

20.320, notes for 10/18

Thursday, October 18, 2012
9:43 AM

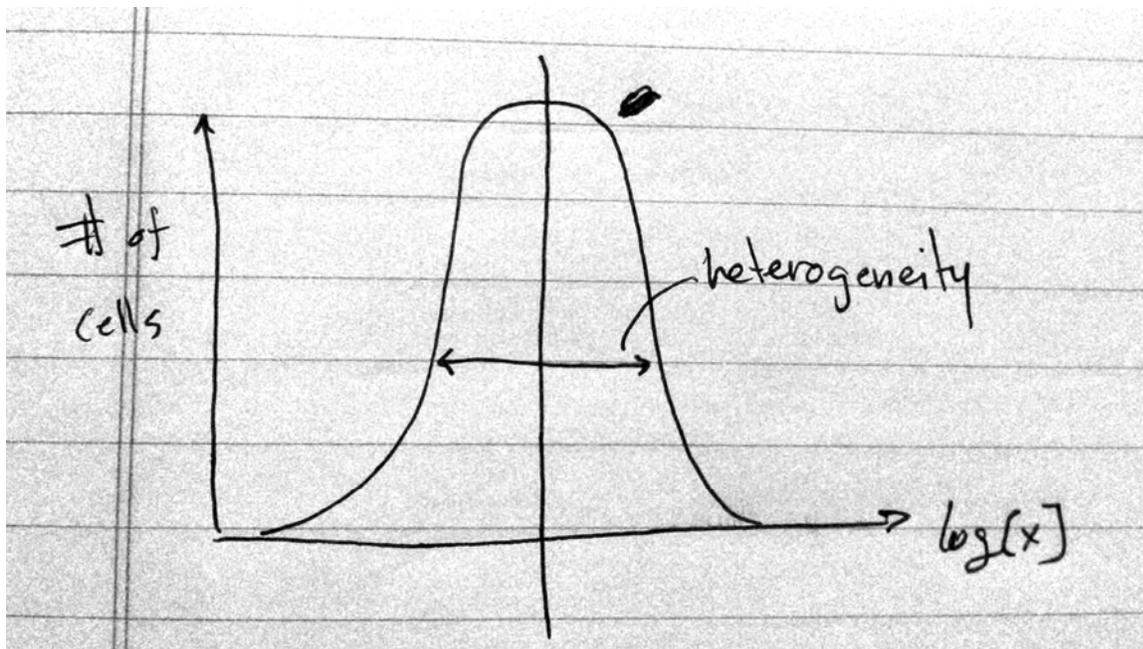
Transcriptional Regulation

1. Simple regulation
2. Negative autoregulation
3. Positive autoregulation

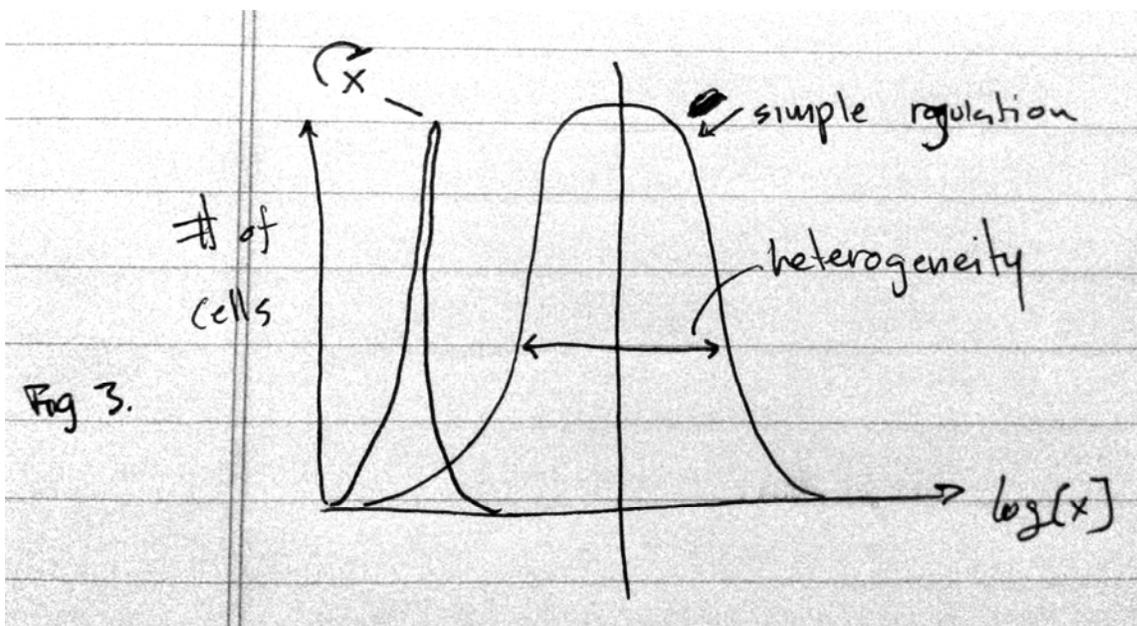
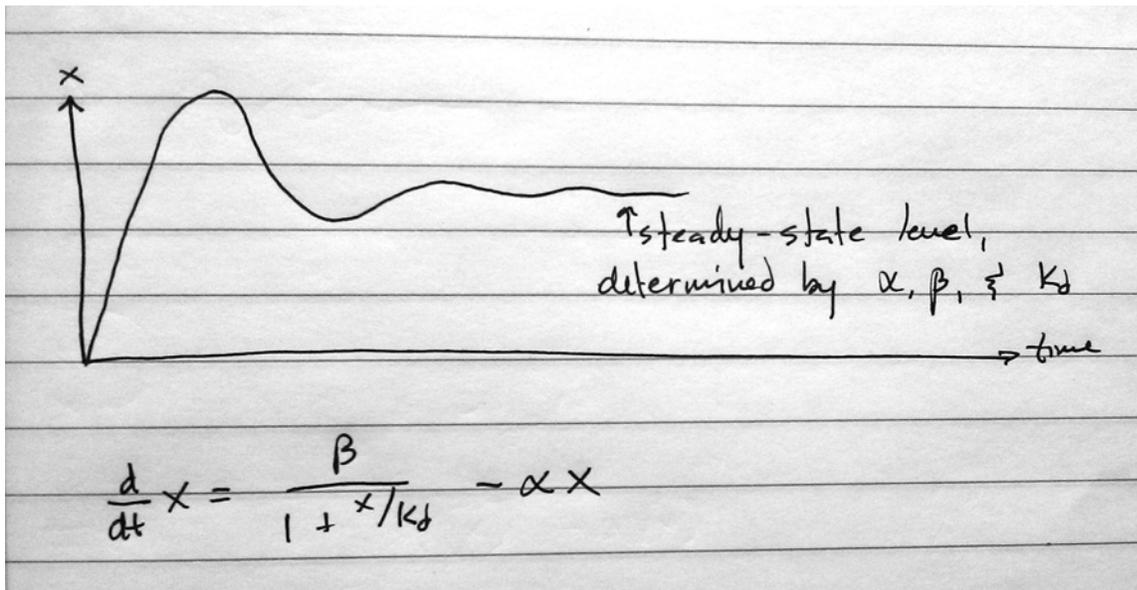
Why heterogeneity?

4. Local concentration of signal
5. Different amounts of receptor
6. Different amounts/availability of RNA polymerase
7. History and context
 1. Negative regulators (phosphatases)
 2. Cell-cell interaction and environment

All these factors contribute to widen the peak of simple regulation.



The story is different for negative autoregulation, though. Here, at the beginning ($x \rightarrow 0$) there is increase of X at the rate β . Eventually, though, everything equilibrates to a value determined only by the inherent system parameters, not by the stochastic heterogeneity of the environment. That heterogeneity will change the initial levels, but the system will always stabilize to more or less the same values. That's why the negative autoregulation plot is much thinner.

