

ODE Analysis of a Cancer Pathway

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1 Introduction

2 The basal cell carcinoma pathway

A first step to creating an effective cancer treatment is understanding underlying biological processes and key interactions in a cell that lead to uncontrollable cell division and therefore cancer. One approach to understanding reactions taking place in a cancerous cell is to consider so-called signal transduction pathways or signaling pathways. In general, the term signaling pathway refers to any ordered sequences of biochemical reactions inside the cell, which are carried out by enzymes and activated by second messengers. Most signaling pathways involve the binding of extracellular signaling molecules (or ligands) to cell-surface receptors that face outward from the plasma membrane and trigger events inside the cell. The usual cellular responses to the activation of a signalling pathway include activation of genes, alterations in metabolism, the continued proliferation and death of the cell. If mutations occur in a cell they can cause an uncontrolled activation of some pathways leading to fast proliferation and cancer tissue formation. Different signaling pathways interact with each other thus creating a complex net of processes in a cell that can be represented by a biochemical pathway map. Database [5] contains a collection of pathway maps representing the most up-to-date knowledge on the molecular interaction and reaction networks for cellular processes including those in pathogenic cells. Most of the pathway maps for the well-known human cancers are very complicated and understanding them doesn't seem to be a feasible task for non-biologists. One of the simplest maps is the map for a widespread skin cancer called Basal Cell Carcinoma (see Fig.1) on which we will concentrate our attention.

On the Fig.1 we can see four signaling pathways engaged in Basal Cell Carcinoma development. The first pathway, called *p53* signaling pathway, leads to a reduced apoptosis which means cell death, hence no further cancer growth. The other three — Hedgehog, TGF and Wnt pathways — lead to proliferation of cancerous cells and therefore are responsible for the development of cancer. Many pathways that play an essential role during the embryonic development are switched off later in life, during adulthood. Aberrant activation of these pathways in adult tissue is often oncogenic. It is known (see e.g. [3]) that the Hedgehog signalling pathway is important in embryological development and is highly conserved through evolution. Activation of this pathway has been implicated in the development of various cancers including Basal Cell Carcinoma (BCC), which was

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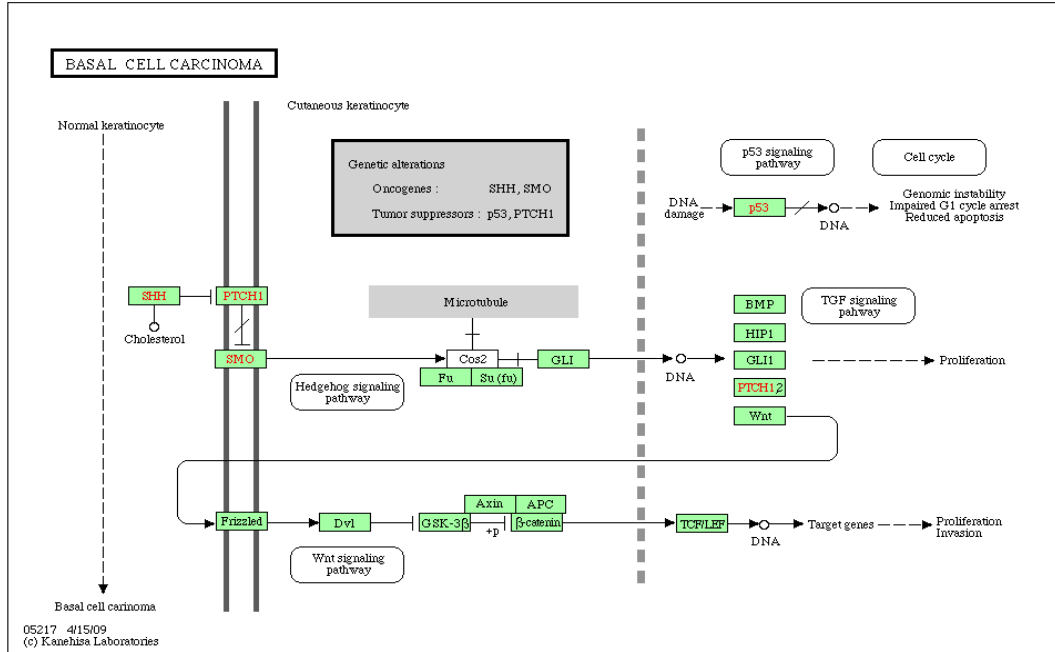


Figure 1: Basal cell carcinoma.

kegg

proved to have the closest association with hedgehog signaling [2]. Since it is believed that inhibiting the HH (Hedgehog) pathway can provide an efficient therapy for a wide range of malignancies [1] including the one under consideration, we chose to concentrate our attention on this particular pathway and its signaling mechanisms.

Returning to the diagram on Fig.1 we will consider the part of it which is engaged in the HH pathway. On the diagram one can see two transmembrane proteins built in cell membrane — PTCH (Patched), in particular PTCH1 homologue, and SMO (Smoothed) — first of which serves as a receptor for the secreted protein SHH (Sonic Hedgehog). In the absence of SHH, PTCH1 inhibits the HH pathway by repressing the activity of SMO. Binding of the SHH ligand to PTCH1 relieves its inhibition of SMO, which in turn triggers the release of the GLI protein family transcription factors from the protein complex (Cos-2, SU and SUFU on Fig.1). The activation of GLI protein drives an overexpression of downstream genes in the nucleus and thus proliferation and differentiation.

