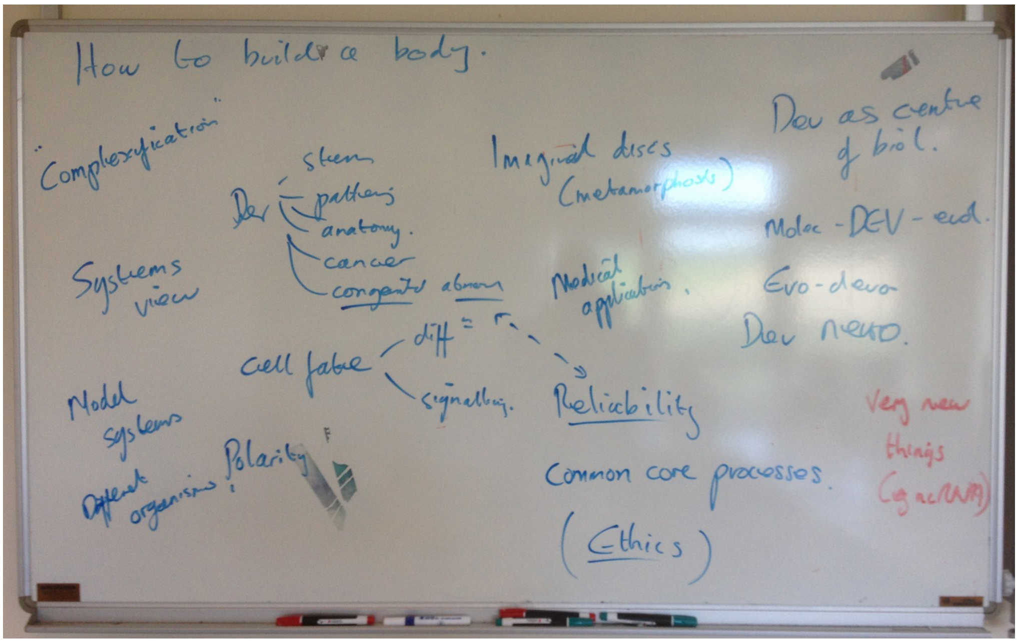
Class notes from DB4 Cellular Mechanisms

Session 1 - 25th September 2015.

We began with you making your own list of the most important problems in developmental biology: here is the list that appeared on the boards (you should be able to zoom):



The top one – how to build a body – is our general topic, and the 'Complexification' is a theme that will come up over and over again. For this reason neither will be mentioned specifically in the syllabus below, because they are everywhere.

We can use this as our syllabus:

- Control of differentiation, from the molecular view of genes to a **systems view** of action of whole genomes. Examples from **different organisms** and **model systems**. 'New' controls like ncRNA.
- Evolvability of cell states (**evo-devo**)
- **Cell signalling** and **cell fate**
- **Patterning** and **reliability of patterning (**including examples from **imaginal discs)**
- **Cell polarities**
- Morphogenesis and the creation of **anatomy.**
- **Congenital abnormalities** as failures of morphogenetic processes
- The wiring of the **nervous system. Reliability** and variation. Maybe the immune system too.
- **Ecological** approaches to development.
- **Cancer** (as a way to revise most of the above).

Throughout, we can draw on lots of model systems and organisms.

We went to on discuss where it comes from. Specifically, the apparent paradox that something simple (the egg) makes something complex (the person / frog / whatever).

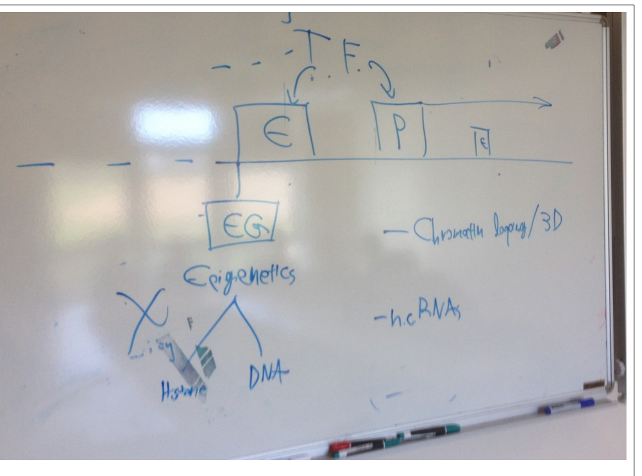
We used Game of Life (see https://duckduckgo.com/?q=conway+game+of+life) to illustrate how very simple rules can generate very complicated behaviours. Rather as, perhaps, simple behaviours of cells can generate very complicated bodies. ('*Discuss*'!).

By the way, by coincidence Radio 4 did a programme that included a lot about John Conway (the authors of the game) later that afternoon - http://www.bbc.co.uk/programmes/b06c4k46 (listen to it soon if you want to hear it – most programmes have limited-length availability).

We noted, though, a very important difference between Game of Life and real life: in Game of life, tiny differences in starting conditions have massive implications: real life is remarkably tolerant of noise. We will discuss this throughout the course.

Differentiation (1): control of single genes.

After the coffee break, you drew a diagram to summarize typical controls on the transcription of a single gene (below). We noted the existence of other modes of gene control (eg epigenetics). You then suggested different mechanisms by which an enhancer might act 'at a distance', including looping out of intervening DNA, untwisting or unzipping DNA, walking of the transcription factor from the enhancer to the promoter etc.

Some of these experiments have actually been done (and I gave you printed sheets to summarize how). The results showed that transcription still occurred when the biotin-streptavidin system was used to link enhancer and promoter and when the enhancer was in a pan-handle. We can therefore reject the twist and walk models, leaving only the loop. We noted that this does not prove the loop – it only disproves the others.	

(We noted, in passing, the power of designing experiments to *dis*prove hypotheses. You may want to look up "Karl Popper" + "Conjecture and Refutation").

Having focused on an individual gene, we know we need to broaden to consider how collections of genes might interact, if we are to understand differentiation. We therefore need to distill some broad features of genes controlling genes, in order to think of genome-scale models.

Tasks: all about genes controlling other genes

- Group 1 : find examples of genes controlling genes by chromatin modification

- **Group 2:** find examples of genes controlled by several different upstream elements (eg transcription factor-binding domains in their promoters) and ask whether combinatorial control can be idealized as Boolean.
- **Group 3**: find examples of transcriptional interference

Please come prepared to present your findings (ideally on a white board).