Pulse Width Modulation of Gene Expression: Closed Form Solutions and Proofs

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7. Useful period constraints:
   - τ_{max} at $\mu \to 0$,
   - τ_{min} at $\mu \to \mu_{\mathrm{max}}$ or μ_{f}!

A Pulse Wave function of transcriptional activity

A gene of class $x \in \{\texttt{HOC}, \texttt{LOC}\}$ is transcribed to an mRNA with abundance R_x (molecules/cell) and the mRNA is translated to a protein with abundance P_x:

HOC or LOC phase duration · **transcription** · **translation**

$$\overline{P_x} = \frac{\tau_x}{\tau_{\text{osc}}} \times \frac{k}{\mu + \delta_R} \times \frac{\rho \ell}{\mu + \delta_P}$$

protein abundance · **oscillation period** · **growth + degradation**

with the temporal constraint $\tau_{\texttt{HOC}} + \tau_{\texttt{LOC}} = \tau_{\text{osc}}$.

Gene Expression - ODE Model

A gene of class $x \in \{\texttt{HOC}, \texttt{LOC}\}$ is transcribed to an mRNA with abundance R_x (molecules/cell) and the mRNA is translated to a protein with abundance P_x:

$$\dot{R}_x = k - (\mu + \delta_\mathrm{R})R_x$$
$$\dot{P}_x = \rho \ell R_x - (\mu + \delta_\mathrm{P})P_x \ ,$$

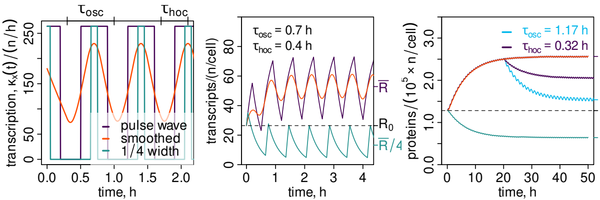
where k is the transcription rate, ρ is the number of translating ribosomes on the mRNA, ℓ is the translation rate per ribosome, $\delta_{\mathrm{R/P}}$ are the degradation rates, and μ is the growth rate.

A Pulse Wave function of transcriptional activity

A gene of class $x \in \{\texttt{HOC}, \texttt{LOC}\}$ is transcribed to an mRNA with abundance R_x (molecules/cell) and the mRNA is translated to a protein with abundance P_x:

$$\dot{R}_x = \kappa_x(t) - (\mu + \delta_{\mathrm{R}})R_x$$
$$\dot{P}_x = \rho\ell R_x - (\mu + \delta_{\mathrm{P}})P_x$$

$$\kappa_x(t) = \phi_x k + \frac{2k}{\pi}\sum_{n=1}^{\infty}\left(\frac{1}{n}\sin\left(\pi n \phi_x\right)\cos\left(n\omega t\right)\right) \quad :$$



[1]

where the *duty cycle* $\phi_x = \frac{\tau_x}{\tau_{\mathrm{osc}}}$ is the fraction of time where transcription is in the *on* state.

[1] NOTE: difference of two sawtooth waves is used for numerical solutions.

Pulse Width Modulation: analytic solutions

Transcription with periodic on/off states:

$$\dot{R} = \kappa(t) - (\mu + \delta_R)\, R(t)$$
$$\kappa(t) = \phi k + g(t)$$
$$R(t) = \int_0^t \dot{R}(s)\,\mathrm{d}s\,,$$

where ϕk is a constant scaling $\phi = [0, 1]$ of the transcription rate k, and $g(t)$ is a periodic function with $\int_0^\tau g(s)\,\mathrm{d}s = 0$, e.g.:

a simple sine wave: $\kappa(t) = \overline{k} + A\sin(\omega t)$

any periodic function: $\kappa(t) = \overline{k} + \sum_{n=1}^{\infty} (a_n \cos(n\omega s) + b_n \sin(n\omega s))$

a pulse wave function: $\kappa(t) = \phi k + \frac{2k}{\pi} \sum_{n=1}^{\infty} \left(\frac{1}{n} \sin(\pi n \phi) \cos(n\omega t) \right)$

Pulse Width Modulation: Analytic Solutions

Transcription with periodic on/off states:

$$\dot{R} = \kappa(t) - (\mu + \delta_{\mathrm{R}})\, R(t)$$
$$\kappa(t) = \phi k + g(t)$$
$$R(t) = \int_0^t \dot{R}(s)\,\mathrm{d}s\,,$$

where ϕk is a constant scaling $\phi = [0, 1]$ of the transcription rate k, and $g(t)$ is a periodic function with $\int_0^\tau g(s)\,\mathrm{d}s = 0$.

Stable oscillations at $t \gg 0$:

$$\langle R \rangle = \frac{1}{\tau} \int_t^{t+\tau} R(s)\,\mathrm{d}s$$
$$\mathcal{A}_R = \max(R(t)) - \min(R(t))$$

... and the same for protein: $P(t)$, $\langle P \rangle$, and $\mathcal{A}_P$,
and additionally the phase delay $\Delta\theta = \theta_P - \theta_R$.

Analytic Solution: general solution

$\dot{R}$ is an inhomogenous linear first order differential equation. We can use the Variation of Constants methods to solve for $R(t)$:

$$
\begin{aligned}
\dot{R} =& \kappa(t) - \gamma R(t) \\
R(t) =& e^{-\gamma t}\left(R(0) + \int_0^t e^{\gamma s}\kappa(s)\,\mathrm{d}s\right) \\
\text{with } & \kappa(t) = \phi k + g(t): \\
R(t) =& e^{-\gamma t}\left(R(0) + \int_0^t e^{\gamma s}\phi k\,\mathrm{d}s + \int_0^t e^{\gamma s} g(s)\,\mathrm{d}s\right) \\
R(t) =& e^{-\gamma t}\left(R(0) + (e^{\gamma t} - 1)\frac{\phi k}{\gamma} + \int_0^t e^{\gamma s} g(s)\,\mathrm{d}s\right) \\
R(t) =& e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + e^{-\gamma t}\int_0^t e^{\gamma s} g(s)\,\mathrm{d}s \\
R(t) =& e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + \int_0^t e^{\gamma(s-t)} g(s)\,\mathrm{d}s
\end{aligned}
$$

Problem: $\int_0^\tau g(t)\,\mathrm{d}t = 0$ but is $\int_0^\tau e^{\gamma(t-\tau)} g(t)\,\mathrm{d}t$ also 0?

Analytic Solution: general solution

$\dot{R}$ is an inhomogenous linear first order differential equation. We can use the Variation of Constants methods to solve for $R(t)$:

$$
\begin{aligned}
\dot{R} =& \kappa(t) - \gamma R(t) \\
R(t) =& e^{-\gamma t}\left(R(0) + \int_0^t e^{\gamma s}\kappa(s)\,\mathrm{d}s\right) \\
\text{with } & \kappa(t) = \phi k + g(t) : \\
R(t) =& e^{-\gamma t}\left(R(0) + \int_0^t e^{\gamma s}\phi k\,\mathrm{d}s + \int_0^t e^{\gamma s} g(s)\,\mathrm{d}s\right) \\
R(t) =& e^{-\gamma t}\left(R(0) + (e^{\gamma t} - 1)\frac{\phi k}{\gamma} + \int_0^t e^{\gamma s} g(s)\,\mathrm{d}s\right) \\
R(t) =& e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + e^{-\gamma t}\int_0^t e^{\gamma s} g(s)\,\mathrm{d}s \\
R(t) =& e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + \int_0^t e^{\gamma(s-t)} g(s)\,\mathrm{d}s
\end{aligned}
$$

Stable oscillations at $t \gg 0 : \; e^{-\gamma t} \to 0$.

