shows the simulation results for M (mRNA) and P (Protein) under these two conditions.

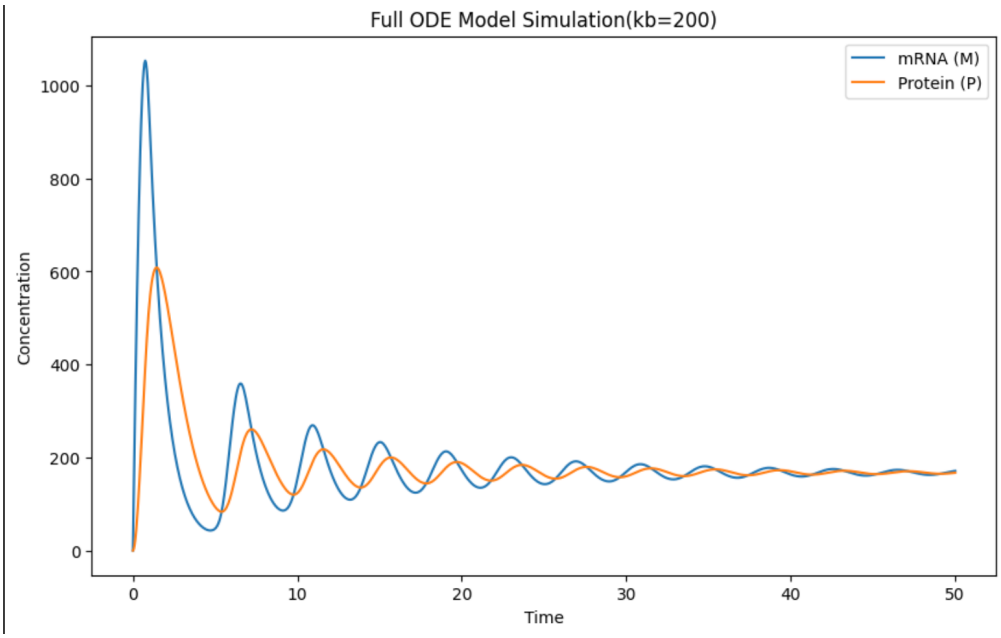

Figure 2: Simulated time courses of mRNA (M) and protein (P)

Observations and Interpretation

- **Stability of the DNA–Repressor Complex:** With $k_b = 50$ (i.e., $K_d = 0.25$), the DNA–repressor complex is more stable, meaning that once F binds the free DNA D_A, it remains bound longer. This leads to a stronger and more prolonged negative feedback on transcription.
- **Transient and Steady-State Behavior:** Although both simulations eventually reach a steady state, the transient dynamics differ: the system with a lower K_d exhibits more pronounced oscillations, whereas the higher K_d case shows damped oscillations with reduced amplitude.

These findings suggest that the stability of the DNA–repressor complex is crucial for generating strong oscillatory behavior. A lower dissociation constant (i.e., more stable binding) supports a sustained oscillations, while a higher dissociation constant leads to a quicker release of the repressor and damped oscillations.

Problem 3: Applying sQSSA to the DNA Equations

We begin with the two ODEs for D_R (the DNA–repressor complex) and D_A (the free DNA):

$$\frac{dD_R}{dt} = k_f\, D_A\, F - k_b\, D_R - b_F\, D_R, \quad \frac{dD_A}{dt} = -k_f\, D_A\, F + k_b\, D_R + b_F\, D_R.$$

Under the *standard quasi-steady state approximation* for these binding/unbinding reactions, we set

$$\frac{dD_R}{dt} = 0 \quad \text{and} \quad \frac{dD_A}{dt} = 0.$$

Hence,

$$k_f\, D_A\, F = k_b\, D_R + b_F\, D_R \quad \Longrightarrow \quad k_f\, D_A\, F = D_R\,(k_b + b_F).$$

