Network modelling of cancer progression

### **Questions**

1. ***MDM2 is an oncogene. That means it can become more active and cause cancer. Based on the network, how would it do this?***
	1. MDM2 in the cell acts to inhibit the action of TP53. The loss of TP53, either by mutation or through the activity of MDM2 increases cell survival, as can be seen in the model. So, over-activating MDM2 causes increased cell survival through inhibition of TP53.
	2. TP53 can be seen to behave like the opposite of an oncogene here; when you lose it, the cell progresses towards cancer. Proteins that do this are called **tumour suppressors**, and play a number of roles in the cell in protecting the cell from cancer causing damage. One of TP53’s roles is that it responds to DNA damage in the cell by first activating repair machinery and stopping cell growth. If the damage is irreparable, causing the cell to commit suicide. It does this by controlling the activity of a large number of other genes by altering their expression.
2. ***KRAS is an important oncogene- how does it change individual proteins and the behaviour of the cell?***
	1. Mutated KRAS activates a large number of pathways in the cell, including other oncogenes and drug targets. It does this directly and indirectly, though connected proteins. Overactive KRAS causes increased invasiveness through the activation of RACL and the downstream protein PAK1. In addition to making the cell more invasive, KRAS and PAK1 both activate members of the RAF/MEK/ERK pathway leading to enhanced growth of the cell.
	2. Finally, in the presence of other mutants, KRAS activation of PI3K supports inhibition of TP53, increasing survival, and TOR, increasing growth.
	3. Due to its widespread interactions in the cell, KRAS is active in a wide range of cancers including lung cancer, pancreatic cancer and colorectal cancer. It cannot be inhibited directly so drugs typically target proteins downstream of KRAS, as seen in the model. The broad range of interactions it makes may also promote drug resistance, as alternative pathways effectively route around the drugged proteins.
3. ***List which drugs would be effective, partially effective, or ineffective against a cancer with a KRAS mutation? How would they perform against a PTEN mutation? Why do different drugs have different effectiveness?***
	1. Trametinib is effective against different individual aspects of the cancer progression in response to KRAS, but no one drug is able to reverse all of the effects of KRAS mutation. In contrast, idelalisib, imidazothiazole, and rapamycin are effective against a PTEN mutation. This can be understood in terms of the underlying network; KRAS is upstream of (i.e. activates) a lot of the pathways in the model, but does not alter TOR driven growth or TP53 mediated survival as PI3K is inactive, so drugs that target those are ineffective. In contrast, PTEN mutation turns PI3K on and so those pathways both drive the cancer and are sensitive to drugging.
	2. Clinically, some of these drugs are effective against some cancers despite being ineffective in the model. This is because cell types vary in their gene expression and some pathways may be more active in specific cancers, and therefore druggable.
4. ***Thinking about the hallmarks of cancer, which mutation would you expect to be first in the development of cancer out of TP53 and KRAS? Give your reasoning.***
	1. The mutations that cause cancer do this through DNA damage, which is detected by TP53 and leads to cell death (hence its connection to “survival”). In contrast KRAS leads to increased growth in the cell and promotes the invasion into other tissues (metastasis). It can be expected therefore an initial mutation to TP53 will allow the cell to survive DNA damage, which in turn could lead to mutation that promote the activity of KRAS without triggering cell death.
	2. However, in some systems can either can occur first, as the increased growth may balance out the increased rate of cell death. Which process is more important depends on the cancer itself.
5. ***Pathways that involve ERK and TOR are known to be important in breast cancer. Its been suggested that there might be feedback between the two proteins. If you add activating arrows between either or both of these proteins, how does this change the way that the model responds to cancer mutations? Do drugs work the same way for mutations with and without these interactions?***
	1. Adding an activation from TOR to ERK does not have any effect on the model. This is because the growth hallmark requires only one of these proteins to be active.
	2. When ERK activates TOR however, KRAS and EGFR mutations can lead to increased cell survival. These mutations activate RAF, MEK, and ERK, and with the new connection also activate TOR. This in turn activates MDM2, and this inhibits TP53. This new behaviour is sensitive to rapamycin and imidazothiazole
	3. Adding activations in both directions to mutant models does not have any new effect. However, the unmutated system with these extra connections is no longer stable- clicking further testing shows that the model has cycles (where genes turn off and on repeatedly) and bifurcations (where genes can end up in multiple different stable states). This is a strong indication that the model with both new connections is incorrect- because the normal cells exist at homeostasis and therefore should be stable.