Journal of
Computer Science & Systems Biology

Cárdenas-García González-Pérez, J Comput Sci Syst Biol 2013, 6:4
DOI: 10.4172/jcsb.1000118

Research Article Open Access

Integration of Pro-Apoptosis and Pro-Survival Signalling Pathways: A Useful Approach to *In silico* Biomedical Research

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Abstract

Cells communication is absolutely essential for multi-cellular organisms, but what if a cell fails to send out a signal at the proper time? Or what if a signal doesn't reach its target? What if a target cell does not respond to a signal or a cell responds even though it has not received a signal? These cellular phenomena can lead to serious metabolic alterations, but of course there are molecules that block these errors and prevent a catastrophe. Apoptosis, a form of programmed cell death, is a genetically regulated cell-suicide mechanism that is essential for our well-being. In this process, cells acquire the means of their own destruction in the form of an arsenal of deadly proteins, which they turn upon themselves. There are different pathways pro-apoptotic and pro-survival that crosstalk. In this work, we simulated the incremental integration of pro-apoptotic and pro-survival signalling pathways in a tuple space-based bioinformatics platform, which provides a robust working environment for *in silico* experimentation, allowing us to work both separately and together on these pathways, including/removing deadly or regulatory proteins, and observing the consequences of such changes for the overall system behaviour.

Keywords: Computer simulation; Tuple space-based bioinformatics platform; *In silico* experiments; Pro-apoptosis signalling pathways; Pro-survival signalling pathways

Introduction

The role of apoptosis in multicellular organisms is not limited to its action in the development of cancer, it is also important for normal development of cell differentiation, to maintain the adult tissue homeostasis by eliminating damaged or abnormal cells. It is also involved in the defence against infection and in the regulation of the physiological process of aging. This type of cell death is genetically programmed and occurs continuously and dynamically in all organisms [1,2].

The mechanism by which cells die by apoptosis is active, complex and sophisticated. Thus, multiple molecules promote cell death cascade involving effects so as to ensure that once the process starts, it is fast and irreversible. As prevention mechanism, the cell produces regulatory molecules whose function is to prevent that small changes result in unnecessary death. Therefore, deregulation of the apoptotic machinery leads to the development of human pathologies. Apoptosis is inhibited in cancer, autoimmune diseases (lupus, type I diabetes, rheumatoid arthritis) and viral infections (herpes-virus, adenovirus). Therefore, our understanding of the mechanisms involved in the process of apoptosis in these diseases at the molecular level, allows us to know more about them [1,3,4].

Caspases are a large family of evolutionarily conserved proteases. The role of effectors caspases is mediating nuclear morphological change during apoptosis. All caspases are synthesized in cells as catalytically inactive zymogens and require proteolytic processing in the presence of apoptotic signals to control distinct downstream processes. The many level interaction allows an amplification of the original signal to quickly produce a strong response to a small stimulus. Intrinsic or Mitochondrial and extrinsic or death receptor pathways, are the most extensively described apoptotic pathways. However, considerable crosstalk exists between the intrinsic and extrinsic pathway including PI3K, PKC and MAPK [5,6]. In previous works we have used successfully a computational framework based on the notion of tuple spaces for modelling and simulation the signalling pathway mentioned above [7-11]. In this paper, using the tuple space-based framework, we integrate all these pathways in order to dissect each one considering the points of crosstalk, this allows us to highlight the regulatory proteins already described, and to "eliminate" proteins which are difficult to remove *in vivo* or *in vitro*.

Material and Methods

The simulation framework

Modelling intracellular signal transduction requires a robust approach accounting for the crucial features that govern the activity, interaction, selectivity, inhibition and evolution of a complex distributed system. These features include situatedness, adaptation, diversity, eternity, topology and locality. Such features have found a suitable support in the concept of Biochemical Tuple Spaces for Self-Organising Coordination (BTSSOC) introduced by Viroli and Casadei [12]. In fact, the cell detects the spatial context (the cellular compartments) of signalling elements, enabling or disabling actions and interactions accordingly (situations); dynamically adapts to external changes (adaptively); can change its function over time and then the activities being executed (presumption and diversity); is able to tolerate runtime changes in terms of structure, elements and function (eternity). Also, BTSSOC supports topology and locality, respectively to model the intracellular compartments, and to provide a view of

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Received August 14, 2013; **Accepted** August 26, 2013; **Published** August 31, 2013

Citation: Cárdenas-García M, González-Pérez PP (2013) Integration of Pro-Apoptosis and Pro-Survival Signalling Pathways: A Useful Approach to *In silico* Biomedical Research J Comput Sci Syst Biol 6: 206-214. doi:10.4172/jcsb.1000118

the signalling system as a composition of local interactions. Finally, and more generally, its biochemical inspiration makes a BTSSOC infrastructure particularly suited for simulating systems where the very same concepts BTSSOC is based on – such as chemical reaction and concentration – are among the most relevant ones.

The main characteristics of our BTSSOC-based framework for simulating intracellular signalling pathways are reported in Table 1. A detailed explanation of this framework can be found at [7-11].

An overview of pro-apoptosis and pro-survival signalling pathways

Apoptosis is the process of programmed cell death, genetically defined. Physiologically, apoptosis is involved in the following process: the removal of damaged tissue, development of an embryo, tissue renewal and the immune system regulation [14-19]. According to the function, extracellular signal molecules promote apoptosis. In some instances, however, regulation deficits lead to diseases. The rate of apoptosis can contribute to degenerative diseases such Parkinson's or autoimmune diseases [20,21]. The inactivation of apoptosis is central to the development of cancer [22]. With regard to the above mentioned, expression and activation may be modulated by key apoptotic proteins considered important therapeutic targets in disease control.

