Supporting Information for:
Optimal Length and Signal Amplification in Weakly Activated Signal Transduction Cascades

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1 Proof of the equality $\mathbf{C}_{\max}(\ell, R) = \mathbf{C}_*(\ell, R)$

Fix any $\ell > 0$, and any $R \in \mathcal{U}$. Recall the notation $\mathcal{C} = (n, \alpha_1, \ldots, \alpha_n, \beta_1, \ldots, \beta_n)$. Given any $\mathcal{C}, \mathcal{C}' \in \mathbf{C}_{K,\ell}$, the following equivalences hold:

$$\begin{aligned} & \sigma_0(n, \beta_1, \ldots, \beta_n) \leq \sigma_0(n', \beta'_1, \ldots, \beta'_n), \\ \Leftrightarrow \quad & \sqrt{\frac{1}{\ell^2} + \sigma_0(n, \beta_1, \ldots, \beta_n) + q(R)} \leq \sqrt{\frac{1}{\ell^2} + \sigma_0(n', \beta'_1, \ldots, \beta'_n) + q(R)}, \\ \Leftrightarrow \quad & \sigma(\mathcal{C}, \ell, R) \leq \sigma(\mathcal{C}', \ell, R) \end{aligned} \tag{1}$$

and also

$$\begin{aligned} \sigma(\mathcal{C}, \ell, R) \leq \sigma(\mathcal{C}', \ell, R) \quad & \Leftrightarrow \quad \frac{K\ \|R\|_2}{\sigma(\mathcal{C}, \ell, R)} \geq \frac{K\ \|R\|_2}{\sigma(\mathcal{C}', \ell, R)} \\ & \Leftrightarrow \quad \mathcal{A}(\mathcal{C}, \ell, R) \geq \mathcal{A}(\mathcal{C}', \ell, R). \end{aligned} \tag{2}$$

Therefore, (1) and (2) imply that, for any two cascades $\mathcal{C}, \mathcal{C}' \in \mathbf{C}_{K,\ell}$,

$$\sigma_0(n, \beta_1, \ldots, \beta_n) \leq \sigma_0(n', \beta'_1, \ldots, \beta'_n) \qquad \Leftrightarrow \qquad \mathcal{A}(\mathcal{C}, \ell, R) \geq \mathcal{A}(\mathcal{C}', \ell, R). \tag{3}$$

To show that $\mathbf{C}_*(\ell, R)$ is contained in $\mathbf{C}_{\max}(\ell, R)$, pick any $\mathcal{C} \in \mathbf{C}_*(\ell, R)$. Then

$$\sigma_0(n, \beta_1, \ldots, \beta_n) \leq \sigma_0(n', \beta'_1, \ldots, \beta'_n), \text{ for all } \mathcal{C}' \in \mathbf{C}_{K,\ell}.$$

By (3), this is equivalent to $\mathcal{A}(\mathcal{C}, \ell, R) \geq \mathcal{A}(\mathcal{C}', \ell, R)$, for all $\mathcal{C}' \in \mathbf{C}_{K,\ell}$, and so $\mathcal{C} \in \mathbf{C}_{\max}(\ell, R)$.

Conversely, we need to show that $\mathbf{C}_{\max}(\ell, R)$ is contained in $\mathbf{C}_*(\ell, R)$. So, pick any $\mathcal{C} \in \mathbf{C}_{\max}(\ell, R)$. It satisfies:

$$\mathcal{A}(\mathcal{C}, \ell, R) \geq \mathcal{A}(\mathcal{C}', \ell, R), \quad \text{for all } \mathcal{C}' \in \mathbf{C}_{K,\ell}.$$

Again by (3), this is equivalent to $\sigma_0(n, \beta_1, \ldots, \beta_n) \leq \sigma_0(n', \beta'_1, \ldots, \beta'_n)$ for all $\mathcal{C}' \in \mathbf{C}_{K,\ell}$. We conclude that $\mathcal{C} \in \mathbf{C}_*(\ell, R)$, as we wanted to show. ∎

2 Properties of function $f(k)$

The function $f : (1, \infty) \to (0, \infty)$

$$f(k) = k^2 \ \left[\left(1 + \frac{1}{k}\right) \ln\left(1 + \frac{1}{k}\right) - \frac{1}{k}\right]$$

has the following properties:

1. f is strictly increasing;

2. $f(1) = 2\ln 2 - 1 \approx 0.386$ and $\lim_{k\to\infty} f(k) = 1/2$.