Using $D_A + D_R = D_T$, we write $D_R = D_T - D_A$. Substitute into the above:

$$k_f\, D_A\, F = (D_T - D_A)\,(k_b + b_F).$$

Rearrange to solve for D_A:

$$k_f\, D_A\, F = (k_b + b_F)\, D_T \;-\; (k_b + b_F)\, D_A,$$

$$D_A\Big(k_f\, F + (k_b + b_f)\Big) = (k_b + b_F)\, D_T,$$

$$\boxed{D_A(F) = \frac{(k_b + b_F)\, D_T}{(k_b + b_F) + k_f\, F}.}$$

Once $D_A(F)$ is found, $D_R(F) = D_T - D_A(F)$ or, equivalently,

$$D_R(F) = \frac{k_f\, D_A(F)\, F}{k_b + b_F}.$$

Reduced ODEs in $\{M,\, P,\, F\}$

With D_A and D_R now expressed in terms of F, we eliminate them as dynamical variables. The ODEs for M, P, and F become:

- **mRNA** $M(t)$:

$$\frac{dM}{dt} = a_M\, D_A(F) \;-\; b_M\, M = a_M\, \frac{(k_b + b_F)\, D_T}{(k_b + b_F) + k_f\, F} \;-\; b_M\, M.$$

- **Protein** $P(t)$:

$$\frac{dP}{dt} = a_P\, M \;-\; b_P\, P.$$

- **Repressor** $F(t)$:

$$\frac{dF}{dt} = a_F\, P \;-\; b_F\, F \;+\; k_b\, \frac{k_f\, D_A(F)\, F}{k_b + b_F}, \quad - k_f\, \frac{(k_b + b_F)\, D_T}{(k_b + b_F) + k_f\, F}\, F$$

  This is our *three-variable system.*

By setting $\frac{dD_A}{dt} = 0$ and $\frac{dD_R}{dt} = 0$, we have effectively enforced the *standard quasi-steady state approximation* on the DNA binding/unbinding reactions. The free DNA D_A and complex D_R become algebraic (instantaneous) functions of the repressor F. Consequently, the model is reduced to three ODEs in (M, P, F), capturing the slower transcription, translation, and repressor-production dynamics, while the DNA-binding reactions are treated as fast processes.

Problem 4: Simulation under sQSSA

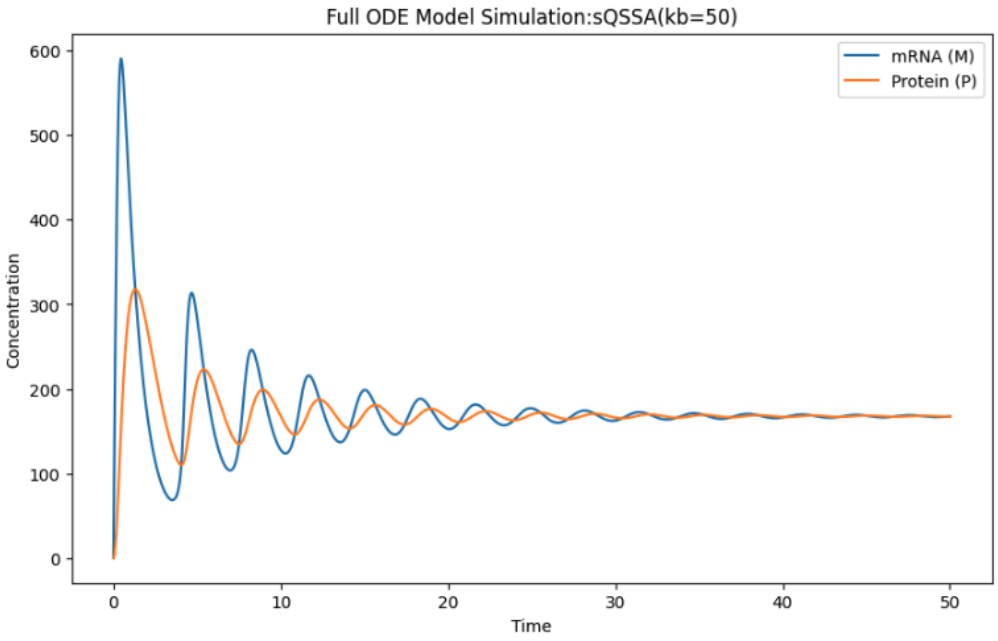

Figure 3: Simulated time courses of mRNA (M) and protein (P)