Apoptosis can be divided into two phases: the activation phase and the implementation phase. In the activation phase, the cell is stimulated to carry out processes such as: destruction of damaged cells, embryonic development, tissue renewal and immune system regulation. Stimuli responsible for triggering these processes are shown in Figure 1. On the other hand, the implementation phase is characterized by morphological and biochemical changes that lead the cell to lose contact with its neighbouring cells.

Caspases are a large family of evolutionarily conserved proteases. The role of effectors caspases is mediating nuclear morphological change during apoptosis. The best characterized signal transduction pathways to trigger the caspase cascade in the apoptotic process are two: the intrinsic pathway (also called mitochondrial pathway) and the extrinsic pathway (also known as death receptor mediated apoptosis). Diverse apoptotic stimuli converge and/or cross talk through the permeability of outer mitochondrial membrane to induce apoptosis, which leads to activation of caspase 9 or initiator.

The intrinsic pathway of apoptosis is regulated by members of the Bcl-2 family (gene 2 B cell lymphoma) - shown in Figure 1 in green, and in more detail in Figure 2. In this family there are 20 polypeptides, divided into three groups according to their structure and function:

- Group I: anti-apoptotic members of the Bcl-2 family (Bcl-2, Bcl-XL, etc.), characterized by containing four BH domains.
- Group II: pro-apoptotic members, characterized by lacking the N-terminal BH4 domain (Bax, Bak and Bok / MTD).
- Group III: pro-apoptotic members that share only a limited degree of sequence homology to the BH3 domain (Bid, Bad, Bik, Bim, PUMA, NOXA, etc.).

The balance between expression levels of both pro-and anti-apoptotic proteins of this family determines mitochondrial cytochrome c release.

The extrinsic pathway begins outside the cell, when specific ligands binding to death receptor, growth factors, cytokines, ionic channels, etc. activate different pathways, among which are:

- Phosphatidyl inositol 3-kinase (PI3K, shown in Figure 1 in red).
- Mitogen-Activated Protein Kinases (MAPKs, shown in Figure 1 in yellow), which is also activated after stress exposure, through the Ras / Raf / MEK or phorbol esters through PKC signalling pathway-Raf-MEK (shown in Figure 1 in orange) [23-25].

Modelling pro-apoptosis and pro-survival signalling pathways

In our working methodology, modelling and simulation of an intracellular signalling network is handled as an incremental process of definition and refinement of the signalling pathways and components in the network. That is, the signalling pathways are modelled one at a time, breaking down each pathway in characteristic segments that compose it, and then identifying and describing the elements belonging to each segment and the relationships established between them. At the beginning of the modelling process it is appropriate to consider only the main features of the components involved in the pro-apoptosis and pro-survival signal transduction, i.e. those needed for achieving a

Requirements for simulation of intracellular signalling pathways	Computational representation/abstractions and algorithms of the BTSSOC framework
Computational Abstraction	Tuple Spaces
Representation of intracellular compartments	Tuple centres
Representation of signalling components (i.e., membrane receptors, proteins, enzymes, and genes)	Chemical reaction sets
Representation of signalling molecules (i.e., first and secondary messengers), activation and deactivation signals	Reactants and concentrations recorded as tuples in the tuple centre
Type of chemical reaction allowed	i. Collaborative activation ii. Alternative activation iii. Complex formation iv. Decomposition reactions v. Standard equation for enzymatic reaction vi. Interaction from and to extracellular space
Model of chemical reactions	Discrete system model
Action selection mechanism for chemical reactions	Gillespie algorithm [13] – an algorithm typically used to simulate systems of chemical/ biochemical reactions efficiently and accurately – to execute chemical reactions with the proper rate.
User interaction and visualization of the simulation	Graphical user interfaces, viewer components, graphical components

Table 1: Mapping requirements for simulation of intracellular signaling pathways onto BTSSOC abstractions.

