Lecture 15

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Biologists spend a lot of time analysing the current status of a biological system, and why it does what it does. One may ask the additional question of what caused it to reach its current state. We will be asking how multicellular organisms formed in a robust way. This may be reinterpreted as the design principles for robust, multicellular organisation.

Let there be two types of cells, A and B. We shall consider the multicellular building block where A contains B. Given a cluster, of 2 types of cells, A, and B, arranged somehow, will achieve this containing structure thanks to something called *Differential Adhesion*. It rearranges to this form of structure, since it is the structure that minimises the energy of the system. The energy of the system is measured like a loss function from IML:

$$H = \sum_{i,j \in \mathbb{N}} J\left(\sigma\left(i\right), \sigma\left(j\right)\right)$$

Where $\sigma\left(i\right) \in \{A, B\}$. Here, σ is the *state*. In turn, we may consider J to be a matrix:

$$\begin{bmatrix} & A & B \\ A & & \\ B & & \end{bmatrix}$$

Where the only important point in this matrix is that $J_{BB} < J_{BA}, J_{AA}$.

One can use the *Cellular Potts Model*, which is a form of cellular automata, to model this. 0 is empty, 1 is A, and 2 is B. We may ask at each time step whether or not a pair want to switch. We may express this mathematically

$$\mathbb{P}\left[\sigma\left(i\right) \leftrightarrow \sigma\left(j\right)\right] = \begin{cases} e^{\frac{-\Delta H}{T}}, & \text{if } \Delta H \geq 0 \\ \Lambda, & \text{if } \Delta H < 0 \end{cases} \tag{1}$$

If one were to create an implementation, one would note that sometimes one reaches the actual minimum, where A contains B, but most of the time one would reach a local minimum, with a different state. However, we do not want to stay in a local minimum, but want to reach the global minimum. When working with physical objects, a standard way of resolving this is quite literally, shaking the system (think about packing problems, shaking the container can improve the packing). However, this is quite difficult to implement in biological systems.

To try and resolve this **Simulated Annealing** was suggested. An algorithm looking for the minimum, like gradient descent, will get stuck in a local minimum. We may add noise into the system to try and resolve this. By adding in noise (like increasing the temperature), this greatly increases the value of ΔH in the above formula. This noise should be large enough to encourage it out of local minima (which are relatively small), but not out of the global minimum. For it to be *annealing*, as time increases, the noise decreases. We are left with the problem (given as a fact) that this is difficult to implement in biological systems, and this is not how we think that the biological systems implemented it.

We may instead consider a system that begins very flat in terms of differences in energies, and slowly becomes noisier and noisier, introducing the dips, and local / global minima. For example, we begin with a system that is only A, with a few cells that are B^*, which has the exact same properties as A. However, we may now change this system such that when A interacts with B^*, then there is some probability that is that B^* will be changed into B.

It may be said that the speed of the containment of B is proportional to the inverse of the core size, to some exponent f. As f increases, then the difference in number of cores between the two models constitutive (the pure cellular automata) and the induced (where A changes B^* to B) increases, such that there are many more cores in the constitutive model than in the induced model for large values of f.

Overall, the "punchline" of today is that gradual increases of complexity result in a robust dynamic convergence.