Analytic Solution: pulse wave function

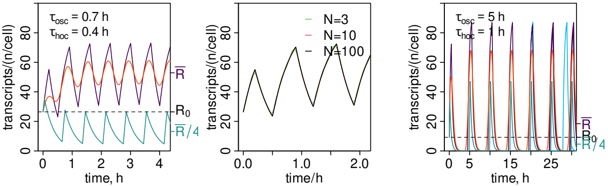
$$R(t) = e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + \int_0^t e^{\gamma(s-t)} g(s)\,\mathrm{d}s$$

$$g(t) = \frac{2k}{\pi}\sum_{n=1}^{\infty}\left(\frac{1}{n}\sin(\pi n\phi)\cos(n\omega t)\right)$$

$$R(t) = e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + \frac{2k}{\pi}\sum_{n=1}^{\infty}\left(\frac{1}{n}\sin(\pi n\phi)\int_0^t e^{\gamma(s-t)}\cos(n\omega s)\,\mathrm{d}s\right)$$

$$I(t) = \frac{\gamma\cos(n\omega t) + n\omega\sin(n\omega t) - \gamma e^{-\gamma t}}{\gamma^2 + n^2\omega^2}$$

$$R(t) = e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + \frac{2k}{\pi}\sum_{n=1}^{N}\left(\frac{1}{n}\sin(\pi n\phi)\,\frac{\gamma\cos(n\omega t) + n\omega\sin(n\omega t) - \gamma e^{-\gamma t}}{\gamma^2 + n^2\omega^2}\right):$$



Analytic Solution: pulse wave function with phase θ

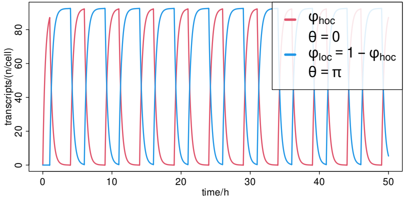
$$R(t) = e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + \int_0^t e^{\gamma(s-t)} g(s)\,\mathrm{d}s$$

$$g(t) = \frac{2k}{\pi}\sum_{n=1}^{\infty}\left(\frac{1}{n}\sin(\pi n\phi)\cos(n(\omega t - \theta))\right)$$

$$R(t) = e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + \frac{2k}{\pi}\sum_{n=1}^{\infty}\left(\frac{1}{n}\sin(\pi n\phi)\int_0^t e^{\gamma(s-t)}\cos(n(\omega s - \theta))\,\mathrm{d}s\right)$$

$$I(t,\theta) = \frac{\gamma\cos(n(\omega t - \theta)) + n\omega\sin(n(\omega t - \theta)) - e^{-\gamma t}(\gamma\cos(n\theta) - n\omega\sin(n\theta))}{\gamma^2 + n^2\omega^2}$$

Model two alternating states with $\theta = \pi$:



Analytic Solution: pulse wave function with phase θ

$$R(t) = e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + \frac{2k}{\pi}\sum_{n=1}^{\infty}\left(\frac{1}{n}\sin(\pi n\phi)\, e^{-\alpha n} I(t,\theta)\right)$$

$$I(t) = \frac{\gamma\cos(n\omega t) + n\omega\sin(n\omega t) - \gamma e^{-\gamma t}}{\gamma^2 + n^2\omega^2}$$

$$I(t,\theta) = \frac{\gamma\cos(n(\omega t - \theta)) + n\omega\sin(n(\omega t - \theta)) - e^{-\gamma t}(\gamma\cos(n\theta) - n\omega\sin(n\theta))}{\gamma^2 + n^2\omega^2}$$

$$R(t) = e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + \frac{2k}{\pi}\sum_{n=1}^{\infty}\left(\frac{1}{n}\sin(\pi n\phi)\,\frac{\gamma\cos(n(\omega t)) + n\omega\sin(n(\omega t)) - e^{-\gamma t}}{\gamma^2 + n^2\omega^2}\right)$$

$$R(t) = e^{-\gamma t}R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma}$$

$$+ \frac{2k}{\pi}\sum_{n=1}^{\infty}\left(\frac{1}{n}\sin(\pi n\phi)\, e^{-\alpha n}\,\frac{\gamma\cos(n(\omega t - \theta)) + n\omega\sin(n(\omega t - \theta)) - e^{-\gamma t}(\gamma\cos(n\theta) - n\omega\sin(n\theta))}{\gamma^2 + n^2\omega^2}\right)$$

Analytic Solution: smoothed pulse wave function

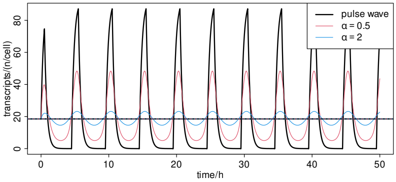
$$R(t) = e^{-\gamma t} R(0) + (1 - e^{-\gamma t}) \frac{\phi k}{\gamma} + \int_0^t e^{\gamma(s-t)} g(s)\,\mathrm{d}s$$

$$g(t) = \frac{2k}{\pi} \sum_{n=1}^{\infty} \left(\frac{1}{n} \sin(\pi n \phi)\, e^{-\alpha n} \cos(n \omega t) \right)$$

$$R(t) = e^{-\gamma t} R(0) + (1 - e^{-\gamma t}) \frac{\phi k}{\gamma} + \frac{2k}{\pi} \sum_{n=1}^{\infty} \left(\frac{1}{n} \sin(\pi n \phi)\, e^{-\alpha n} \int_0^t e^{\gamma(s-t)} \cos(n \omega s)\,\mathrm{d}s \right)$$

$$I(t) = \frac{\gamma \cos(n\omega t) + n\omega \sin(n\omega t) - \gamma e^{-\gamma t}}{\gamma^2 + n^2\omega^2}$$

Smoothing (parameter α) does not affect the mean abundance:



Average Abundance: general solution

For stable oscillations at $t \gg 0: \ e^{-\gamma t} \to 0$, and the general solution to our differential equation simplifies to:

$$R(t) = \frac{\phi k}{\gamma} + \int_0^t e^{\gamma(s-t)} g(s)\,\mathrm{d}s$$

$$\langle R \rangle = \frac{1}{\tau}\int_0^\tau \left(\frac{\phi k}{\gamma} + \int_0^t e^{\gamma(s-t)} g(s)\,\mathrm{d}s\right)\mathrm{d}t$$

