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Mathematical models in cancer therapy

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ABSTRACT

In this article, deterministic mathematical models are derived from biochemical models within a human cell in two distinct cases, for comparison: healthy cell and cancerous cell. The former model is based in the cell cycle model by Novak and Tyson and its adaptation by Conradie, and makes use of the MAPK cascade pathway and the PI3K/AKT pathway for signalling transduction, to create a wider updated model for the regulation of a healthy cell. The latter model, for the cancer cell, is derived from the healthy cell model by altering specific pathways and interpreting the outcome in the light of literature in cancer. This last study is done in two approaches: simulation of common deregulations and specific cancer simulation, colon cancer. After studying both models, we propose targeting therapies and simulate their consequences. We thus explore mathematical modelling efficacy and usefulness in providing enough information from which to derive ideas for therapies. The purpose is to validate mathematics, once again, as a powerful tool with which one can model the underlying nature of chaotic systems and extract useful conclusions to real-life problems.

1. Introduction

Cancer is one of the most deadly diseases among humanity in great part due to the large amount of variables which have to be taken into account in its development and dynamics, making it particularly difficult to approach therapeutically. The understanding of how cancer mechanism works starts with understanding how a healthy cell behaves, since the differences between cancer dynamics and healthy tissue dynamics are a reasonable object of analysis in cancer theory.

When a single mammalian cell fails to stop cell cycle when it needs to, proceeding to replicate and originate offspring with anomalies, it can quickly develop a tumour whose priority is to grow and divide uncontrollably, selfishly wearing all resources in its environment, destabilizing its neighbouring healthy cells in the tissue and, consequently, the whole organism. The study of individual healthy and cancerous cells dynamics is therefore an understandable approach for cancer therapy development and is the one we discuss in this paper.

2. Preliminaries

2.1. The cell cycle regulation

The Cell Cycle of Eukaryotic cells can be divided in two main events: replication of DNA, known as S phase, and Mitosis, known as M Phase, followed by cytokinesis (Alberts et al., 2002). Between S phase and M phase the cell enters G_1 and G_2 phase, in which different concentrations of biomolecules change. When it is not in any of these phases, it means it is in quiescence state, the so called G_0 phase, or is preparing itself for apoptosis, i.e. programmed cell death.

The biomolecules that regulate this cycle are the Cyclins (Cyc's) and the Cyclin Dependent Kinases (CDK's), proteins and enzymes, respectively. To enter the cycle from G_0 phase, some external signal must be transducted through the cell's cytosol reaching the nucleus and promoting transcription of CycD and CDK4,6. During the transition between G_1 and S phase, CycE/CDK2 complexes increase their concentration in the cytosol, allowing for the transcription of CycA and CDK2, which, in the form of complex, promotes the movement to the G_2 phase of the cycle, where CycA/CDK1 complexes are predominant, leading to the passage to Mitosis, where, in turn, CycB/CDK1 complexes are in abundance. This completes the cycle of concentrations of Cyclin/CDK complexes, right before the cytokinesis event, that divides the cell in two daughter cells.

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Activation of the anaphase-promoting complex (APC) by binding of cell-division cycle protein 20 (CDC20) and cadherin 1 (CDH1) is necessary for exit from mitosis.

2.2. The restriction point regulation

The previous section resumed what is known about the Cell Cycle regulation. The dances of Cyclins and CDK's are the mechanism that promote the advance of the cell through the cycle. However, at some specific point in the cycle, the cell no longer needs extracellular signals to proceed. In the late G_1 phase there is some device that allows the cycle to continue regardless of mitogenic activity at the membrane. This point, called *Restriction Point*, was set between the 3rd and the 4th hour of G_1 phase (Zatterberg and Larsson, 1995).

In human eukaryote cells, the Retinoblastoma Protein, Rb, whose transcription is done from a genetic sequence found in chromosome 13 (Anon, 2017a), plays an important role in regulating the restriction point along with E2F transcription factor. Active E2F migrates to the nucleus of the cell where it promotes DNA replication, initiating S phase. Active Rb binds to E2F, deactivating E2F and thus inhibiting the passage to S phase. Rb is activated in its hypophosphorylated form, and is deactivated in its phosphorylated form. CycD–CDK4/6 complexes inhibit active Rb, phosphorylating it partially, leading to a partial activation of E2F. PP1 phosphatase dephosphorylates Rb, increasing the concentration of active Rb and thus promoting the inhibition of E2F. Along with CycE/CDK2 complexes, E2F promotes the passage through the G_1-S phases frontier, hence leading to DNA replication, independent of further mitogenic signals. At this point, the cell enters in automatic program.

2.3. Cell cycle arrest and apoptosis

The cell cycle can be disrupted by the cell itself if something is not according to the regulation we summarized in the previous sections, and in some cases this conduces the cell to a specific fate called apoptosis, i.e., programmed cell death. Apoptosis is a mechanism of defense developed to protect multicellular organisms from malformations in cell development and/or activity, for it conduces the cell to destroy itself without damaging neighbouring cells. It does so by shrinking, condensing, tearing up its outer layers and breaking the DNA into fragments (Alberts et al., 2002).

