Mathematical Modelling of p53 Signalling in Response to DNA Damage

AMATH/BIOL 382

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Overview of presentation

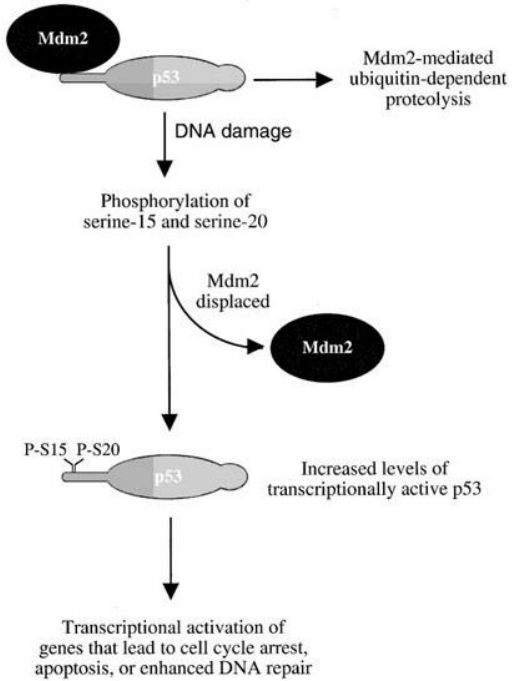
- Introduction
  - Overview of gene regulatory networks (GRNs)
  - p53's role in molecular oncology
  - Motivation for model
- Negative feedback model of p53-Mdm2
  - Summary and analysis of model
  - Implementation
  - Limitations
- Extending the model
  - Summary and analysis of model
- Next steps

Introduction

What are GRNs?

- Gene regulatory networks (GRNs) are mathematical descriptions of the interactions between genetic molecules
  - Molecules represent nodes, and their interactions represent edges in the graph
- Genetic interactions affect the production of molecules
  - Through activation or inhibition mechanisms
- GRNs are found across all cellular processes, and are an important resource to investigate cell behaviour
  - Helps to understand genetic reasoning behind deviation of cell behaviour (Ex. cancer)

p53’s role in molecular oncology



https://www.nature.com/articles/1203015

- Key player in molecular oncology
- p53 provides many regulatory functions
  - Regulates cellular process such as apoptosis and cell cycle arrest
- Extra- and intracellular stresses activate p53
  - Downstream effects depend on nature of stress
- This paper focused on the response of p53 to DNA damage
  - Irradiation causes DNA damage
  - Leads to phosphorylation of p53 that reduces its binding to Mdm2 (inhibitor)

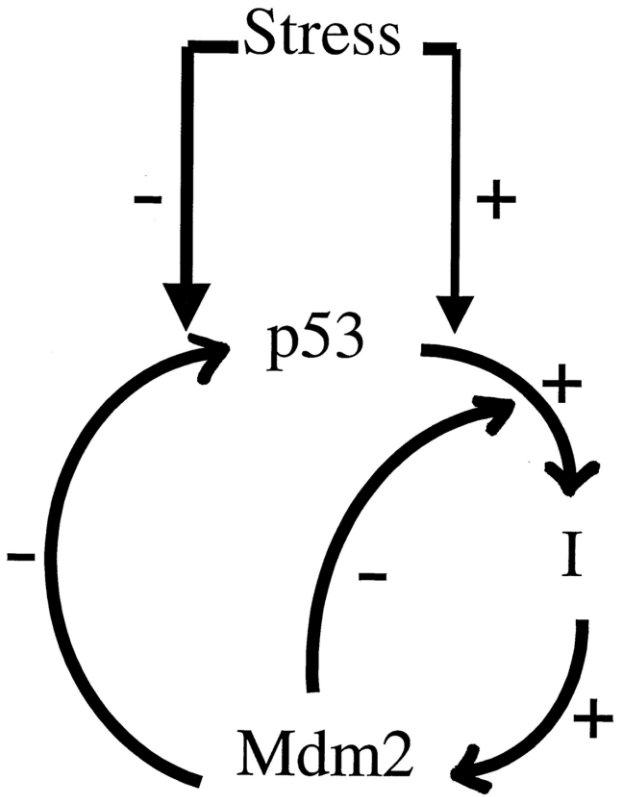
Motivation for model development

- Time-lapse fluorescence microscopy experiments determined altered dynamics of p53
  - Depending on source of irradiation, p53 exhibited periodic or sustained expression
- Dynamic behaviour of p53 is an important part of its function
  - Useful to investigate mechanisms within its pathway to determine what drives periodic vs sustained expression
  - Determining mechanisms which provoke oscillations in p53 GRNs has been a major focus
- A common feature of GRNs is negative feedback
- Response to DNA damage induced by radiotherapy
- Timing and pathway sensitivity to targeted drugs