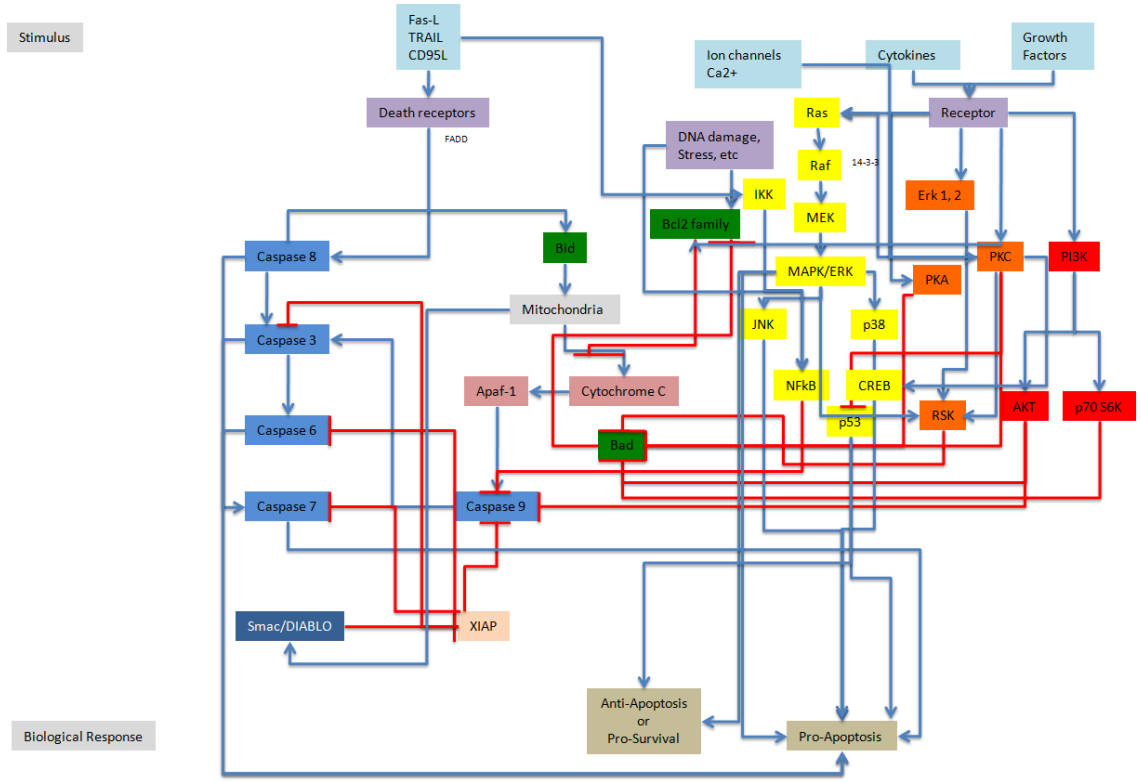

Figure 1: Simplification of Pro-survival and Pro-apoptosis pathways, blue arrows represent activation and red truncated lines inhibition..

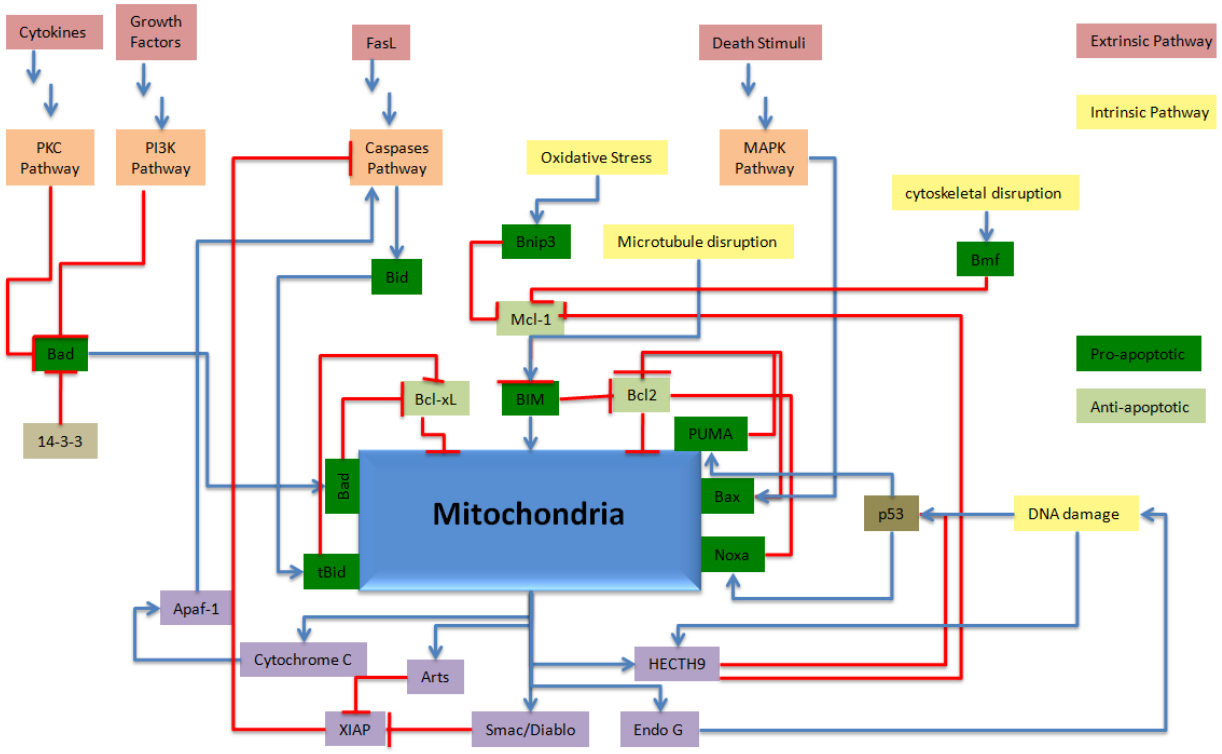

Figure 2: A detailed representation of both interactions intrinsic pathway (yellow) and extrinsic pathway (pink), regulating members of the Bcl-2 family (green) and mitochondrial Cyt c release. DNA damage, microtubules damage, or caspase activation are pro-apoptotic processes (dark green). Growth factors and cytokines are pro-survival processes (light green)..

comprehensible and functional simulation. In this paper, we start with a simple model where each signalling component is described by the following attributes:

- Identity;
- Usual cellular compartment:
- Cellular compartment, which is located over time
- Concentration in each cellular compartment;
- Free concentration;
- "Bound" concentration;
- Biochemical reactions involving the component and the order in which they occur according to reaction stoichiometry and the affinity of its components;
- Reaction temporality situation.

It is necessary to include all elements involved in these pathways and its biochemical reactions in our virtual cell. Examples of modelling of these elements are shown in Tables 2 and 3.