The Fourier series can represent any periodic function $g(t)$, incl. pulse waves:

$$r(t) = \int_0^t e^{\gamma(s-t)} \sum_{n=1}^{\infty} \left(a_n \cos(n\omega s) + b_n \sin(n\omega s)\right)\,\mathrm{d}s$$

$$r(t) = \sum_{n=1}^{\infty}\left(a_n \int_0^t e^{\gamma(s-t)} \cos(n\omega s)\,\mathrm{d}s + b_n \int_0^t e^{\gamma(s-t)} \sin(n\omega s)\mathrm{d}s\right)$$

$$x(t) = \int_0^t e^{\gamma(s-t)} \cos(\omega s)\,\mathrm{d}s$$

$$x(t) = \frac{\gamma \cos(\omega t) + \omega \sin(\omega t) - \gamma e^{-\gamma t}}{\gamma^2 + \omega^2} \qquad \Leftarrow \text{ key step!}$$

$$\langle x \rangle = \frac{1}{\tau}\int_0^\tau \frac{\gamma \cos(\omega t) + \omega \sin(\omega t)}{\gamma^2 + \omega^2}\mathrm{d}t$$

$$\langle x \rangle = \frac{1}{\tau}\left(\frac{0}{\gamma^2\omega + \omega^3} + \frac{1-1}{\gamma^2 + \omega^2}\right) = 0$$

$$\langle R \rangle = \frac{\phi k}{\gamma} \quad \square$$

Average Abundance: detailed solution for cos

$$x(t) = \int_0^t e^{\gamma(s-t)} \cos(\omega s)\,\mathrm{d}s$$

$$x(t) = e^{-\gamma t} \int_0^t e^{\gamma s} \cos(\omega s)\,\mathrm{d}s$$

$$x(t) = e^{-\gamma t} \frac{e^{\gamma t}\left(\gamma \cos(\omega t) + \omega \sin(\omega t)\right) - \gamma}{\gamma^2 + \omega^2}$$

$$x(t) = \frac{\gamma \cos(\omega t) + \omega \sin(\omega t) - \gamma e^{-\gamma t}}{\gamma^2 + \omega^2}$$

$$\langle x \rangle = \frac{1}{\tau} \int_0^\tau \frac{\gamma \cos(\omega t) + \omega \sin(\omega t)}{\gamma^2 + \omega^2}\mathrm{d}t$$

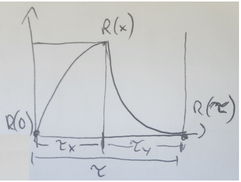
$$\langle x \rangle = \frac{1}{\tau}\left(\frac{\gamma \sin(\omega \tau)}{\gamma^2\omega + \omega^3} + \frac{1 - \cos(\omega \tau)}{\gamma^2 + \omega^2}\right)$$

$$\langle x \rangle = \frac{1}{\tau}\left(\frac{\gamma \sin(2\pi)}{\gamma^2\omega + \omega^3} + \frac{1 - \cos(2\pi)}{\gamma^2 + \omega^2}\right)$$

$$\langle x \rangle = \frac{1}{\tau}\left(\frac{0}{\gamma^2\omega + \omega^3} + \frac{1 - 1}{\gamma^2 + \omega^2}\right) = 0 \quad \square$$

Amplitudes: On/Off

$$R_{on}(t) = R(0)e^{-\gamma t} + \frac{k}{\gamma}\left(1 - e^{-\gamma t}\right)$$
$$R_{off}(t) = R(\tau_x)e^{-\gamma t}$$

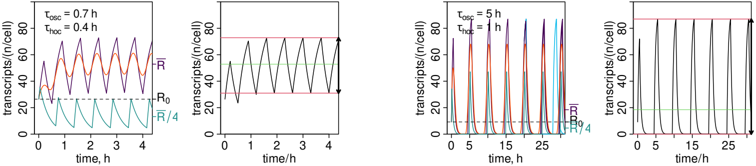


$$R(\tau_x) = R(0)e^{-\gamma\tau_x} + \frac{k}{\gamma}\left(1 - e^{-\gamma\tau_x}\right)$$
$$R(0) = R(\tau) = R(\tau_x)e^{-\gamma(\tau-\tau_x)}$$
$$R(\tau_x) = \frac{k}{\gamma}\frac{1 - e^{-\gamma\tau_x}}{1 - e^{-\gamma\tau}}$$

with $\tau_x = \phi\tau$:

$$R_{max} = \frac{k}{\gamma}\frac{1 - e^{-\gamma\phi\tau}}{1 - e^{-\gamma\tau}}$$
$$R_{min} = \frac{k}{\gamma}\frac{1 - e^{-\gamma\phi\tau}}{1 - e^{-\gamma\tau}}e^{\gamma\tau(\phi-1)}$$
$$\mathcal{A}_R = \frac{k}{\gamma}\frac{1 - e^{-\gamma\phi\tau}}{1 - e^{-\gamma\tau}}\left(1 - e^{\gamma\tau(\phi-1)}\right)$$

Amplitudes: On/Off



$$R(\tau_x) = R(0)e^{-\gamma\tau_x} + \frac{k}{\gamma}\left(1 - e^{-\gamma\tau_x}\right)$$

$$R(0) = R(\tau) = R(\tau_x)e^{-\gamma(\tau-\tau_x)}$$

$$R(\tau_x) = \frac{k}{\gamma}\frac{1 - e^{-\gamma\tau_x}}{1 - e^{-\gamma\tau}}$$

with $\tau_x = \phi\tau$:

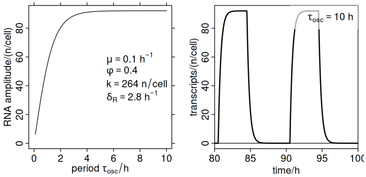
$$R_{max} = \frac{k}{\gamma}\frac{1 - e^{-\gamma\phi\tau}}{1 - e^{-\gamma\tau}}$$

$$R_{min} = \frac{k}{\gamma}\frac{1 - e^{-\gamma\phi\tau}}{1 - e^{-\gamma\tau}}e^{\gamma\tau(\phi-1)}$$

$$\mathcal{A}_R = \frac{k}{\gamma}\frac{1 - e^{-\gamma\phi\tau}}{1 - e^{-\gamma\tau}}\left(1 - e^{\gamma\tau(\phi-1)}\right)$$

Amplitudes: On/Off

For $\tau_y \gg \frac{\ln(2)}{\gamma}$:



$$R(\tau_x) = R(0)e^{-\gamma\tau_x} + \frac{k}{\gamma}\left(1 - e^{-\gamma\tau_x}\right)$$

$$R(0) = R(\tau) = R(\tau_x)e^{-\gamma(\tau-\tau_x)}$$

$$R(\tau_x) = \frac{k}{\gamma}\frac{1-e^{-\gamma\tau_x}}{1-e^{-\gamma\tau}}$$

with $\tau_x = \phi\tau$:

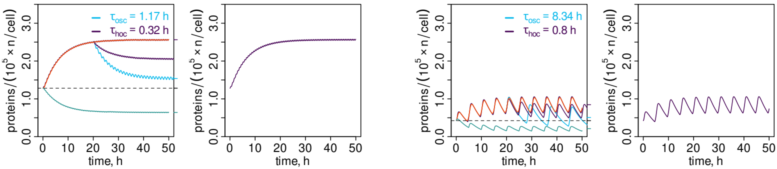
$$R_{max} = \frac{k}{\gamma}\frac{1-e^{-\gamma\phi\tau}}{1-e^{-\gamma\tau}}$$

$$R_{min} = \frac{k}{\gamma}\frac{1-e^{-\gamma\phi\tau}}{1-e^{-\gamma\tau}}e^{\gamma\tau(\phi-1)}$$

$$\mathcal{A}_R = \frac{k}{\gamma}\frac{1-e^{-\gamma\phi\tau}}{1-e^{-\gamma\tau}}\left(1 - e^{\gamma\tau(\phi-1)}\right)$$

Protein

$$\dot{P} = \ell\rho R(t) - \gamma_p P(t)$$
$$P(t) = e^{-\gamma_p t}\left(P(0) + \ell\rho \int_0^t e^{\gamma_p s} R(s)\, \mathrm{d}s\right)$$



Current implementation: just integrate calculated $R(t)$ via trapezoid rule.

