Homogeneous time constants promote oscillations in negative feedback loops

Supplementary Material

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Contents

1 Proofs of the theoretical results **3**

2 Analysis of the Goodwin oscillator **6**
2.1 Goodwin oscillator: model and equilibrium 6
2.2 Goodwin oscillator: linearisation 6
2.3 Goodwin oscillator: conditions for sustained oscillations 8

3 Analysis of a two-node oscillator **9**
3.1 Two-node oscillator: model and equilibrium 9
3.2 Two-node oscillator: linearisation 10
3.3 Two-node oscillator: conditions for sustained oscillations 11

4 A case study: the Neurospora crassa biological clock **12**

1 Proofs of the theoretical results

The negative feedback interconnection of $n \in \mathbb{N}$ first order systems (cf. Fig. 1 of the Main Paper, where $n \geq 3$) can be represented in the Laplace domain as

$$\begin{aligned} X_n(s) &= -\frac{b_1}{1+\tau_1 s}\frac{b_2}{1+\tau_2 s}\cdots\frac{b_n}{1+\tau_n s}[X_n(s)+U(s)] \\ &= -\kappa\prod_{i=1}^{n}\left(\frac{1}{1+\tau_i s}\right)[X_n(s)+U(s)], \end{aligned}$$

where $\kappa \doteq \prod_{i=1}^{n} b_i > 0$ is the loop gain, as defined in the main paper, and $\tau_i > 0$ for all i, hence $\tau = [\tau_1 \;\; \tau_2 \;\; \ldots \;\; \tau_n]$ is a positive vector in $\mathbb{R}^n$. The transfer function from $U(s)$ to $X_n(s)$ is

$$F(s) = \frac{-\kappa}{\kappa + \prod_{i=1}^{n}(1+\tau_i s)}.$$

Hence the characteristic polynomial associated with the loop, which corresponds to the denominator of the above transfer function, is

$$p_n(s,\tau) = \kappa + \prod_{i=1}^{n}(1+\tau_i s)$$

and depends on the product $\kappa \doteq \prod_{i=1}^{n} b_i$, but not on the individual values of the parameters b_i. For $n > 2$ and large $\kappa > 0$, $p_n(s,\tau)$ has positive-real-part roots, associated with instability phenomena. When $\kappa = \kappa^*$, the *critical gain*, $p_n(s,\tau)$ has a pair of purely imaginary roots.

In the Main Paper, we aim at solving the following problem.

Problem 1 *Find a value τ^* that minimises the critical gain $\kappa^*(\tau)$, namely that minimises*

$$\kappa^*(\tau) = \min\{\kappa > 0 \;:\; p_n(\jmath\omega,\tau) = 0 \text{ for some } \omega > 0\}.$$

Our main result is summarised in the following theorem.

Theorem 1 *Problem 1 is solved by a value τ^* with*

$$\tau_1^* = \tau_2^* = \cdots = \tau_n^*.$$

Hence, $\kappa^*(\tau^*) = \min_{\tau>0}\kappa^*(\tau)$.

We give here the proof of Theorem 1, which also requires an intermediate proposition and a corollary.

Proof of Theorem 1.

The minimum destabilising gain as a function of τ can be denoted as

$$\kappa^*(\tau) = \min\{\kappa \;:\; \exists\, \omega \text{ such that } p_n(\jmath\omega,\tau) = 0\}.$$

For a given τ, $\kappa^*(\tau)$ is the smallest value of κ such that the characteristic polynomial $p_n(\jmath\omega,\tau)$ is not Hurwitz (i.e., does not have all negative-real-part roots) and necessarily admits a pair of complex, purely imaginary, roots. To proceed with our proof, we state the following proposition, showing that $\kappa^*(\sigma\tau)$ is constant with respect to σ; namely, even when τ is scaled, the polynomial p_n admits a pair of imaginary roots for the same value of $\kappa = \kappa^*$.

Proposition 1 *For any $\sigma > 0$, $\kappa^*(\sigma\tau) = \kappa^*(\tau)$.*

Proof of Proposition 1: For a given $\tau \in \mathbb{R}^n$, if $p_n(s,\tau)$ has a pair of imaginary roots $s = \pm\jmath\omega$, then $p_n(s,\sigma\tau)$ has roots scaled as $s = \pm\jmath\omega/\sigma$. Indeed, $\kappa + \prod_{i=1}^n (1+\tau_i\jmath\omega) = 0$ for some ω if and only if

$$\kappa + \prod_{i=1}^n (1 + (\sigma\tau_i)\jmath\frac{\omega}{\sigma}) = \kappa + \prod_{i=1}^n (1 + (\sigma\tau_i)\jmath\omega') = 0$$

for some $\omega' = \omega/\sigma$. ■

We have thus proved that $\kappa^*(\sigma\tau)$ is invariant with respect to $\sigma > 0$, while the pulsation of the oscillations ω changes as $\omega' = \omega/\sigma$.