With all this information, we proceed to the incremental development of the modelling process by incorporating other signalling components. Clearly, the more the modelling process preserves the essential features of signal transduction, the more the intracellular signalling model becomes significant. The cube in Figure 3 represents our initial (minimalist) model with the previously described features.

Results

The goal of the first *in silico* experiment was the simulation of each of the pro-apoptosis and pro-survival signalling pathways separately in order to identify proteins involved in more than one signalling pathway, which have not been reported in the literature.

Chemical reaction	K_m	V_{max}	Rate
Bcl2R* + CytC → CytC @ cytosol	0.1 μM	8×10^{-7} μM	1/1

Table 2: Kinetic parameters for the reactions involving cytochrome C. V_{max} is the maximum initial velocity (V_o) that an enzyme can achieve, K_m is determined as the substrate concentration at which 1/2 V_{max} is achieved. Rate is the stoichiometric rate [26].

E×trinsic pathway of apoptosis			
Cellular compartment	**Reactions**	**K_m (μM)**	**V_{max} (μmol/mg/min)**
E×tracellular space and membrane	DL + DR → DR*@Cytosol	1	1×10^{-5}
	DL + DecoryR → DecoryR*@ Cytosol	1	1×10^{-5}
Cytosol	DR* + FADD + Cas8 → Cas8*	4.5	5.8×10^{-5}
	Cas8* + ProCas3 → Cas3*	50	5×10^{-5}
Intrinsic pathway of apoptosis			
Cellular compartment	**Reactions**	**K_m (μM)**	**V_{max} (μmol/mg/min)**
Mitochondria/ Cytosol	BakR* + Smac → Smac @ cytosol	0.5	5×10^{-6}
	BidR* + AIF → AIF @ cytosol	0.3	2×10^{-5}
	Bcl2R* + CytC→ CytC @ cytosol	0.1	8×10^{-7}
Mitochondrial membrane	Bak + BakR → BakR* @ mitochondria	0.1	5.8×10^{-5}

Table 3: Modelling the signal components belonging to pro-apoptosis signalling pathways.

Note: The symbol "@" on the right side of an equation indicates the cellular compartment in which the resultant reactant must be registered.

Our discussion of the results in this section will be focused on the activation of the PKC signalling pathway as an example (see Figure 4). PKC are a family of serine-threonine kinases involved in cell proliferation, survival of malignant cells and in metastasis. However, in some cancers, PKC activators cause the translocation of PKC to the plasma membrane of cancer cells and trigger an apoptotic response, so that each member of the PKC family exerts different effects on pro-apoptotic or pro-survival pathways.

PKCδ participates in pro-apoptotic action through activation of the p38 MAPK pathway. If PKCδ is removed – i.e., as a virtual knockout - then a pro-apoptotic response disappears. The activation of PKCδ promotes the dephosphorylation and inactivation of the pro-survival kinase Akt. Moreover, PKCε isoform activates pro-survival response; PKC stimulates the release of TNF, while blocking the secretion of TNF or TNF receptors suppresses the apoptotic response. Since members of the PKC family can be activated by many signals, using bioinformatics platform enables us to display activation of each member of this family.

Since many signals can activate members of this family, it is essential to determine whether the active member promotes apoptosis or cell survival. For example, when cellular enzymes fail to protect the cell from reactive oxygen species (ROS), oxidative stress arises. Redox state becomes unbalanced; DNA and proteins are damaged, so that different signalling pathways are activated. Such events can lead to the onset and/or progression of apoptosis. In particular, Figure 5 illustrates PKCδ activation by oxidative stress and how the activation of this protein can lead to survival or apoptosis.

Tables 4 and 5 list the kinetic parameters to carry out this experiment, which begins when oxidative damage is caused.

Due to the flexibility of our bioinformatics platform we were able to perform a number of simulations modifying the quantity of DNA damage in a normal cell because of oxidative stress or radiation. The values vary as 0, 10, 100, 1000 or 10000, and depending on the amount of damage the cell undergoes to apoptosis or survives, as shown in Figures 6-9 below.

As shown in Figures 6 and 7 without DNA damage, or with 10 or 100, the self-repair cell mechanisms permit it to survive, but for damage values 1000 or 10000 the cell is unable to repair the damage and undergoes apoptosis, as shown in Figures 8 and 9.

But what about a cancer cell? In the case of cancerous cell with inactive p53 (p53=0), even when the DNA damage grows up to 1000, 10000 or 100000, the cell survives, since the cellular cycle does not stop. This is shown in Figures 10 and 11.

As shown in Figures 10 and 11, the absence of p53 prevents the cell cycle arrest, the cell continues functioning activating MAPK through JNK1. More damage to cell DNA results in bigger cell alteration. *Our in silico results* were generally *consistent* with available *in vitro experimental* annotations [27,28].