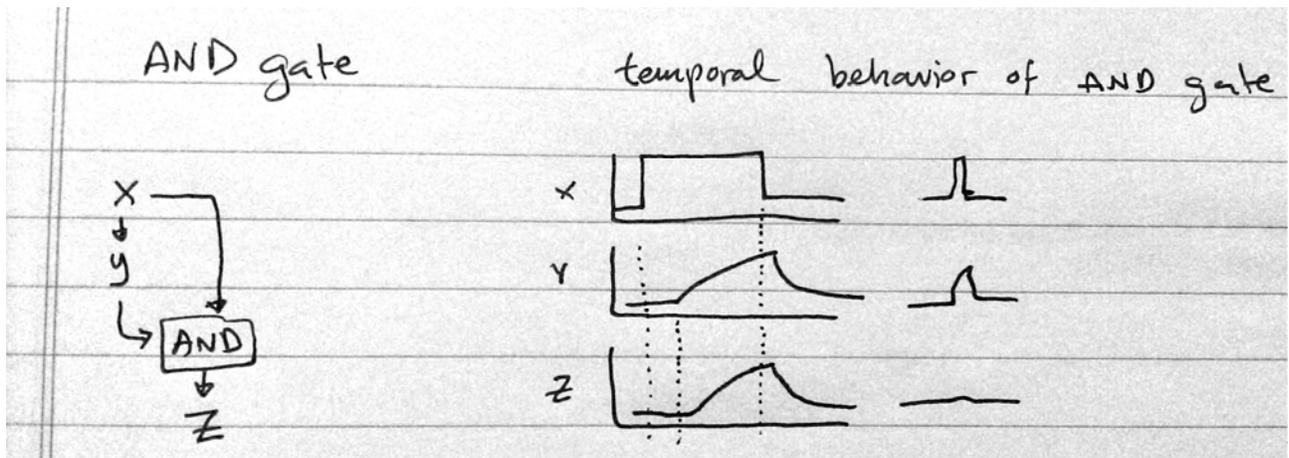


Now, in the case of positive autoregulation there is **no** control. A small signal gets amplified, a large signal gets amplified even more. Heterogeneity gets blown into a great variety, as we've seen before.

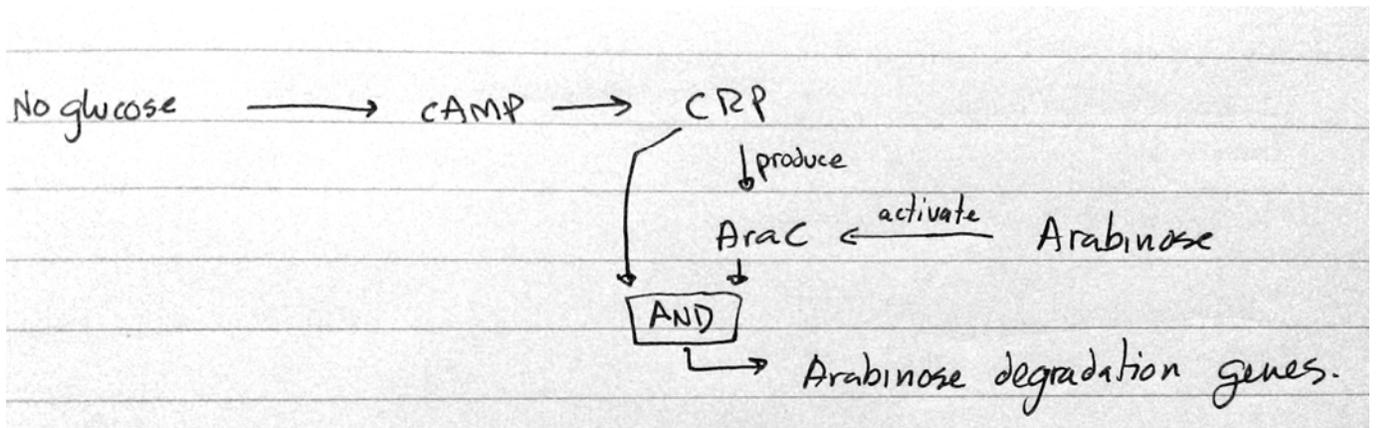
All these methods are used in the cell, for different genes. Why would the cell use all of them? The instinct is to put everything under negative autoregulation, to keep lots of control. The BIG downside is that this is a great evolutionary weakness. The perfect system for one environment might be deadly if the environment changes even a little bit. If we used all-positive autoregulation, then we'd have enormous variation of everything (including the crucial stuff that needs to be tightly controlled). In real cells, a single signal applied at one time results in complex waves of protein expression, some of which start at the beginning and some of which have a built-in delay. This is achieved through a slightly more complex system: Feed-forward loops.