Corollary 1 *When the time constants are scaled as $\tau_i \to \sigma\tau_i$, for arbitrary $\sigma > 0$, the critical gain κ^* is invariant, $\kappa^*(\sigma\tau^*) = \kappa^*(\tau^*)$, while the critical pulsation scales proportionally to σ: $\omega^* \to \sigma\omega^*$.*

Then, the solution of the problem is time-scale invariant: we can equivalently consider the problem in which the critical frequency is scaled to $\omega = 1$, namely, minimise κ such that $p_n(\jmath,\tau) = 0$:

$$\min_{\tau>0} \kappa > 0 \tag{1}$$

$$\text{s.t.} \quad \kappa + \prod_{i=1}^n (1+\jmath\tau_i) = 0 \tag{2}$$

The complex expression (2) corresponds to two real constraints. Let us parameterise the numbers $(1+\jmath\tau_i)$ as follows:

$$(1+\jmath\tau_i) = \sqrt{1+\tau_i^2}\; e^{\jmath\arctan(\tau_i)}, \quad i = 1,\dots,n.$$

Now, (2) can be rewritten as $\prod_{i=1}^n (1+\jmath\tau_i) = -\kappa$, where $-\kappa$ is negative real. Then, the problem in (1) and (2) is equivalent to minimising $\kappa > 0$ under the conditions

$$\prod_{i=1}^n \sqrt{1+\tau_i^2} = \kappa, \qquad \sum_{i=1}^n \arctan(\tau_i) = m\pi,$$

for $m > 0$ integer and odd, with $\tau_i > 0$. It is not difficult to see that the minimum is achieved for $m = 1$: in fact, in order to increase the phase, the τ_i's must be increased, and this increases the modulus κ as well. Then, we can consider the problem

$$\min \prod_{i=1}^n (1+\tau_i^2) \quad \text{s.t.} \quad \sum_{i=1}^n \arctan(\tau_i) = \pi, \quad \tau_i > 0.$$

This minimisation problem can be recast as a convex optimisation problem by defining the new variable $\theta_i = \arctan(\tau_i)$, $\theta_i \in (0,\pi/2]$, and considering the logarithm of the objective function. We obtain

$$\min \sum_{i=1}^n \log[1+\tan^2(\theta_i)] \tag{3}$$

$$\text{s.t.} \quad \sum_{i=1}^n \theta_i = \pi, \quad \theta_i \in (0,\pi/2], \tag{4}$$

which is a convex problem, since (4) are linear constraints and (3) is a strictly convex function. Indeed, it is the sum of n strictly convex functions of one variable: for the function $\log[1+\tan^2(\theta_i)]$, the first derivative is $2\tan(\theta_i)$, while the second derivative is $1/\cos^2(\theta_i)$, which is always positive. (Alternatively: the objective function as a multivariable function and its Hessian is a diagonal matrix with positive diagonal entries, hence it is positive definite, which implies strict convexity of the function.)

At the minimum, in view of the optimality conditions, the gradient of the objective function (with respect to the variables θ_i, *i.e.*, $\nabla(\cdot) = \partial(\cdot)/\partial\tau$) is aligned with the gradient of the constraint. The method of Lagrange multipliers, with multiplier λ, gives

$$\frac{\partial}{\partial\tau}\left[\sum_{i=1}^{n}\log[1+\tan^2(\theta_i)]\right] = \lambda\frac{\partial}{\partial\tau}\left[\sum_{i=1}^{n}\theta_i\right].$$

By equating the two gradients component by component, we get

$$2\tan(\theta_i) = \lambda, \quad k = 1, 2, \ldots n,$$

which implies that θ_i are all equal; since $\tau_i = \tan(\theta_i)$, this in turn implies that τ_i are all equal, $\tau_i = \hat{\tau}\ \forall i$.

The Lagrange multiplier condition is just necessary for a minimum. However, since the objective function is strictly convex, as previously shown, the stationary point found by the Lagrange multiplier method is indeed a minimum, and the proof is over.

End of the Proof of Theorem 1. ■

For all i, $\tau_i^* = \hat{\tau}$, with $\hat{\tau} = \tan(\pi/n)$, since $n\arctan(\hat{\tau}) = \pi$, and the optimal value of κ turns out to be $\kappa^* = \left[1+\tan(\pi/n)^2\right]^{\frac{n}{2}}$, which is independent of the common value of the time constant $\hat{\tau}$.

In the previous computations we have normalised the frequency to $\omega = 1$ essentially by setting $(1 + j\omega\tau) = (1 + j\tilde{\tau})$. To derive the actual critical frequency associated with choosing $\tau_i = \hat{\tau}$ for all i, we can see that $(\omega^*\tau) = \tan(\pi/n)$, hence $\omega^* = \frac{\tan(\pi/n)}{\hat{\tau}}$. As expected, ω^* is a decreasing function of n.