Conclusion

In this paper we have successfully simulated the principal pathways involved in caspase dependent apoptosis: the extrinsic receptor pathway, or the death path, and the intrinsic or mitochondrial one. However, the integration of lysosomal pathway, the endoplasmic reticulum and nuclear pathway are necessary as well, since they are also involved in apoptosis. We consider that our model is flexible enough to include in the future the additional data, and to refine the model in such

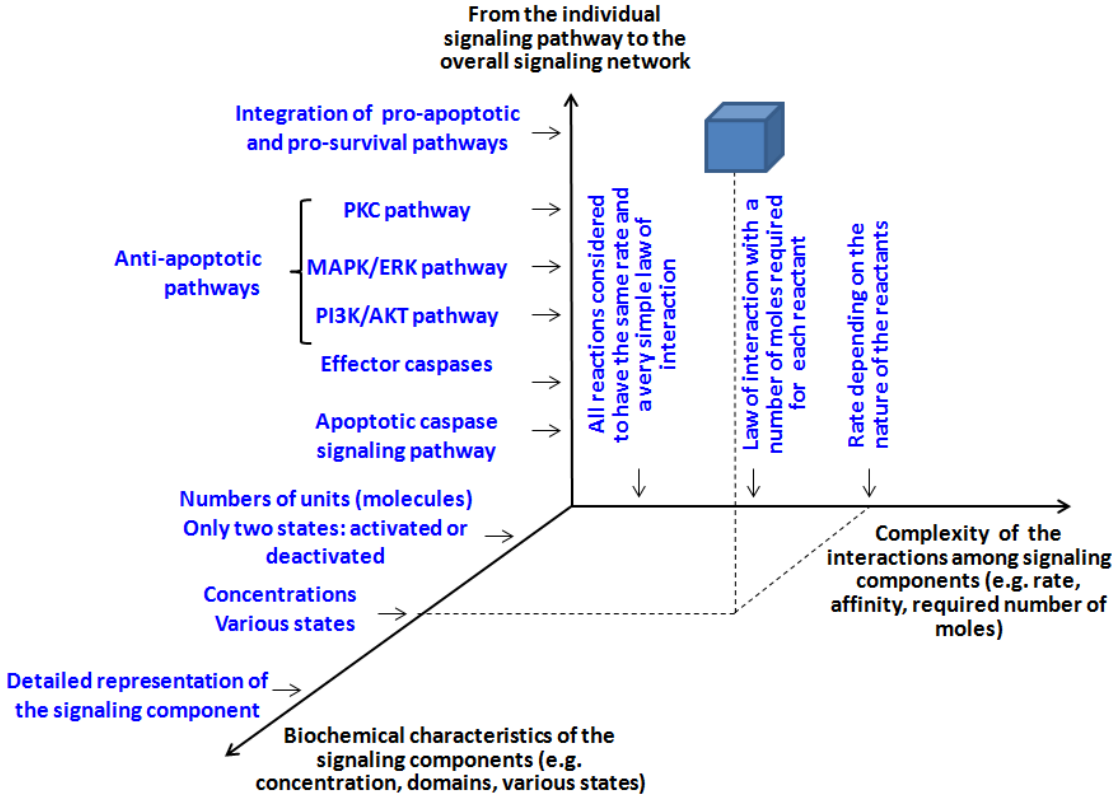

Figure 3: Incremental modelling process of apoptosis signalling pathways. The cube represents the characteristics of our current work and moves it according to our needs.

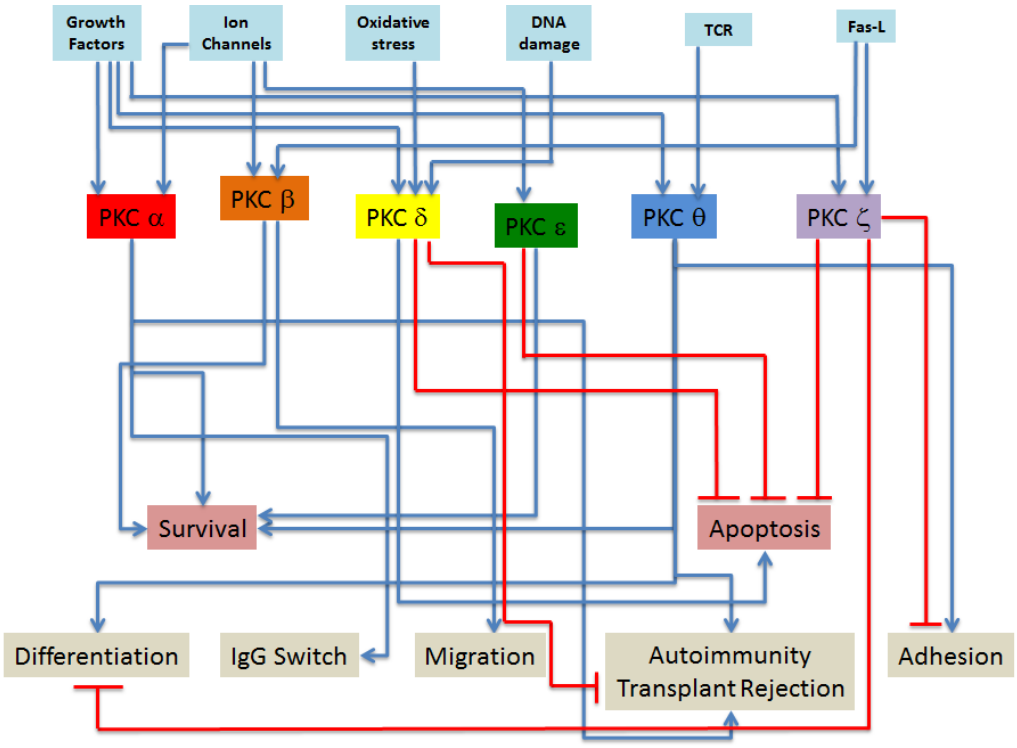

Figure 4: Participation of the PKC family members in the different cellular functions, including survival and apoptosis. Note also the extracellular factors activating each of these functions.

