

# Physics of Behavior

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## Exercise 5

1. **Circuit zoo.** In this exercise we will see which circuits have exact adaptation and fold change detection (FCD). Recall the conditions for FCD we learned in class: A general system with input  $x$ , output  $z$  and inner variable  $y$  is described by the equations:

$$\frac{dy}{dt} = f(x, y, z), \quad \frac{dz}{dt} = g(x, y, z)$$

a sufficient condition for FCD (Shoval et. al. PNAS 2010) is that the system is stable, that the output  $z$  shows exact adaptation, and that  $g$  and  $f$  satisfy the following homogeneity conditions for any  $\lambda > 0$ :

$$f(\lambda x, \lambda y, z) = \lambda f(x, y, z), \quad g(\lambda x, \lambda y, z) = g(x, y, z)$$

Consider the following circuits (they are all stable): Which of these circuits has exact adaptation (steady state output  $z$  that does not depend on constant input  $x$ )? Which has FCD?

$$\begin{array}{ll} \text{i) } \frac{dy}{dt} = x^2 - y, \quad \frac{dz}{dt} = \frac{x}{y} - z & \text{ii) } \frac{dy}{dt} = x - y^2, \quad \frac{dz}{dt} = \frac{x}{y} - z \\ \text{iii) } \frac{dy}{dt} = z y (z - 1), \quad \frac{dz}{dt} = \frac{x}{y} - z & \text{iv) } \frac{dy}{dt} = x - y, \quad \frac{dz}{dt} = x - yz \\ \text{v) } \frac{dy}{dt} = x - y, \quad \frac{dz}{dt} = \left(\frac{x}{y}\right)^n - z^m & \text{vi) } \frac{dy}{dt} = x(z - 1), \quad \frac{dz}{dt} = \frac{x}{y} - z \\ \text{vii) } \frac{dy}{dt} = z - 1, \quad \frac{dz}{dt} = x - y - z & \end{array}$$

2. **I1FFL input function for FCD.** We've seen previously how the I1FFL can have roles such as sign-sensitive response acceleration, pulse generation and biphasic dose response. Here we will see how the I1FFL as a pulse generator can also show FCD under certain conditions.

- a.** In the I1FFL, the activator  $x$  and repressor  $y$  together regulate the  $z$  promoter. Binding of  $x$  to the promoter can be described by the following process:  $x$  binds the free DNA site on the promoter  $[P]$  at rate  $k_{on}$  to form the complex  $[Px]$  ( $[P] + x \xrightarrow{k_{on}} [Px]$ ), and  $x$  falls off of the site at rate  $k_{off}$  ( $[Px] \xrightarrow{k_{off}} [P] + x$ ). Thus,  $\frac{d[Px]}{dt} = k_{on} [P] x - k_{off} [Px]$ . The total amount of the site is  $[P] + [Px] = 1$ .

Show that the amount of bound site at steady state is  $[Px] = \frac{x}{K_x + x}$ . What is  $K_x$ ?

- b.** Suppose that the activator  $x$  and the repressor  $y$  bind the promoter independently. The promoter is active and  $z$  is expressed from the promoter state in which  $x$  is bound and  $y$  is not. Explain why the promoter activity goes as

$$[Px \text{ not } y] = \frac{x}{(K_x + x)(K_y + y)}$$

- c.** When is the following approximation a good approximation:  $[Px \text{ not } y] \sim x/y$ ?

- d.** Show that an I1FFL which meets the above conditions, and has the following equation, shows FCD (see question 1).

$$\frac{dy}{dt} = x - y, \quad \frac{dz}{dt} = \frac{x}{y} - z.$$

3. **Solve the IFFL of question 2d.**

- a. Solve it numerically for a step change in  $x$  using a differential-equation-solving software.
- b. (Only if your math level is sufficiently strong, or if you want a challenge): Solve the dynamics of  $z$  exactly. (guidance: verify by direct differentiation that the general solution of an equation of the type  $dw/dt = f(t) - w$  is:

$$w(t) = e^{-t} \left( 1 + \int_0^t e^{\tau} f(\tau) d\tau \right).$$

Substitute  $f(t) = x/y(t)$ , and use the identity:  $\int \frac{a e^{2t}}{1+a e^t} dt = \frac{1}{a} (a e^t - \ln(1 + a e^t))$

c. What is the dependence of the peak  $z$  amplitude on the fold change  $F$  of a step of input  $x$ ? (hint:  $dz/dt = 0$  at two points along the dynamics of  $z$ : asymptotically for  $t \rightarrow \infty$ , and at the peak, that is  $z_{peak} = x/y(t_{peak})$ .)

d. Plot peak time (time of peak amplitude after a step of  $x$ ) as a function of fold change  $F$  of the step. Explain intuitively why peak time decreases with  $F$ .

4. **The PTH system.** The basic features needed for DC exist in many hormone systems, in which glands made of cells secrete hormones that work on other tissues. For example, blood calcium concentration is controlled tightly around 10mM by a hormone called PTH, secreted by the parathyroid gland. The circuit has a negative feedback loop similar to insulin-glucose, but with inverted signs: PTH causes increased release of calcium from body stores such as bone, and calcium inhibits PTH secretion. The effect of a unit of PTH on the release rate of calcium to the blood is  $S$ , a parameter called PTH-sensitivity. An additional slow feedback loop occurs because parathyroid cell proliferation is inhibited by calcium.

- a. Sketch the circuit for the PTH system.
- b. Schematically draw the dynamics over weeks if the PTH-sensitivity parameter  $S$  changes in a step-like manner. What component changes to compensate for the change in  $S$ ?
- c. Schematically draw the dynamics over hours after a pulse of calcium is added, in three different days: before, soon after and long after a step change in  $S$ .
- d. Write dynamical equations for this circuit.
- e. By converting the equations to rescaled variables, show that it has dynamic compensation for  $S$ .
- f. Read and summarize in 100 words or less about a common disease called hyperparathyroidism and suggest how it might be caused by problems in this circuit.