When DNA is damaged, the ATM ("ataxia-telangiectasia mutated") kinase is activated, culminating in p53 concentration increase, which in turn gives place to a sequence of events that turn on Caspase-9 and ultimately induces apoptosis. The details on this mechanism are far too extensive for the purpose of our model, which is why we kept the apoptotic dynamics fairly simple, as we explain in the updated model section.

2.4. The p53 pathway

The p53 gene, found in 1979 by separate groups of investigators (Sherr and McCormick, 2002; Alberts et al., 2002; Zatterberg and Larsson, 1995; Peña et al., 2005), and set to be a *tumour supressor gene* in 1989 (Baker et al., 1989; Takahashi et al., 1989), expresses the p53 protein, a central biomolecule in cancer research, specifically in the study of pathways within the cell. This is due to the fact that virtually all cancers exhibit some sort of mutation of p53 gene or modifications to its pathway. The study of p53 pathway revealed the core of its regulation as well as several links that it establishes between other major pathways, such as the one of Rb protein, E2F and Ras. The concentration of p53 protein within an unstressed cell is low, however it has a fast turnover when the cell is under stress.

The core regulation of p53 protein is co-protagonized by the protein Hdm2 (Mdm2 in the mouse) that inhibits p53 protein by binding to it directly. P53 protein promotes the transcription of Hdm2, defining a negative feedback loop between p53 protein and Hdm2 (Momand et al., 1992; Picksley and Lane, 1993). $p14^{ARF}$ ($p19^{ARF}$ in the mouse) in turn inhibits Hdm2 and its activity is inhibited by p53 protein. The transcription factor E2F also plays a role in p53 regulation, by sustaining a negative feedback loop with $p14^{ARF}$ by inducing it while being inhibited by it (Sherr and McCormick, 2002).

The core regulation of p53 protein leads to several different downstream events that culminate in different fates of the cell: *cell cycle arrest*, *apoptosis*, *inhibition of angiogenesis* and *metastasis*, and *DNA repair*.

In Harris and Levine (2005), these downstream events were explored in distinct pathways, as well as useful positive and negative feedback loops for P53 protein, which are fairly easy to model.

Let us resume the main downstream event triggered by p53 protein activity which culminates in cell cycle arrest: the p21 gene product, a Cyclin Dependent Kinase Inhibitor (CKI), that inhibits CycE/CDK2 complex is a relevant molecule in p53-mediated G_1-S phase arrest. Its transcription is induced by p53 protein activity. There is also CDC25 inhibited by 14-3-3-sigma, and CDC2 induced by CDC25 and CycB, the latter inhibited by Gadd45. CDC2 promotes Cell Cycle arrest between G_2-S phase. This last pathway is not of our interest, as it concerns another checkpoint in the cell cycle, not the restriction point. The cell cycle arrest pathway in which we focused our attention was the one concerning the checkpoint during G_1-S phase transition, and is obviously of the most relevant for studying the regulation of the Restriction Point.

The p53 pathway that culminates in apoptosis is triggered by ATM and induces Caspase-9, an essential protease of apoptosis (see model diagram 1).

2.5. The MAPK cascade pathway

MAPK Cascade signalling pathway (Mitogenic-Activating-Protein Kinase Cascade), is a main mechanism for protein synthesis motivated by extracellular signals. It depends on MAPKKK, MAPKK and MAPK whose phosphorylated form is the activated form.

Extracellular signals, also called Ligands, such as *Growth Factors*, bind to transmembrane receptors, whose cytosolic domain may be allosterically altered, enabling its phosphorylation, inducing the binding of Growth factor receptor-bound protein 2 (GRB2) molecule, activating it. Active GRB2 activates *Son of Sevenless* (SOS), which in turn phosphorylates Ras–GDP complex to Ras–GTP complex. The latter can then activate Raf (MAPKKK) by binding. Raf will proceed the mechanism by phosphorylating MEK (MAPKK). Activated MEK promotes the phosphorylation of ERK (MAPK). Finally, active ERK promotes the activation of transcription factors and subsequent migration to the nucleus where it will bind to DNA transcription sites, leading to protein synthesis (Dhillon et al., 2007).

Phosphorylated ERK promotes cell growth (Meloche and Pouysségur, 2007). Important transcription factors are the *Early Response Genes* (ERG) *c-Fos*, part of the Fos family of transcription factors, the protein *c-jun* and the protein *Myc*. This cascade would continue indefinitely while Ras–GTP complex continues active. This is why this cascade also induces the transcription of GAP (GTPase-Activating Proteins) regulatory proteins, which act like a switch off button, phosphorylating Ras–GTP complex back to Ras–GDP complex, inhibiting the rest of the cascade and thus stopping the synthesis of the specific proteins that the mitogenic signals triggered. It has been documented that the silencing of GAP proteins is related to some human cancers (Jin et al., 2007), since it leaves the regulation of Ras protein to chance, resulting in the deregulation of the concentration of Ras, and consequently of the whole Cascade.

Overall, this signalling pathway needs to be well regulated to avoid cancers, because if one of the biomolecules involved in it were