Average Abundance $\langle P \rangle$

For stable oscillations at $t \gg 0$: $e^{-\gamma t} \to 0$, and the general solution to our differential equation simplifies to:

$$
\begin{aligned}
R(t) =& \frac{\phi k}{\gamma} + \int_0^t e^{\gamma(s-t)} g(s)\,\mathrm{d}s \\
P(t) =& e^{-\gamma_p t} \ell\rho \int_0^t e^{\gamma_p s} R(s)\,\mathrm{d}s \\
P(t) =& \ell\rho \int_0^t e^{\gamma_p (s-t)} R(s)\,\mathrm{d}s \\
P(t) =& \ell\rho \int_0^t e^{\gamma_p (s-t)} \frac{\phi k}{\gamma}\,\mathrm{d}s + \ell\rho \int_0^t e^{\gamma_p (s-t)} \left(\int_0^t e^{\gamma(u-s)} g(u)\,\mathrm{d}u \right)\,\mathrm{d}s \\
P(t) =& \frac{\phi k}{\gamma} \frac{\ell\rho}{\gamma_p} (1 - e^{-\gamma_p t}) + I(t) \\
\langle P \rangle =& \frac{\phi k}{\gamma} \frac{\ell\rho}{\gamma_p} \quad \square ?
\end{aligned}
$$

TODO: Fix this and reason whether the most general proof above, for a general Fourier series, suffices?

Protein: full analytic solution

$$P(t) = e^{-\gamma_p t}\left(P(0) + \ell\rho \int_0^t e^{\gamma_p s} R(s)\, \mathrm{d}s\right)$$

$$R(t) = e^{-\gamma t} R(0) + (1 - e^{-\gamma t})\frac{\phi k}{\gamma} + \frac{2k}{\pi}\sum_{n=1}^{N}\left(\frac{1}{n}\sin(\pi n\phi)\,\frac{\gamma\cos(n\omega t) + n\omega\sin(n\omega t) - \gamma e^{-\gamma t}}{\gamma^2 + n^2\omega^2}\right)$$

$$\int_0^t e^{\gamma_p s} R(s)\,\mathrm{d}s = R(0)\int_0^t e^{s(\gamma_p - \gamma)}\,\mathrm{d}s + \frac{\phi k}{\gamma}\int_0^t \left(e^{\gamma_p s} - e^{s(\gamma_p-\gamma)}\right)\mathrm{d}s +$$

$$\frac{2k}{\pi}\sum_{n=1}^{N}\left(\frac{\sin(\pi n\phi)}{n\gamma^2 + n^3\omega^2}\int_0^t e^{\gamma_p s}\left(\gamma\cos(ns\omega) + n\omega\sin(ns\omega) - \gamma e^{-\gamma s}\right)\mathrm{d}s\right)$$

$$I(t) = \int_0^t e^{\gamma_p s}\gamma\cos(ns\omega)\,\mathrm{d}s + \int_0^t e^{\gamma_p s} n\omega\sin(ns\omega)\,\mathrm{d}s - \int_0^t e^{s(\gamma_p-\gamma)}\mathrm{d}s$$

$$I(t) = \frac{\gamma(e^{\gamma_p t}(n\omega\sin(n\omega t) + \cos(n\omega t)) - \gamma_p)}{\gamma_p^2 + n^2\omega^2} + \frac{n\omega(e^{\gamma_p t}(\gamma_p\sin(n\omega t) - n\omega\cos(n\omega t)) + n\omega)}{\gamma_p^2 + n^2\omega^2} - \frac{1 - e^{t(\gamma_p-\gamma)}}{\gamma - \gamma_p}$$

$$\underline{P(t) = e^{-\gamma_p t}\left(P(0) + \ell\rho\left(R(0)\frac{1 - e^{t(\gamma_p-\gamma)}}{\gamma - \gamma_p} + \frac{\phi k}{\gamma}\left(\frac{e^{t(\gamma_p-\gamma)} - 1}{\gamma - \gamma_p} + \frac{e^{\gamma_p t} - 1}{\gamma_p}\right)\frac{2k}{\pi}\sum_{n=1}^{N}\left(\frac{\sin(\pi n\phi)}{n\gamma^2 + n^3\omega^2} I(t)\right)\right)\right)}$$

TODO: check and implement this analytic solution; find expressions for protein amplitude $\mathcal{A}_{P_x}$, and phase delay $\Delta\theta = \theta_P - \theta_R$.

Yeast Oscillation Frequency vs Growth Rate

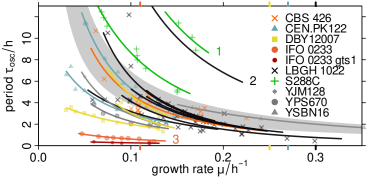
$$\langle P_x \rangle = \frac{\phi_x k}{\gamma} \frac{\ell \rho}{\gamma_p}$$

$$\langle P_x \rangle = \frac{\tau_x}{\tau_{osc}} \frac{k}{\mu + \delta_R} \frac{\ell \rho}{\mu + \delta_P}$$

$$\tau_{osc} = \frac{\tau_x}{\langle P_x \rangle} \frac{k}{\mu + \delta_R} \frac{\rho \ell}{\mu + \delta_P}$$

To maintain a stable protein abundance $\langle P_x \rangle$ at different growth rates with otherwise unchanged parameters, we require the duty cycle $\phi = \frac{\tau_x}{\tau_{osc}}$ to increase with growth rate to compensate for the dilution by growth. For example, we can consider ribosome abundance, as approximated by the life cycle of an average ribosomal protein, $B \approx \langle P_{RP} \rangle$.