A large number of different factors can affect the work of HH signaling pathway. Studies have shown [1, 2] that deregulation of the HH pathway in BCC occurs by mutation or altered activity of one or more of the members. Proteins expressed by mutated genes or altered by external factors are shown in red on the Fig.1. While the Hedgehog signaling results in overexpression of PTCH, SMO and GLI genes, it should also be noted that it activates the Wnt signaling pathway which eventually leads to expression of SHH gene [4]. Expression of both PTCH1 and SHH creates a positive feedback loop in a cancer development through HH signaling. A simplified scheme of the Hedgehog signaling is shown on Fig.2

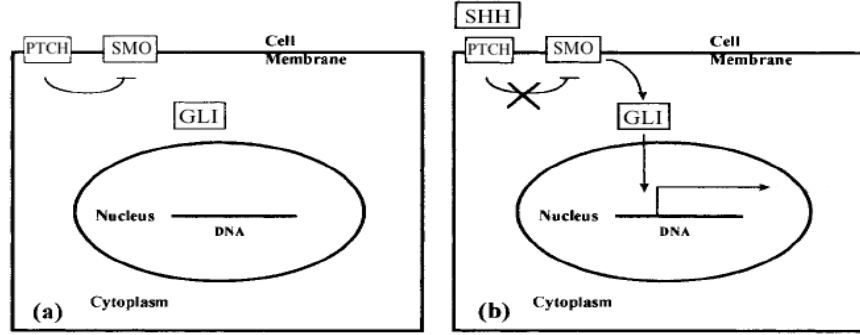


Figure 2: Hedgehog signaling pathway.

hh

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

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

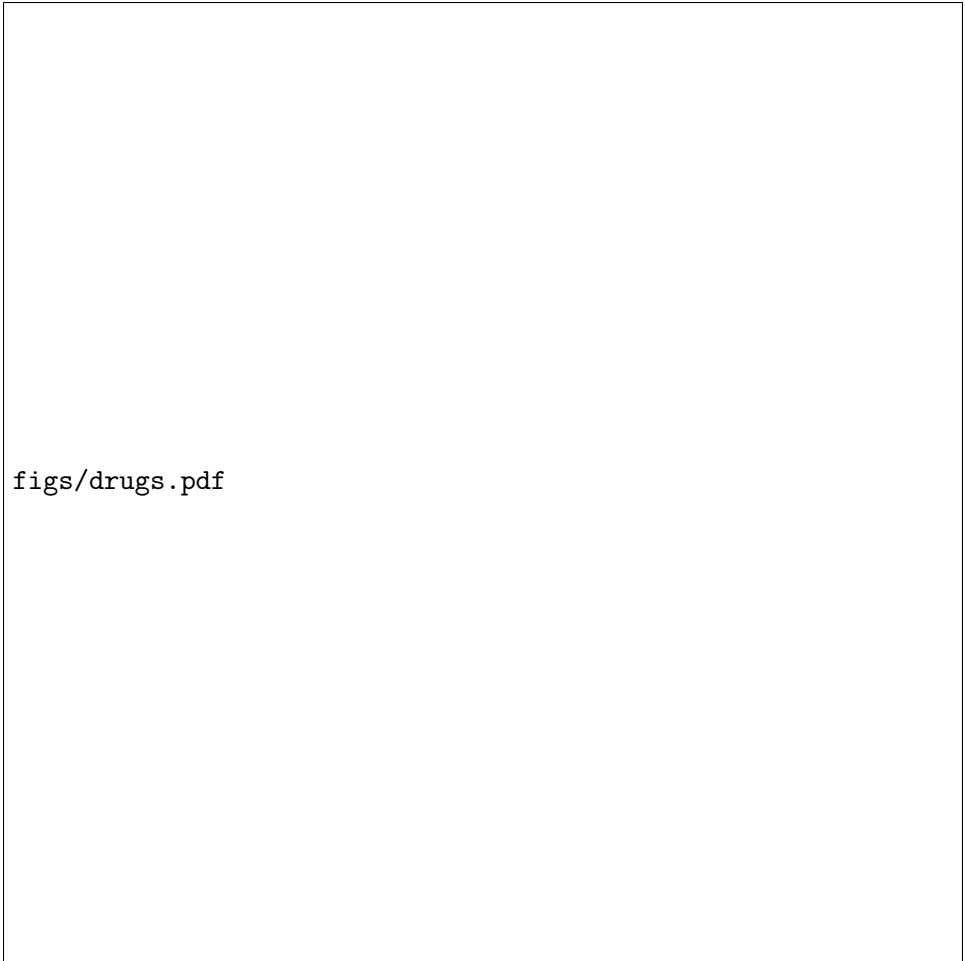
As a preliminary investigation into the dynamics of the system, we first neglect the effects of drugs. The results from such a time integration can be seen in Figure 3. This figure shows the evolution of the various receptors and ligands, (check this...is the biology correct?) and it also displays the 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 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

figs/time_int.pdf

Figure 3: 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.

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 4. 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 4 must be interpreted with caution. For instance, it is not clear how much drug is actually needed



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Figure 4: 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

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.

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.

References

- [A] [1] M. Athar, X. Tang, J. L. Lee, L. Kopelovich, A.L. Kim, Hedgehog signalling in skin development and cancer, *Exp. Dermatol.* **15** (2006), 667-677.
- [D] [2] L. Daya-Grosjean, S. Couvé-Privat, Sonic hedgehog signaling in basal cell carcinomas, *Cancer Letters* **225** (2005), 181-192.
- [S] [3] G. Saldanha, The Hedgehog signalling pathway and cancer, *J. Pathology* **193** (2001), 427-432.
- [T] [4] C.M.L.J. Tilli, M.A.M. Van Steensel, G.A.M. Krekels, H.A.M. Neumann and F.C.S. Ramaekers, Molecular aetiology and pathogenesis of basal cell carcinoma, *J. Dermatol.* **152** (2005), 1108-24.
- [K] [5] <http://www.genome.jp/kegg/pathway.html>