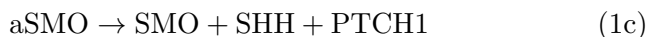


1 Model

Looking at the large biological pathway diagram referenced previously (Figure ??), the complexities in even a relatively simple cancer pathway are clear and thus a thoroughly accurate model is difficult to generate, especially considering the lack of modelling literature found on this topic.

Hence, after discussion with the biological research department at the University of Calgary, we decided upon a way to create a simplified pathway that could be modelled. We noticed that at the beginning of the pathway, the mutated SHH combines with a mutated PTCH1 creating a complex which activates SMO. The creation of this activated SMO continued on through the pathway to stimulate cancer proliferation through a multitude of intermediate steps. Therefore, we decided that by modelling the concentration of this activated SMO we could have an estimate on cancer production because of this direct cancer growth relation. The simplified pathway is presented in Figure 1. The oversimplification step is the positive feedback loop where the activated SMO produces new SHH and PTCH1 as this in actuality is an indirect reaction. In our model we consider five concentrations, x_1 for SHH, x_2 for PTCH1, x_3 for the SSH PTCH1 binding complex, x_4 for the inactive SMO, and \tilde{x}_4 for the activated SMO. A simple mass action law approach was used whereby reactants in a synthesis equation are combined as products in the differential equation indicating that no reaction is possible when either reactant is absent. The reactions from Figure 1 can be simplified to



where SPc is the SHH-PTCH1 complex and $aSMO$ is the activated SMO. The SHH is lost by the synthesis of SPc with PTCH1 and then produced again by the dissociation of the SPc back into its constituents along with the production of new species from the $aSMO$. This is the same reaction as with the PTCH1. The complex is created by the synthesis of the SHH and PTCH reactants but naturally dissociates back to the individual compounds and the SMO concentration is increased as the $aSMO$ loses its energy but is decreased by the activation with the SHH-PTCH1 complex. These are all

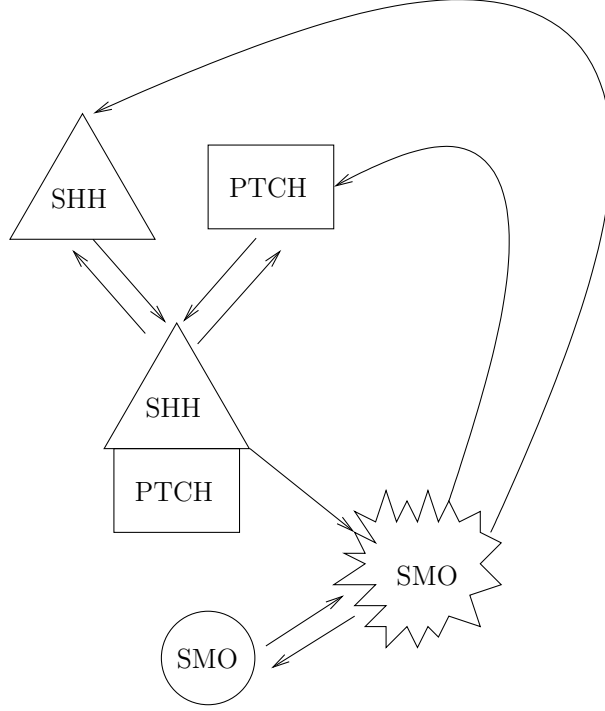


Figure 1: The simplified pathway created to model cancer growth in a skin cell.

modelled with ordinary differential equations in (2),

$$\dot{x}_1 = -ax_1x_2 + bx_3 + c\tilde{x}_4 \quad (2a)$$

$$\dot{x}_2 = -ax_1x_2 + bx_3 + c\tilde{x}_4 \quad (2b)$$

$$\dot{x}_3 = -bx_3 + ax_1x_2 \quad (2c)$$

$$\dot{x}_4 = c\tilde{x}_4 - bx_3x_4 \quad (2d)$$

$$\dot{\tilde{x}}_4 = bx_3x_4 - c\tilde{x}_4 \quad (2e)$$

where a , b , and c represent the three key reaction rates. For generality, each reaction would have a different rate constant but conservation of mass can simplify them down to three (possibly) unique rates. For instance, the SHH-PTCH1 complex forms with equal parts of each constituent so the

rate of synthesis of SPc must be the same as the loss rate of each SHH and PTCH1 respectively. This is also similar for the complex dissociation. Since the activated SMO is synthesized from a one to one reaction with the complex and inactive SMO then the same reasoning is used to justify the third rate constant. Without proper empirical data, a robust justification for rate constant values is impossible however, we approximated them with some physical justification. The rate constant a was set to 1 without loss of generality with everything else being evaluated in reference to that. The rate constant b was then set to $1/2$. This was justified under a conservation of mass ideology whereby if two reactants form a single complex with rate constant a then in the reverse reaction, the rate at which the two original reactants are reproduced must be half of the original rate. This is similar to current branching in electrical circuits. The rate constant c which relates to the production of activated SMO was left as an adjustable parameter.

1.1 Cancer Proliferation and Drugs

As mentioned, the complex pathway diagram shows that after the SMO is activated it eventually ends up in a step with cancer proliferation. Therefore, the concentration of the aSMO is directly proportional the cancer production in the basal cell for any time t . The rate of cancer development is then going to be,

$$C = \int_0^t c\tilde{x}_4(s)ds. \quad (3)$$

By introducing a drug into the pathway, the goal is to limit the cancer proliferation. While this can be done in a various number of ways from a physical perspective, the only qualitative change would be a decrease in the rate of production of cancer. Therefore, adding drugs into the system can be modelled as varying the rate constant c attached to the production of activated SMO. For model results, we varied the rate constant from 0 (the perfect drug) to 1 (no drug acting) and monitored effects. As well we considered a drug that affected the synthesis of the SHH and PTCH1 complex.