SUPPLEMENTARY MATERIALS: HOPF BIFURCATIONS OF REACTION NETWORKS WITH ZERO-ONE STOICHIOMETRIC COEFFICIENTS*

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SM1. Application: MAPK cascade. Theorem 3.1 states that if a zero-one network admits a Hopf bifurcation, then the rank of the stoichiometric matrix is at least four. In this subsection, we show that a rank-four subnetwork that admits a Hopf bifurcation can be obtained from the well-known mitogen-activated-protein-kinase (MAPK) cascade, which represents a crucial step of the chemical signal transduction in cellular systems and is widely conserved in eukaryotes [SM5]. In fact, this rank-four subnetwork is first found in [SM11], where the authors do not emphasize it has the minimum rank that admits a Hopf bifurcation. Here, we use the same notation as that used in [SM11]. The MAPK cascade network, denote by $\mathrm{Net}_{\mathrm{MAPK}}$, consists of 14 species and 18 reactions (see (SM1.1a) to (SM1.1f)).

$$B + A^* \underset{\kappa_{13}}{\overset{\kappa_1}{\rightleftharpoons}} A^*B \xrightarrow{\kappa_2} A^* + B_1 \tag{SM1.1a}$$

$$A^* + B_1 \underset{\kappa_{14}}{\overset{\kappa_3}{\rightleftharpoons}} A^*B_1 \xrightarrow{\kappa_4} A^* + B_2 \tag{SM1.1b}$$

$$B_2 + C \underset{\kappa_{15}}{\overset{\kappa_5}{\rightleftharpoons}} CB_2 \xrightarrow{\kappa_6} C + B_1 \tag{SM1.1c}$$

$$B_1 + C \underset{\kappa_{16}}{\overset{\kappa_7}{\rightleftharpoons}} CB_1 \xrightarrow{\kappa_8} C + B \tag{SM1.1d}$$

$$D_1 + A \underset{\kappa_{17}}{\overset{\kappa_9}{\rightleftharpoons}} D_1A \xrightarrow{\kappa_{10}} D_1 + A^* \tag{SM1.1e}$$

$$D_2 + A^* \underset{\kappa_{18}}{\overset{\kappa_{11}}{\rightleftharpoons}} D_2A^* \xrightarrow{\kappa_{12}} D_2 + A. \tag{SM1.1f}$$

The authors in [SM11] present a small oscillating network obtained from $\mathrm{Net}_{\mathrm{MAPK}}$, denoted by $\mathrm{SubNet}_{\mathrm{MAPK}}$, which consists of 6 species and 7 reactions (see (SM1.2a) to (SM1.2e)).

$$B + A^* \xrightarrow{\tau_1} A^*B \xrightarrow{\tau_2} A^* + B_1 \tag{SM1.2a}$$

$$A^* + B_1 \xrightarrow{\tau_3} A^* + B_2 \tag{SM1.2b}$$

$$B_2 \xrightarrow{\tau_4} B_1 \tag{SM1.2c}$$

$$B_1 \xrightarrow{\tau_5} B \tag{SM1.2d}$$

$$A \underset{\tau_7}{\overset{\tau_6}{\rightleftharpoons}} A^*. \tag{SM1.2e}$$

First, we explain how to obtain $\mathrm{SubNet}_{\mathrm{MAPK}}$ from $\mathrm{Net}_{\mathrm{MAPK}}$.

(i) We obtain (SM1.2a) by removing the reverse reaction indexed by the rate constant κ_{13} from (SM1.1a).

(ii) We obtain (SM1.2b) by removing the reverse reaction indexed by the rate constant κ_{14} and the intermediate A^*B_1 from (SM1.1b).

(iii) We obtain (SM1.2c) by removing the reverse reaction indexed by the rate constant κ_{15}, the intermediate CB_2, and the specie C from (SM1.1c). Similarly, we obtain (SM1.2d) from (SM1.1d), and we obtain (SM1.2e) from (SM1.1e)–(SM1.1f).

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It is straightforward to check that the rank of the stoichiometric matrix of the network $\mathrm{SubNet}_{\mathrm{MAPK}}$ is four. Next, we show that $\mathrm{SubNet}_{\mathrm{MAPK}}$ admits a simple Hopf bifurcation according to Definition 2.6. We denote by $y_1, \ldots, y_6$ the concentrations of the 6 species in $\mathrm{SubNet}_{\mathrm{MAPK}}$, see Table SM1. Let $\tau = (\tau_1, \ldots, \tau_7)$, and let $y = (y_1, \ldots, y_6)$.