To prove property 1, notice that another expression for f is $f(k) = k[(k+1)\ln\,(k+1)/k \; - \; 1]$, and compute the first and second derivatives:

$$\begin{aligned}\frac{d\,f}{dk} &= (2k+1)\;\ln\,\frac{k+1}{k} - 2\\ \frac{d^2\,f}{dk^2} &= (2k+1)\;\ln\,\frac{k+1}{k} + \frac{2k+1}{k(k+1)}.\end{aligned}$$

It is clear that the second derivative is always positive, and hence the first derivative is strictly increasing. Since $df/dk(1) = 3\ln 2 - 1 > 0$, it follows that the first derivative is also always positive and therefore the function f is strictly increasing.

To prove property 2, the value $f(1)$ is straightfoward, and for the limit as $k \to \infty$, it is easier to consider $x = 1/k$ and compute:

$$\lim_{k\to\infty} f(k) = \lim_{x\to 0} f(1/x) = \lim_{x\to 0} \frac{(1+x)\ln(1+x) - x}{x^2} = \frac{0}{0}.$$

This indeterminacy can be solved by twice applying L'Hôpital's rule:

...first time: $$\frac{\ln(1+x) + (1+x)\frac{1}{1+x} - 1}{2x} \to \frac{0}{0}, \quad \text{as } x \to 0$$

...second time: $$\frac{\frac{1}{1+x}}{2} \to \frac{1}{2}, \quad \text{as } x \to 0.$$

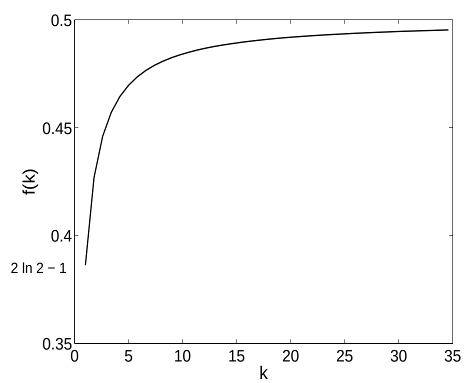

Figure 1: The function $f(k)$.

3 Minimization of σ_0

Let Q be a positive real number and $n > 2$ an integer. Consider the function $F : (0,\infty)^{n-1} \to (0,\infty)$ given by

$$F(B_1, \ldots, B_{n-1}) = B_1 + \cdots + B_{n-1} + \frac{Q}{B_1 \cdots B_{n-1}}.$$

Lemma 3.1 The choice of $B_i > 0$, $i = 1, \ldots, n-1$ that minimizes the function F is: $B_i = Q^{1/n}$, $i = 1, \ldots, n-1$.

Proof. First, we claim that the search for a point $(B_1, \ldots, B_{n-1})$ where F is minimized can be constrained to the compact set:

$$\left[\frac{1}{n^{n-1}}\, Q^{1/n},\ n\, Q^{1/n}\right]^{n-1}. \tag{4}$$

To justify the upper bound of the interval, observe that

$$F(Q^{1/n}, \ldots, Q^{1/n}) = n\, Q^{1/n} \tag{5}$$

and that, for any $j = 1, \ldots, n-1$,

$$B_j \geq n\, Q^{1/n} \quad \Rightarrow \quad F(B_1, \ldots, B_{n-1}) > n\, Q^{1/n}. \tag{6}$$

So, it is enough to look for a minimum of F in the region $B_i < n\, Q^{1/n}$, $i = 1, \ldots, n-1$ (because inside this region there is at least one point – equation (5) – where F has a lower value than anywhere outside of this region).

To justify the lower bound, suppose that $B_j \leq \frac{1}{n^{n-1}} Q^{1/n}$, for some $j = 1, \ldots, n-1$. Then using the already established upper bounds

$$F(B_1, \ldots, B_{n-1}) > \frac{Q}{B_1 \cdots B_j \cdots B_{n-1}} \geq \frac{Q}{\frac{1}{n^{n-1}} Q^{1/n}\ [n\, Q^{1/n}]^{n-2}} = n\, Q^{1/n}, \tag{7}$$

and similarly we conclude that it is enough to look for a minimum of F in the region $B_i > \frac{1}{n^{n-1}} Q^{1/n}$, for $i = 1, \ldots, n-1$.

