The Laplace transform operator is $\mathscr{L}$, defined as $\mathscr{L}[f(t)] = \tilde{f}(s) = \int_0^\infty dt e^{-st} f(t)$. The convolution operator is $\star$, defined as $f \star g(t) = \int_0^t dt' f(t-t') g(t')$. The real part of a complex variable $z = x + iy$ is denoted $\Re(z) = x$.

1. The MAPK signaling cascade usually has three levels denoted $k \in \{1,2,3\}$. The activation state of level k at time t is denoted $x_k(t)$. When activation is weak, a linear model may be appropriate:

$$\begin{aligned} \dot{x}_1(t) &= \beta(t) - \alpha_1 x_1(t) \\ \dot{x}_2(t) &= b_2 x_1(t) - \alpha_2 x_2(t) \\ \dot{x}_3(t) &= b_3 x_2(t) - \alpha_3 x_3(t). \end{aligned}$$

The input is under external control, $\beta(t) = \beta_0 \sin(\omega t)$. At time 0, $x_k(0) = \dot{x}_k(0) = 0$ for $k \in 1 \ldots 3$. Provide all results in terms of model parameters $\{\beta_0, \omega, b, \alpha_1, \alpha_2, \alpha_3\}$, as well as s or t as appropriate. For simplicity assume that each α_k is different.

(a) What is $\tilde{\beta}(s)$?

$$\begin{aligned} \tilde{\beta}(s) &= \int_0^\infty dt\; e^{-st} \beta_0 \sin(\omega t) && (1) \\ &= \beta_0 \, \Im \int_0^\infty dt\; e^{-(s-i\omega)t} && (2) \\ &= \beta_0 \, \Im \left[-\frac{1}{s-i\omega} e^{-(s-i\omega)t} \right] \Bigg|_0^\infty && (3) \\ &= \frac{\beta_0 \omega}{s^2 + \omega^2} && (4) \end{aligned}$$

(b) What is $\tilde{x}_1(s)$?

$$\begin{aligned} \tilde{x}_1(s) &= \frac{\tilde{\beta}(s)}{s + \alpha_1} && (5) \\ &= \frac{\beta_0 \omega}{(s+\alpha_1)(s^2+\omega^2)} && (6) \end{aligned}$$

(c) What is $\tilde{x}_2(s)$?

$$\tilde{x}_2(s) = \frac{b_2 \beta_0 \omega}{(s+\alpha_1)(s+\alpha_2)(s^2+\omega^2)}$$

(d) What is $\tilde{x}_3(s)$?

$$\tilde{x}_3(s) = \frac{b_2 b_3 \beta_0 \omega}{(s+\alpha_1)(s+\alpha_2)(s+\alpha_3)(s^2+\omega^2)}$$

(e) What are the poles in $\tilde{x}_3(s)$?

$$s = -\alpha_1,\ -\alpha_2,\ -\alpha_3,\ \pm i\omega$$

(f) What is the time-domain output $x_3(t)$?

$$\begin{aligned}
x_3(t) &= \int_{-i\infty}^{i\infty} \frac{ds}{2\pi i} \frac{b_2 b_3 \beta_0 \omega\, e^{st}}{(s+\alpha_1)(s+\alpha_2)(s+\alpha_3)(s^2+\omega^2)} && (7)\\
&= \frac{1}{2\pi i}\left[\frac{b_2 b_3 \beta_0 \omega e^{-\alpha_1 t}}{(-\alpha_1+\alpha_2)(-\alpha_1+\alpha_3)(\alpha_1^2+\omega^2)} \oint ds \frac{1}{s+\alpha_1} + \right. && (8)\\
&\quad \frac{b_2 b_3 \beta_0 \omega e^{-\alpha_2 t}}{(-\alpha_2+\alpha_1)(-\alpha_2+\alpha_3)(\alpha_2^2+\omega^2)} \oint ds \frac{1}{s+\alpha_2} + && (9)\\
&\quad \frac{b_2 b_3 \beta_0 \omega e^{-\alpha_3 t}}{(-\alpha_3+\alpha_1)(-\alpha_3+\alpha_2)(\alpha_3^2+\omega^2)} \oint ds \frac{1}{s+\alpha_3} + && (10)\\
&\quad \frac{b_2 b_3 \beta_0 \omega e^{-i\omega t}}{(-i\omega+\alpha_1)(-i\omega+\alpha_2)(-i\omega+\alpha_3)(-2i\omega)} \oint ds \frac{1}{s+i\omega} + && (11)\\
&\quad \left. \frac{b_2 b_3 \beta_0 \omega e^{i\omega t}}{(i\omega+\alpha_1)(i\omega+\alpha_2)(i\omega+\alpha_3)(2i\omega)} \oint ds \frac{1}{s-i\omega} \right] && (12)
\end{aligned}$$

Each contour integral evaluates to $2\pi i$.