The next two propositions show that the critical gain is a decreasing function of the number of elements in the loop, and that oscillations are prevented if one delay is significantly larger than the others.

Proposition 2 *Denote by $\kappa^*_{n_1}$ and $\kappa^*_{n_2}$ the critical gain values associated with loops involving $n = n_1$ and $n = n_2$ elements, respectively. Then, if $n_1 > n_2$, $\kappa^*_{n_1} < \kappa^*_{n_2}$.*

Proof of Proposition 2. We need to prove that the minimum value κ^* of κ, solution of the considered optimisation problem (3)–(4), is a decreasing function of n, the number of elements in the loop. If the value of τ providing the minimum $\kappa^*_{n_1}$ (for $n = n_1$) is such that $\tau_1^* = \tau_2^* = \cdots = \tau_{n_1}^*$, solving the problem with $n_2 < n_1$ corresponds to solving the previous problem in the restricted domain where, for instance, the first $r = n_1 - n_2$ τ_i's are zero: $\tau_1 = \cdots = \tau_r = 0$. However, since the objective function is strictly convex and the minimum is internal, as shown in the proof of Theorem 1, a smaller value cannot be achieved on the boundary of the closure of the domain. ■

Proposition 3 *If $\tau_1 = T_{tot}$ and $\tau_i = 0$, $i \geq 2$, there are no oscillations (not even damped): all the roots of $p_n(s,\tau)$ are real. If $\tau_1 + \tau_2 = T_{tot}$ and $\tau_i = 0$, $i \geq 3$, there are no permanent oscillations: there are no complex roots of $p_n(s,\tau)$ with a nonnegative real part.*

Proof of Proposition 3. If just $\tau_1 = T_{tot}$ is nonzero, the loop equation is $(1+\tau_1 s)+\kappa = 0$, whose only root is real and negative; hence, there are no oscillations. If $\tau_1+\tau_2 = T_{tot}$, the equation is $(1+\tau_1 s)(1+\tau_2 s)+\kappa = 0$ and can have two complex roots for κ large; yet their real part is negative: the oscillations are damped. ■

2 Analysis of the Goodwin oscillator

We propose in this section a detailed analysis of the well renowned Goodwin oscillator [8]. In our analysis, we exploit Theorem 1, which states that the minimum gain required for the onset of oscillations in a negative feedback loop is minimised when the time constants of the subsystems involved in the loop are homogeneous. The results in Theorem 1 allow us to quantitatively bound the oscillatory domain of the Goodwin oscillator and derive exact oscillatory conditions in the parameter space.

2.1 Goodwin oscillator: model and equilibrium

The equations of a Goodwin oscillator [8] with n stages and Hill coefficient N are

$$\dot{x}_1 = a_1 \frac{K^N}{K^N + x_n^N} - b_1 x_1 \tag{5}$$

$$\dot{x}_i = a_i x_{i-1} - b_i x_i, \qquad i = 2, \ldots, n \tag{6}$$

where a_i and b_i, for $i = 1, \ldots, n$, and K are positive coefficients.

At the equilibrium, we have $\dot{x}_i = 0$ for all i. Then, from Eq. (6) at the equilibrium we get

$$\bar{x}_{i-1} = \frac{b_i}{a_i} \bar{x}_i, \quad i = 2, \ldots, n, \tag{7}$$

hence we can derive $\bar{x}_1$ as a function of $\bar{x}_n$:

$$\bar{x}_1 = \frac{b_2 b_3 \ldots b_n}{a_2 a_3 \ldots a_n} \bar{x}_n. \tag{8}$$

From Eq. (5) at the equilibrium we get

$$\bar{x}_1 = \frac{a_1}{b_1} \frac{K^N}{K^N + \bar{x}_n^N}. \tag{9}$$

Then, considering Eq. (8) and Eq. (9) together, we obtain that the equilibrium value $\bar{x}_n$ is the solution of the following equation:

$$\frac{K^N}{K^N + x_n^N} = \frac{b_1 b_2 b_3 \ldots b_n}{a_1 a_2 a_3 \ldots a_n} x_n = y, \tag{10}$$

where the variable y has been introduced to aid the visualisation in Figure 1. The first expression is a bounded, decreasing function of x_n, the second expression is a linear function of x_n and is a line with positive slope, increasing up to infinity. Hence, there always exists a single positive intersection $\bar{x}_n > 0$, as shown in Figure 1. Once $\bar{x}_n$ has been found, the equilibrium values of all the other variables can be derived recursively, by exploiting the relations in Eq. (7).