TABLE SM1
Species concentrations of $SubNet_{MAPK}$

y_1	y_2	y_3	y_4	y_5	y_6
A^*	B	B_1	A^*B	B_2	A

Denote the system of ODEs by $\dot{y} = \hat{f}(\tau, y)$. Let $\mathrm{Jac}^{\mathrm{red}}_{\hat{f}}(\tau, y)$ be a reduced Jacobian matrix of $\hat{f}(\tau, y)$ with respect to y. Let

$$\tau^* = (100,\ 1,\ 100,\ 1,\ 10,\ 2.39,\ 0.239).$$

And, pick a corresponding positive steady state

$$y^* = (0.1,\ 0.1,\ 0.1,\ 1,\ 1,\ 1).$$

Notice here that this point exactly lies on the Hopf bifurcation curve given in [SM11, Figure 7]. The eigenvalues of $\mathrm{Jac}^{\mathrm{red}}_{\hat{f}}(\tau^*, y^*)$ are approximately

$$-22.314 + 6.993\mathrm{i},\ -22.314 - 6.993\mathrm{i},\ \mathbf{0.815}\mathrm{i},\ \mathbf{-0.815}\mathrm{i}.$$

As the value of τ_7 varies, in the neighborhood of τ_7^*, consider the curve of rate constants

$$\tau(\tau_7) = (100,\ 1,\ 100,\ 1,\ 10,\ 10\tau_7,\ \tau_7). \tag{SM1.3}$$

We remark that for every point on this curve, y^* is a corresponding positive steady state. When $\tau_7 = 0.228$, the eigenvalues of $\mathrm{Jac}^{\mathrm{red}}_{\hat{f}}(\tau(\tau_7), y^*)$ are approximately

$$-22.282 + 6.995\mathrm{i},\ -22.282 - 6.995\mathrm{i},\ \mathbf{0.0284{+}0.797}\mathrm{i},\ \mathbf{0.0284{-}0.797}\mathrm{i}.$$

In this case, a nearby oscillation is generated around the positive steady state y^*, see Figure SM1, where we set the initial concentrations to

$$y^{(0)} = (0.15,\ 0.15,\ 0.15,\ 1.1,\ 1.1,\ 1.1). \tag{SM1.4}$$

When $\tau_7 = 0.248$, the eigenvalues of $\mathrm{Jac}^{\mathrm{red}}_{\hat{f}}(\tau(\tau_7), y^*)$ are approximately

$$-22.340 + 6.991\mathrm{i},\ -22.340 - 6.991\mathrm{i},\ \mathbf{-0.0238{+}0.829}\mathrm{i},\ \mathbf{-0.0238{-}0.829}\mathrm{i}.$$

We observe that when the value of τ_7 changes from 0.228 to 0.248, the real parts of a pair of conjugate-complex eigenvalues changes from positive to negative, and become zero when $\tau_7 = \tau_7^*$. Moreover, all other eigenvalues remain with negative real parts. So, by Definition 2.6, $\mathrm{SubNet}_{\mathrm{MAPK}}$ has a simple Hopf bifurcation at (τ^*, y^*) with respect to τ_7.

Below, we show that the original network $\mathrm{Net}_{\mathrm{MAPK}}$ also admits a simple Hopf bifurcation. Let $x_1, \ldots, x_{14}$ denote the concentrations of the species in $\mathrm{Net}_{\mathrm{MAPK}}$, see Table SM2. Let $\kappa = (\kappa_1, \ldots, \kappa_{18})$, and let $x = (x_1, \ldots, x_{14})$. Denote the system of

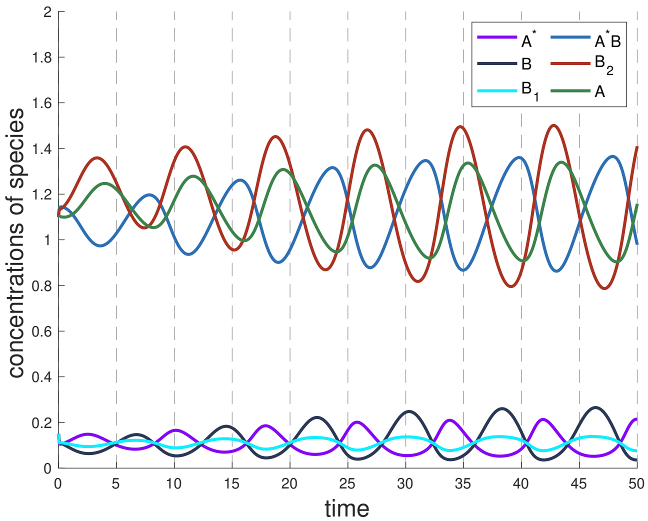

FIG. SM1. *The network SubNet$_{MAPK}$ gives rise to oscillations with respect to the species in Table SM1. The rate constants are given by $\tau(\tau_7)$ in* (SM1.3) *where the value of τ_7 is 0.228. We set the initial concentrations to $y^{(0)}$ in* (SM1.4).

