

### Asymmetric noise without deterministic asymmetry

Given that slight noise asymmetries can create interesting system asymmetries (for example, in state occupancy bias) even without any deterministic asymmetry, one faces a natural question: how can one rig up a system with no deterministic asymmetry, but a little noise asymmetry?

From the point of view of Gillespie's derivation of the chemical Langevin equation, the problem might at first seem impossible. Supposing the concentration of a species  $x$  is affected by reactions with propensities  $a_1(x)$ ,  $a_2(x)$ , and  $a_3(x)$  (with species change numbers  $\nu_1, \nu_2, \nu_3 \in \{+1, -1\}$ ), the chemical Langevin equation reads

$$dx = [\nu_1 a_1(x) + \nu_2 a_2(x) + \nu_3 a_3(x)] dt + \sqrt{a_1(x) + a_2(x) + a_3(x)} dW ,$$

where  $W$  is a Wiener process. Naively, one expects that whatever terms show up in the deterministic part must show up in the noise part as well.

But with just a little more thinking, we can realize that terms can *cancel* in the deterministic part, but remain in the noise part. For example, suppose that  $\nu_1 = 1$ ,  $\nu_2 = 1$ , and  $\nu_3 = -1$ . Then we have

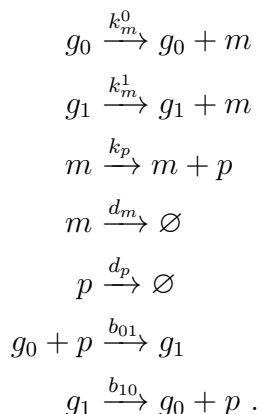
$$dx = [a_1(x) + a_2(x) - a_3(x)] dt + \sqrt{a_1(x) + a_2(x) + a_3(x)} dW .$$

If the reactions associated with  $a_2(x)$  and  $a_3(x)$  are in equilibrium (so that  $a_2(x) = a_3(x)$ ), then we have

$$dx = [a_1(x)] dt + \sqrt{a_1(x) + a_2(x) + a_3(x)} dW .$$

In other words, the reactions  $a_2(x)$  and  $a_3(x)$  no longer affect what happens on average, but *do* affect the noise about the mean. In general, one can imagine many reactions roughly at equilibrium contributing mostly to a system's noise.

Let's consider a specific example: a gene that regulates itself (via first-order binding). The associated reactions are



The protein concentration  $p$  changes according to

$$dp = [k_p m - d_p p - b_{01} g_0 p + b_{10} g_1] + \sqrt{k_p m + d_p p + b_{01} g_0 p + b_{10} g_1} dW .$$

If the self-binding is at equilibrium (and there are  $G = g_0 + g_1$  total available gene sites), then

$$\begin{aligned} b_{01} g_0 p &= b_{10} g_1 \\ \implies b_{01} g_0 p &= b_{10} (G - g_0) \\ \implies b_{01} g_0 p &= b_{10} G - b_{10} g_0 \\ \implies g_0 &= \frac{b_{10} G}{b_{01} p + b_{10} g_0} , \end{aligned}$$

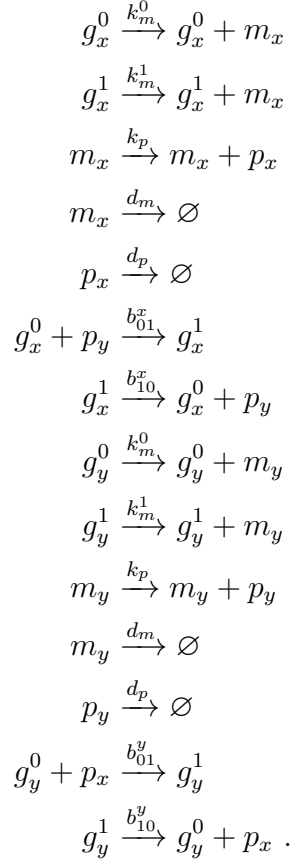
so that the amount of  $g_0$  changes approximately instantaneously as the protein concentration  $p$  changes. Our SDE reads

$$dp = [k_p m - d_p p] + \sqrt{k_p m + d_p p + b_{01} g_0 p + b_{10} g_1} dW .$$

The parameters  $b_{01}$  and  $b_{10}$ , on which there are no restrictions, now tune how much *extra noise* there is.

Can we use this to rig up a bistable switch with asymmetric noise, but symmetric deterministic terms? I think so. Here's a list of reactions analogous to the list above, for two genes

that inhibit each other's transcription:



As you can see, all of the transcription, translation, and degradation parameters are symmetric. What is *not* symmetric are the binding parameters. Assuming as before that binding is at quasi-equilibrium, the protein concentration SDEs read

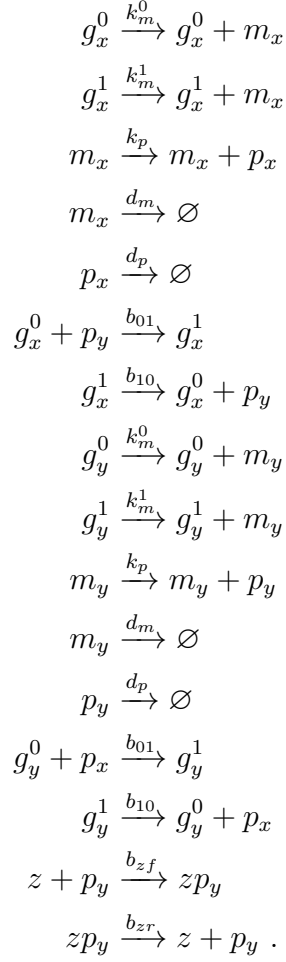
$$\begin{aligned}
dp_x &= [k_p m_x - d_p p_x] + \sqrt{k_p m_x + d_p p_x + b_{01}^x g_x^0 p + b_{10}^x g_x^1} dW_x \\
dp_y &= [k_p m_y - d_p p_y] + \sqrt{k_p m_y + d_p p_y + b_{01}^y g_y^0 p + b_{10}^y g_y^1} dW_y ,
\end{aligned}$$

which look pretty symmetric.

Of course, it turns out that we are cheating a little.  $m_x$  and  $m_y$  follow slightly different dynamics, because they depend on  $g_x^0/g_x^1$  and  $g_y^0/g_y^1$ , respectively (which depend on the binding parameters).

We can construct a purer example. Take the previous mutual inhibition system, and make the binding parameters *exactly* the same, so that the system is *completely* symmetric. But now suppose that species  $y$  binds reversibly to species  $z$ , and that this binding is at quasi-equilibrium. The list of reactions is almost the same as before, but now we add the extra

binding:



The protein concentration SDEs are

$$\begin{aligned}
dp_x &= [k_p m_x - d_p p_x] + \sqrt{k_p m_x + d_p p_x + b_{01} g_x^0 p + b_{10} g_x^1} dW_x \\
dp_y &= [k_p m_y - d_p p_y] + \sqrt{k_p m_y + d_p p_y + b_{01} g_y^0 p + b_{10} g_y^1 + b_{zf} z p_y + b_{zr} (z_{tot} - z)} dW_y ,
\end{aligned}$$

which now *only* differ in the additional noise terms.

In short, we *can* obtain asymmetric noise without deterministic noise. This can be achieved by tweaking binding parameters (although this does not leave the deterministic parts *completely* symmetric), and by having one species experience a reversible reaction in quasi-equilibrium that the other does not experience.