

ODE Analysis of a Cancer Pathway

Matt Hennessy*, Luda Korobenko† and Iain Moyles‡

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1 Introduction

2 The basal cell carcinoma pathway

3 Model

3.1 Results

Due to the nonlinearities in the governing equations (??), an analytical solution could not be found. Furthermore, a linear stability analysis of the equations is nontrivial because the equations which govern the steady state are not independent. In particular, the equations governing the SHH ligand and PTCH1 receptors are identical. Thus, there are not enough equations to uniquely determine a steady state, if one does exist. These difficulties can be overcome by investigating the dynamics of the system via numerical integrations in time. To begin such a simulation, it is assumed that there is an initial abundance of free SHH ligands and PTCH1 receptors. Furthermore, we assumed that all of the SMO was in the inactive state. Mathematically, these initial conditions correspond to

$$x_1(0) = 2, x_2(0) = 1, x_3(0) = 0, x_4(0) = 1, \tilde{x}_4(0) = 0.$$

As a preliminary investigation into the dynamics of the system, we first neglect the effects of drugs. The results from such a time integration can be seen in Figure 1. This figure shows the evolution of the various receptors and ligands, (check this...is the biology correct?) and it also displays the proliferation of cancer cells. From this figure, it can be seen that the SHH ligands quickly bind to the free PTCH1 receptors and reach a quasi-steady state almost immediately. Due to the positive feedback loop described above make sure this is actually described, the steady state is not actually reached because as long as there are some active SMO ligands, a series of biological processes will occur which eventually leads to generation of more SHH and PTCH1 ligands. The amount of cancerous cells, which is quantified using (??)cite this properly, appears to exhibit exponentially fast growth. This results from the fact that the amount of active SMO remains essentially constant in time, which from a biological standpoint, implies a constant inhibition of the P53 tumour suppressor gene. Furthermore, this figure depicts an increasing amount of SHH/PTCH1

*Mathematical Institute, University of Oxford, hennessy@maths.ox.ac.uk

†Department of Mathematics and Statistics, University of Calgary, lkoroben@math.ucalgary.ca

‡Institute of Applied Mathematics, University of British Columbia, imoyles@math.ubc.ca

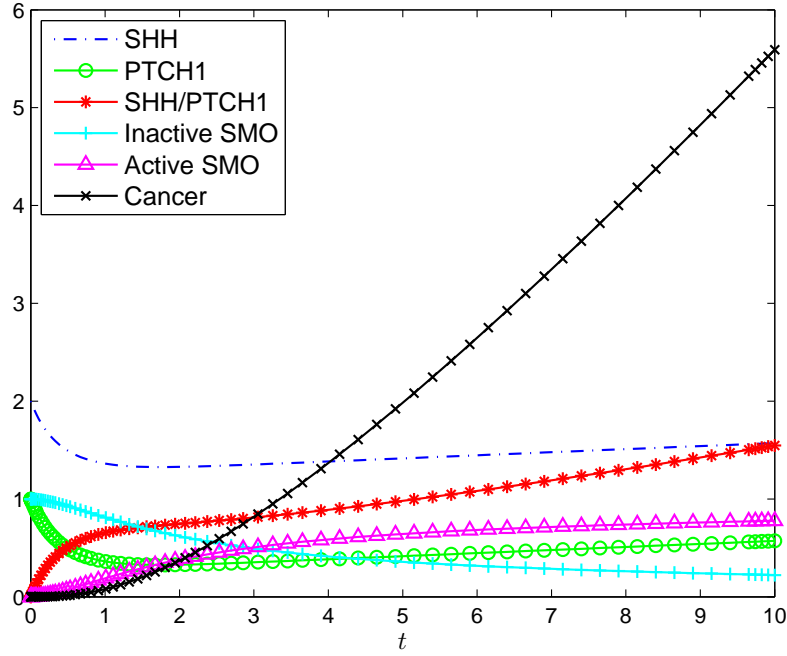


Figure 1: Evolution of SHH ligands (line/dots), PTCH1 receptors (line/circles), SHH/PTCH1 complexes (line/star), inactive and active SMO receptors (line/plus and line/triangle, respectively). Also shown is the growth of cancer cells. **units?** The effects of drugs are not considered here.

fig:time_in

complexes. These excess complexes can be thought of as inactive, since they do not appear to be activating additional SMO ligands (which do lead to cell proliferation). It then follows that if a drug treatment were to target these complexes after they have formed, the treatment would be highly ineffective at reducing cell proliferation because the drugs would have the effect of reducing the “inactive” complexes. Instead, the SMO ligands should be targeted directly, if possible.