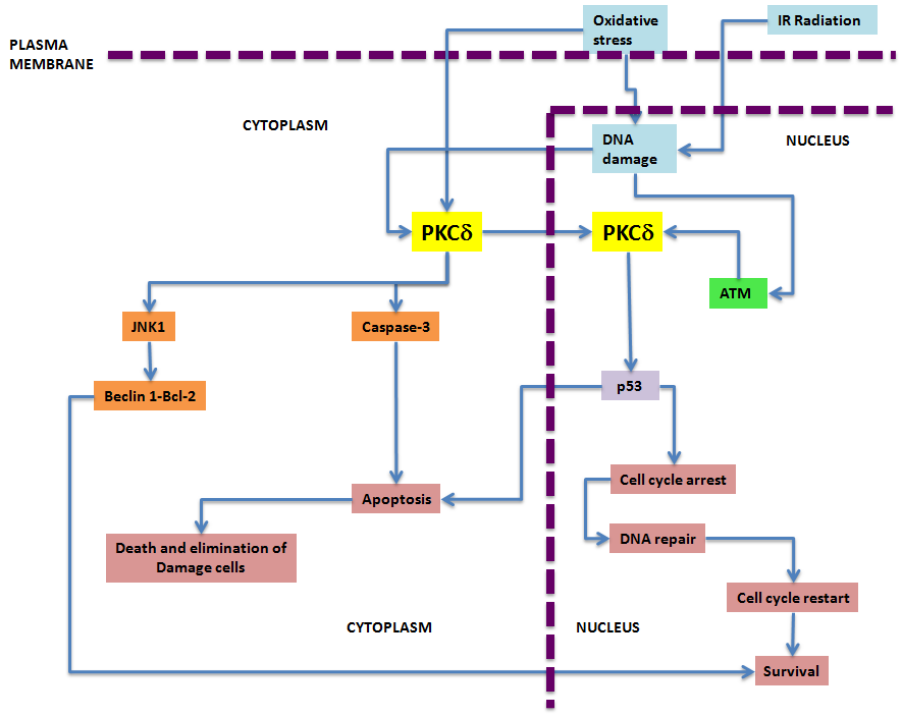

Figure 5: The oxidative stress caused by an abnormal accumulation of reactive oxygen species leads to PKCδ is relocated in the cell nucleus. Moreover, oxidative stress can damage DNA, and DNA damage activates ATM (a family of kinases whose sequence is homologous to PI3K), ATM activates PKCδ in the nucleus. PKCδ leads to apoptosis through the execution of the following: activation of the caspase pathway, activation of MAPK (through JNK1 activation) or activation of p53. Furthermore, p53 can lead to the survival of a tissue damaged by oxidative stress, to stop the cell cycle and allow repair of damage [1-5].

Cellular compartment	Reactions	K_m (μM)	V_{max} (μmol/mg/min)
Plasma membrane / Cytosol	OS + PKCδ → PKCδ@Nucleus	1	1×10^{-5}
Cytosol	PKCδ + DNA damage (Nucleus) → PKCδ@Nucleus	1	1×10^{-5}
	PKCδ + PKCδ (Nucleus) + ProCas3 → Cas3*	10	1×10^{-5}
	Cas3* → Apoptosis	1	0.33
	PKCδ + JNK1 → JNK1*	1	1×10^{-5}
	JNK1* + Becli1-Bcl-2 → Beclin1-Bcl-2*	2	4
	Beclin1-Bcle-2* → Survival	10	1×10^{-8}
Nucleus	DNA damage + ATM → ATM*	1	1×10^{-5}
	ATM* + PKCδ → PKCδ*	2	1×10^{-3}
	PKCδ* + p53 → p53*	1	1×10^{-3}
	p53* + DNA damage → Cell cycle arrest	1	1×10^{-8}
	Cell cycle arrest → DNA repair	10	1×10^{-8}
	DNA repair → Cell cycle restart	10	1×10^{-8}
	Cell cycle restart → Survival	10	1×10^{-8}
	p53* +DNA damage → Apoptosis	1000	1×10^{-10}

Table 4: Kinetic data for the PKCδ reactions.

Component	Concentration (μM)
OS	1
PKCδ @ Cytosol	1
PKCδ @ Nucleus	0
DNA damage @ Nucleus	1
ProCas3	1
JNK1	1
Beclin1-Bcl2	0.5
ATM	1
p53	1
Cell cycle arrest	0

Table 5: The initial concentrations of the reactants.

