Waites and measures.

As some of these blog articles (eg *Painting by numbers*, and *Elise's holey relic*) have indicated, this lab has an interest in the mechanisms of biological pattern formation, and in testing theories about it by trying to teach naive cells how to make patterns they never evolved to make. One of the problems involved in studying pattern formation is finding a good way to measure how 'patterned' something is. At first sight, it may seem odd that this is any problem at all, as patterns are easy to see: the coat of a tiger clearly has a colour pattern on it in a way that the coat of a polar bear does not. But imagine having to compare the ability of different experimental systems, in a culture dish, intended to make tiger-like stripes (say), to work out which works best or fastest. This needs not simple recognition, but some kind of quantitative measure. Ideally, this measure should be as free as possible from human interpretation, because humans are very good at seeing patterns, shapes and connections even when there are none (think of the constellations we make of randomly placed stars that have no connection to one another).

In our previous work (see the *Painting by numbers* piece in this blog series), we measured the positions of cells of the same colour (green or red) and asked whether that distribution of cells, with the clustering of like colours together into patches when pattern formation had taken place, was statistically distinguishable from randomness. Using the Kolmogorov-Smirnoff test (which, disappointingly, works mathematically, not by measuring how much Smirnoff one has to drink before the images become indistinguishable), we could show that patterns formed. Fortunately, we had no particular requirement to make any measurements more detailed than that. The experience had, though, warned us that it would be very helpful for the future if we could.

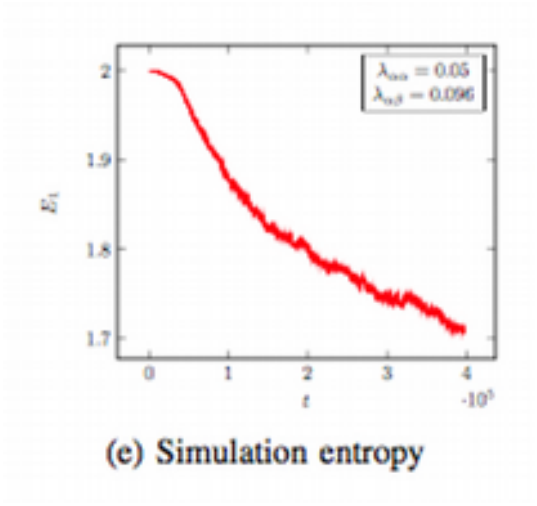
Some time later, Elise and I were discussing this at an informal meeting of some of the synthetic and systems biologists of this parish, and William Waites (right), a physicist new to the group, expressed an interest in the problem. This first chat was followed up by a more detailed meeting between William, me, and his colleague Matteo Cavaliere: in the grand traditions of science, it was held in a beer garden, in this case in the old Dick Vet School at Summerhall.

The collaboration, which quickly brought in Vincent Danos on the theory side and Elise Cachat on

the practical, has just resulted in our publishing a new measure for patterning (see links): I say 'we' but really the lion's share of the credit belongs to William.

One of the important decisions William made, in guiding this work, was that the measure should work equally well for images from real experiments and from simulations and should, within reason, work independently of image resolution so that pictures of the same object taken, for example, with different microscopes would yield the same measure of how patterned it is. Since it would be very useful in future, to compare computer predictions with real images, this feature was very important.

In designing his measure, William drew on graph theory, information theory, and the theory of probability. Or, as I would summarize it, 'scary maths'. From these foundations, he developed a measure called Path Entropy, which can be calculated (by computer) from analysis of 2-dimensional images. Like other instances of 'entropy', in both physics and information theory, Path Entropy is high when things are distributed randomly and falls as a random mess resolves into a pattern. In simulations of the real biological patterning system Elise and I had already built, Path Entropy fell with time as patterning took place (see the graph to the left of this text: the y axis shows Path Entropy and the x axis shows a measure of time, in this case in processing steps rather than actual seconds).



(e) Simulation entropy

Having this measure allowed us to begin to explore the effect of different conditions (eg cell adhesion strengths) on patterning. To do this, William brought a large, fast and very loud computer to my lab, on the grounds that it was far too noisy to be used 24/7 in an office, but just about acceptable in the already-noisy environment of a laboratory. The computer churned away on simulation after simulation, giving us welcome winter warmth from its roaring fans, and after

a while we almost forgot it was there. Then came the day that William arrived again, to announce that the simulations were complete. They had produced clear predictions for how Path Entropy would decrease (ie patterning would increase) would be faster or slower according to the difference in cell adhesion in our system. This is shown in the graph to the right: again, Path Entropy is on the y axis and time on the x axis. The different coloured lines adhesion strengths between cells of different colours. We have not yet verified this in real life because, while making adjustments to cell-cell adhesion is relatively trivial – in the system we use it can be adjusted by reducing the concentration of free calcium in the medium –actually measuring the adhesion quantitatively is difficult. Verification will therefore have to wait until we have the resources (time) to do it.

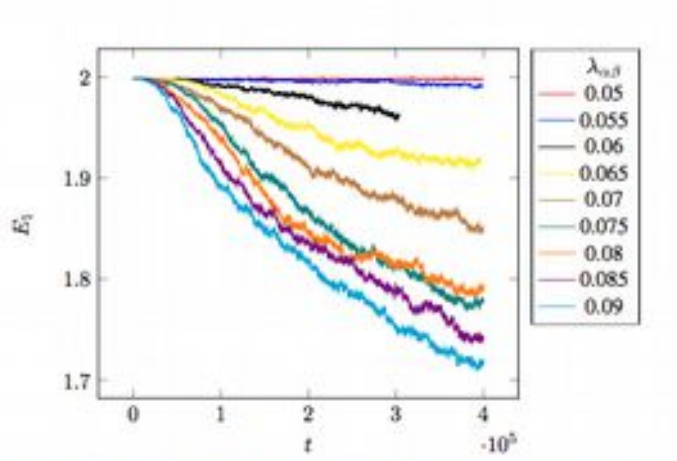


Fig. 3: Path entropy time series for simulations with various values for the heterotypic edge cost, $\lambda_{\alpha\beta}$. In all cases the homotypic value is $\lambda_{\alpha\alpha} = 0.05$.

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Links

The paper (early access version from journal site) https://ieeexplore.ieee.org/document/8405520/