The phase of yeast respiratory oscillations where ribosomal proteins are transcribed (HOC) is approximately constant (for given strain and conditions), with $\tau_{\mathrm{HOC}} = 0.5\,\mathrm{h}$ to $1.5\,\mathrm{h}$, thus the total period τ_{osc} must vary:



Yeast Oscillation Frequency vs Growth Rate

$$\tau_{\mathrm{osc}} = \frac{\tau_{hoc}}{B} \frac{k}{\mu + \delta_{\mathrm{R}}} \frac{\rho \ell}{\mu + \delta_{\mathrm{P}}}$$

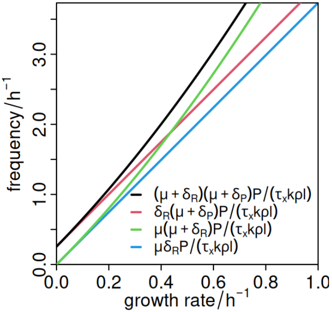
$$S = \frac{B}{\tau_{hoc} k \rho \ell}$$

$$f = (\mu + \delta_{\mathrm{R}})(\mu + \delta_{\mathrm{P}}) S$$

$$f = (\mu \delta_{\mathrm{R}} + \delta_{\mathrm{R}} \delta_{\mathrm{P}}) S$$

$$f = (\mu^2 + \mu \delta_{\mathrm{R}}) S$$

$$f = \mu \delta_{\mathrm{R}} S$$



Conditions $\delta_{\mathrm{R}} \gg \mu \gg \delta_{\mathrm{P}}$:

RNAs are very short lived (half-live ≈ 25 min), and the transcription term $(\mu + \delta_{\mathrm{R}})$ is dominated by degradation. In contrast, protein half-lives (median 9 h) are comparable to or higher than growth rates (doubling times 1-10 h).

Yeast Oscillation Frequency vs Growth Rate

$$\tau_{\mathrm{osc}} = \frac{\tau_{hoc}}{B} \frac{k}{\mu + \delta_{\mathrm{R}}} \frac{\rho\ell}{\mu + \delta_{\mathrm{P}}}$$

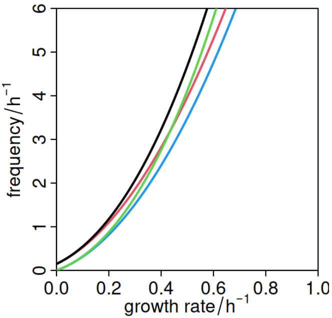
$$S = \frac{B_0 + \beta\mu}{\tau_{hoc} k \rho \ell}$$

$$f = (\mu + \delta_{\mathrm{R}})(\mu + \delta_{\mathrm{P}})S$$

$$f = (\mu\delta_{\mathrm{R}} + \delta_{\mathrm{R}}\delta_{\mathrm{P}})S$$

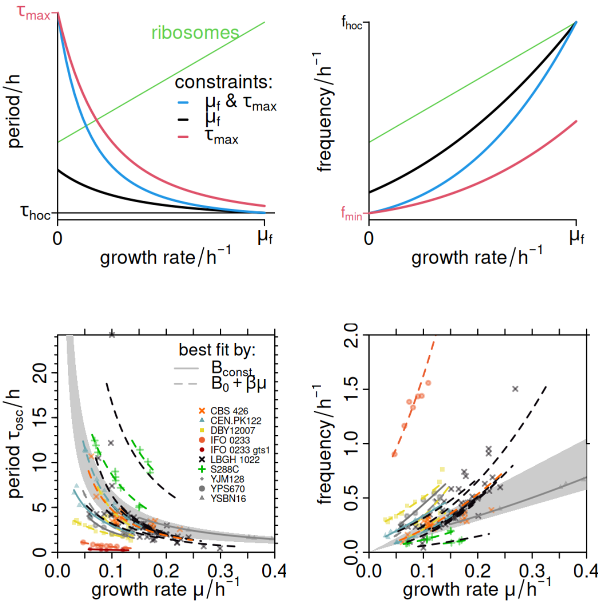
$$f = (\mu^2 + \mu\delta_{\mathrm{R}})S$$

$$f = \mu\delta_{\mathrm{R}}S$$



Accounting for linearly increasing ribosome concentration leads to a **cubic dependence of frequency on growth rate**.

Frequency vs Growth



Constraints

We can use additional constraints to calculate periods that must be realized to achieve a certain ribosome concentration:

- A maximal period $\tau_{\max}$ at $\mu = 0$ reflects the compensation for (protein/ribosome) degradation alone[1],
- A minimal period is reached at the maximal or the critical dilution rate, $\tau_{\texttt{LOC}} \to 0$ and $\tau_{\min} \to \tau_{\texttt{HOC}}$ at μ_{f}:

$$\begin{aligned}\tau_{\mathrm{osc}} &= \frac{\tau_{hoc}}{B} \frac{k}{\mu + \delta_{\mathrm{R}}} \frac{\rho\ell}{\mu + \delta_{\mathrm{P}}} \\ \tau_{\max} &= \frac{\tau_{hoc}}{B} \frac{k}{\delta_{\mathrm{R}}} \frac{\rho\ell}{\delta_{\mathrm{P}}} \\ B_f &= \frac{k}{\mu_{\mathrm{f}} + \delta_{\mathrm{R}}} \frac{\rho\ell}{\mu_{\mathrm{f}} + \delta_{\mathrm{P}}}\end{aligned}$$

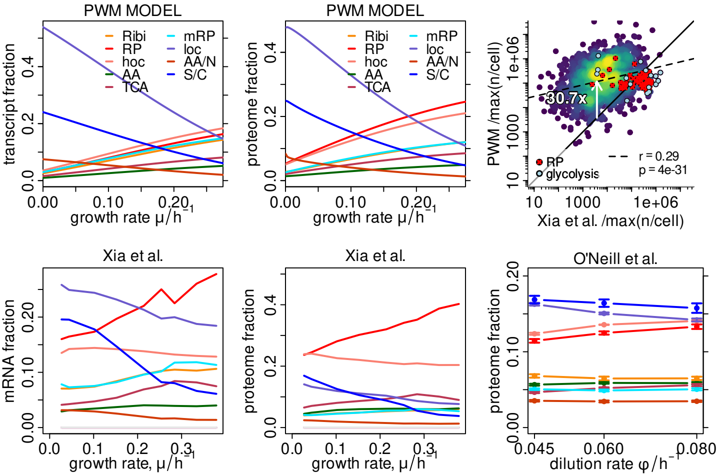
Note: $\tau_{\texttt{HOC}}$ is not necessarily constant, this is just an approximate observation from the data. For example, during the short period oscillations in IFO 0233, close to its μ_{f}, the HOC and LOC phases appear contracted.

---

[1] Calabrese et al. (2022): Protein degradation sets the fraction of active ribosomes at vanishing growth.

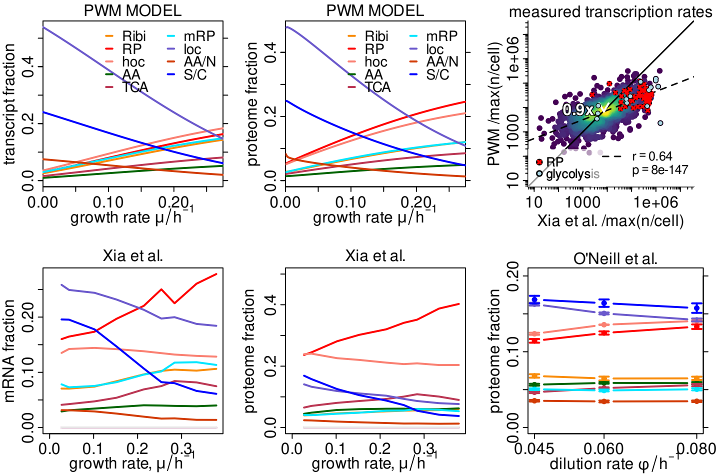
Translation Pulses

$$\langle P_x \rangle = \frac{\tau_x}{\tau_{\mathrm{osc}}} \frac{k}{\mu + \delta_{\mathrm{R}}} \frac{\ell \rho}{\mu + \delta_{\mathrm{P}}} \quad :$$



