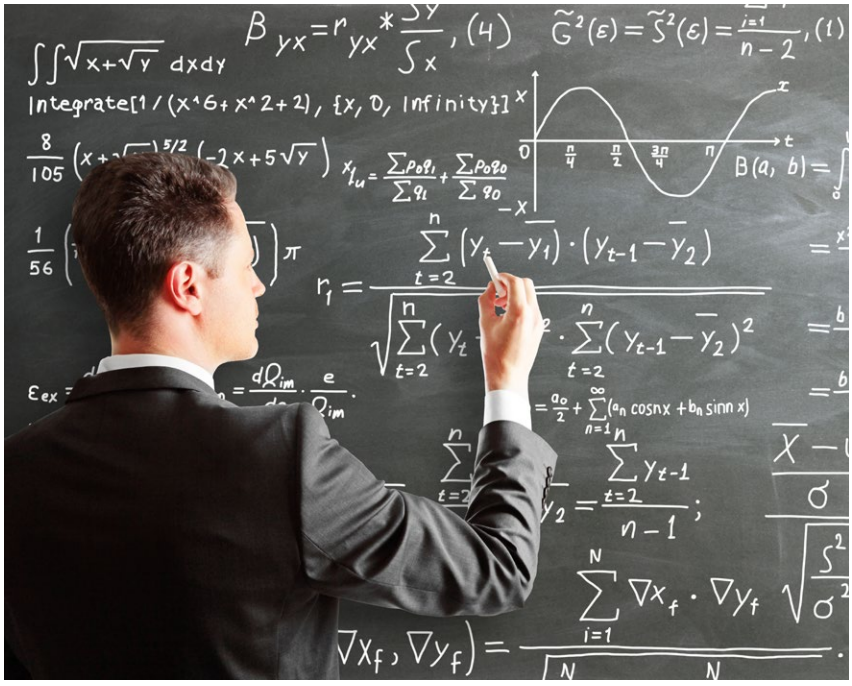
Predicting Pattern formation of real-world multicellular systems using Statistical Physics and a new metric

A revolutionary new approach to predicting pattern formation has been developed by Professor Hyun Youk's group at the Delft University of Technology based in the Netherlands. By creating a new metric, statistical physics can now be applied to previously unapproachable, real-world, multicellular systems which greatly advances the world of biophysics. Using cellular automata, Youk and his team found that the spatial patterns of cells formed via computer simulation followed an identical formation trajectory that is found in the complex systems of biological cells in nature.

Whether it's the hypnotic swirls of a distant galaxy or the playful collection of patches that give a chameleon its signature look, patterns can be found throughout the universe. But just exactly how do these majestic sequences form? There isn't an external presence that organises all the pieces of the puzzle into a final picture so there must be something driving them to arrange themselves into the structures we see today.

Professor Hyun Youk and his team based at the Delft University of Technology in the Netherlands are trying to answer that very question by turning their attention to the very foundations of spatial patterns – cells. While these cells can represent living cells in nature, in the context of pattern formation, they are a single, generic entity that can interact with other cells around them to form patterns.



Dis-satisfied with the conventional approach for analysing patterns Youk and his team have crafted a brand new approach to examine how these formations can emerge.

The current method for studying pattern formation is known as the Turing Mechanism (developed by Alan Turing in 1952). It's a highly sophisticated approach that requires at least several thousand cells (if not millions) that are closely packed together – like a continuous fluid of cells – and uses complex reaction-diffusion equations to simulate the shape of the pattern produced. There are several negatives to this approach, such as the equations needing complex simulations, but the particular bug-bear is that the Turing Mechanism does not provide a concrete way of measuring the spatial order of the patterns (i.e., how organised one pattern is compared to another) and it's this measurement that Youk and his team wish to study further.

CELLULAR AUTOMATON

To uncover spatial order, he and his students, turned to Cellular Automaton – a modelling technique often used in theoretical biology and physics. Cellular Automaton involves creating a grid of cells (also known as a lattice), where each cell can have a set number of states – typically these states are either *on* or *off*. Each cell in the lattice is surrounded by many others and this collection of surrounding cells is known as a neighbourhood. Each neighbourhood is defined relative to a specific cell.

The initial stage of the cellular lattice is when time (t) is set to zero (t=0). As the time is increased (t=1), the state of each of these cells is updated by a mathematical function which is run with

each increment of time. Over time, the state of one cell may have an effect on its neighbourhood, and in turn, the state of neighbouring cells may have an effect on one another. This is Cellular Automaton at its most basic approach.

To build on this Youk introduced intracellular signalling (within the cell) and intercellular signalling (outside of the cell) by a creating what he likes to call "secrete-and-sense cells" (SAS cells). These cells will a) secrete a signalling molecule and b) have a receptor on them that binds to the molecule. This means that a SAS cell will be able to capture its own molecule once it has secreted it – this is known as "Self-Communication". The secreted molecules can also bind to the other SAS cells in its neighbourhood – this is "Neighbour Communication".