The function F is continuous, in fact differentiable, in the compact set (4), and so F has (absolute) maximum and minimum values in this set. The maximum and minimum may be attained either at a critical point of F, or at the boundary points of (4). Equations (6) and (7) show that the minimum is not attained at any of the boundary points. So the minimum will be attained at an interior point of the set (4), which must also be a critical point of F. The critical points of F are given by:

$$\frac{dF}{dB_j} = 0 \quad \Leftrightarrow \quad 1 - \frac{1}{B_j} \frac{Q}{B_1 \cdots B_{n-1}}, \quad j = 1, \ldots, n-1,$$

or, equivalently,

$$B_j = \frac{Q}{B_1 \cdots B_{n-1}} = B_*, \quad j = 1, \ldots, n-1,$$

where B_* satisfies

$$1 - \frac{1}{B_*} \frac{Q}{B_*^{n-1}} = 0 \quad \Leftrightarrow \quad B_* = Q^{1/n}.$$

Thus, there exists a unique critical point of F, $(B_*, \ldots, B_*)$, which indeed belongs to the compact set (4). By the discussion above, this point must be the minimizer of F, as we wanted to show. ∎

4 Minimization of $F(n, M)$

For a fixed M, let the minimizer of $F(n, M)$ over $n \in \mathbb{N}$ be

$$n^*(M) := \{n \in \mathbb{N} : \ F(n, M) \le F(n', M), \quad \text{for every} \quad n' \in \mathbb{N}\},$$

Lemma 4.1 Let M be any fixed real number. Then $n^*(M) = \Psi(M)$.

Proof. Since $n^*(M)$ is the minimizer of $F(n, M)$ over the (positive) natural numbers, we start by computing the derivative of $F(n, M)$:

$$\frac{dF}{dn}(n, M) = \frac{1}{n} - \frac{1}{n^2}M = \frac{1}{n^2}\,[n - M].$$

We consider two distinct cases:

- Case $M \le 0$

$$\frac{dF}{dn}(n, M) > 0, \quad \text{for all } n \ge 1,$$

  so $F(\cdot, M)$ is a strictly increasing function and thus its minimizer over $\mathbb{N}$ is the smallest natural number, i.e., $n^*(M) = 1$.

- Case $M > 0$

$$\frac{dF}{dn}(n, M) = 0 \quad \Leftrightarrow \quad n = M,$$

  and the derivative is negative for $n < M$ and positive for $n > M$: in other words, the function F has indeed a minimum at $n = M$. However, in general, M is not an integer, so it cannot be a solution to our minimization problem. We should choose

$$n^*(M) = \begin{cases} 1, & M \le 1 \\ \lfloor M \rfloor, & M > 1, \text{ and } F(\lceil M \rceil, M) \ge F(\lfloor M \rfloor, M) \\ \lceil M \rceil, & M > 1, \text{ and } F(\lceil M \rceil, M) < F(\lfloor M \rfloor, M). \end{cases}$$

  Note that we pick $n^* = 1$ whenever $M \le 1$, since a cascade of length zero is meaningless.

To further analyze this condition, observe that we can write, for $M > 1$,

$$M = k + \delta, \ \lfloor M \rfloor = k, \quad \lceil M \rceil = k + 1$$

where $k \ge 1$ is the integral part of M and $\delta \in [0, 1)$ is the fractional part of M. Now, the point δ for which n^* "jumps" from $\lfloor M \rfloor$ to $\lceil M \rceil$ can be found by setting

$$\begin{aligned} 0 &= F(\lceil M \rceil, M) - F(\lfloor M \rfloor, M) = F(k+1, k+\delta) - F(k, k+\delta) \\ &= \ln(k+1) + \frac{1}{k+1}(k+\delta) - \ln k - \frac{1}{k}(k+\delta). \end{aligned}$$

Simplifying this equation we obtain:

$$\begin{aligned} \ln\frac{k+1}{k} - \frac{k+\delta}{k(k+1)} = 0 \quad &\Leftrightarrow \quad \delta = k(k+1)\,\ln\frac{k+1}{k} - k \\ &\Leftrightarrow \quad \delta = k^2\left[\frac{k+1}{k}\ln\frac{k+1}{k} - \frac{1}{k}\right] \\ &\Leftrightarrow \quad \delta = k^2\left[\left(1+\frac{1}{k}\right)\ln\left(1+\frac{1}{k}\right) - \frac{1}{k}\right] = f(k). \end{aligned}$$

Analysis of this function (see Appendix 2), shows that f is positive and strictly increasing, so we have

$$F(\lceil M\rceil, M) - F(\lfloor M\rfloor, M) \geq 0 \quad \Leftrightarrow \quad f(\lceil M\rceil) - \delta \geq 0.$$

Therefore, we should choose

$$n^*(M) = \begin{cases} 1, & M \leq 1 \\ \lfloor M\rfloor, & M > 1, \text{ and } \delta \leq f(\lfloor M\rfloor) \\ \lceil M\rceil, & M > 1, \text{ and } \delta > f(\lfloor M\rfloor). \end{cases}$$

This proves the Lemma. ∎

5 Dictionary: Laplace transforms and transfer functions

For further details about these topics see, for instance, [2] and [1], [3], [4].