Feed forward loops

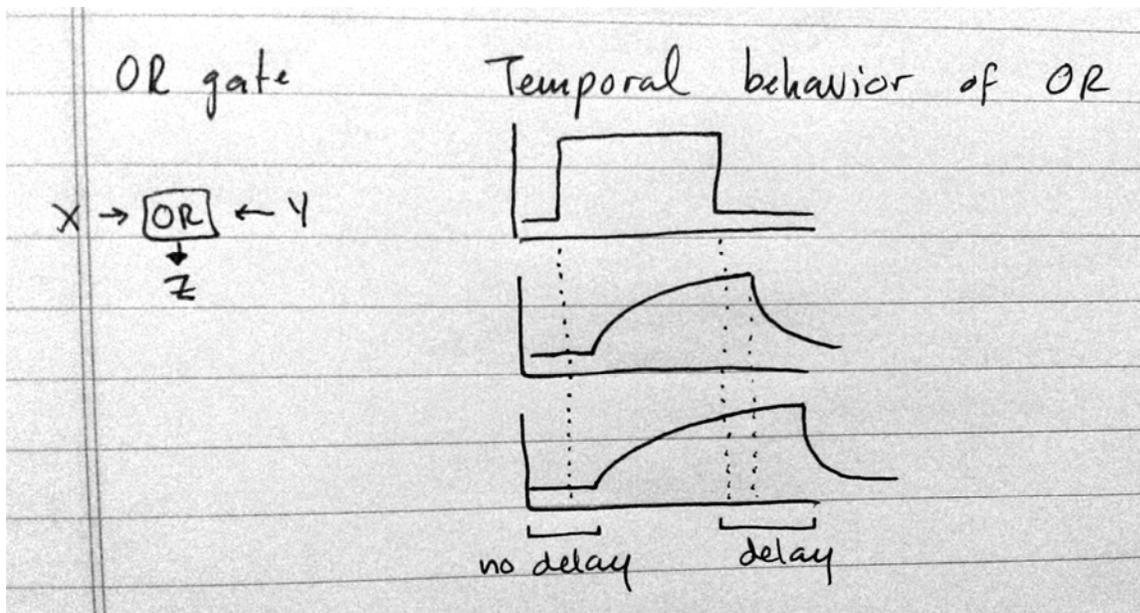
Imagine the genes X, Y, and Z. Several of our feed forward loops are Boolean gates. X is input, Z is output, and Y is an intermediate. The nice thing about AND gates is how they can build in a time delay at the start but allow for the whole system to end at the same time. Z won't start until X and Y are both there.



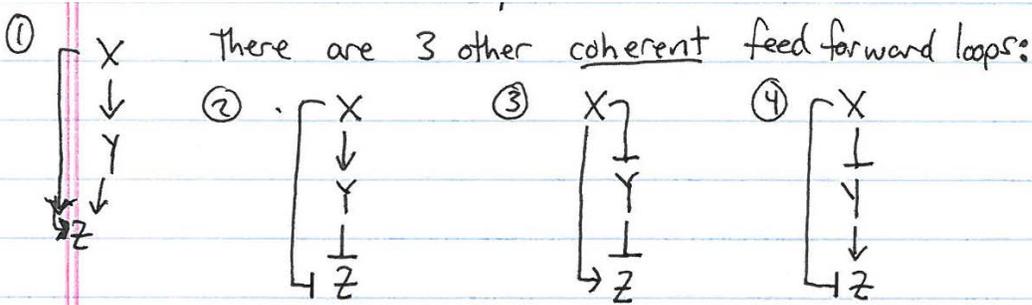
If the X pulse is quick enough, there's a little Y production but no time for Z. We've seen this before in PC12 cells, where the time of the Erk signal is the difference between proliferation and differentiation. This is also seen a lot in E coli, who typically grow on glucose but can use arabinose in its absence. They use an AND gate to sense for the absence of glucose AND the presence of arabinose before producing the proteins that can digest arabinose.



