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 $\tilde{\beta}(s)$?

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

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

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

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

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

   (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?

   (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.

   (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 $\omega \to \infty$?

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