Laplace transforms

For a function $X : (-\infty, \infty) \to \mathbb{R}^n$ (with $|X(t)| \leq ce^{kt}$, for all t, for some positive constants c, k), the Laplace transform is another function $\hat{X} : \mathcal{R} \to \mathbb{C}^n$ defined as

$$\hat{X}(s) := \int_{-\infty}^{\infty} e^{-st} X(t) dt$$

where $\mathcal{R} \subset \mathbb{C}$ is the region of convergence of the integral. For example, if $X(t) = e^{-3t}$, for $t \geq 0$ and $X(t) = 0$ otherwise, then $\hat{X}(s) = 1/(s+3)$, and $\mathcal{R} = \{s = s_{re} + \jmath s_{im} : \ s_{re} > -3\}$ ($\jmath$ is the imaginary number $\sqrt{-1}$).

Some of its properties are:

1. For any constant matrix $A \in \mathbb{R}^{n\times n}$

$$\widehat{AX}(s) = A\,\hat{X}(s);$$

2. The Laplace transform of the derivative of X is

$$\widehat{\frac{dX}{dt}}(s) = X(0) + s \int_{-\infty}^{\infty} e^{-st} X(t) dt = X(0) + s\,\hat{X}(s)\ ;$$

3. If $X(t+\delta) =: W(t)$ is a translation of X, then

$$\hat{W}(s) = e^{-s\delta} \hat{X}(s)\ ;$$

4. The inverse Laplace transform is

$$X(t) = \frac{1}{2\pi \jmath} \int_{s_{re} - \jmath\infty}^{s_{re} + \jmath\infty} e^{st} \hat{X}(s) ds$$

with $s = s_{re} + \jmath s_{im}$, where s_{re} is chosen so that $s_{re} + \jmath s_{im}$ is in the region of convergence $\mathcal{R}$.

Transfer function

Let $A \in \mathbb{R}^{n\times n}$, $B \in \mathbb{R}^{n\times m}$ and $C \in \mathbb{R}^{p\times n}$ be matrices, and let $X \in \mathbb{R}^n$, $Y \in \mathbb{R}^m$, $R \in \mathbb{R}^p$, and consider the n-dimensional linear system with m inputs and p outputs:

$$\frac{dX}{dt} = AX + BR, \tag{8}$$

$$Y = C\,X. \tag{9}$$

Applying the Laplace transform operator on both sides of the linear system (8)-(9) yields an *algebraic equation* relating the new functions $\hat{X}(s)$, $\hat{Y}(s)$ and $\hat{R}(s)$:

$$\begin{aligned} s\hat{X}(s) &= A\hat{X}(s) + B\,\hat{R}(s) \\ \hat{Y}(s) &= C\,\hat{X}(s). \end{aligned}$$

Moreover, for every s for which the matrix $sI - A$ is invertible (I is the identity matrix),

$$(sI - A)\,\hat{X}(s) = B\,\hat{R}(s) \quad \Rightarrow \quad \hat{X}(s) = (sI - A)^{-1}B\,\hat{R}(s)$$

and thus, one can solve immediately for the output

$$\hat{Y}(s) = C(sI - A)^{-1}B\,\hat{R}(s). \tag{10}$$

The transfer function of the system (8) is

$$\hat{G}(s) := C(sI - A)^{-1}B,$$

and *depends only on the internal structure of the system (i.e., A, B and C).*

Impulse response

A useful case is that of the impulse response:

$$R(t) = \delta(t), \qquad \Rightarrow \quad \hat{R}(s) \equiv 1$$

and therefore:

$$\hat{Y}(s) \equiv \hat{G}(s) \quad \Leftrightarrow \quad Y(t) \equiv G(t),$$

so that the transfer function of the system is the output corresponding to a single pulse of input.

The gain $\|\hat{G}\|_\infty$

We have

$$\|\hat{Y}\|_2^2 = \frac{1}{2\pi}\int_{-\infty}^{\infty} |\hat{G}(\jmath\omega)\hat{R}(\jmath\omega)|^2 d\omega \le \frac{1}{2\pi}\sup_\omega |\hat{G}(\jmath\omega)|^2 \int_{-\infty}^{\infty} |\hat{R}(\jmath\omega)|^2 d\omega$$

which is equivalent to

$$\|\hat{Y}\|_2 \le \|\hat{G}\|_\infty \|\hat{R}\|_2 \quad \Leftrightarrow \quad \|Y\|_2 \le \|\hat{G}\|_\infty \|R\|_2.$$

So, the infinity norm of the transfer function is an upper bound on the strength of the output.