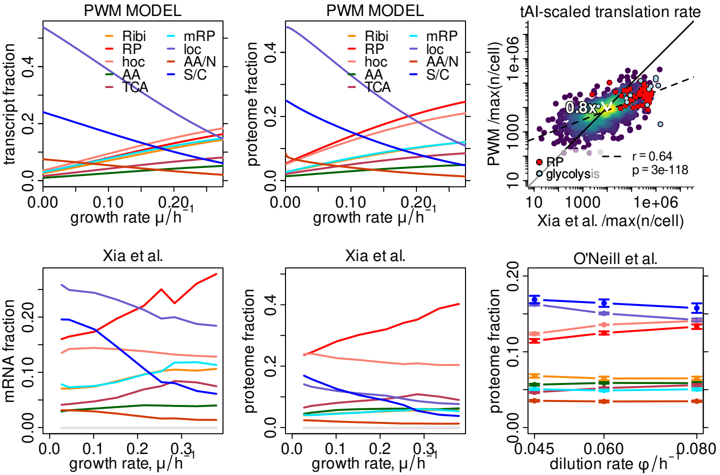
Translation Pulses

$$\langle P_x \rangle = \frac{\tau_x}{\tau_{osc}} \frac{k}{\mu + \delta_R} \frac{\tau_{HOC}}{\tau_{osc}} \frac{\ell\rho}{\mu + \delta_P} \quad :$$



Translation Pulses

$$\langle P_x \rangle = \frac{\tau_x}{\tau_{\text{osc}}} \frac{k}{\mu + \delta_{\text{R}}} \frac{\tau_{\texttt{HOC}}}{\tau_{\text{osc}}} \frac{\ell \rho}{\mu + \delta_{\text{P}}} \quad :$$



Outlook

- Couple equations to a coarse-grained metabolic model to account for the core auto-catalysis of life, **ribosomes making more ribosomes**.

$$\frac{dX}{dt} = (\mu_a - \phi)X$$

$$\frac{dS}{dt} = \phi(S_{in} - S) - (\mu_a + \mu_c)X$$

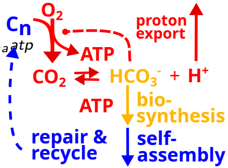
$$\frac{datp}{dt} = (n_c\mu_c - n_a\mu_a - \mu_m)\frac{C_c}{V_c} - \mu_a atp$$

$$adp = a_{\text{tot}} - atp$$

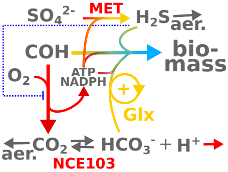
where $\mu_a = f(\texttt{Ribi}, \texttt{RP}, \texttt{AA}, \texttt{TCA})$, $\mu_c = f(\texttt{mRP}, \texttt{S/C})$, $\texttt{Ribi} + \texttt{RP} + \texttt{AA} + \texttt{TCA} + \texttt{mRP} + \texttt{S/C} \leq X$, and transcription depends on an ATP-dependent toggle switch.

axiomatic modeling strategy

Temporal constraints on the synthesis of macro-molecular machinery:



Data suggest bicarbonate (HCO_3^{2-}) buffering as feedforward gate:



Summary and todos

1. Analytic solutions for both $R(t)$ and $P(t)$:
   - $P(t)$ uses manually integrated $R(t)$.
2. Derivation of average abundance:
   - Missing: proof for average protein abundance.
3. Derivation of amplitude:
   - Only valid for on/off transcription function.
   - Wrong for $\tau_{\text{off}} \gg \frac{\ln 2}{\gamma}$?
4. Phases:
   - Missing: phase difference between RNA and protein peaks.

Summary and todos

1. Analytic solutions for both $R(t)$ and $P(t)$:
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But why?

1. Can oscillation periods explain growth-related resource allocation?
2. Is a global binary transcription state (on/off) enough to explain the observed temporal program of transcript abundances?
3. Can we infer periodic on/off expression programs from single cell snap shot data of asynchronous cultures?

APPENDIX

1. Average abundance for pulse wave,
2. Average abundance for on/off assumption,
3. Amplitudes: analytic solution.

Average Abundance: pulse wave at $t \gg 0$

$$R(t) = e^{-\gamma t} R(0) + (1 - e^{-\gamma t}) \frac{\phi k}{\gamma} + \frac{2k}{\pi} \sum_{n=1}^{N} \left(\frac{1}{n} \sin(\pi n \phi) I(t, \theta) \right)$$

$$I(t, \theta) = \frac{\gamma \cos(n(\omega t - \theta)) + n\omega \sin(n(\omega t - \theta)) - e^{-\gamma t} (\gamma \cos(n\theta) - n\omega \sin(n\theta))}{\gamma^2 + n^2 \omega^2}$$

---

1. Ignore phase:
    - $\theta = 0 \Rightarrow \cos(0) = 1$ and $\sin(0) = 0$.

Average Abundance: pulse wave at $t \gg 0$

$$R(t) = e^{-\gamma t} R(0) + (1 - e^{-\gamma t}) \frac{\phi k}{\gamma} + \frac{2k}{\pi} \sum_{n=1}^{N} \left(\frac{1}{n} \sin(\pi n \phi) \, I(t) \right)$$

$$I(t) = \frac{\gamma \cos(n\omega t) + n\omega \sin(n\omega t) - e^{-\gamma t}\gamma}{\gamma^2 + n^2\omega^2}$$

1. Ignore phase:
   - $\theta = 0 \Rightarrow \cos(0) = 1$ and $\sin(0) = 0$.
2. Stable oscillations **far from** initial transients:
   - $t \gg 0 \Rightarrow e^{-\gamma t} \to 0$.

Average Abundance: pulse wave at $t \gg 0$

$$R(t) = \frac{\phi k}{\gamma} + \frac{2k}{\pi} \sum_{n=1}^{N} \left(\frac{1}{n} \sin\left(\pi n \phi\right) I(t,\theta) \right)$$

$$I(t,\theta) = \frac{\gamma \cos(n\omega t) + n\omega \sin(n\omega t)}{\gamma^2 + n^2\omega^2}$$

1. Ignore phase:
   - $\theta = 0 \Rightarrow \cos(0) = 1$ and $\sin(0) = 0$.
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Average Abundance: pulse wave at $t \gg 0$

$$R(t) = \frac{\phi k}{\gamma} + \frac{2k}{\pi} \sum_{n=1}^{N} \left(\frac{1}{n} \sin\left(n\pi\phi\right) \frac{\gamma \cos(n\omega t) + n\omega \sin(n\omega t)}{\gamma^2 + n^2\omega^2} \right)$$

- Valid for stable oscillations, i.e., akin to a steady state solution?