Comparison of Figure 1 and Figure 3:

- **Peak Amplitude:** In the full model (Figure 1), the peak amplitudes for mRNA M and protein P are considerably higher (approximately 1100 for M and 600 for P). In contrast, the sQSSA-reduced model (Figure 3) exhibits lower peak amplitudes (around 600 for M and 300 for P). This indicates that while the reduced model captures the qualitative behavior, it underestimates the transient peak values.

- **Transient and Steady-State Behavior:** The full model shows sustained oscillations throughout the simulation period, despite with gradually decreasing amplitude. In the sQSSA-reduced model, however, the oscillations damp out more rapidly—by around t=30 the oscillatory behavior is significantly diminished, and the system approaches a steady state more quickly

- **Accuracy of sQSSA:** Despite these quantitative differences, the reduced model does a good job of mimicking the overall trajectory of the full model. It reproduces the key qualitative features: an initial transient phase with oscillatory behavior followed by a convergence toward a steady state. This suggests that the sQSSA is an acceptable approximation for this system, capturing the essential dynamics even if some details (such as peak amplitudes and damping rates) differ

Problem 5: Introducing the Total Repressor $R = F + D_R$

The original system of ODEs is given by:

$$\frac{dM}{dt} = a_M\, D_A - b_M\, M, \tag{6}$$

$$\frac{dP}{dt} = a_P\, M - b_P\, P, \tag{7}$$

$$\frac{dF}{dt} = a_F\, P - b_F\, F + k_b\, D_R - k_f\, D_A\, F, \tag{8}$$

$$\frac{dD_R}{dt} = k_f\, D_A\, F - k_b\, D_R - b_F\, D_R, \tag{9}$$

$$\frac{dD_A}{dt} = -k_f\, D_A\, F + k_b\, D_R + b_F\, D_R, \tag{10}$$

subject to the conservation law:

$$D_A(t) + D_R(t) = D_T.$$

Introducing Total Repressor R We define the total repressor as:

$$R = F + D_R.$$

Thus, the free repressor can be written as:

$$F = R - D_R.$$

Taking the derivative of R yields:

$$\frac{dR}{dt} = \frac{d}{dt}(F + D_R) = \frac{dF}{dt} + \frac{dD_R}{dt}.$$

Substitute the expressions from (8) and (9):

$$\begin{aligned}
\frac{dR}{dt} &= \Big[a_F\, P - b_F\, F + k_b\, D_R - k_f\, D_A\, F\Big] + \Big[k_f\, D_A\, F - k_b\, D_R - b_F\, D_R\Big] \\
&= a_F\, P - b_F\, F - b_F\, D_R \\
&= a_F\, P - b_F\, \big(F + D_R\big) \\
&= a_F\, P - b_F\, R.
\end{aligned}$$

Thus, we obtain:

$$\boxed{\frac{dR}{dt} = a_F\, P - b_F\, R.}$$

New ODE System in Terms of M, P, R, D_A, D_R Substitute $F = R - D_R$ into the original ODEs. The equations for M and P remain unchanged:

$$\frac{dM}{dt} = a_M\, D_A - b_M\, M,$$

$$\frac{dP}{dt} = a_P\, M - b_P\, P.$$

For the DNA binding/unbinding dynamics, replace F by $R - D_R$:

$$\frac{dD_R}{dt} = k_f\, D_A\,(R - D_R) - k_b\, D_R - b_F\, D_R,$$
$$\frac{dD_A}{dt} = -k_f\, D_A\,(R - D_R) + k_b\, D_R + b_F\, D_R.$$

Along with the new ODE for R:

$$\frac{dR}{dt} = a_F\, P - b_F\, R.$$

The conservation law $D_A + D_R = D_T$ still holds.