2.2 Goodwin oscillator: linearisation

The Jacobian matrix associated with the linearisation of the system in Eqs. (5)–(6), around the unique equilibrium point computed in the previous section, is given by

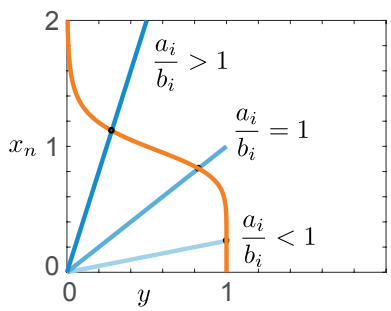

Figure 1: Goodwin oscillator: equilibrium conditions for different ratios a_i/b_i.

$$J_G = \begin{bmatrix} -b_1 & 0 & 0 & \dots & 0 & \frac{-a_1 N K^N \bar{x}_n^{N-1}}{(K^N+\bar{x}_n^N)^2} \\ a_2 & -b_2 & 0 & \dots & 0 & 0 \\ 0 & a_3 & -b_3 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & -b_{n-1} & 0 \\ 0 & 0 & 0 & \dots & a_n & -b_n \end{bmatrix}, \tag{11}$$

and corresponds to the characteristic polynomial

$$p_G(s) = \det(sI - J_G) = \prod_{i=1}^{n}(s+b_i) + \prod_{i=1}^{n} a_i \frac{N K^N \bar{x}_n^{N-1}}{(K^N + \bar{x}_n^N)^2}.$$

Enforcing the relation derived from (10)

$$\frac{\prod_{i=1}^{n} a_i K^N}{K^N + \bar{x}_n^N} = \bar{x}_n \prod_{i=1}^{n} b_1 \tag{12}$$

that stems from the equilibrium conditions, the characteristic polynomial becomes

$$p_G(s) = \prod_{i=1}^{n}(s+b_i) + N \frac{\bar{x}_n^N}{K^N + \bar{x}_n^N} \prod_{i=1}^{n} b_i.$$

Dividing $p_G(s)$ by $\prod_{i=1}^{n} b_i$, we can write the characteristic equation as

$$\prod_{i=1}^{n}(1 + s/b_i) + N \frac{\bar{x}_n^N}{K^N + \bar{x}_n^N} = 0. \tag{13}$$

The dynamic behaviour and the stability properties of the linearised system around the equilibrium point, including its capability of giving rise to persistent oscillations, are ruled by the roots of $p_G(s)$, namely, by the solutions of the characteristic equation (13).

Remark 1 *The coefficients $1/b_i$ correspond to the time constants τ_i in Eq. (3) of the Main Paper, while the term $N\frac{\bar{x}_n^N}{K^N+\bar{x}_n^N}$ corresponds to the gain κ in Eq. (3) of the Main Paper.*

2.3 Goodwin oscillator: conditions for sustained oscillations

We would like to find the minimum value N^* of N for which the system exhibits sustained oscillations, namely, the characteristic equation (13) admits a pair of complex solutions with nonnegative real part (i.e., the linearised system admits a pair of complex eigenvalues with nonnegative real part). In view of the results in Theorem 1, the minimum value N^* is achieved when all b_i's are equal: $b_i = b^*$ for all i. Then, the equation we need to solve is

$$(1 + s/b^*)^n + N\frac{\bar{x}_n^N}{K^N + \bar{x}_n^N} = 0,$$

hence

$$\frac{s}{b^*} = -1 + \sqrt[n]{-1}\sqrt[n]{N}\sqrt[n]{\frac{\bar{x}_n^N}{K^N + \bar{x}_n^N}}. \tag{14}$$

Since $0 < \frac{\bar{x}_n^N}{K^N+\bar{x}_n^N} < 1$, the critical condition for the characteristic equation (13) to admit complex solutions with a nonnegative real part is:

$$\cos(\pi/n)\sqrt[n]{N} > 1. \tag{15}$$

We can therefore state the following result, which allows us to characterise the subset of the parameter space where oscillations are indeed possible.

Proposition 4 *The two following conditions are equivalent.*

(i) There exists at least one choice of parameters for the Goodwin oscillator for which the characteristic equation (13) *admits complex solutions with nonnegative real part.*

(ii) The inequality (15) *is satisfied.*

Proof We first show that (ii) is necessary for (i). Indeed, the smallest value of the gain required to have oscillations is achieved when all the b_i's are equal, according to Theorem 1. For $b_1 = b_2 = \cdots = b_n$, the roots of the characteristic polynomial satisfy Eq. (14). The two roots having the largest real part (i.e., the two *dominant* roots) satisfy

$$\frac{s}{b^*} = -1 + \sqrt[n]{N}e^{\pm j\pi/n}\sqrt[n]{\frac{\bar{x}_n^N}{K^N + \bar{x}_n^N}}.$$

Since $0 < \frac{\bar{x}_n^N}{K^N+\bar{x}_n^N} < 1$, their real part

$$Re\left(\frac{s}{b^*}\right) = -1 + \sqrt[n]{N}\cos(\pi/n)\sqrt[n]{\frac{\bar{x}_n^N}{K^N + \bar{x}_n^N}}$$

can be larger than 0 only if the condition (15) is satisfied.