Average Abundance: pulse wave at $t \gg 0$

$$R(t) = \frac{\phi k}{\gamma} + \frac{2k}{\pi} \sum_{n=1}^{N} \left(\frac{1}{n} \sin(n\pi\phi) \frac{\gamma \cos(n\omega t) + n\omega \sin(n\omega t)}{\gamma^2 + n^2\omega^2} \right)$$

$$\langle R \rangle = \frac{1}{\tau} \int_0^\tau \left(\frac{\phi k}{\gamma} + \frac{2k}{\pi} \sum_{n=1}^{N} \left(\frac{1}{n} \sin(n\pi\phi) \frac{\gamma \cos(n\omega t) + n\omega \sin(n\omega t)}{\gamma^2 + n^2\omega^2} \right) \right) \mathrm{d}t$$

$$\tau \langle R \rangle = \int_0^\tau \frac{\phi k}{\gamma} \mathrm{d}t + \frac{2k}{\pi} \sum_{n=1}^{N} \left(\frac{1}{n} \sin(n\pi\phi) \int_0^\tau \frac{\gamma \cos(n\omega t) + n\omega \sin(n\omega t)}{\gamma^2 + n^2\omega^2} \mathrm{d}t \right)$$

$$\tau \langle R \rangle = \tau \frac{\phi k}{\gamma} + \frac{2k}{\pi} \sum_{n=1}^{N} \left(\frac{1}{n} \sin(n\pi\phi) \frac{\gamma \sin(n\omega\tau) - n\omega \cos(n\omega t) + n\omega}{\gamma^3 + n^3\omega^3} \right)$$

with $\omega = \frac{2\pi}{\tau}$, $\sin(n2\pi) = 0$, and $\cos(n2\pi) = 1$

$$\tau \langle R \rangle = \tau \frac{\phi k}{\gamma} + \frac{2k}{\pi} \sum_{n=1}^{N} \left(\frac{1}{n} \sin(n\pi\phi) \frac{0 - n\omega + n\omega}{\gamma^3 + n^3\omega^3} \right)$$

$$\langle R \rangle = \frac{\phi k}{\gamma} \quad \square$$

Average Abundance: On/Off

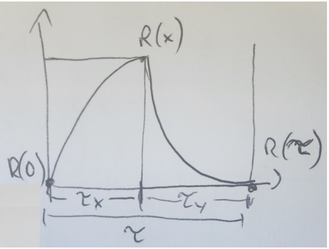
$$\langle R \rangle = \frac{1}{\tau}\left(\int_0^{\tau_x} R_{on}(t)\,\mathrm{d}t + \int_{\tau_x}^{\tau} R_{off}(t)\,\mathrm{d}t\right)$$

$$\int_0^t \dot{R}_{on}\,\mathrm{d}t = \int_0^t (k - \gamma R_{on}(t))\,\mathrm{d}t$$

$$\int_0^t \dot{R}_{off}\,\mathrm{d}t = \int_0^t -\gamma R_{off}(t)\,\mathrm{d}t$$

$$R_{on}(t) = \frac{k}{\gamma} + \left(R(0) - \frac{k}{\gamma}\right) e^{-\gamma t}$$

$$R_{off}(t) = R(\tau_x) e^{-\gamma t}$$



$$\int_0^{\tau_x} R_{on}(t)\,\mathrm{d}t = \frac{k\tau_x}{\gamma} + \frac{R(0) - k/\gamma}{\gamma}\left(1 - e^{-\gamma\tau_x}\right)$$

$$\int_{\tau_x}^{\tau} R_{off}(t)\,\mathrm{d}t = \frac{R(\tau_x)}{\gamma}\left(1 - e^{-\gamma(\tau - \tau_x)}\right)$$

$$\langle R \rangle = \frac{1}{\tau}\left(\frac{k\tau_x}{\gamma} + \frac{R(0) - k/\gamma}{\gamma}\left(1 - e^{-\gamma\tau_x}\right) + \frac{R(\tau_x)}{\gamma}\left(1 - e^{-\gamma(\tau - \tau_x)}\right)\right)$$

$$\langle R\rangle = \frac{1}{\tau}\left(\frac{k\tau_x}{\gamma} + \frac{R(0)-k/\gamma}{\gamma}\left(1-e^{-\gamma\tau_x}\right) + \frac{R(\tau_x)}{\gamma}\left(1-e^{-\gamma(\tau-\tau_x)}\right)\right)$$

$$R(\tau_x) = \frac{k}{\gamma} + \left(R(0)-\frac{k}{\gamma}\right)e^{-\gamma\tau_x}$$

$\Rightarrow$ replace $R(\tau_x)$ and isolate $R(0)$:

$$\begin{aligned}
\tau\langle R\rangle =& \frac{k\tau_x}{\gamma} + \frac{R(0)-k/\gamma}{\gamma}\left(1-e^{-\gamma\tau_x}\right) + \\
& \frac{1-e^{-\gamma(\tau-\tau_x)}}{\gamma}\left(\frac{k}{\gamma} + \left(R(0)-\frac{k}{\gamma}\right)e^{-\gamma\tau_x}\right) \\
\gamma\tau\langle R\rangle =& k\tau_x + \frac{k}{\gamma}\left(1-e^{-\gamma(\tau-\tau_x)}\right) \\
& + \left(R(0)-\frac{k}{\gamma}\right)\left(1-e^{-\gamma\tau_x} + \left(1-e^{-\gamma(\tau-\tau_x)}\right)e^{-\gamma\tau_x}\right) \\
\gamma\tau\langle R\rangle =& k\tau_x + \frac{k}{\gamma}\left(1-e^{-\gamma\tau}e^{\gamma\tau_x}\right) \\
& + \left(R(0)-\frac{k}{\gamma}\right)\left(1-e^{-\gamma\tau_x} + \left(1-e^{-\gamma\tau}e^{\gamma\tau_x}\right)e^{-\gamma\tau_x}\right) \\
\gamma\tau\langle R\rangle =& k\tau_x + \frac{k}{\gamma}\left(1-e^{-\gamma\tau}e^{\gamma\tau_x}\right) + \left(R(0)-\frac{k}{\gamma}\right)\left(1-e^{-\gamma\tau_x} + e^{-\gamma\tau_x} - e^{-\gamma\tau}\right) \\
\gamma\tau\langle R\rangle =& k\tau_x + \frac{k}{\gamma}\left(1-e^{-\gamma\tau}e^{\gamma\tau_x}\right) + \left(R(0)-\frac{k}{\gamma}\right)\left(1-e^{-\gamma\tau}\right) \\
\gamma\tau\langle R\rangle =& k\tau_x + \frac{k}{\gamma} - \frac{k}{\gamma}e^{-\gamma\tau}e^{\gamma\tau_x} + R(0) - R(0)e^{-\gamma\tau} - \frac{k}{\gamma} + \frac{k}{\gamma}e^{-\gamma\tau} \\
\gamma\tau\langle R\rangle =& k\tau_x + R(0)\left(1-e^{-\gamma\tau}\right) + \frac{k}{\gamma}e^{-\gamma\tau}\left(1-e^{\gamma\tau_x}\right)
\end{aligned}$$

$$R(0) = R(\tau) = R(\tau_x)e^{-\gamma(\tau-\tau_x)} \quad \Rightarrow \text{periodicity condition}$$

$$R(\tau_x) = \frac{k}{\gamma} + \left(R(0) - \frac{k}{\gamma}\right) e^{-\gamma\tau_x}$$