$$\boxed{\begin{aligned}
\frac{dM}{dt} &= a_M\, D_A - b_M\, M,\\
\frac{dP}{dt} &= a_P\, M - b_P\, P,\\
\frac{dR}{dt} &= a_F\, P - b_F\, R,\\
\frac{dD_R}{dt} &= k_f\, D_A\,(R - D_R) - (k_b + b_F)\, D_R,\\
\frac{dD_A}{dt} &= -k_f\, D_A\,(R - D_R) + (k_b + b_F)\, D_R,
\end{aligned}}$$

subject to

$$D_A(t) + D_R(t) = D_T.$$

Problem 6: Total QSSA with $R = F + D_R$

From Problem 5, we introduced $R = F + D_R$ (the total repressor) and obtained the following five-variable ODE system:

$$\begin{cases}
\dfrac{dM}{dt} = a_M\, D_A \;-\; b_M\, M,\\
\dfrac{dP}{dt} = a_P\, M \;-\; b_P\, P,\\
\dfrac{dR}{dt} = a_F\, P \;-\; b_F\, R,\\
\dfrac{dD_R}{dt} = k_f\, D_A\,\big(R - D_R\big) - \big(k_b + b_F\big)\, D_R,\\
\dfrac{dD_A}{dt} = -\,k_f\, D_A\,\big(R - D_R\big) + \big(k_b + b_F\big)\, D_R,
\end{cases}$$

with the conservation law

$$D_A + D_R = D_T.$$

Here, M (mRNA), P (protein), and R (total repressor) are considered *slow* variables, while D_A (free DNA) and D_R (bound DNA) change rapidly.

Total QSSA: $\frac{dD_R}{dt} = 0$ and $\frac{dD_A}{dt} = 0$

We now apply the *total QSSA* by setting

$$\frac{dD_R}{dt} = 0 \quad \text{and} \quad \frac{dD_A}{dt} = 0.$$

From the last two ODEs:

$$0 = \frac{dD_R}{dt} = k_f\, D_A \left(R - D_R\right) - (k_b + b_F)\, D_R,$$
$$0 = \frac{dD_A}{dt} = -\,k_f\, D_A \left(R - D_R\right) + (k_b + b_F)\, D_R.$$

Additionally, $D_A + D_R = D_T$. These conditions imply:

$$k_f\, D_A \left(R - D_R\right) = (k_b + b_F)\, D_R, \quad D_A + D_R = D_T.$$

Let us solve for D_R in terms of R. Write $D_A = D_T - D_R$, so

$$k_f\, (D_T - D_R) \left(R - D_R\right) = (k_b + b_F)\, D_R.$$

Rearrange and solve for D_R:

$$k_f\, (D_T - D_R)\, (R - D_R) \;-\; (k_b + b_F)\, D_R = 0.$$

This is typically a quadratic equation in D_R, which we can denote by $D_R(R)$ (the algebraic solution). Once $D_R(R)$ is found, $D_A(R) = D_T - D_R(R)$.

Let $X = D_R$ for clarity, so the equation is:

$$k_f \left(D_T - X\right) \left(R - X\right) \;-\; (k_b + b_F)\, X = 0.$$

Expand and Collect Terms:

$$k_f \left(D_T R - D_T X - R X + X^2\right) \;-\; (k_b + b_f)\, X = 0,$$
$$k_f\, D_T\, R \;-\; k_f\, D_T\, X \;-\; k_f\, R\, X \;+\; k_f\, X^2 \;-\; (k_b + b_F)\, X = 0.$$

Group powers of X:

$$\underbrace{k_f}_{A}\, X^2 \;+\; \underbrace{\left[-\,k_f\, D_T \;-\; k_f\, R \;-\; (k_b + b_F)\right]}_{B}\, X \;+\; \underbrace{k_f\, D_T\, R}_{C} = 0.$$