The effects of targeting different parts of the pathway can be studied theoretically by performing various time integrations with different drug concentrations and recording the amount of cancer at the final time. As mentioned previously **check this**, drugs are introduced into the equations by assuming they only vary the rate constants of the interactions. We chose to focus on drug treatments which affect either the formation of the SHH/PTCH1 complex, or the positive feedback loop created by the active SMO ligands. The results can be seen in Figure 2. This figure shows the amount of cancer at the final time (taken to be 10 units of time) as a function of the amount of drug, where the drug amount has been normalized so that an amount of unity corresponds to completely stopping the given process. As predicted, we find that targeting the SMO feedback loop is far more effective than inhibiting the formation of the SHH/PTCH1 complex. However, Figure 2 must be interpreted with caution. For instance, it is not clear how much drug is actually needed to completely inhibit these two processes, and these amounts could differ by orders of magnitude. However, the important point is that targeting different interactions in the pathway can significantly improve the efficacy of a treatment.

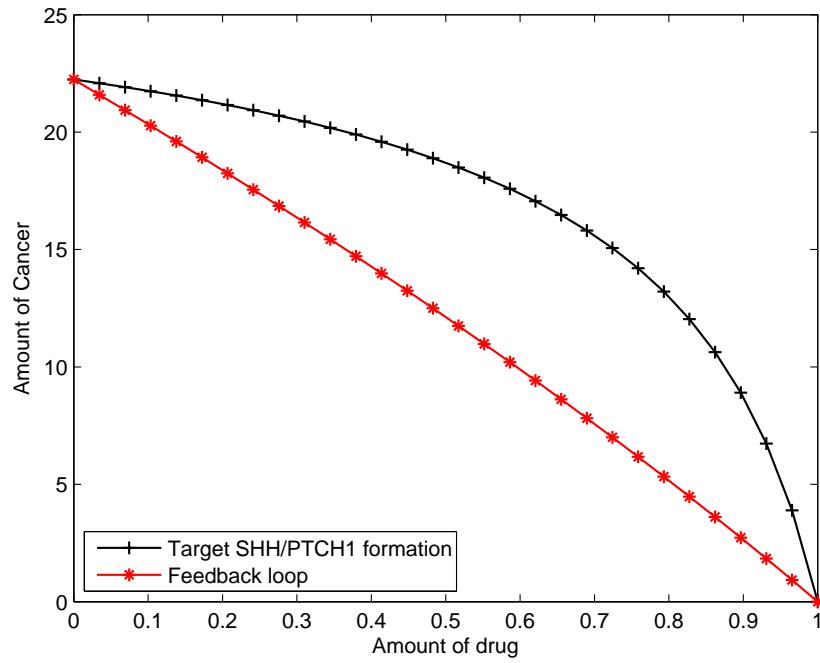


Figure 2: The effect of a chemotherapeutic treatment can be determined by measuring the amount of cancer at some time as a function of the drug concentration. We considered two treatments; one of which focused on inhibiting the formation of SHH/PTCH1 complexes (line/plus) and the other which inhibits the SMO feedback loop (line/star).

fig:drugs

4 Discussion and Conclusions

In this report we developed a small set of ordinary differential equations that model a simplified version of the basal cell carcinoma pathway. This model looked at how the constituent ligands and receptors in the pathway interact with one another and it incorporated the effects that drug treatments would have on these various interactions. By performing numerical experiments on the differential equations, it was found that targeting different interactions can have a significant effect on the amount of cell proliferation that occurs in a given time. In particular, our model suggests that targeting the positive feedback loop between activated SMO, PTCH1, and SHH, is much more effective at reducing the number of cancerous cells than using a treatment which inhibits the formation of SHH/PTCH1 complexes. Unfortunately, our model uses unrealistic parameter values and therefore it cannot be used in its current form to make predictions about real life treatments. However, it does show if one can accurately model the key interactions in a biological pathway, then one can use the model to investigate the key interactions in the pathway that are essential for cell proliferation. Using this information, a treatment can be created which focuses on targeting this critical interaction. Furthermore, this report shows the type of approach that can be taken in order to build such models. In fact, it could be possible to create a generic toolbox of equations that can be used to string together various types of interactions, such as a ligand binding to a receptor followed by an activation via phosphorylation. When armed with such a toolbox, one could build arbitrarily complex models of biological pathways.

Of course, modelling the role of drugs in a biological pathway is not as simple as we have described, as we have neglected the very important fact that the drugs which are used in cancer treatments are usually damaging to healthy cells as well. Therefore, an ideal model would have to take this fact into account. One possible way of doing this would be to study an optimization problem that aims to minimize both the amount of cancerous cells at some terminal time and the total amount of drug that is used during the treatment. There are countless other methods in which this problem can be modelled, but one fact remains the same: the analysis of accurate mathematical models can, in theory, be used to develop new treatments that are both highly effective yet still allow the patient to live with a high quality of life.