$$R(0) = \left(\frac{k}{\gamma} + \left(R(0) - \frac{k}{\gamma}\right) e^{-\gamma\tau_x}\right) e^{-\gamma(\tau-\tau_x)}$$

$$R(0) = \frac{k}{\gamma} e^{-\gamma\tau} e^{\gamma\tau_x} + \left(R(0) - \frac{k}{\gamma}\right) e^{-\gamma\tau_x} e^{-\gamma\tau} e^{\gamma\tau_x}$$

$$R(0) = \frac{k}{\gamma} e^{-\gamma\tau} e^{\gamma\tau_x} + R(0)e^{-\gamma\tau} - \frac{k}{\gamma} e^{-\gamma\tau}$$

$$R(0) - R(0)e^{-\gamma\tau} = \frac{k}{\gamma} e^{-\gamma\tau} e^{\gamma\tau_x} - \frac{k}{\gamma} e^{-\gamma\tau}$$

$$R(0)\left(1 - e^{-\gamma\tau}\right) e^{\gamma\tau} = \frac{k}{\gamma} \left(e^{\gamma\tau_x} - 1\right)$$

$$R(0) = \frac{k}{\gamma} \frac{e^{\gamma\tau_x} - 1}{e^{\gamma\tau} - 1}$$

$$\gamma\tau\langle R\rangle - k\tau_x = R(0)\left(1 - e^{-\gamma\tau}\right) + \frac{k}{\gamma}e^{-\gamma\tau}\left(1 - e^{\gamma\tau_x}\right)$$

$$R(0) = \frac{k}{\gamma}\frac{e^{\gamma\tau_x} - 1}{e^{\gamma\tau} - 1}$$ $\Rightarrow$ replace $R(0)$:

$$\gamma\tau\langle R\rangle - k\tau_x = \frac{k}{\gamma}\frac{e^{\gamma\tau_x} - 1}{e^{\gamma\tau} - 1}\left(1 - e^{-\gamma\tau}\right) + \frac{k}{\gamma}e^{-\gamma\tau}\left(1 - e^{\gamma\tau_x}\right)$$

$$\gamma\tau\langle R\rangle - k\tau_x = \frac{k}{\gamma}\frac{e^{\gamma\tau_x} - 1}{e^{\gamma\tau} - 1}\frac{e^{\gamma\tau} - 1}{e^{\gamma\tau}} + \frac{k}{\gamma}e^{-\gamma\tau}\left(1 - e^{\gamma\tau_x}\right)$$

$$\gamma\tau\langle R\rangle - k\tau_x = \frac{k}{\gamma}\frac{e^{\gamma\tau_x} - 1}{e^{\gamma\tau}} + \frac{k}{\gamma}e^{-\gamma\tau}\left(1 - e^{\gamma\tau_x}\right)$$

$$\gamma\tau\langle R\rangle - k\tau_x = \frac{k}{\gamma}\frac{e^{\gamma\tau_x} - 1}{e^{\gamma\tau}} + \frac{k}{\gamma}\frac{1 - e^{\gamma\tau_x}}{e^{\gamma\tau}}$$

$$\gamma\tau\langle R\rangle - k\tau_x = \frac{k}{\gamma}\frac{e^{\gamma\tau_x} - 1 + 1 - e^{\gamma\tau_x}}{e^{\gamma\tau}}$$

$$\gamma\tau\langle R\rangle - k\tau_x = +\frac{k}{\gamma}\frac{0}{e^{\gamma\tau}}$$, and with $\tau_x = \phi\tau$:

$$\langle R\rangle = \frac{\phi k}{\gamma} \quad \square$$

Amplitudes: Analytic Solution

- $\mathcal{A}_R = \max(R(t)) - \min(R(t))$,
- $\max(R(t))$ at $\frac{\mathrm{d}R}{dt} = 0$ and $\frac{\mathrm{d}^2R}{\mathrm{d}t^2} < 0$,
- $\min(R(t))$ at $\frac{\mathrm{d}R}{\mathrm{d}t} = 0$ and $\frac{\mathrm{d}^2R}{\mathrm{d}t^2} > 0$:

$$\begin{aligned}
\text{at } \frac{\mathrm{d}R}{\mathrm{d}t} &= 0 : \\
R &= \frac{\kappa(t)}{\gamma} \\
\frac{\mathrm{d}^2R}{\mathrm{d}t^2} &= \frac{\mathrm{d}\kappa(t)}{\mathrm{d}t} + \gamma\frac{\mathrm{d}R}{\mathrm{d}t} \\
\frac{\mathrm{d}\kappa(t)}{\mathrm{d}t} &= \frac{\mathrm{d}\frac{\phi k}{\gamma}}{\mathrm{d}t} + \frac{\mathrm{d}g(t)}{\mathrm{d}t} \\
g(t) &= \frac{2k}{\pi}\sum_{n=1}^{\infty}\left(\frac{1}{n}\sin(\pi n\phi)\cos(n\omega t)\right) \\
\frac{\mathrm{d}g(t)}{\mathrm{d}t} &= -\frac{2k\omega}{\pi}\sum_{n=1}^{\infty}\left(\sin(\pi n\phi)\sin(n\omega t)\right) \\
\frac{\mathrm{d}g(t)}{\mathrm{d}t} &= -\frac{4k}{\tau}\sum_{n=1}^{\infty}\left(\sin(\pi n\phi)\sin\left(n\frac{2\pi}{\tau}t\right)\right) \\
\frac{\mathrm{d}g(t)}{dt} &= 0 \text{ if } t = \tau
\end{aligned}$$

TODO: > 0 and < 0

Amplitudes: Analytic Solution

Note: the relative amplitude is independent of the transcription rate:

$$\widetilde{\mathcal{A}}_R = \frac{\mathcal{A}_R}{\langle R \rangle}$$

$$\widetilde{\mathcal{A}}_R = \frac{k}{\gamma} \frac{1 - e^{-\gamma\phi\tau}}{1 - e^{-\gamma\tau}} \left(1 - e^{\gamma\tau(\phi-1)}\right) \left(\frac{\phi k}{\gamma}\right)^{-1}$$

$$\widetilde{\mathcal{A}}_R = \frac{1 - e^{-\gamma\phi\tau}}{1 - e^{-\gamma\tau}} \left(1 - e^{\gamma\tau(\phi-1)}\right) \phi^{-1}$$

... and just depends on degradation rate, period and duty cycle.

Lück et al. (2014) relative amplitude for sine-wave production amplitude ($\widetilde{\mathcal{A}}_R$):

$$\widetilde{\mathcal{A}}_P = \widetilde{\mathcal{A}}_R \frac{\gamma}{\sqrt{\gamma^2 + \omega^2}}.$$

References:

Calabrese, L., J. Grilli, M. Osella, C. P. Kempes, M. C. Lagomarsino, and L. Ciandrini. 2022. "Protein Degradation Sets the Fraction of Active Ribosomes at Vanishing Growth." *PLoS Comput Biol* 18 (5): e1010059. https://doi.org/10.1371/journal.pcbi.1010059.

Lück, S., K. Thurley, P. F. Thaben, and P. O. Westermark. 2014. "Rhythmic Degradation Explains and Unifies Circadian Transcriptome and Proteome Data." *Cell Rep* 9 (2): 741–51.