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► To cite this version:

Honglu Sun, Jean-Paul Comet, Maxime Folschette, Morgan Magnin. Supplementary material of condition for sustained oscillations in repressilator based on a hybrid modeling of gene regulatory networks. 2022. hal-03890505

HAL Id: hal-03890505

<https://hal.science/hal-03890505>

Preprint submitted on 8 Dec 2022

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Supplementary material of condition for sustained oscillations in repressilator based on a hybrid modeling of gene regulatory networks

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1 Supplementary information about the Poincaré map

The expressions of b_1 , b_2 , c_1 and c_2 can be found in the following.

$$b_1 = \frac{B_1}{D_0} \tag{1}$$

$$b_2 = \frac{B_2}{D_0} \tag{2}$$

$$c_1 = \frac{C_1}{D_0} \tag{3}$$

$$c_2 = \frac{C_2}{D_0} \tag{4}$$

$$\begin{aligned} B_1 = & C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb1c1} \\ & + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb1c0}C_{cb1c1} \\ & + C_{ac0a1}C_{ac1a0}C_{ba1b0}C_{ba1b1}C_{cb1c0}C_{cb1c1} \\ & + C_{ac1a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb1c0}C_{cb1c1} \\ & + C_{ac1a0}C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb1c0}C_{cb1c1} \end{aligned} \tag{5}$$

$$\begin{aligned} B_2 = & -C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c0}C_{cb0c1}C_{cb1c1} \\ & -C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c1}C_{cb1c0}C_{cb1c1} \\ & -C_{ac0a1}C_{ba0b0}C_{ba1b1}C_{cb0c1}C_{cb1c0}C_{cb1c1} \\ & -C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb0c1}C_{cb1c1} \\ & -C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0}C_{cb1c1} \\ & -C_{ac0a1}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0}C_{cb1c1} \\ & -C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0}C_{cb1c1} \\ & -C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0}C_{cb1c1} \end{aligned} \tag{6}$$

$$\begin{aligned}
C_1 = & -C_{ac0a0}C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c0} \\
& -C_{ac0a0}C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb1c0} \\
& -C_{ac0a0}C_{ac1a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb1c0} \\
& -C_{ac0a1}C_{ac1a0}^2C_{ba0b1}C_{ba1b0}C_{cb0c0} \\
& -C_{ac0a1}C_{ac1a0}^2C_{ba0b1}C_{ba1b0}C_{cb1c0} \\
& -C_{ac0a1}C_{ac1a0}^2C_{ba1b0}C_{ba1b1}C_{cb1c0} \\
& -C_{ac1a0}^2C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb1c0} \\
& -C_{ac1a0}^2C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb1c0}
\end{aligned} \tag{7}$$

$$\begin{aligned}
C_2 = & C_{ac0a0}C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba0b1}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba0b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac1a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac1a0}C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0}
\end{aligned} \tag{8}$$

$$D_0 = C_{ac0a0}C_{ac1a1}C_{ba0b0}C_{ba1b1}C_{cb0c0}C_{cb1c1} \tag{9}$$

2 Expressions of polynomial P_1 and P_2

$$\begin{aligned}
P_1 = & C_{ac0a0}C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& - 2C_{ac0a0}C_{ac1a1}C_{ba0b0}C_{ba1b1}C_{cb0c0}C_{cb1c1} \\
& + C_{ac0a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba0b1}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba0b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb1c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb1c0}C_{cb1c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba1b0}C_{ba1b1}C_{cb1c0}C_{cb1c1} \\
& + C_{ac1a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac1a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb1c0}C_{cb1c1} \\
& + C_{ac1a0}C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac1a0}C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb1c0}C_{cb1c1}
\end{aligned} \tag{10}$$

$$\begin{aligned}
P_2 = & C_{ac0a0}C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& - C_{ac0a0}C_{ac1a1}C_{ba0b0}C_{ba1b1}C_{cb0c0}C_{cb1c1} \\
& + C_{ac0a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba0b1}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba0b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb1c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb1c0}C_{cb1c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba1b0}C_{ba1b1}C_{cb1c0}C_{cb1c1} \\
& + C_{ac1a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac1a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb1c0}C_{cb1c1} \\
& + C_{ac1a0}C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac1a0}C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb1c0}C_{cb1c1}
\end{aligned} \tag{11}$$

3 The proof of Property 1

Proof. From the expressions of b_1, b_2, c_1, c_2 , we know that $b_1 > 0, b_2 < 0, c_1 < 0, c_2 > 0$, so we have $(b_1 - c_2)^2 + 4c_1b_2 > 0$, therefore these two eigenvalues are real. Moreover, the expression of the product of these two eigenvalues is:

$$\lambda_1 \times \lambda_2 = b_1c_2 - c_1b_2 = \frac{D_{\lambda_1 \times \lambda_2}}{D_0} \tag{12}$$

where

$$D_{\lambda_1 \times \lambda_2} = C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \tag{13}$$

$$D_0 = C_{ac0a0}C_{ac1a1}C_{ba0b0}C_{ba1b1}C_{cb0c0}C_{cb1c1} \tag{14}$$

Therefore, $\lambda_1 \times \lambda_2 > 0$. Since λ_1 is strictly positive, so is λ_2 .