TABLE SM2
Species concentrations of Net$_{MAPK}$.

x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	x_9	x_{10}	x_{11}	x_{12}	x_{13}	x_{14}
A^*	B	B_1	A^*B	B_2	A	D_1	D_2	D_1A	D_2A^*	C	CB_1	CB_2	A^*B_1

ODEs by $\dot{x} = f(\kappa, x)$. Let $\mathrm{Jac}_f^{\mathrm{red}}(\kappa, x)$ be a reduced Jacobian matrix of $f(\kappa, x)$ with respect to x. Let

$$\kappa^* = (200,\ 1,\ 200,\ 10,\ 2,\ 1,\ 20,\ 1,\ 1.00579,\ 0.00579,\ 1.0579,\ 0.00579,\ 1,\ 10,\ 1,\ 1,\ 1,\ 0.1).$$

Then, pick a positive steady state corresponding to κ^*

$$x^* = (0.1,\ 0.1,\ 0.1,\ 1,\ 1,\ 1,\ 1,\ 1,\ 1,\ 1,\ 1,\ 1,\ 1,\ 0.1).$$

The eigenvalues of $\mathrm{Jac}_f^{\mathrm{red}}(\kappa^*, x^*)$ are approximately

$$-76.416,\ -32.662,\ -15.519,\ -5.290,\ -3.364,\ -3.015,\ \mathbf{0.225}\mathrm{i},\ \mathbf{-0.225}\mathrm{i}.$$

As the value of κ_{10} varies, in the neighborhood of κ_{10}^*, consider the curve of rate constants

(SM1.5)
$$\kappa(\kappa_{10}) = (200,\ 1,\ 200,\ 10,\ 2,\ 1,\ 20,\ 1,\ 1+\kappa_{10},\ \kappa_{10},\ 1+10\kappa_{10},\ \kappa_{10},\ 1,\ 10,\ 1,\ 1,\ 1,\ 0.1),$$

and notice that for every point on the curve, x^* is a positive steady state. When $\kappa_{10} = 0.00479$, the eigenvalues of $\mathrm{Jac}_f^{\mathrm{red}}(\kappa(\kappa_{10}), x^*)$ are approximately

$$-76.411, -32.661, -15.519, -5.291, -3.363, -3.0128, \mathbf{0.00103{+}0.223}\mathrm{i}, \mathbf{0.00103{-}0.223}\mathrm{i}.$$

In this case, a nearby oscillation is generated around the positive steady state x^*, see Figure SM2, where we set the initial concentrations to

(SM1.6)
$$x^{(0)} = (0.15,\ 0.15,\ 0.15,\ 1.1,\ 1.1,\ 1.1,\ 1.1,\ 1.1,\ 1.1,\ 1.1,\ 1.1,\ 1.1,\ 1.1,\ 0.15).$$

Notice that here, we see that the capacity of $\text{SubNet}_{\text{MAPK}}$ for oscillations is inherited from Net_{MAPK} by the facts that y^* exactly gives the first six coordinates of x^*, and $y^{(0)}$ exactly gives the first six coordinates of $x^{(0)}$. When $\kappa_{10} = 0.00679$, the eigenvalues

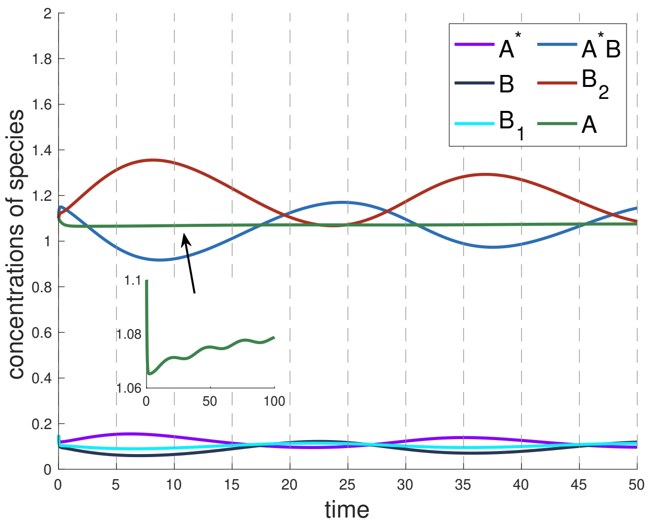

Fig. SM2. *The network Net_{MAPK} gives rise to oscillations, and we show here only the first six species in Table SM2. The rate constants are given by $\kappa(\kappa_{10})$ in (SM1.5) where the value of κ_{10} is 0.00479. We set the initial concentrations to $x^{(0)}$ in (SM1.6). We remark that the maximum amplitude of the green curve is no more than* 0.01.

of $\text{Jac}_f^{\text{red}}(\kappa(\kappa_{10}), x^*)$ are approximately

$$-76.421, -32.664, -15.520, -5.290, -3.365, -3.0181, \mathbf{-0.00104+0.227}\text{i}, \mathbf{-0.00104-0.227}\text{i}.$$

We observe that when the value of κ_{10} changes from 0.00479 to 0.00679, the real parts of a pair of conjugate-complex eigenvalues change from positive to negative, and become zero when $\kappa_{10} = \kappa_{10}^*$. Moreover, all other eigenvalues remain with negative real parts. So, by Definition 2.6, Net_{MAPK} has a simple Hopf bifurcation at (κ^*, x^*) with respect to κ_{10}.