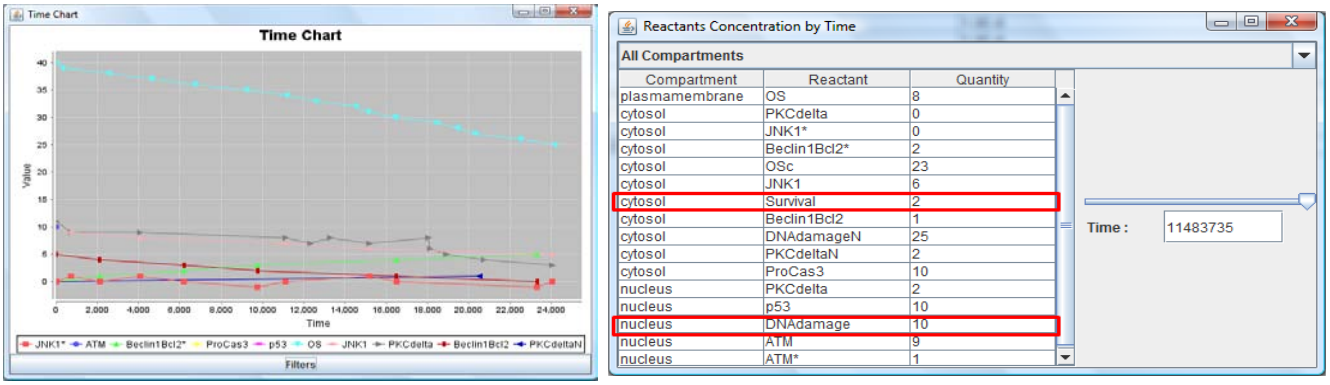

Figure 6: When in a normal cell DNA damage is 10 (DNA damage = 10), the self-repair cell mechanisms permit the cell to survive.

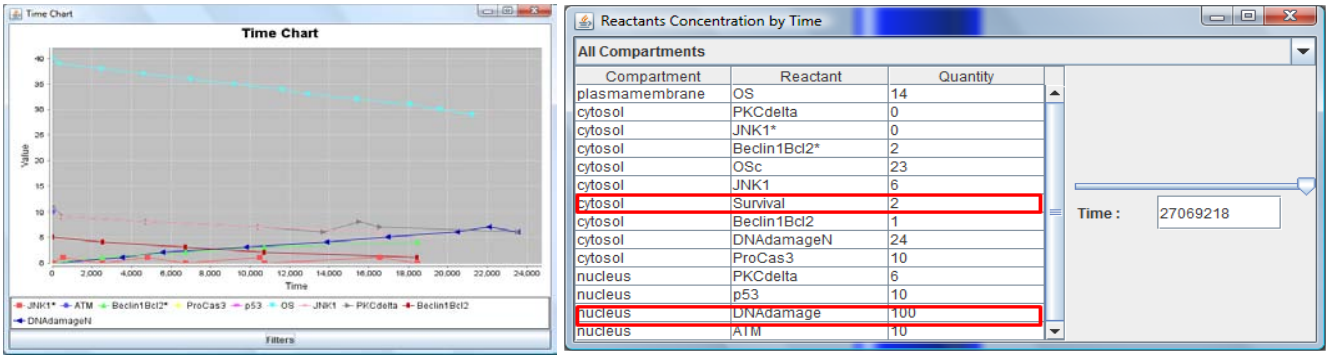

Figure 7: When in a normal cell the DNA damage is 100 (DNA damage = 100), the self-repair cell mechanisms permit the cell to survive.

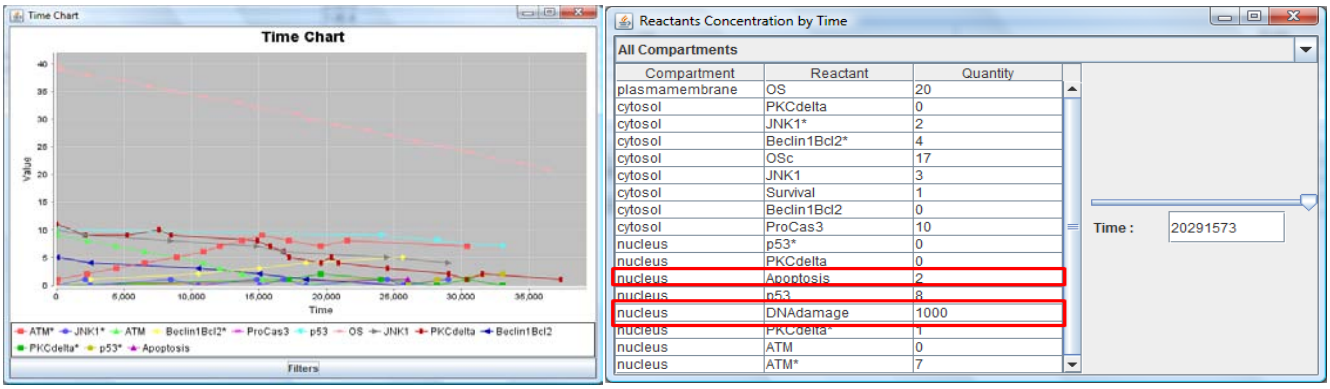

Figure 8: When in a normal cell the DNA damage is 1000 (DNA damage = 1000), the cell is unable to repair the damage and undergoes to apoptosis.

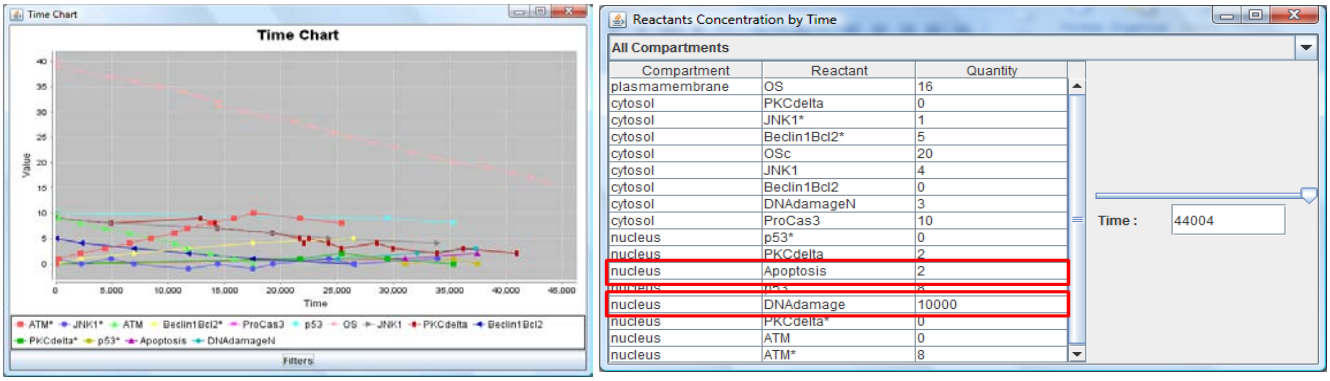

Figure 9: When in a normal cell the DNA damage is 10000 (DNA damage = 10000), the cell is unable to repair the damage and undergoes to apoptosis.