4 The proof of Property 2

Proof. Since v_1 is a eigenvector related to λ_1 , we have:

$$\lambda_1 \begin{pmatrix} v_1^1 \\ v_1^2 \end{pmatrix} = \begin{bmatrix} b_1 & c_1 \\ b_2 & c_2 \end{bmatrix} \begin{pmatrix} v_1^1 \\ v_1^2 \end{pmatrix} \tag{15}$$

From which, we have:

$$v_1^2 = \frac{\lambda_1 - b_1}{c_1} v_1^1 \quad (16)$$

By developing the expression $\frac{\lambda_1 - b_1}{c_1}$, we have:

$$\frac{\lambda_1 - b_1}{c_1} = \frac{c_2 - b_1 + \sqrt{(c_2 - b_1)^2 + 4c_1 b_2}}{2c_1} \quad (17)$$

We can see that whether $c_2 - b_1$ is positive or negative, $\lambda_1 - b_1$ is always strictly positive because $|c_2 - b_1| < \sqrt{(c_2 - b_1)^2 + 4c_1 b_2}$. Since c_1 is strictly negative, we have $v_1^1 \times v_1^2 < 0$.

Similarly for v_2 , we can have:

$$v_2^2 = \frac{\lambda_2 - b_1}{c_1} v_2^1 \quad (18)$$

and

$$\frac{\lambda_2 - b_1}{c_1} = \frac{c_2 - b_1 - \sqrt{(c_2 - b_1)^2 + 4c_1 b_2}}{2c_1} \quad (19)$$

So, similarly, whether $c_2 - b_1$ is positive or negative, $\lambda_2 - b_1$ is always strictly negative. And since c_1 is strictly negative, we have $v_2^1 \times v_2^2 > 0$.

5 The proof of Theorem 1

Proof. For any trajectory τ sufficiently close to the characteristic state but different from the characteristic state, which reaches the chosen Poincaré section at a state $s = ((x_1, 0, z_1), (0, 1, 1))$, and then reaches this Poincaré section again for the first time at another state $s' = ((x_2, 0, z_2), (0, 1, 1))$, such that there is no sliding mode between s and s' , since the state $((1, 0, 0), (0, 1, 1))$ (which is related to the characteristic state) is a fixed point of the Poincaré map, we can have the following relation:

$$\begin{pmatrix} x_2' \\ z_2' \end{pmatrix} = \begin{bmatrix} b_1 & c_1 \\ b_2 & c_2 \end{bmatrix} \begin{pmatrix} x_1' \\ z_1' \end{pmatrix} \quad (20)$$

where (x_1', z_1') and (x_2', z_2') are the new coordinates of (x_1, z_1) and (x_2, z_2) by taking $(1, 0)$ as the new origin, which means that $x_i' = x_i - 1$, $z_i' = z_i - 0$, where $i \in \{1, 2\}$. In fact, this change of coordinates allows to remove the affine vector b , as opposed to the general form given in Equation (1) of the main text.

Vectors (x_1', z_1') and (x_2', z_2') can be decomposed by:

$$\begin{pmatrix} x_1' \\ z_1' \end{pmatrix} = \alpha_1 v_1 + \beta_1 v_2 \quad (21)$$

$$\begin{pmatrix} x_2' \\ z_2' \end{pmatrix} = \alpha_2 v_1 + \beta_2 v_2 \quad (22)$$

where $\alpha_1, \beta_1, \alpha_2, \beta_2 \in \mathbb{R}$ and α_1 is not null as $x'_1 < 0$, $z'_1 > 0$, $v_1^1 \times v_1^2 < 0$ and $v_2^1 \times v_2^2 > 0$.

By multiplying Equation (21) on the left by $\begin{bmatrix} b_1 & c_1 \\ b_2 & c_2 \end{bmatrix}$ and from Equation (20), we can derive that:

$$\alpha_2 = \lambda_1 \alpha_1 \quad (23)$$

$$\beta_2 = \lambda_2 \beta_1 \quad (24)$$

Consider the case where $\lambda_1 \geq 1$. Since $|\alpha_1|$ is strictly positive, then we have $|\alpha_2| \geq |\alpha_1|$, which means that s' is not closer to the characteristic state than s in the direction of v_1 . Therefore, any sequence of the intersection points of τ with this Poincaré section will never converge to the characteristic state, which indicates that the characteristic state is unstable. This proves that “the characteristic state is unstable” is a necessary condition for “ $\lambda_1 \geq 1$ ”.

Now consider the case where the characteristic state is unstable, meaning that there is no damped oscillation that converges to it. We suppose that $\lambda_1 < 1$. Since $\lambda_1 > \lambda_2 > 0$, we have $|\alpha_2| < |\alpha_1|$ and $|\beta_2| < |\beta_1|$, which means that if τ is sufficiently close to the characteristic state, then it converges to the characteristic state, which contradicts the hypothesis stating that the characteristic state is unstable. This proves that “the characteristic state is unstable” is a sufficient condition for “ $\lambda_1 \geq 1$ ”.