To prove that (ii) is sufficient for (i), consider again the equilibrium condition in Eq. (12) and write it as

$$\frac{1}{K^N + \bar{x}_n^N} = \frac{b_1 b_2 \ldots b_n}{a_1 a_2 \ldots a_n}\bar{x}_n.$$

It is not difficult to see that, if we take

$$\frac{b_1 b_2 \dots b_n}{a_1 a_2 \dots a_n} = \frac{b^n}{a_1 a_2 \dots a_n}$$

large, then the root $\bar{x}_n$ can become arbitrarily large (as is also shown in Figure 1). Hence, we can ensure that, for a suitable choice of the parameters, the fraction

$$\sqrt[n]{\frac{\bar{x}_n^N}{K^N + \bar{x}_n^N}}$$

gets arbitrarily close to 1. Then, if the condition (15) holds, the real part of the two dominant roots can indeed cross the imaginary axis. ■

It is worth pointing out that, in the case of $n = 3$, the condition in (15) becomes $\sqrt[3]{N} > 2$ and the minimum value of N to have oscillations is $N = 8$, consistently with the results in [10]. The general condition that we have derived based on Theorem 1, however, can be applied to Goodwin oscillators with an arbitrary number of stages.

3 Analysis of a two-node oscillator

We propose in this section a detailed analysis of a two-node oscillator, resulting from the (overall negative) feedback interconnection of an activated module and an inhibited module [2, 5, 6, 7, 11]. Also in this case, the results in Theorem 1 allow us to precisely characterise the oscillatory domain of the two-node oscillator in the parameter space.

3.1 Two-node oscillator: model and equilibrium

A two-node oscillator is given by the feedback interconnection of an activated module and an inhibited module

$$\dot{r}_1 = \frac{\alpha_1}{K_1^N + p_2^N} - \beta_1 r_1 \tag{16}$$

$$\dot{p}_1 = \gamma_1 r_1 - \delta_1 p_1 \tag{17}$$

$$\dot{r}_2 = \frac{\alpha_2 p_1^N}{K_2^N + p_1^N} - \beta_2 r_2 \tag{18}$$

$$\dot{p}_2 = \gamma_2 r_2 - \delta_2 p_2 \tag{19}$$

where α_i, β_i, γ_i, δ_i and K_i, for $i = 1, 2$, are positive parameters.

At the equilibrium, $\dot{r}_i = \dot{p}_i = 0$, for $i = 1, 2$. Hence, we can derive the following equilibrium conditions: the equilibrium pair $(\bar{p}_1, \bar{p}_2)$ is the solution of the coupled equations

$$p_1 = \frac{\alpha_1 \gamma_1}{\beta_1 \delta_1} \frac{1}{K_1^N + p_2^N} \tag{20}$$

$$p_2 = \frac{\alpha_2 \gamma_2}{\beta_2 \delta_2} \frac{p_1^N}{K_2^N + p_1^N}, \tag{21}$$

which always exists and is unique because in Eq. (20) the variable p_1 is expressed as a decreasing function of p_2, while in Eq. (21) the variable p_2 is expressed as an increasing function of p_1, hence the two curves always have exactly one intersection. Then, once $\bar{p}_1$ and $\bar{p}_2$ have been found, the equilibrium values of the other variables can be computed as

$$\bar{r}_i = \frac{\delta_i}{\gamma_i}\bar{p}_i, \quad i = 1, 2.$$

3.2 Two-node oscillator: linearisation

The Jacobian matrix that describes the linearisation of the system in Eqs. (16)–(19) in a neighbourhood of the equilibrium point computed in the previous section is

$$J_{TN} = \begin{bmatrix} -\beta_1 & 0 & 0 & -\frac{\alpha_1 N \bar{p}_2^{N-1}}{(K_1^N+\bar{p}_2^N)^2} \\ \gamma_1 & -\delta_1 & 0 & 0 \\ 0 & \frac{\alpha_2 N K_2^N \bar{p}_1^{N-1}}{(K_2^N+\bar{p}_1^N)^2} & -\beta_2 & 0 \\ 0 & 0 & \gamma_2 & -\delta_2 \end{bmatrix} \tag{22}$$

and corresponds to the characteristic polynomial

$$\begin{aligned} p_{TN}(s) &= \det(sI - J_{TN}) \\ &= (s+\beta_1)(s+\beta_2)(s+\delta_1)(s+\delta_2) + N^2 \frac{\alpha_1\alpha_2\gamma_1\gamma_2 K_2^N \bar{p}_1^{N-1}\bar{p}_2^{N-1}}{(K_2^N+\bar{p}_1^N)^2(K_1^N+\bar{p}_2^N)^2}. \end{aligned}$$

