SI Appendix: Common metabolic network motifs with amplitude and phase responses

Here mathematical formulas that describe amplitude and phase responses of common metabolic network motifs are given. Differential equations, amplitude, and phase responses of the network motifs shown in Fig. 2 and Fig. S2 are listed. The amplitude and phase responses are given in terms of the absolute value and argument, respectively, of the complex valued response coefficients computed by CRA as first-order approximations in the circadian frequency ω.

Irreversible Reaction

Differential Equation:

$$\begin{aligned}\frac{dx}{dt} &= f_1(t) - f_2(t)x(t)\\ f_1(t) &= k_1[1 + A_1\cos(\omega t + \Theta_1)]\\ f_2(t) &= k_2[1 + A_2\cos(\omega t + \Theta_2)]\end{aligned}$$

Amplitude response:

$$\begin{aligned}\begin{pmatrix}|R_1^x|\\ |R_2^x|\end{pmatrix} &= \begin{pmatrix}1\\ 1\end{pmatrix}\\ \begin{pmatrix}|R_1^J|\\ |R_2^J|\end{pmatrix} &= \begin{pmatrix}1\\ 0\end{pmatrix}\end{aligned}$$

Phase response:

$$\begin{aligned}\begin{pmatrix}\arg(R_1^x)\\ \arg(R_2^x)\end{pmatrix} &= \begin{pmatrix}-\arctan(\omega/k_2)\\ \pi-\arctan(\omega/k_2)\end{pmatrix}\\ \begin{pmatrix}\arg(R_1^J)\\ \arg(R_2^J)\end{pmatrix} &= \begin{pmatrix}-\arctan(\omega/k_2)\\ \pi/2-\arctan(\omega/k_2)\end{pmatrix}\end{aligned}$$

Linear reaction chain (n=2)

Differential Equation:

$$
\begin{aligned}
\frac{dx_1}{dt} &= f_0(t) - k_1^+ x_1(t) + k_1^- x_2(t) \\
\frac{dx_2}{dt} &= k_1^+ x_1(t) - k_1^- x_2(t) - f_2(t) x_2(t) \\
f_0(t) &= k_0[1 + A_0 \cos(\omega t + \Theta_0)] \\
f_2(t) &= k_2[1 + A_2 \cos(\omega t + \Theta_2)]
\end{aligned}
$$

Amplitude Response:

$$
\begin{pmatrix} |R_0^{x_1}| \\ |R_2^{x_1}| \\ |R_0^{x_2}| \\ |R_2^{x_2}| \end{pmatrix} = \begin{pmatrix} 1 \\ \frac{k_1^-}{k_1^- + k_2} \\ 1 \\ 1 \end{pmatrix}
$$

$$
\begin{pmatrix} |R_0^J| \\ |R_2^J| \end{pmatrix} = \begin{pmatrix} 1 \\ \frac{\omega}{k_2}(1 + 1/K) \end{pmatrix}
$$

Phase Response:

$$
\begin{pmatrix} \arg(R_0^{x_1}) \\ \arg(R_2^{x_1}) \\ \arg(R_0^{x_2}) \\ \arg(R_2^{x_2}) \end{pmatrix} = \begin{pmatrix} -\arctan(\omega\tau) \\ \pi - \arctan(\omega\tau) \\ -\arctan(\omega\tau) \\ \pi - \arctan(\omega\tau) \end{pmatrix}
$$

$$
\begin{pmatrix} \arg(R_0^J) \\ \arg(R_2^J) \end{pmatrix} = \begin{pmatrix} -\arctan(\omega\tau) \\ \pi/2 - \arctan(\omega\tau) \end{pmatrix}
$$

Here $\tau = (k_1^+ + k_1^- + k_2)/(k_1^+ k_2)$ is the turnover time of the chain as defined by Easterby (Biochem J. 1981;199:155–161), and $K = k_1^+/k_1^-$ is the equilibrium constant of the intermediate reaction. Note that we found the same response coefficients for a chain with n=3 metabolites (for appropriately defined τ, see Text S1).

Metabolic Storage

Differential Equation:

$$\begin{aligned}\frac{dx_1}{dt} &= f_0(t) - k_1^+ x_1(t) + k_1^- x_2(t) - f_2(t)x_1(t)\\ \frac{dx_2}{dt} &= k_1^+ x_1(t) - k_1^- x_2(t)\\ f_0(t) &= k_0[1 + A_0\cos(\omega t + \Theta_0)]\\ f_2(t) &= k_2[1 + A_2\cos(\omega t + \Theta_2)]\end{aligned}$$

Amplitude Response:

$$\begin{pmatrix}|R_0^{x_1}|\\ |R_2^{x_1}|\\ |R_0^{x_2}|\\ |R_2^{x_2}|\end{pmatrix} = \begin{pmatrix}1\\1\\1\\1\end{pmatrix}$$
$$\begin{pmatrix}|R_0^J|\\ |R_2^J|\end{pmatrix} = \begin{pmatrix}1\\ \frac{\omega}{k_2}(1+K)\end{pmatrix}$$

Phase Response:

$$\begin{pmatrix}\arg(R_0^{x_1})\\ \arg(R_2^{x_1})\\ \arg(R_0^{x_2})\\ \arg(R_2^{x_2})\end{pmatrix} = \begin{pmatrix}-\arctan(\omega\tau)\\ \pi-\arctan(\omega\tau)\\ -\arctan(\omega\tau)\\ \pi-\arctan(\omega\tau)\end{pmatrix}$$
$$\begin{pmatrix}\arg(R_0^J)\\ \arg(R_2^J)\end{pmatrix} = \begin{pmatrix}-\arctan(\omega\tau)\\ \pi/2-\arctan(\omega\tau)\end{pmatrix}$$

Here the turnover time τ and equilibrium constant K are defined as in the linear chain motif above.

