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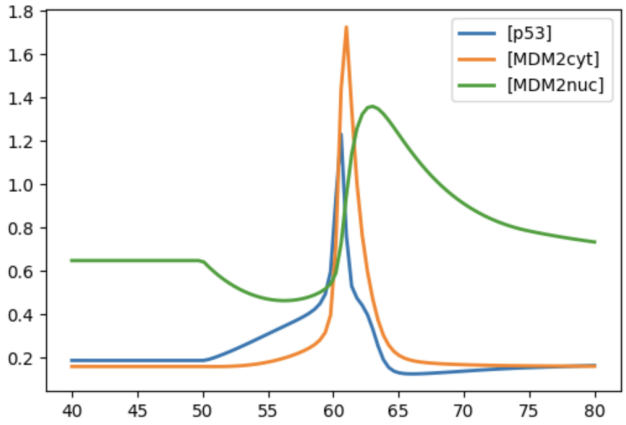
Bio Background

P53 is a protein that suppresses tumor growth within cells, preventing cancer. Mdm2 is a protein that suppresses p53 production. These proteins are in a positive/negative feedback loop as p53 promotes the production of Mdm2 and Mdm2 suppresses the production of p53.

In a healthy cell p53 levels are low as Mdm2 suppresses its production. However, when Dna damage occurs, Mdm2 levels decrease. This causes an increase in p53. Since p53 and Mdm2 are in a feedback loop, the increase in p53 causes a rapid increase in Mdm2. Thereby suppressing the p53 back to its steady state. See graph below.



If the Dna damage is large, then this process will occur multiple times in pulses or oscillations until the damage is fixed or the cell dies.

The Models

The model used to generate the above graph is taken from Biomodels. It depicts what happens to p53 and Mdm2 levels during DNA damage. The inputs for this model are essentially the initial values of mdm2, p53, and amount of dna damage.

I am using this paper and model to help generate ideas for my project. I want to expand on this model and use others.

My Thoughts

There exists many current models related to p53, however I want to analyze some of these models/papers and try to combine them to see make new conclusions. Below are some guiding questions that I have come up with. I would appreciate any feedback as to if this is enough for a project.

- How can I combine this model (alluding to the graph above) with another model that models DNA damage to see correlations?
- How will other variables impact this model/system?
- How does the environment impact the p53/mdm2 relationship and response?

An Application

Another way I can build on these models is creating a digestible walkthrough of the whole DNA damage process. I can look at the different types of DNA damage and see how that affects the p53 levels and oscillations. Or can adjust the enviroment and make conclusions

Possible Sources

Tongli Zhang, Paul Brazhnik & John J. Tyson (2007) Exploring Mechanisms of the DNA-Damage Response: p53 Pulses and their Possible Relevance to Apoptosis, Cell Cycle, 6:1, 85-94, DOI: 10.4161/cc.6.1.3705

Ma L, Wagner J, Rice JJ, Hu W, Levine AJ, Stolovitzky GA. A plausible model for the digital response of p53 to DNA damage. Proc Natl Acad Sci U S A. 2005 Oct 4;102(40):14266-71. doi: 10.1073/pnas.0501352102. Epub 2005 Sep 26. PMID: 16186499; PMCID: PMC1242279.

Kim E, Kim JY, Lee JY. Mathematical Modeling of p53 Pathways. Int J Mol Sci. 2019 Oct 18;20(20):5179. doi: 10.3390/ijms20205179. PMID: 31635420; PMCID: PMC6834204.

Ciliberto A, Novak B, Tyson JJ. Steady states and oscillations in the p53/Mdm2 network. Cell Cycle. 2005 Mar;4(3):488-93. doi: 10.4161/cc.4.3.1548. Epub 2005 Mar 18. PMID: 15725723.