In view of the equilibrium conditions in Eq. (20) and Eq. (21), we can write

$$\frac{\alpha_1}{K_1^N+\bar{p}_2^N} = \frac{\beta_1\delta_1}{\gamma_1}\bar{p}_1 \quad \text{and} \quad \frac{\alpha_2\bar{p}_1^N}{K_2^N+\bar{p}_1^N} = \frac{\beta_2\delta_2}{\gamma_2}\bar{p}_2,$$

hence

$$\begin{aligned} N^2 \frac{\alpha_1\alpha_2\gamma_1\gamma_2 K_2^N \bar{p}_1^{N-1}\bar{p}_2^{N-1}}{(K_2^N+\bar{p}_1^N)^2(K_1^N+\bar{p}_2^N)^2} &= N^2\gamma_1\gamma_2 \frac{\alpha_1}{K_1^N+\bar{p}_2^N}\frac{\alpha_2\bar{p}_1^N}{K_2^N+\bar{p}_1^N}\frac{K_2^N\bar{p}_1^{-1}\bar{p}_2^{N-1}}{(K_2^N+\bar{p}_1^N)(K_1^N+\bar{p}_2^N)} \\ = N^2\gamma_1\gamma_2 \frac{\beta_1\delta_1}{\gamma_1}\bar{p}_1 \frac{\beta_2\delta_2}{\gamma_2}\bar{p}_2 \frac{K_2^N\bar{p}_1^{-1}\bar{p}_2^{N-1}}{(K_2^N+\bar{p}_1^N)(K_1^N+\bar{p}_2^N)} &= N^2\beta_1\beta_2\delta_1\delta_2 \frac{K_2^N}{K_2^N+\bar{p}_1^N}\frac{\bar{p}_2^N}{K_1^N+\bar{p}_2^N} \end{aligned}$$

and therefore

$$p_{TN}(s) = (s+\beta_1)(s+\beta_2)(s+\delta_1)(s+\delta_2) + N^2\beta_1\beta_2\delta_1\delta_2 \frac{K_2^N}{K_2^N+\bar{p}_1^N}\frac{\bar{p}_2^N}{K_1^N+\bar{p}_2^N}.$$

Dividing $p_{TN}(s)$ by $\beta_1\beta_2\delta_1\delta_2$, we can write the characteristic equation as

$$p_{TN}(s) = (1+s/\beta_1)(1+s/\beta_2)(1+s/\delta_1)(1+s/\delta_2) + N^2 \frac{K_2^N}{K_2^N+\bar{p}_1^N}\frac{\bar{p}_2^N}{K_1^N+\bar{p}_2^N} = 0. \tag{23}$$

Remark 2 *The coefficients $1/\beta_i$ and $1/\delta_i$, for $i = 1, 2$, correspond to the time constants τ_i in Eq. (3) of the Main Paper, while the term $N^2 \frac{K_2^N}{K_2^N+\bar{p}_1^N}\frac{\bar{p}_2^N}{K_1^N+\bar{p}_2^N}$ corresponds to the gain κ in Eq. (3) of the Main Paper.*

Denoting $f(\bar{p}_1, \bar{p}_2) = \frac{K_2^N}{K_2^N + \bar{p}_1^N} \frac{\bar{p}_2^N}{K_1^N + \bar{p}_2^N}$, since $0 < f(\bar{p}_1, \bar{p}_2) < 1$ and since the closer $f(\bar{p}_1, \bar{p}_2)$ is to 1, the more likely the system is to oscillate, we can notice that the onset of oscillations is facilitated by small values of $\bar{p}_1$ and large values of $\bar{p}_2$. This is very reasonable, since both decreasing $\bar{p}_1$ and increasing $\bar{p}_2$ leads to an increase in the gain value.

3.3 Two-node oscillator: conditions for sustained oscillations

In view of Theorem 1, we can state that the minimum value of N for which the system exhibits sustained oscillations (namely, admits a pair of complex eigenvalues with nonnegative real part, where the eigenvalues are the solution of the characteristic equation (23)) is achieved when $\beta_1 = \beta_2 = \delta_1 = \delta_2 = b^*$. Then, the system eigenvalues are the solutions of

$$(1 + s/b^*)^4 + N^2 f(\bar{p}_1, \bar{p}_2) = 0,$$

hence

$$\frac{s}{b^*} = -1 + \sqrt[4]{-1}\sqrt[4]{N^2}\sqrt[4]{f(\bar{p}_1, \bar{p}_2)}.$$

Therefore, since $f(\bar{p}_1, \bar{p}_2) < 1$, the critical condition for the system to admit complex eigenvalues with a nonnegative real part is $\cos(\pi/4)\sqrt{N} > 1$, hence

$$N > 2. \tag{24}$$

We can now state and prove the following result, which provides a characterisation of the oscillatory region in the parameter space.