Branching Point

Differential Equation:

$$\begin{aligned}\frac{dx}{dt} &= f_0(t) - f_1(t)x(t) - f_2(t)x(t)\\ f_0(t) &= k_0[1 + A_0\cos(\omega t + \Theta_0)]\\ f_1(t) &= k_1[1 + A_1\cos(\omega t + \Theta_1)]\\ f_2(t) &= k_2[1 + A_2\cos(\omega t + \Theta_2)]\end{aligned}$$

In the following, J refers to branch 1.
Amplitude Response:

$$\begin{pmatrix} |R_0^x| \\ |R_1^x| \\ |R_2^x| \end{pmatrix} = \begin{pmatrix} 1 \\ \frac{k_1}{k_1+k_2} \\ \frac{k_2}{k_1+k_2} \end{pmatrix}$$
$$\begin{pmatrix} |R_0^J| \\ |R_1^J| \\ |R_2^J \end{pmatrix} = \begin{pmatrix} 1 \\ \frac{k_2}{k_1+k_2} \\ \frac{k_2}{k_1+k_2} \end{pmatrix}$$

Phase Response:

$$\begin{pmatrix} \arg(R_0^x) \\ \arg(R_1^x) \\ \arg(R_2^x) \end{pmatrix} = \begin{pmatrix} 0 \\ \pi \\ \pi \end{pmatrix}$$
$$\begin{pmatrix} \arg(R_0^J) \\ \arg(R_1^J) \\ \arg(R_2^J) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ \pi \end{pmatrix}$$

Irreversible Reaction with feedback

Differential Equation:

$$\frac{dx}{dt} = f_1(t)g(x(t)) - f_2(t)x(t)$$
$$f_1(t) = k_1[1 + A_1\cos(\omega t + \Theta_1)]$$
$$f_2(t) = k_2[1 + A_2\cos(\omega t + \Theta_2)]$$

Here $g(x(t))$ determines the feedback, e.g.

$$g(x(t)) = \frac{\gamma x(t) + 1}{x(t) + 1},$$

where the parameter γ sets the fold change in reaction rate with respect to feedback ($\gamma < 1$: negative feedback, $\gamma > 1$: positive feedback). In the expressions below, $\bar{x}$ is an estimate for the magnitude (time average) of x, e.g. $\bar{x} = k_1/k_2$.

Amplitude Response:

$$\begin{pmatrix} |R_1^x| \\ |R_2^x| \end{pmatrix} = \begin{pmatrix} \frac{k_2}{|k_2 - k_1 g'(\bar{x})|} \\ \frac{k_2}{|k_2 - k_1 g'(\bar{x})|} \end{pmatrix}$$
$$\begin{pmatrix} |R_1^J| \\ |R_2^J| \end{pmatrix} = \begin{pmatrix} \frac{k_2}{|k_2 - k_1 g'(\bar{x})|} \\ \frac{k_1 g'(\bar{x})}{|k_2 - k_1 g'(\bar{x})|} \end{pmatrix}$$

Phase Response:

$$\arg(R_1^x) = \begin{cases} -\arctan\left(\frac{\omega}{|k_2 - k_1 g'(\bar{x})|}\right) & , k_2 > k_1 g'(\bar{x}) \\ \pi - \arctan\left(\frac{\omega}{|k_2 - k_1 g'(\bar{x})|}\right) & , k_2 < k_1 g'(\bar{x}) \end{cases}$$

$$\arg(R_2^x) = \pi - \arg(R_1^x)$$

$$\arg(R_1^J) = \arg(R_1^x)$$

$$\arg(R_2^J) = \begin{cases} \frac{\pi}{2} + \arctan\left(\frac{|k_1 g'(\bar{x})|}{\omega}\right) - \arctan\left(\frac{\omega}{|k_2 - k_1 g'(\bar{x})|}\right) & , k_2 > k_1 g'(\bar{x}), k_1 g'(\bar{x}) > 0 \\ \frac{\pi}{2} - \arctan\left(\frac{|k_1 g'(\bar{x})|}{\omega}\right) - \arctan\left(\frac{\omega}{|k_2 - k_1 g'(\bar{x})|}\right) & , k_2 > k_1 g'(\bar{x}), k_1 g'(\bar{x}) < 0 \\ \frac{3\pi}{2} + \arctan\left(\frac{|k_1 g'(\bar{x})|}{\omega}\right) - \arctan\left(\frac{\omega}{|k_2 - k_1 g'(\bar{x})|}\right) & , k_2 < k_1 g'(\bar{x}), k_1 g'(\bar{x}) > 0 \\ \frac{3\pi}{2} - \arctan\left(\frac{|k_1 g'(\bar{x})|}{\omega}\right) - \arctan\left(\frac{\omega}{|k_2 - k_1 g'(\bar{x})|}\right) & , k_2 < k_1 g'(\bar{x}), k_1 g'(\bar{x}) < 0 \end{cases}$$