# Scooped!  Twice in one day.

One of the interesting, and occasionally maddening, features of working in fast-moving fields of science is that that same idea can occur to multiple people at the same time, so that they end up working in parallel, usually unknowingly. Often it is only when the first of these people publishes that the other(s) realize that they were not the only ones working on a problem. Reading a paper that describes success in something one has been trying to do oneself is a bitter-sweet experience. Proof that the task can be completed is exciting, but it is not possible for most of us mere humans to shake off the feeling that, as Prof Ron Laskey once put it in one of his songs about science, everything about the paper is perfect, except for the authors' names at the top.

This has just happened to us. One of the long-standing interests of this lab is using the techniques of synthetic biology to engineer patterning systems that theoreticians have proposed so that they can be tested  in real living cells. Patterning is the process by which a zone of initially identical cells (a 'field', in the jargon of embryology) organizes itself to produce a pattern of cells that are no longer identical,  for example, black and white stripes on animal skin. Elise Cachat in my laboratory published the first example of a synthetic patterning system in mammalian cells a few years ago (see my earlier blog article 'Painting by numbers', or the published paper in the 'links' section at the end of this article). Our design and construction of that system was actually a branch line off a longer-term plan, a plan to build a system that creates patterns according to the ideas of the British mathematician, Alan Turing. Elise's achievement in building her patterning system was one factor in her winning a prestigious group-leader position in this university's College of Science and Engineering. Her move put the longer project on hold for a while, but recently Alazne Dominguez-Monedero, who replaced Elise, picked up the baton to continue the Turing project and is at the moment about 3 months, I would estimate, from completing it.

Classical Turing patterning uses two molecules, an 'activator' and an 'inhibitor'. The activator activates both its own synthesis and that of the inhibitor, while the inhibitor inhibits all actions of the activator. If the activator diffuses (spreads out) only slowly but the inhibitor diffuses quickly, the system is unstable. An area that happens to make lots of activator will experience a high concentration of that activator, because it does not move quickly. It will also necessarily make a lot of inhibitor, but this diffuses away so that it does not build up enough to block all of the activator

locally, and activation wins. Neighbouring areas, though, are flooded by inhibitor flowing from the area of strong activation, so they are prevented from being activated themselves. Far enough away, there is too little inhibitor to block activation, and another activator peak can arise. The dynamics are complicated, and describing them properly requires differential equations rather than English sentences - the bottom line is that a Turing system can bootstrap itself from random noise to patterns (spots, stripes etc).

We have been trying to make this system using two proteins as our signals, the activator being a protein of the Wnt family, chosen because we can control whether it diffuses quickly or slowly, and the inhibitor being a fast-diffusing antagonist of Wnt activity. Alazne has so far built a system that produces Wnt in response to Wnt, and is right now in the course of adding the inhibitor to the system.

A couple of days ago, she knocked at my door, carrying a thin sheaf of printed papers hanging limply from her hand, and appeared with a long face quite uncharacteristic of her usual sunny disposition.
“I have a preprint from *BioRXiv*”, she said. “there’s a working Turing system in Kobe”.
We settled down to read and discuss the paper, from Ryoji Sekine, Tatsuo Shibata and Miki Ebisuya at the RIKEN Center, Kobe, Japan. It describes a superb piece of work, which created either a Turing pattern, or at least something very similar (the authors themselves are not certain, as they explain in the Discussion section of their paper). Their system used not Wnt, but two molecules called Nodal and Lefty, which are thought to make Turing patterns in real embryos (see the Muller paper in the 'links' section). Despite the discomfort of being 'scooped', we both enjoyed reading the paper and really enjoyed the conclusion that Turing (/ Turing-like) systems can really work in the simple two-component forms that Turing suggested. The researchers also went to show that their activator diffuses slowly because it interacts with the matrix under cells, and that if they modified it so that it could not interact this way, it diffused quickly and Turing patterning failed. It is, as I said, a beautiful piece of work and we applaud it.