p53-Mdm2 negative feedback loop

Summary of model

- Negative feedback occurs through p53's interaction with Mdm2
  - Mdm2 represses p53
  - Activated p53 activates Mdm2



https://www.pnas.org/doi/10.1073/pnas.2101715977

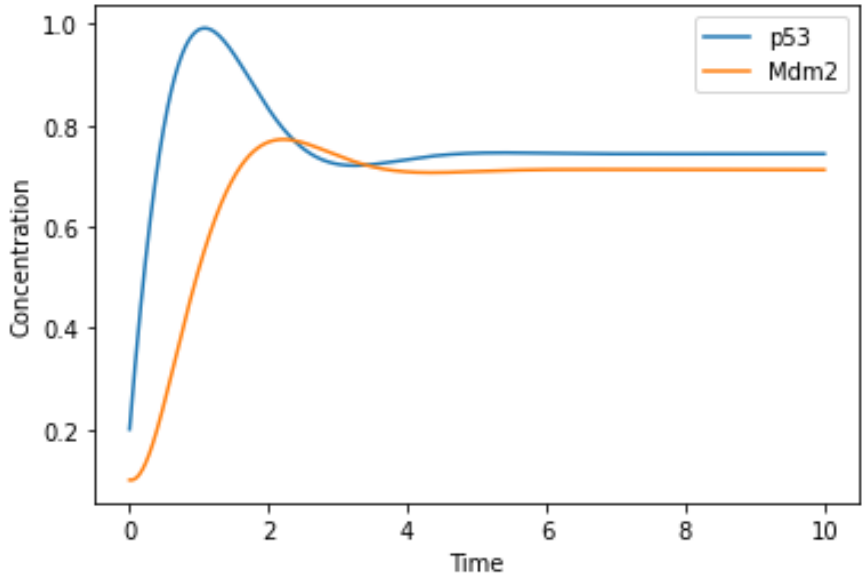
Implementation of model

System of Ordinary Differential Equations (ODEs):

$$\dot{x}(t) = k_s - k_1 y(t) \frac{x(t)}{K_1 + x(t)} - d_x x(t),$$

$$\dot{y}(t) = k_2 \frac{x(t)^n}{K_2^n + x(t)^n} - d_y y(t).$$

Graphical model:



Limitations

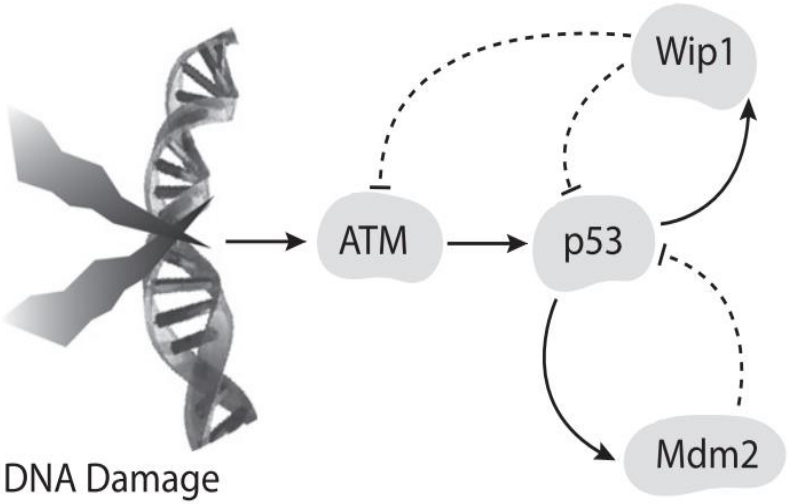
- Modelling GRNs using ODEs showed that presence of negative feedback alone is insufficient to produce fluctuating protein levels

- An intermediate is required to push GRNs from sustained expression to periodic fluctuations
    - Time delay: time for processes to occur
    - Spatial effects: requirement for molecules to diffuse to certain spatial locations
    - Positive feedback: interactions with other molecules