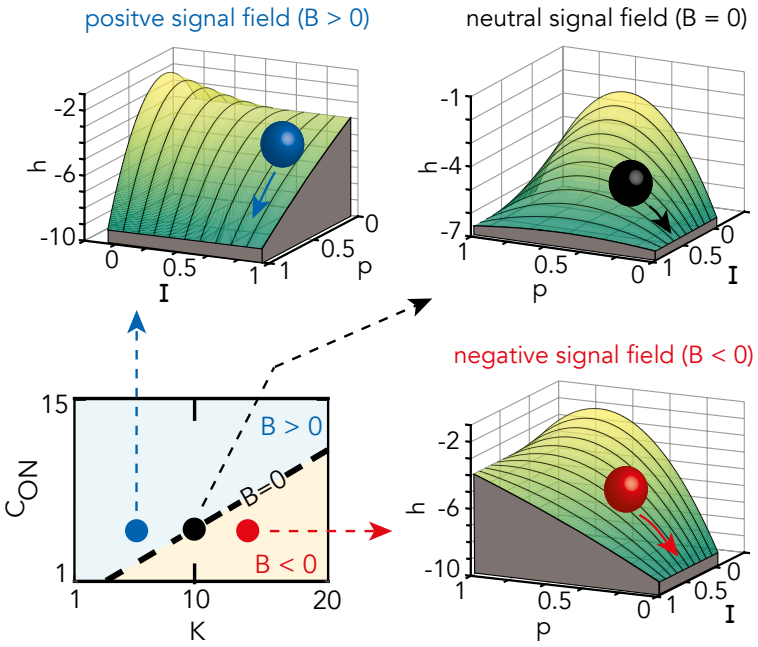
Since these SAS cells are a little more complex than the average ones found in basic cellular automaton, their behaviours are also a little more intricate. When a SAS cell is in the "On" state, it will secrete molecules at its maximum rate and a particular gene (a trait given to the SAS cell) known as the reporter gene is said to be highly expressed. Whereas SAS cells in the "Off" state will barely secrete any molecules meaning their reporter genes will be poorly expressed. Therefore, SAS cells can turn themselves on or off by self-communication as well as doing the same to any other SAS cell in its neighbourhood.

A BOLD NEW PHYSICS APPROACH

It's not very scientific to say that one pattern is "patternier" than another, thus Hyun Youk has developed a new measurement to quantify the spatial order of a pattern. While using SAS cells in cellular automaton, Youk and his team realised each of the lattices could be classified by two numbers.

The first number, *p*, is the fraction of cells that are in a state of "On", so if half of the SAS cells in a cellular lattice expressed the reporter gene very highly (i.e., were in the state of "On") then *p* would equal 0.5. Therefore, *p* can be any number between 0 and 1.

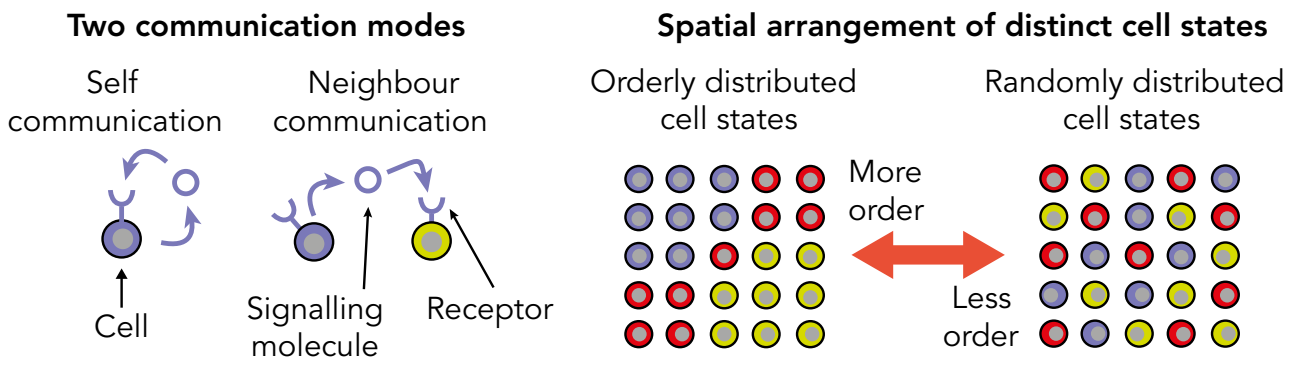
Pseudo-energy landscapes



Pseudo-energy (h) landscape is shaped by the fraction (p) of cells secreting signal at the maximal rate (on-cells), and the spatial index (I). Two gene-circuit parameters – minimum signal concentration (K) required to turn a cell "on" and maximum signal-concentration a cell can create on itself (C_{ON}) – control the landscape's shape.

This is exactly what Youk and his team want to know, the spatial order of patterns – i.e. how organised one pattern is compared to another.

