4xx Control 2 - Rate equations: switches and stability

One of the simplest control circuits is a single negative-feedback loop, where the presence of a particular protein (which we give the label *R*) inhibits its own production. An example of how this might work in the cell is the situation where a protein can bind to its own gene. When the concentration of *R* is low, then its small number of copies in the cell does little to inhibit the transcription of its mRNA. In contrast, when *R* is abundant, transcription is blocked by the binding of *R* to its gene. Thus, *R* builds to a certain critical concentration and then is held fixed at that level through negative feedback. In this situation, the production rate of *R* might be described by a single differential equation with a form like $du/dt = -u + u_{ss}$, where u_{ss} is the steady-state value of u.

A more general form of a regulatory system involves the variation of two quantities, which we denote by u and v, with a time dependence governed by the coupled equations

$$du/dt = -u + \alpha / (1 + v^n) \tag{1a}$$
$$dv/dt = -v + \alpha / (1 + u^n). \tag{1b}$$

Here, u and v might be concentrations of proteins in dimensionless units. For our applications, $n > 1$. If the parameter $\alpha = 0$, then the equations decouple and their solution is just exponential decay of u and v with time. Within the cell, this might be the case if a protein starts at a fixed concentration and decreases with time. More interesting behavior arises when $\alpha \neq 0$.

To understand the generic properties of Eq. (1), we start with the solution under steady state conditions where the time derivatives on the left-hand side of the equations vanish. Unlike the $\alpha = 0$ case, now the equations remain coupled in u and v:

$$u_{ss} = \alpha / (1 + v_{ss}^n) \tag{2a}$$
$$v_{ss} = \alpha / (1 + u_{ss}^n) \tag{2b}$$

These equations resemble the Hill functions (Sec. 9.5, *Mechanics of the Cell*). The *ss* subscripts identify u_{ss} and v_{ss} as steady state solutions.

First, we consider the situation when $\alpha >> 1$. There are three distinct functional regimes present:

Case 1 Assuming u_{ss} is small, then Eq. (2b) gives the form $v_{ss} = \alpha$, which can be substituted into Eq. (2a) to yield a consistent solution for u_{ss}. Thus,

$$u_{ss} = \alpha^{1-n} \qquad v_{ss} = \alpha. \tag{3}$$

Case 2 Next, assume v_{ss} is small and follow the same steps as Case 1 to obtain

$$u_{ss} = \alpha \qquad v_{ss} = \alpha^{1-n}. \tag{4}$$

Case 3 Now, u_{ss} and v_{ss} cannot be small simultaneously if $\alpha >> 1$ as inspection of Eq. (2) confirms. Thus, the only other possibility left is that they are both large simultaneously; solving Eq. (2) for this situation yields

$$u_{ss} = v_{ss} = \alpha^{1/(1+n)}. \quad (5)$$

Next, consider the opposite range of α, where $\alpha << 1$. Again, we start by assuming u_{ss} is small, so that Eq. (2b) yields $v_{ss} = \alpha$, from which $u_{ss} = \alpha$ according to Eq. (2a). Thus, one possible solution is

$$u_{ss} = v_{ss} = \alpha. \quad (6)$$

However, proposing that one of u_{ss} or v_{ss} is large does not yield a consistent solution upon substitution into Eq. (2). So, the regime with $\alpha << 1$ has only one solution, Eq. (6), not the three solutions present in Eqs (3) - (5) when $\alpha >> 1$.

Eqs. (3) to (6) are the asymptotic steady state solutions to Eq. (1) in two limits of the parameter α: there is one solution at small α and three solutions at large α. The next step is to find which solutions are stable. A mathematical test of the stability of solutions to a potential energy function $V(x)$ is that its second derivative must be positive: $d^2V/dx^2 > 0$ for stability. Graphically, a positive second derivative means that the shape of the potential energy curve around the solution is concave up and therefore stable. In Eq. (1), we are interested in the time-dependence of u and v around the values of u_{ss} and v_{ss}: if u is displaced slightly from the steady-state value, does it oscillate around u_{ss} indicating stability? Or does u move away from u_{ss} indicating instability? By introducing the small quantities $\delta_u(t)$ and $\delta_v(t)$ *via* the equations

$$u(t) = u_{ss} + \delta_u(t) \quad (7a)$$
$$v(t) = v_{ss} + \delta_v(t), \quad (7b)$$

the time dependence of the perturbations can be corralled into a set of equations for $\delta_u(t)$ and $\delta_v(t)$. To simplify the notation, Eq. (1) is rewritten as

$$du/dt = -u + g(v) \quad (8a)$$
$$dv/dt = -v + g(u), \quad (8b)$$

with

$$g(x) = \alpha / (1 + x^n), \quad (9)$$

so that the steady-state solutions obey $u_{ss} = g(v_{ss})$ and $v_{ss} = g(u_{ss})$. Combining Eqs. (8) with the series expansion $g(u) = g(u_{ss}) + g'(u_{ss})\delta_u$ [with a similar form for $g(v)$], yields

$$d\delta_u /dt = -\delta_u + g'(v_{ss})\delta_v \quad (10a)$$
$$d\delta_v /dt = -\delta_v + g'(u_{ss})\delta_u, \quad (10b)$$

where $g'(x)$ is the derivative of $g(x)$ with respect to x.

Assuming that unstable states diverge from their steady state solutions exponentially with time, we assign $\delta_u(t)$ and $\delta_v(t)$ the functional forms

$$\delta_u(t) = \delta_{uo} \exp(\lambda t) \qquad (11a)$$
$$\delta_v(t) = \delta_{vo} \exp(\lambda t), \qquad (11b)$$

where δ_{uo} and δ_{vo} are constants and λ is a rate constant. If $\lambda > 0$, the perturbation grows with time (unstable) whereas if $\lambda < 0$, it decays with time (stable); we have assumed that the same rate constant applies to u and v. Substituting Eq. (11) into Eq. (10) gives the set of coupled equations

$$(1 + \lambda)\, \delta_{uo} = g'(v_{ss})\, \delta_{vo} \qquad (12a)$$
$$(1 + \lambda)\, \delta_{vo} = g'(u_{ss})\, \delta_{uo}, \qquad (12b)$$

which can be combined to yield

$$1 + \lambda = \pm\, [g'(u_{ss})g'(v_{ss})]^{1/2}. \qquad (13)$$

The stability condition $\lambda < 0$ then imposes the requirement

$$g'(u_{ss})g'(v_{ss}) < 1, \qquad (14)$$

stable solutions

and that $g'(u_{ss})g'(v_{ss})$ be positive.

We now apply this stability analysis to the steady state solutions in Eqs. (3) - (6). Considering first the regime $\alpha << 1$, the solutions in Eq. (6) give $g'(u_{ss})g'(v_{ss}) = n^2\alpha^{2n}$. For small α and n greater than unity, α^{2n} must be much less than 1, so the single symmetric solution ($u_{ss} = v_{ss}$) is stable. However, in the regime $\alpha >> 1$, the solution in Case 3 leads to $g'(u_{ss})g'(v_{ss}) = n^2$, which must be larger than unity because $n > 1$. Thus, the symmetric solution $u_{ss} = v_{ss}$ is *unstable* at $\alpha >> 1$ even though the symmetric solution is stable at $\alpha << 1$. However, the remaining two solutions at $\alpha >> 1$ are both stable. The overall behavior of the stable solutions to Eqs. (2) is that there is a single, symmetric solution at small values of the parameter α, and two asymmetric solutions at large values of α. The large-α solutions have the properties of a switch, and the transition from a single solution regime to the switch regime occurs at a value of α that depends on n.