Compartmental Model

Summary of model

- ATM and Wip1 modelled
  - DNA breaks activate ATM
  - ATM activates p53
  - p53 upregulates Wip1 and Mdm2
  - Wip1 deactivates p53 and ATM
- Diffusion effects between cytoplasm and nucleus must be considered



https://iopscience.iop.org/article/10.1088/1478-3975/11/4/045001/pdf

Implementation of model

Nucleus Equations:

$$\frac{du_0}{dt} = k_{dph1}u_5\frac{u_3}{K_{dph1}+u_3} - k_1u_1\frac{u_0}{K_1+u_0} - k_{ph1}u_4\frac{u_0}{K_{ph1}+u_0} - p_0V_r(u_0 - v_0)$$

$$\frac{du_1}{dt} = -p_1V_r(u_1 - v_1) - \delta_1u_1$$

$$\frac{du_2}{dt} = k_{Sm} + k_{S_{pm}}\frac{u_3^4}{K_{S_{pm}}^4+u_3^4} - p_2V_ru_2 - \delta_2u_2$$

$$\frac{du_3}{dt} = k_{ph1}u_4\frac{u_0}{K_{ph1}+u_0} - k_{dph1}u_5\frac{u_3}{K_{dph1}+u_3}$$

$$\frac{du_4}{dt} = k_{ph2}E\frac{ATM_{TOT}-u_4}{K_{ph2}+\frac{1}{2}(ATM_{TOT}-u_4)} - 2k_{dph2}u_5\frac{u_4^2}{K_{dph2}+u_4^2}$$

$$\frac{du_5}{dt} = p_5V_rv_5 - \delta_5u_5$$

$$\frac{du_6}{dt} = k_{Sw} + k_{S_{pw}}\frac{u_3^4}{K_{S_{pw}}^4+u_3^4} - p_6V_ru_6 - \delta_6u_6$$

$$u_0 = [p53]^{(n)},\ u_1 = [Mdm2]^{(n)},\ u_2 = [Mdm2_{mRNA}]^{(n)},$$

$$u_3 = [p53_p]^{(n)},\ u_4 = [ATM_p]^{(n)},\ u_5 = [Wip1]^{(n)},$$

$$u_6 = [Wip1_{mRNA}]^{(n)}$$

- E = severity of DNA damage
- p = permeability of molecule
- Vr = volume ratio
- ATM_TOT = total ATM (assumed constant)
- δ = basal degradation rate

Implementation of model

Cytoplasm Equations:

$$\frac{dv_0}{dt} = k_S - k_1 v_1 \frac{v_0}{K_1 + v_0} - p_0 (v_0 - u_0) - \delta_0 v_0$$

$$\frac{dv_1}{dt} = k_{tm} v_2 - p_1 (v_1 - u_1) - \delta_1 v_1$$

$$\frac{dv_2}{dt} = p_2 u_2 - k_{tm} v_2 - \delta_2 v_2$$

$$\frac{dv_3}{dt} = 0$$

$$\frac{dv_4}{dt} = 0$$

$$\frac{dv_5}{dt} = k_{tw} v_6 - p_5 v_5 - \delta_5 v_5$$

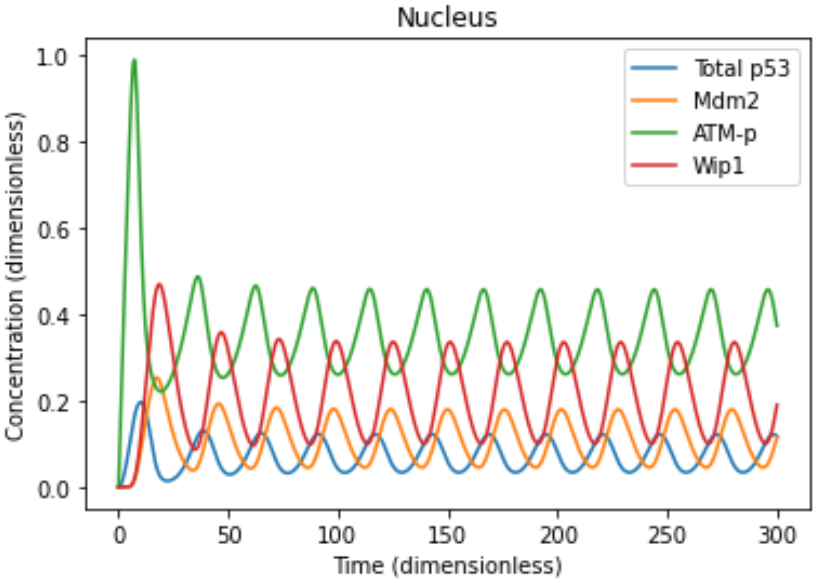
$$\frac{dv_6}{dt} = p_6 u_6 - k_{tw} v_6 - \delta_6 v_6$$

