206. Switching in multi-stable systems

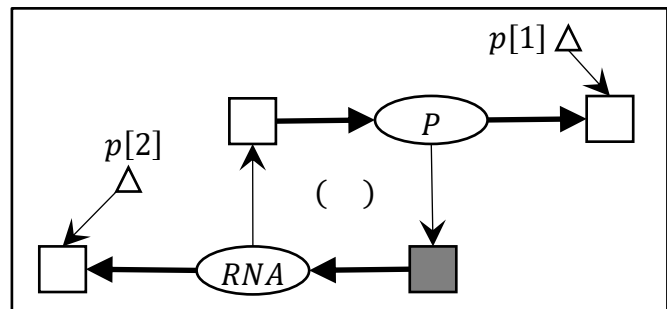## What new skills will I possess after completing this laboratory?
- **Describing** how the Griffith model of genetic switching works
- **Developing** an account of bifurcation from null-cline intersections

Why do I need these skills?
We saw in lab 204 that chaos is related to the idea that a small change in initial conditions can lead to a large change in long-term behaviour. This sensitivity to initial conditions also occurs in **multi-stable** systems, where the small change leads the system to switch between different stable states. Think of a light switch, where a small push flips the switch between the ON and OFF positions.

Multi-stability is the basis of computer storage (flip-flops), and is also important for eukaryotic cells. For although all cells in your body have the same DNA, they decide whether to become a cone cell in the eye or a B-cell in the immune system, and store this state over their lifetime.

In 1971, Griffith proposed the model shown on the right of how a **genetic switch** in the cell nucleus might work. Griffith considers a protein P that is translated from a messenger RNA R, and assumes that P positively regulates transcription of its own RNA (R). He assumes that this regulation is a *cooperative* phenomenon involving *two* molecules of P, and so is described by Hill kinetics together with degradation/dilution:

(1) $\dot{r} = \frac{V_{max}\, p^2}{K^2 + p^2} - br$

In addition, R is translated into P at a constant rate. Using the mathematical technique of *non-dimensionalisation*, we can reduce the complexity of Griffith's model without loss of generality by setting this transcription rate to 1, together with $V_{max} = K = 1$. Griffith's equations then become:

(2) $\begin{cases} \dot{p} = -ap + r \\ \dot{r} = \frac{p^2}{1+p^2} - br \end{cases}$

(i)   Write a julia module **Multistability.jl** that implements the Griffith model, and set $a = b = 1$ and $p(0) = r(0) = 0$. Check that your model runs as you expect.

(ii)   Now we will probe the Griffith model by injecting a single dose of 1 unit of P into the system. In your flow function, define:

injection = (abs(t-5)<0.1) ? 1.0 : 0.0

then add **injection** as a new term in the DE for p. If you run the model now over 50 seconds, you should see both P and R rise at 5s and then fall back to zero.

(iii)   The degradation rate a of P is a critical parameter of the model: set $a = 0.4$, then re-run the model. At 5s the system gets switched on *by a single event*!

(iv)   At the critical value $a_c = 0.5$, the Griffith system **bifurcates** (or *branches*) into a switch. That is, so long as a is greater than 0.5, the system has just one attractor at $p = r = 0$, but if a drops below 0.5, the system suddenly possesses two attractors at (0,0) and (2,0.8). Check the existence of the attractor at the origin by halving the dose of the P injection at 5s.

Bifurcation is an incredibly important phenomenon in biological systems – it describes the way organisms are capable of abruptly changing their behaviour under varying circumstances.

Example: Show that Griffith's system has three fixed points when $a < a_c$, where a_c is a critical value to be determined. What happens when $a = a_c$?

Solution: The nullclines of a DE are the sets of states in which one of the phase variables remains unchanging – i.e., when the corresponding rate of change is equal to zero. For example, if we set $\dot{p} = 0$ in the first equation (2), we find that $r = ap$, which is the equation of the straight line in the phase diagram on the right. If, on the other hand, we set $\dot{r} = 0$, we find that r remains unchanging on the S-shaped curve $r = p^2/[b(1 + p^2)]$ in the diagram. The critical points of the system, where both p and r remain unchanging, lie at the intersection of these two nullclines.
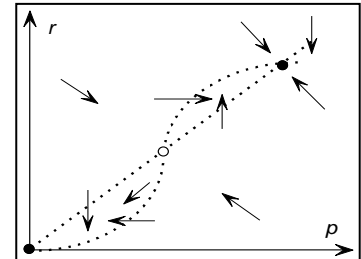
Now suppose we vary a while holding b constant. This is easy to visualise, since a is the slope of the straight line. We see from the diagram that for large values of a the two nullclines intersect at only one point $(0,0)$, but as a gets smaller, the straight nullcline becomes tangent to the curve and suddenly two more intersections pop into existence. A **bifurcation** is any case where critical points appear or disappear, and in this particular case, the **bifurcation parameter** a determines when these new points appear.

(v)   To calculate a_c, we compute the critical points, then see where they merge. The nullclines intersect when $ap = p^2/[b(1 + p^2)]$, which has a trivial solution at $(0,0)$. Show that the other intersections satisfy the quadratic equation $ab(1 + p^2) = p$. Solve this equation and show that the solutions merge when $a_c = 1/2b$ (where $p = 1$).

The nullclines in the diagram tell us a lot about the phase portrait for $a < a_c$. The vector field $(\dot{p}, \dot{r})$ is vertical on the line $r = ap$ and horizontal on the S-shaped curve. We can sketch other arrows by noting the signs of $\dot{r}$ and $\dot{p}$ from equations (2). It seems that the middle fixed point is a saddle and the other two are attractors (see right).
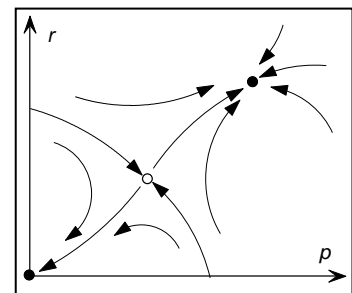
The biological interpretation of this phase portrait is that Griffith's model acts like a *genetic switch*, provided P decays slowly enough. In this case, there are two stable steady states: one at the origin, meaning that the gene is silent and there is no protein around to turn it on; and one where p and r are large, meaning that the gene is active and sustained by the high level of P.

(vi)   Now apply your knowledge of phase diagrams, bifurcation and saturation to develop an ecological model of spruce budworm outbreaks that destroy Canadian forest by eating leaves of the balsam fir tree. Three factors influence budworm growth: the budworm population (x), vegetation quality (v) and the bird predators that eat budworms. Vegetation provides budworms with both food and shelter from birds. Here are the equations:

$$\dot{x} = r_x\, x(1 - x/K_x) - \frac{Bx^2}{A^2 + x^2} \qquad x(0) = 30 \qquad r_x = 0.1 \qquad K_x = 4v \qquad B = 200$$
$$\dot{v} = r_v(K_v - x) \qquad\qquad\quad v(0) = 2000 \quad r_v = 0.1 \quad K_v = 3000 \quad A = 0.5v$$

Write a short report presenting arguments, a simulation and recommendations to the Canadian Forestry Commission regarding budworm behaviour over time, explaining carefully the ecological significance of all expressions, relationships and constants in your report.