To see that it is indeed the least upper bound, see for instance [3]: we can always choose a frequency ω_0 so that

$$\|\hat{G}\|_\infty = |\hat{G}(\jmath\omega_0)|.$$

In our case, this is $\omega_0 = 0$. Then choose a control such that

$$|\hat{R}(\jmath\omega)| = \begin{cases} r, & \text{if } |\omega| < \varepsilon \\ 0, & \text{otherwise,} \end{cases} \tag{11}$$

where $\varepsilon > 0$ and r should be such that $\hat{R}$ has unit 2-norm, for instance $r = \sqrt{\pi/\varepsilon}$. For very small $\varepsilon > 0$, $|\hat{R}(\jmath\omega)|$ is zero, except on a very small neighborhood of $\omega_0 = 0$ and we may approximate:

$$\begin{aligned} \frac{1}{2\pi}\int_{-\infty}^{\infty} |\hat{G}(\jmath\omega)|^2 |\hat{R}(\jmath\omega)|^2 \, d\omega &\approx \frac{1}{2\pi}\int_{-\varepsilon}^{\varepsilon} r^2 \, |\hat{G}(\jmath\omega_0)|^2 \, d\omega \\ &= \frac{1}{2\pi}|\hat{G}(\jmath\omega_0)|^2 \int_{-\varepsilon}^{\varepsilon} r^2 \, d\omega \\ &= \|\hat{G}\|_\infty^2 \end{aligned}$$

where the last equality follows from the definitions of ω_0 and r. Therefore

$$\|Y\|_2 = \left[\frac{1}{2\pi}\int_{-\infty}^{\infty} |\hat{G}(\jmath\omega)|^2 |\hat{R}(\jmath\omega)|^2 \, d\omega\right]^{\frac{1}{2}} \approx \|\hat{G}\|_\infty.$$

As an example of an input that (approximately) satisfies (11), consider $R(t) = 2\frac{r}{\pi t}\sin\varepsilon t$ (for $t \geq 0$), the input plotted in main text. Computation of the Laplace transform yields $\hat{R}(s) = \frac{r}{\pi}\left[\pi - 2\text{Arctan}\frac{s}{\varepsilon}\right]$, where the function Arctan is the principal branch of the complex inverse tangent function. It is possible to show that, for sufficiently small ε, the function $\hat{R}$ approximately satisfies condition (11), except at the discontinuity points $\omega = \pm\varepsilon$.

More generally, in a system with m inputs and p outputs, one defines the *internal gain of the system* $\|\hat{G}\|_\infty$ as the induced $\mathcal{L}^2$ operator norm of the map from the inputs to the outputs. It is possible to prove that

$$\|\hat{G}\|_\infty = \sup_{\omega\in\mathbb{R}} \bar{\theta}[\hat{G}(\jmath\omega)]$$

where $\bar{\theta}$ denotes the largest singular value of the matrix $\hat{G}(\jmath\omega)$.

Stability of the transfer function

As remarked above, expression (10) is valid if and only if the matrix $sI - A$ is invertible, or equivalently

$$s \neq \lambda, \quad \text{for every eigenvalue, } \lambda, \text{ of } A.$$

If $\lambda_m = \max\{\text{Re}(\lambda) : \lambda \text{ is an eigenvalue of } A\}$, then the region of definition of the transfer function is included in the set $\mathcal{R} = \{s = s_{re} + \jmath s_{im} : \; s_{re} > \lambda_m\}$.

If all the eigenvalues of the matrix A have negative real parts, then the transfer function is said to be stable. This is case for the matrix of the signaling cascade $dX/dt(t) = AX(t)+BR(t)$, $Y(t) = CX(t)$, whose eigenvalues are: $-\beta_1, \ldots, -\beta_n$, so the transfer function $\hat{G}(s)$ is stable and well defined on $\mathcal{R} = \{s = s_{re} + \jmath s_{im} : \; s_{re} > -\min\beta_i\}$.

References

[1] B.D.O. Anderson and J.B. Moore, Linear Optimal Control, Prentice Hall, Englewood Cliffs, NJ, 1971.

[2] G. Birkhoff and G-C. Rota, Ordinary Differential Equations, John Wiley and Sons, NY, 1978.

[3] J. Doyle, B. Francis and A. Tannenbaum, Feedback Control Systems, MacMillan Publishing Co, 1992. Also available on `http://www.control.utoronto.ca/-people/profs/francis/dft.html`.

[4] E.D. Sontag, Mathematical Control Theory: Deterministic Finite Dimensional Systems, (2^{nd} edition), Springer, NY, 1998.