Being scooped when close to the end of a project (but not close to the end of the postdoctoral fellowship) raises questions about what to do next. The problem for someone in Alazne's position is that being the second scientist to do something does not carry as much career-progressing fame as being the first. For this reason, we have been planning some other directions in which to take the

cells she has already made, still to do patterning, but in a different way. I would still like her, or someone in the lab, to complete the Turing project though. It would be genuinely informative to have two systems to compare, and having both would also open the door to having two orthogonal (non-interacting) Turing patterning systems operating in the same field of cells, potentially producing very complex and interesting behaviour. It might even be possible to use one to make a pattern at large scale and the other to sub-pattern elements within the larger patter (to make 'stripes' that consist of lines of spots, for example).

The title of this blog mentions two scoops in one day. The other was not scientific at all, and to be honest not wholly serious (we were not really intending to publish!) but, since it came on the same day, I cannot resist mentioning it. It has to do with a joke "book / poster project" began in a silly moment. Katie and I were in a bookshop some months ago and found ourselves near the children's section, facing one of those alphabet-learning classroom posters with letters, pictures, and phrases such as '*A is for Apple*, *B is for Ball*, *C is for Cat*…'. Katie was admiring the drawing of the cat cuddled by a devoted child. I agreed it was a great image, but offered the opinion that it would have been better with the focus being on the child, under the banner 'A'; '*A is for Ailurophile*'.
"'*Ah...*", she said, catching on at once to my 'helpful' educational concept of picking a word that has a first syllable beginning with with 'A' but sounding like 'Eye…' .
"*to go with 'G is for Gnome'.*", she proposed.
And so was born our idea of a 'helpful' alphabet learning tool, in which every letter is represented by a word that starts with a sound completely uncharacteristic of its first letter. Some were easy to find, but some have proved a lot more challenging for us. For the record, this is the list we had assembled so far:

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|---|---|---|---|
| A is for Ailurophile | H is for Honorarium | O is for Oestrogen | V is for ??? |
| B is for Bdellium | I is for Ibo | P is for Phone | W is for Wrath |
| C is for Cnidarian | J is for Jalapeno | Q is for Qi | X is for Xhosa |
| D is for Djinn | K is for Knot | R is for ??? | Y is for Yttrium |
| E is for Eiderdown | L is for Llewellyn | S is for Sugar | Z is for ??? |
| F is for ??? | N is for Ngoma | T is for Tsumani | |
| G is for Gnome | M is for Mnemonic | U is for Uakari | |

While puzzling over the letters we have still not managed to complete, we added other helpful educational ideas, such as the mathematics poster that says;

1 AND 1 = 1

1 AND 2 = 0

1 AND 3 = 1

1 AND 4 = 0

2 AND 2 = 2

….and so on. I don't imagine any readers of this blog would confuse the word 'AND' with 'Plus', so won't labour the Boolean explanation.

Well, about an hour after my conversation with Alazne, Katie sent me an e-mail containing the news that a "helpful" alphabet book of exactly the type described above has been published and has hit the NYT best-seller list. It is called "*P is for pterodactyl: the worst alphabet book ever*", and has been written by Raj Haldar (see Links). I am so glad that something of this type has been published, but apparently (I have not seen the book, only read the review) its authors did not find words for every letter either, but used some negatives (eg 'U is not for you'). Hmmm…. If I am going to be scooped, I would rather that, like the Turing paper, the scoop is an honest-to-goodness great piece of work that fully achieves an aim, not one that involves cheating! If you have kids, though, do consider buying them *P is for Pterodactyl*: something that teaches English as a playground of wonders will do so much more for them than a dull classroom poster that makes our mad language seem predictable and boring.

Jamie Davies
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Links:

Elise's paper: http://www.nature.com/articles/srep20664

The BioRXiv preprint of the paper that scooped us:
https://www.biorxiv.org/content/early/2018/07/20/372490

The Muller paper: http://science.sciencemag.org/content/336/6082/721

P is for Pterodactyl: https://www.amazon.com/Pterodactyl-Worst-Alphabet-Book-Ever/dp/1492674311