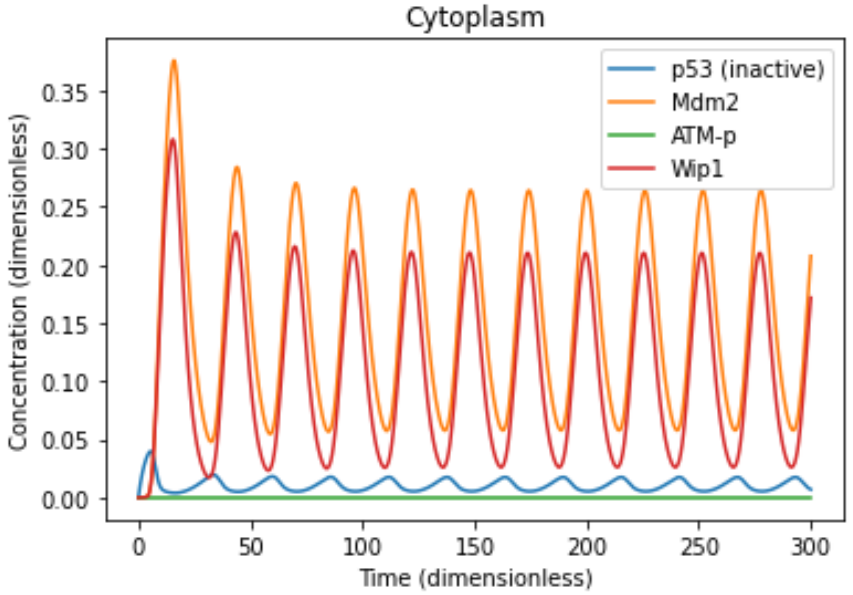
$$v_0 = [p53]^{(c)}, \; v_1 = [Mdm2]^{(c)},$$
$$v_2 = [Mdm2_{mRNA}]^{(c)}, \; v_3 = [p53_p]^{(c)}, \; v_4 = [ATM_p]^{(c)},$$
$$v_5 = [Wip1]^{(c)}, \; v_6 = [Wip1_{mRNA}]^{(c)}$$

- Rate of p53-p and ATM-p are 0 given assumption that the molecules are phosphorylated in nucleus and the activated forms aren't diffusing into cytoplasm