Proposition 5 *The two following conditions are equivalent.*

(i) There exists at least one choice of parameters for the two-node oscillator for which the characteristic equation (23) *admits complex solutions with a nonnegative real part.*

(ii) The inequality (24) *is satisfied.*

Proof Necessity follows from the same considerations as in the proof of Proposition 4: in view of Theorem 1, the smallest value of the gain required to have oscillations is achieved when all the time constants are equal and, in this case, the dominant roots of the characteristic polynomial (23) can have a nonnegative real part only if the condition (24) is satisfied.

To prove sufficiency, we just need to show that we can select values of the parameters for which

$$f(\bar{p}_1, \bar{p}_2) = \frac{K_2^N}{K_2^N + \bar{p}_1^N} \frac{\bar{p}_2^N}{K_1^N + \bar{p}_2^N}$$

becomes arbitrary close to 1. Hence, for given K_1 and K_2, $\bar{p}_1$ has to be small enough and $\bar{p}_2$ has to be large enough. From the equilibrium conditions in Eq. (20) and Eq. (21), we see that it is a matter of suitably selecting, for instance, γ_1 and γ_2 to have $\bar{p}_1$ as small as desired and $\bar{p}_2$ as large as desired; indeed, we can fix the pair $(\bar{p}_1, \bar{p}_2)$ and compute suitable values of γ_1 and γ_2 for which Eq. (20) and Eq. (21) hold. Then, once the parameters have been suitably chosen, the real part of the two dominant roots can actually cross the imaginary axis if the condition (24) is satisfied. ■

4 A case study: the Neurospora crassa biological clock

In our analysis we have pointed out that a long negative loop of elements with homogeneous time constants promotes oscillation. However, a long chain is not necessary if the system includes a positive feedback and, indeed, even a two-element chain can be oscillating. In the concluding discussion in the Main Paper, we have proposed an academic example of a two-node negative loop in which one node has a positive self-loop. To emphasize this aspect, we consider now the example of a real oscillator composed of a (necessarily present) negative loop, which is sustained by the co-presence of a positive loop.

The genetic network present in the bread mould *Neurospora crassa*, studied in [13], has been shown to be a successful biological oscillator. Here, we provide some considerations showing that the result proposed in [13] are fully consistent with our analysis.

The system describing the genetic network, presented in [13], corresponds to the equations

$$\begin{aligned}
\dot{f}_1 &= A(f_g - f_1)w^n - \bar{A}f_1 \\
\dot{f}_r &= S_3(f_g - f_1) + S_4 f_1 - D_3 f_r \\
\dot{f}_p &= L_3 f_r - D_6 f_p \\
\dot{w} &= E_2 u_p - D_8 w - nA(f_g - f_1)w^n + n\bar{A}f_1 - Pwf_p^m \\
\dot{u}_p &= L_1 u_{r_1} - D_4 u_p - E_2 u_p \\
\dot{u}_{r_1} &= C_1 u_{r_0} f_p - D_7 u_{r_1} \\
\dot{u}_{r_0} &= V_1 - D_1 u_{r_0} - C_1 u_{r_0} f_p
\end{aligned}$$

associated with the Jacobian matrix

$$\begin{bmatrix}
-[Aw^n + \bar{A}] & 0 & 0 & nA(f_g - f_1)w^{n-1} & 0 & 0 & 0 \\
S_4 - S_3 & -D_3 & 0 & 0 & 0 & 0 & 0 \\
0 & L_3 & -D_6 & 0 & 0 & 0 & 0 \\
n[Aw^n + \bar{A}] & 0 & -nPwf_p^{m-1} & -\gamma_4 & E_2 & 0 & 0 \\
0 & 0 & 0 & 0 & -[D_4 + E_2] & L_1 & 0 \\
0 & 0 & C_1 u_{r_0} & 0 & 0 & -D_7 & C_1 f_p \\
0 & 0 & -C_1 u_{r_0} & 0 & 0 & 0 & -(D_1 + C_1 f_p)
\end{bmatrix}$$

where $\gamma_4 = [D_8 + n^2 Aw^{n-1}(f_g - f_1) + Pf_p^m]$.

By suitably renaming the variables, the Jacobian can be rewritten as

$$J_x = \begin{bmatrix}
-\gamma_1 & 0 & 0 & \delta_1 & 0 & 0 & 0 \\
\beta_1 & -\gamma_2 & 0 & 0 & 0 & 0 & 0 \\
0 & \beta_2 & -\gamma_3 & 0 & 0 & 0 & 0 \\
\delta_2 & 0 & -\beta_3 & -\gamma_4 & \beta_4 & 0 & 0 \\
0 & 0 & 0 & 0 & -\gamma_5 & \beta_5 & 0 \\
0 & 0 & \delta_3 & 0 & 0 & -D_7 & \beta_6 \\
0 & 0 & -\delta_3 & 0 & 0 & 0 & -(\beta_6 + D_1)
\end{bmatrix}.$$

The only term that is not sign-definite is $\beta_1 = S_4 - S_3$. However, we assume it is positive, $\beta_1 > 0$, in view of the numerical values reported in [13, Table 1]: $S_4 = 8.34$ and $S_3 = 0.000529$.