Hence, in the standard form $A\, X^2 + B\, X + C = 0$, we identify:

$$A = k_f, \quad B = -\,k_f\, (D_T + R) \;-\; (k_b + b_F), \quad C = k_f\, D_T\, R.$$

Apply the Quadratic Formula:

$$X = D_R = \frac{-\,B \;\pm\; \sqrt{B^2 \;-\; 4\, A\, C}}{2\, A}.$$

That is,

$$D_R(R) = \frac{\Big[k_f\,(D_T + R) + (k_b + b_F)\Big] - \sqrt{\Big[k_f\,(D_T + R) + (k_b + b_F)\Big]^2 \;-\; 4\,k_f^2\,D_T\,R}}{2\,k_f}.$$

Physical Root Selection: We typically choose the root that ensures $0 \le D_R \le D_T$ (the physically meaningful concentration). Once $D_R(R)$ is found, we also get

$$D_A(R) = D_T - D_R(R).$$

Substituting these expressions into the original ODEs for M, P, and F (with $F = R - D_R$) yields the following reduced system:

$$\begin{aligned}
\frac{dM}{dt} &= a_M\,D_A(R) - b_M\,M \;=\; a_M\,\Big(D_T - D_R(R)\Big) - b_M\,M,\\
\frac{dP}{dt} &= a_P\,M - b_P\,P,\\
\frac{dR}{dt} &= a_F\,P - b_F\,\Big(R)\Big).
\end{aligned}$$

Problem 7: simulation under tQSSA:

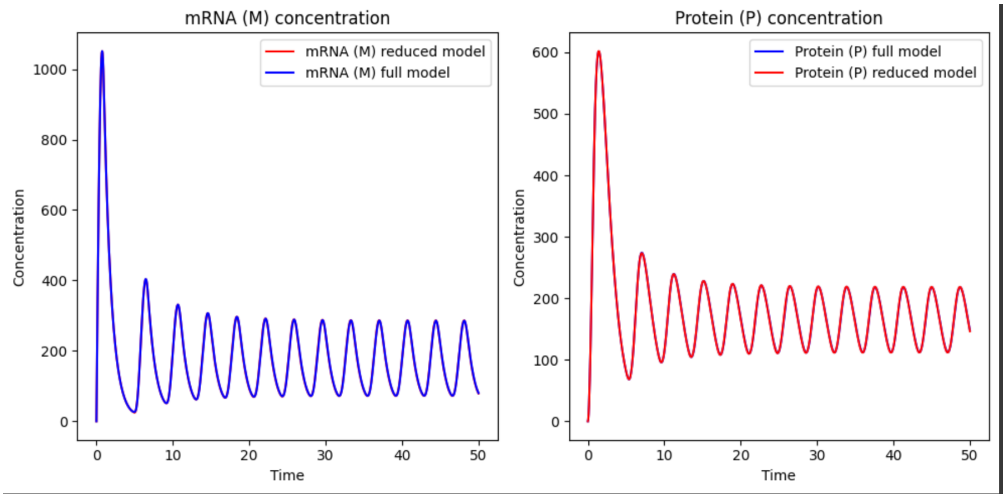

Figure 4: Simulated time courses of mRNA (M) and protein (P)

Comparing Figure 1 and Figure 4:

When we compare the simulation results of the tQSSA-reduced model with those of the full model (in Figure 1) , we observe that the solution trajectories for both mRNA (M) and protein (P) almost perfectly overlap. For example, in the mRNA plot , the reduced model (red) is plotted first and then the full model (blue) is overlaid, and the curves are nearly

indistinguishable. In the protein plot, the order is reversed—blue (full model) is plotted first, then red (reduced model)—and again the curves overlap almost exactly.

This close overlap indicates that the tQSSA is very accurate under these parameter settings; the binding/unbinding reactions are fast enough compared to the slower production and degradation processes that replacing them with their quasi-steady state expressions does not alter the overall dynamics. Therefore, the nearly perfect match between the red and blue curves confirms that the reduced model reproduces the oscillatory behavior of the full model with high fidelity.