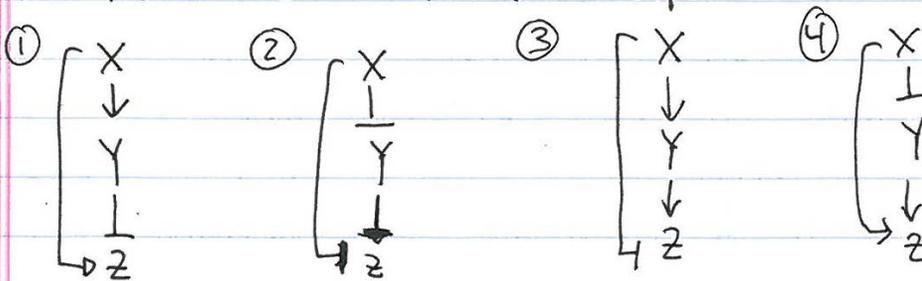
Another possible feed-forward loop is an OR gate.



The OR gate has the opposite behavior. It shows no lag during onset, but it does cause a delay on the other end. Z remains in the system until after Y is all gone. There are eight total feed forward loops, divided into coherent and incoherent depending on whether the two 'arms' of the system agree with each other or not.

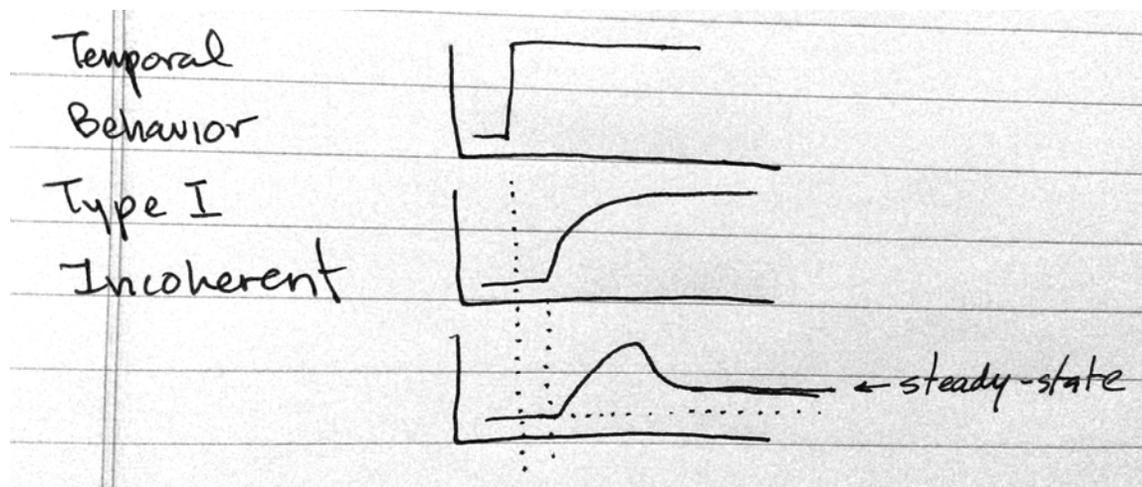


And 4 other incoherent feed forward loops:

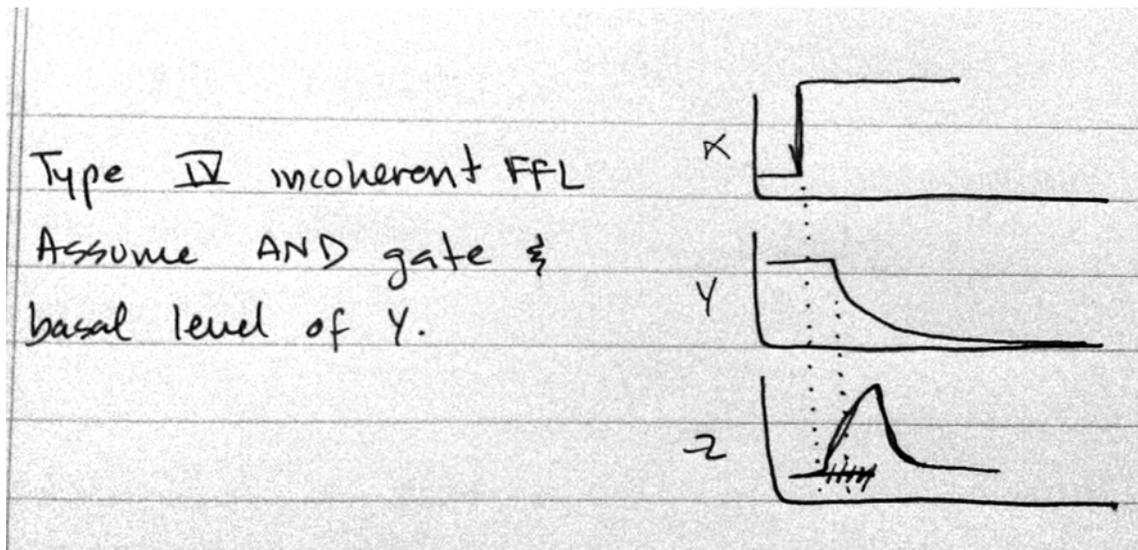


Note that these are just the three-component motifs \rightarrow many more complex possibilities exist for 4, 5, etc... component motifs.

Type I, in both cases, is the most common. Let's look at the temporal behavior of two of them.



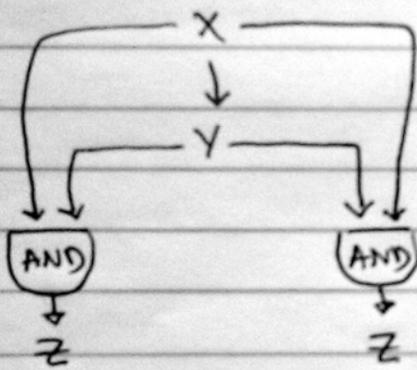
Notice how this behavior looks exactly like that of negative autoregulation. You start with a pulse, which then stabilizes onto a steady state different from whatever state it started at. Why is this any better? Because we have more control. The behavior of Z is determined by X and Y. We can regulate the activation of X, the activation of Y, the K_d of X:zDNA or Y:zDNA. The complexity gives you different ways of achieving regulation, and with it more control and robustness.



Here, the things you can regulate are X:yDNA and the signal of X. There is much less to control than in the case of Type I incoherent, which is why Type I is much more common in bacteria than Type IV.

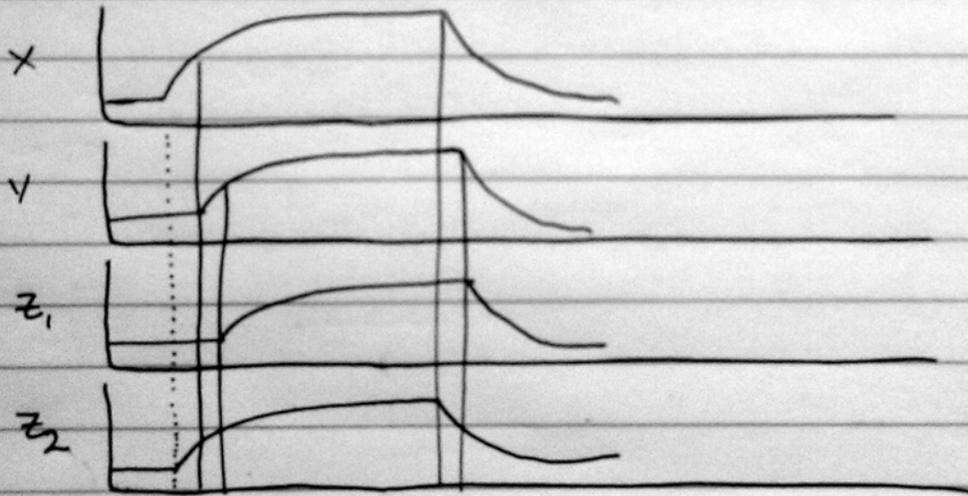
So, if you had 4 genes and wanted to activate them sequentially, what would you do? We could put them all under control of X, with different K_d values such that the K_d values are $1 < 2 < 3 < 4$, and then ramp up X. Gene 1 would outcompete gene 2 in binding to X until there was a lot of it, and so forth. The problem is that you can't turn genes on and off in the same order. There's other ways, such as multi-output FFLs.

Multi-output FFL



$K_d X:Z_1 < K_d \text{ for } X:Z_2$

$K_d Y:Z_2 < K_d \text{ for } Y:Z_1$



And note how here you CAN turn things on in one order and off in the same order.

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20.320 Analysis of Biomolecular and Cellular Systems
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