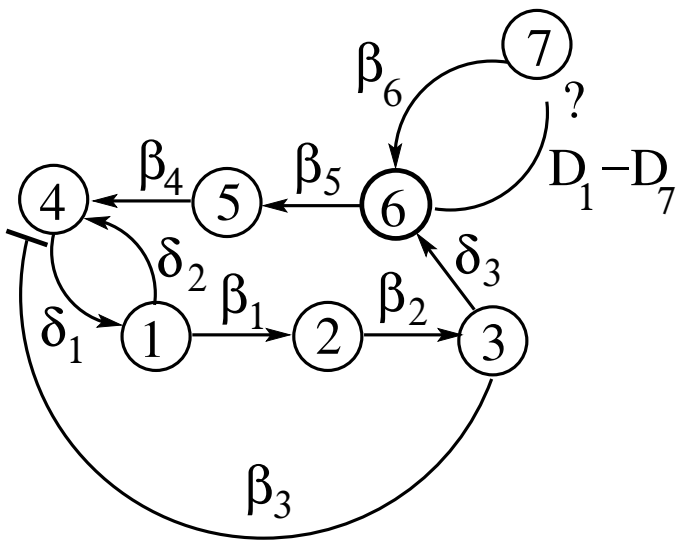

Figure 2: The graph associated with the *Neurospora crassa* system.

The data in [13, Table 2] show that, as the parameter D_7 increases, oscillations are less likely to occur. This can be also shown with our analytic approach. Indeed, if we replace the last variable x_7 by $\hat{x}_7 = x_7 + x_6$, the Jacobian becomes

$$\begin{bmatrix} -\gamma_1 & 0 & 0 & \delta_1 & 0 & 0 & 0 \\ \beta_1 & -\gamma_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_2 & -\gamma_3 & 0 & 0 & 0 & 0 \\ \delta_2 & 0 & -\beta_3 & -\gamma_4 & \beta_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\gamma_5 & \beta_5 & 0 \\ 0 & 0 & \delta_3 & 0 & 0 & -(D_7+\beta_6) & \beta_6 \\ 0 & 0 & 0 & 0 & 0 & D_1 - D_7 & -D_1 \end{bmatrix}.$$

This new Jacobian corresponds to the diagram reported in Figure 2, where the nodes 1-6 correspond to the variables x_1-x_6 and node 7 corresponds to the new variable $\hat{x}_7$, while the arcs correspond to the interactions between pairs of nodes (the arc from node j to node i is associated with the nonzero (i, j) entry of the Jacobian matrix). All the arcs are positive, with the exception of the arc from node 3 to 4, associated with the coefficient $-\beta_3$, which is negative, and of the arc from node 6 to node 7, associated with the coefficient $D_1 - D_7$, which is not sign-definite: it is positive if $D_1 > D_7$ and negative if $D_1 < D_7$.

There are therefore two possible cases.

Case 1: $D_7 < D_1$. When D_7 is small, hence $D_1 - D_7 > 0$ is positive, there is a positive feedback from $\hat{x}_7$ to x_6, because in this case the arc denoted by a "?" in Figure 2 is positive. If the unique negative off-diagonal entry is set to zero, namely $\beta_3 = 0$, the overall system is a monotone system; in fact, the associated Jacobian matrix has exclusively nonnegative off-diagonal entries. The presence of a nonzero entry $-\beta_3$ introduces a negative loop.

Negative feedback interconnections of monotone systems have been deeply investigated in the literature [1] and shown to be typical candidate oscillators [3, 4]. Also in this case, the negative loop created by β_3 induces oscillations, as confirmed by the results in [13].

In this case, two loops are present in the system: a negative loop, $4 \to 1 \to 2 \to 3 \dashv 4$, which is essential for the onset of sustained oscillations (indeed, the presence of a negative loop is necessary for

oscillations [9, 12]), and a positive loop, $1 \to 2 \to 3 \to 6 \to 5 \to 4 \to 1$, which has a beneficial effect on the onset of oscillations, since it tends to amplify the effect of the negative one.

Case 2: $D_7 > D_1$. If D_7 is large, $D_1 - D_7 < 0$ and the arc denoted by a "?" in Figure 2 is now negative. In this case, two negative loops coexist. The additional negative loop $z_7 \to x_6 \dashv z_7$ is short: according to the arguments presented in our paper, short negative loops (as well as loops with one or two dominant time constants) have a strong stabilising effect, because a higher gain is needed to induce sustained oscillations. This is fully consistent with the results reported in [13, Table 2], which show that, for D_7 substantially greater than D_1, oscillations are less likely to occur: for D_7 large enough, the system becomes arrhythmic.

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