(g) The time-domain output for each level k should have the form $x_k(t) = x'_k(t) + x''_k(t)$, where $x'_k(t)$ is a transient with $\lim_{t\to\infty} x'_k(t) = 0$, and $x''_k(t)$ is the long-time response with $\lim_{t\to\infty} x''_k(t) \neq 0$. Each pole in $\tilde{x}_k(s)$ contributes to either $x'_k(t)$ or $x''_k(t)$. What condition on $\Re(s_0)$ determines whether it contributes to the transient or to the long-time response?

$\Re(s_0) < 0$ contributes to the transient response. $\Re(s_0) \geq 0$ contributes to the long-time response.

(h) The long-time response $x''_k(t)$ should have the form $A_k \sin(\omega t - \phi_k)$, where A_k is the response amplitude and ϕ_k is the phase shift. The amplitude gain is $G_k = A_k/\beta_0$. Provide the amplitude gain and the phase shift for each stage k.

Convert the complex numbers in the denominator of (11) and (12) to polar coordinates $r_k e^{i\phi_k}$ where $r_k = \sqrt{\alpha_k^2 + \omega^2}$ and $\phi_k = tan^{-1}\frac{\omega}{\alpha_k}$. Then rewrite (11) and (12) as:

$$\begin{aligned}
x''_3(t) &= \frac{b_2 b_3 \beta_0 \omega e^{-i(\omega t - \phi_1 - \phi_2 - \phi_3)}}{-2i\omega r_1 r_2 r_3} + \frac{b_2 b_3 \beta_0 \omega e^{i(\omega t - \phi_1 - \phi_2 - \phi_3)}}{2i\omega r_1 r_2 r_3} && (13)\\
&= \frac{b_2 b_3 \beta_0 \sin(\omega t - \phi_1 - \phi_2 - \phi_3)}{r_1 r_2 r_3} && (14)
\end{aligned}$$

Similarly, $x_1''(t)$ and $x_2''(t)$ can be written as:

$$x_1''(t) = \frac{\beta_0 \sin(\omega t - \phi_1)}{r_1} \quad (15)$$

$$x_2''(t) = \frac{b_2 \beta_0 \sin(\omega t - \phi_1 - \phi_2)}{r_1 r_2} \quad (16)$$

The gains G_k for $k = 1,2,3$ are:

$$G_1 = \frac{1}{\sqrt{\alpha_1^2 + \omega^2}},\ G_2 = \frac{b_2}{\sqrt{\alpha_1^2 + \omega^2}\sqrt{\alpha_2^2 + \omega^2}},\ G_3 = \frac{b_2 b_3}{\sqrt{\alpha_1^2 + \omega^2}\sqrt{\alpha_2^2 + \omega^2}\sqrt{\alpha_3^2 + \omega^2}}$$

The phase shift for each stage k is:

$$\phi_k = \sum_{i=1}^{k} \tan^{-1}\left(\frac{\omega}{\alpha_i}\right)$$

(i) What condition determines whether the input signal is amplified (amplitude gain $G_k >$ 1) or damped (amplitude gain $G_k < 1$) at each stage? What happens in the limit that the input frequency $\omega \to 0$ and when $\omega \to \infty$?

To guarantee that the signal is damped at stage 1:

$$\begin{aligned} 1 &> G_1 \\ \sqrt{\alpha_1^2 + \omega^2} &> 1 \\ \alpha_1^2 &> 1 - \omega^2 \end{aligned}$$

For stage 2:

$$\begin{aligned} 1 &> G_2 \\ \sqrt{\alpha_1^2 + \omega^2}\sqrt{\alpha_2^2 + \omega^2} &> b_2 \end{aligned}$$

For stage 3:

$$\begin{aligned} 1 &> G_3 \\ \sqrt{\alpha_1^2 + \omega^2}\sqrt{\alpha_2^2 + \omega^2}\sqrt{\alpha_3^2 + \omega^2} &> b_2 b_3 \end{aligned}$$

In the limit that $\omega \to 0$, the gain depends entirely on the model parameters:

$$\begin{aligned} G_1 &= \frac{1}{\alpha_1} \\ G_2 &= \frac{b_2}{\alpha_1 \alpha_2} \\ G_3 &= \frac{b_2 b_3}{\alpha_1 \alpha_2 \alpha_3} \end{aligned}$$

In the limit that $\omega \to \infty$, $G_k \to 0$ for all stages.

2. Suppose that $f(t) = t^2$. Evaluate $e^{3d/dt} f(t)$ at $t = 1$.

$$\begin{aligned} e^{a \frac{d}{dt}} f(t) &= \sum_{n=0}^{\infty} \frac{a^n}{n!} (\frac{d}{dt})^n f(t) \\ &= f(t+a) \\ (e^{3 \frac{d}{dt}}) f(t)|_{t=1} &= f(t+3)\ |_{t=1} = f(4) \\ &= 16 \end{aligned}$$