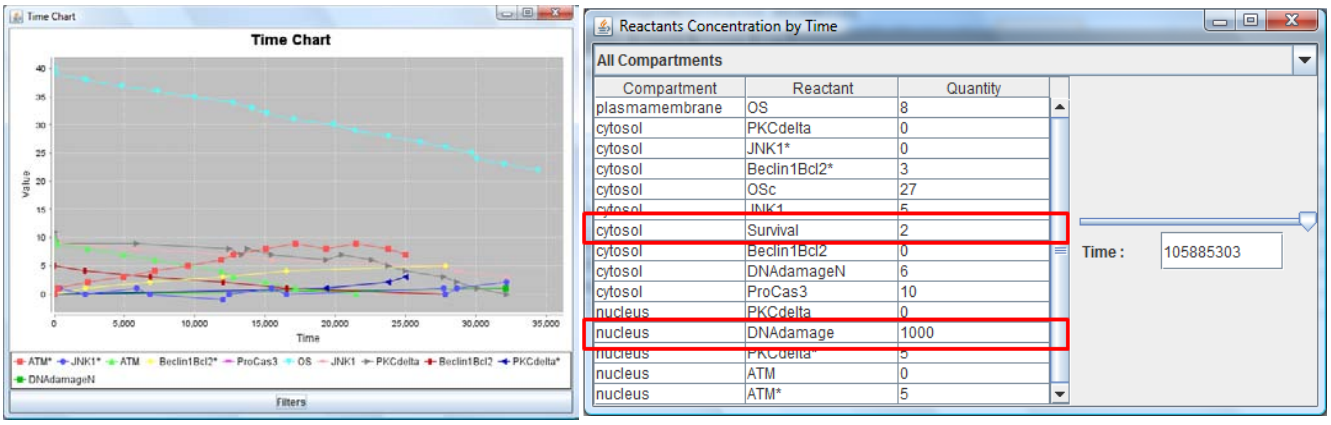

Figure 10: A cancerous cell with inactive p53 (p53=0), even when the DNA damage grows up to 1000, the cell survives, since the cellular cycle does not stop.

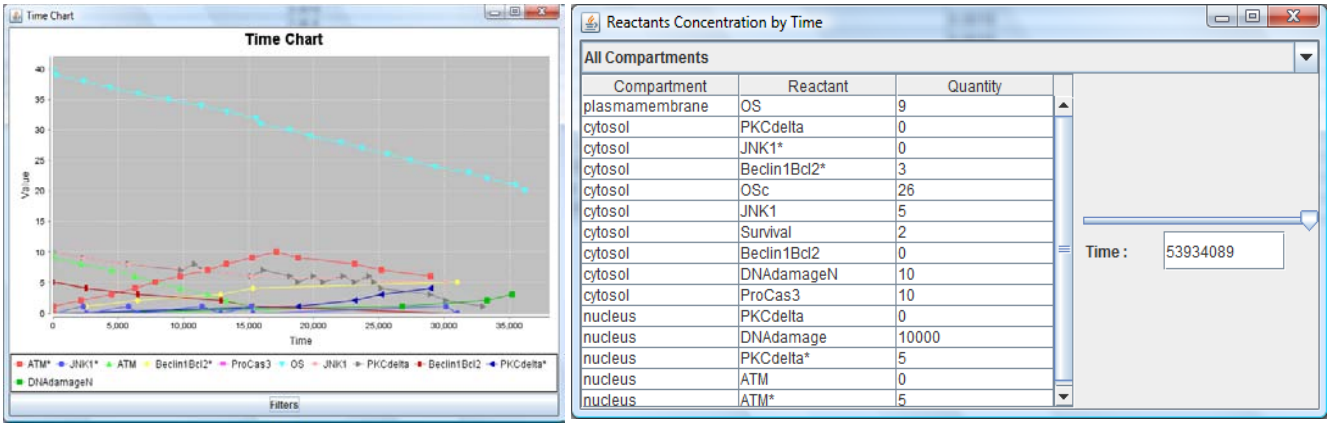

Figure 11: A cancerous cell with inactive p53 (p53=0), even when the DNA damage grows up to 10000, the cell survives, since the cellular cycle does not stop.

aspects as individual components, their biochemical characteristics, and interaction details. Of course, the real biochemical mechanisms are very complicated, and the computer models are limited simply due to the lack of perfect knowledge on the mechanisms involved. In particular, it is necessary to refine the modeling of concentrations and reaction rates K_m to better account for real processes occurring in a cell. However, even the incomplete models can be useful for better understanding of these complicated processes.

Acknowledgement

The authors would like to thank Sara Montagna, Andrea Boccaci and Liliana Karina Cabrera-Cosme for making a valuable contribution to this Project.

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