Model Results

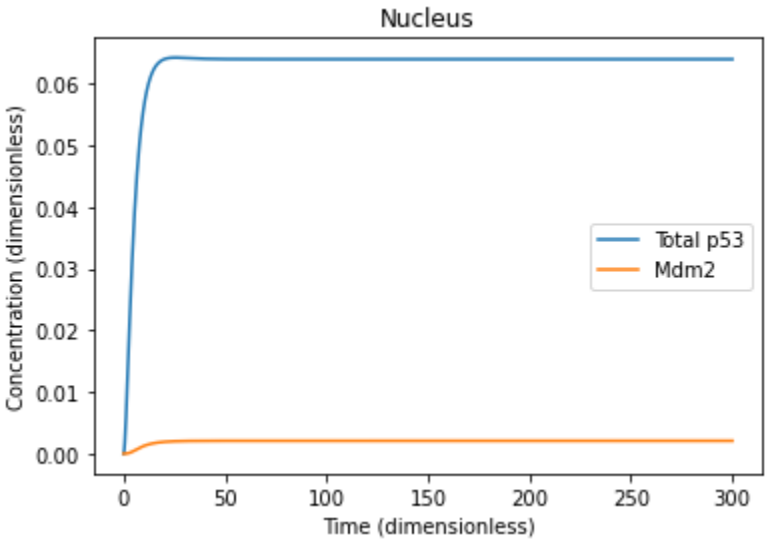
E = 0.1 μM



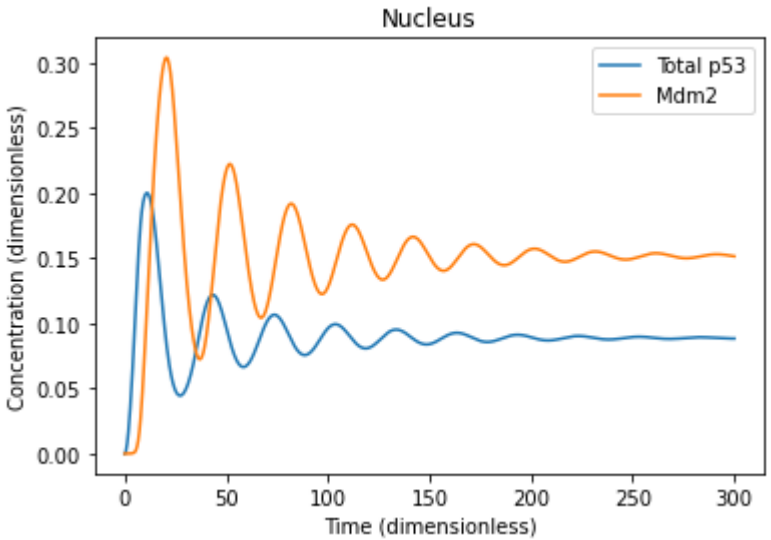


Model Results - Damage Parameter

E = 0



E = 5



Model expansion: Preventing Dephosphorylation from Wip1

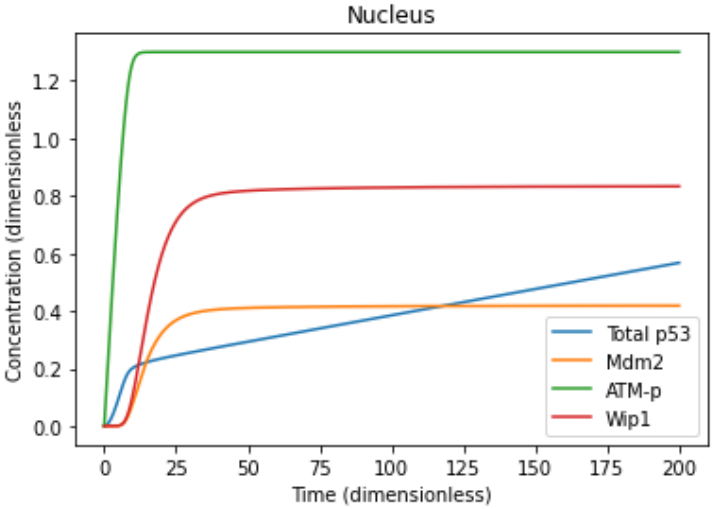
Model Setup

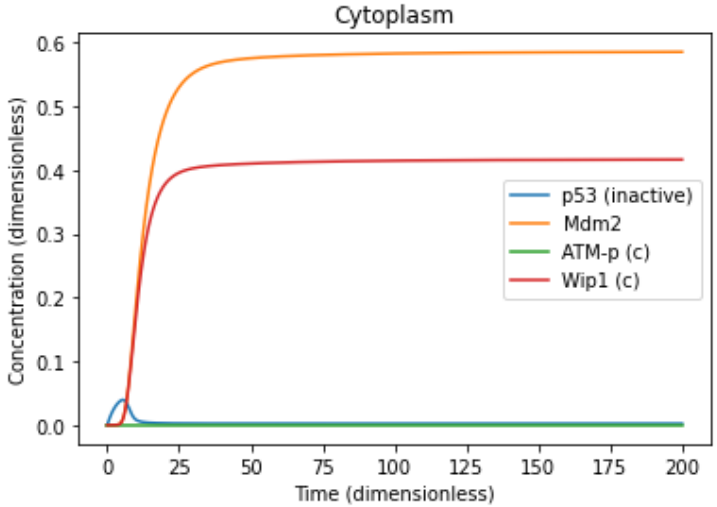
- Set rate of dephosphorylation by Wip1 to 0
- Concentration of Wip1 will have no effect on activated p53
- Will assume that Wip1 loses interaction with both p53 and ATM

$$k_{dph1} = dephosphorylation\ velocity\ of\ p53_p = 0$$

$$k_{dph2} = dephosphorylation\ velocity\ of\ ATM_p = 0$$

Model Extension Results





- Relevant for Wip1-targeting drugs such as GSK2830371 that have been seen to promote cancer cell death

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5442293/

Future Considerations

- Stochastic population modelling
- Compartmental model that depends on both spatial and time parameters
- Bifurcation analysis on damage parameter
- Accounting for protein translation in endoplasmic reticulum is expected to make system more robust to high damage values

References (put in proper format later)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8508851/pdf/ijms-22-10590.pdf

https://iopscience.iop.org/article/10.1088/1478-3975/11/4/045001/pdf

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5442293/