Cells communicate through secreted signalling molecule



(Left): A cell (in blue) can secrete a molecule and have a receptor that captures the molecule (self-communication). Another cell (in green), does not secrete a molecule but can capture the blue cell's molecule. (Right): Distinct cell types (blue, red, green) can be arranged in many ways, in orderly or disorderly manners.

A secrete-and-sense cell can secrete the signalling molecule at two rates – 'low' and 'high'. The signal concentration sensed by the cell determines which of the two rates the cell has – if the sensed concentration is below (above) a "threshold" concentration, then the cell secretes at the 'low' ('high') rate.

The second number, *I*, is what Youk calls a "Spatial Index" and can be any value between -1 and 1 (but for the purposes of his study, only positive variables of *I* were discussed). The *I* measures the average, weighted correlation between the states of any two cells in a cellular lattice. It does this by assigning a higher weight to the pairs of cells that are communicating more with each other.

In the briefest of terms, Spatial Index is a statistical measure of cell-cell co-ordination of gene expression (where the gene in question is the Reporter gene that controls how much a SAS cell secretes).

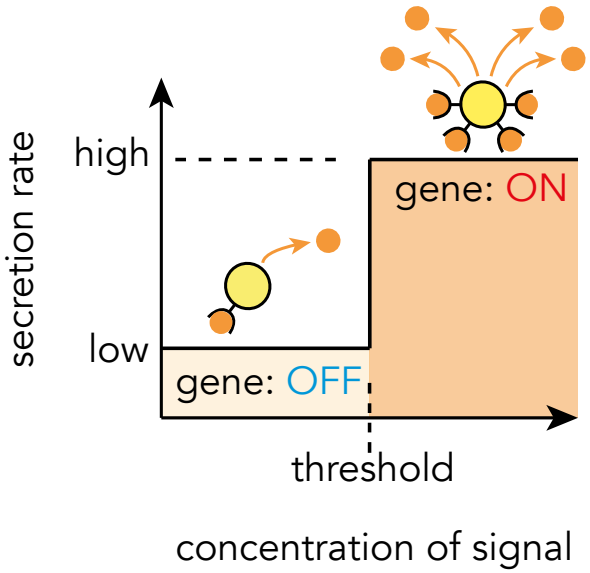
Keeping *p* the same (p=0.50), while varying the Spatial Index, *I*, has the following effects on the cellular lattice:

- When $I = 0$, all the "On" and "Off" SAS cells are randomly distributed meaning the lattice is maximally disordered.
- When $I \approx 1$ (or *I* is large), the lattice becomes more organised and large clusters of cells that are in the same state form (the cells are said to be more spatially ordered)
- When *I* is an intermediate value, the lattice is full of small clusters of cells that are either "On" or "Off"

These two numbers, *p* and *I*, are combined to define a single state (macrostate) for a lattice. However, you could have many lattices (microstates) that have a wildly different set of clusters and patterns within them whilst possessing the same p and I values. This would mean all those microstates belong to a single macrostate.

It's this revelation that allowed Youk and his team to actually predict how organised a pattern will become over time. Since a single macrostate has two numbers (*p* and *I*), this allows it to be plotted like coordinates on a map. Therefore, the macrostate can be visualised as a particle that moves in an abstract space (phase space).

A cell's response to the signalling molecule



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THE HYPOTHETICAL MOUNTAIN

By studying how the macrostate variables (*p* and *I*) changed over time, they discovered that macrostates followed distinct trajectories which, collectively, resemble the shape of a mountain.

They hypothesised that if the particle were to move around the phase space, perhaps there would be a "landscape" it would roll across. To explore this, they expanded the 2D phase space of *p* and *I* to include a third dimension - *h*, the pseudo energy of the particle. The pseudo energy is calculated entirely from the *p* and *I* variables.

When $p \approx 0.5$ and $I = 0$, the pseudo energy, *h*, is at its maximum due to the amount of disorganisation in the macrostate and the high potential for patterns to form – this is the peak of the mountain. Either side of this peak ($p \rightarrow 0$, $p \rightarrow 1$) are the slopes of the mountain and as the spatial index, *I*, increases from 0 to 1 (chaos to patterns) the pseudo energy decreases and mountain cascades down.

Placing the particle on this phase space mountain allows you to follow its trajectory as it rolls down the slope, like a river would flow down a peak. This means that given a macrostate's initial parameters you can predict the trajectory of the particle to its final point in the phase space, allowing you to determine how organised the patterns will become.

WHY THIS IS IMPORTANT

Physicists have forever attempted to explain living, real-world systems (such as cells) by mathematical approaches that they've applied to non-living systems (such as electronics or magnets).

However, such an approach to the exploration of living systems has (until now) gone un-noticed. This is mostly due to the fact that conventional metrics used in physics (energy, force, etc.,) simply cannot be applied to the dynamics of living systems that form from chemical and genetic elements.

Hence, a new metric needed to be created, which is exactly what Youk's team has done. These new metrics have armed physicists with a brand new framework that will allow them to understand chemically and genetically-generated dynamics of multicellular systems.