INTERDISCIPLINARY TEACHING OF DIFFERENTIAL EQUATIONS FOR LIFE SCIENCES: MODELING THE CELL GROWTH

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ABSTRACT:

The challenges in education include continuous improvement and searching for new strategies in the management of teaching and learning. Interdisciplinary teaching offers the possibility of improving the efficiency of the teaching-learning process by combining biological concepts or situations, making the simulation of natural phenomena and their mathematical and computational analysis. Using a previously made model, the proposed implementation included the study of cell cycle and its modeling with differential equations in order to give an interdisciplinary strategy for simulating the effect of five hypothetical anti-cancer candidates with inhibitory activity against regulators of the cell cycle. The *in silico* evaluation of the compounds was made by simulating the changes in the global cell mass in the model of the cell cycle. In all the cases, the inhibitors caused an increment in the cell mass. The uncontrolled increment in the replication of DNA and in the cell mass during the simulations can drive the cell destiny of the tumor cells to death.

With this practical scenario, understanding the cell cycle with a model of system of differential equations allowed to highlight the power of modeling, making possible a connection to a language more suited to the interests of the students and develop skills for interpreting and make predictions. The link of systems of differential equations with different problems of the academic areas students is a motivational axis to consider in the teaching-learning process in mathematics.

KEYWORDS

Cell cycle modeling, MathTeaching-Learning, Differential Equations.

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INTRODUCTION

The challenges in education include continuous improvement and searching for new strategies in the management of teaching and learning. Particularly in mathematics, new proposals have been implemented including modeling and ICT (Information and Communication Technologies) which, in part, is a response to the great advances of mathematical software in the past two decades (Gatica & Ares, 2012). ICT in conjunction with teaching by modeling offers the possibility of improving the efficiency of the teaching-learning process by combining biological concepts or situations, making the simulation of natural phenomena and their mathematical and computational analysis. The modeling does encourage discovery learning, the student has a more active role in delivering refreshing and creative features to educational problems, develop the art of experimentation, to stimulate analytical skills, conceptual understanding of learning and working in partnership or collaboration peer (Ré, Arena, & Giubergia, 2012). Proposed Implementation includes the study of cell cycle and its modeling with differential equations, which have been presented in a course of differential equations for students of Biological Sciences.

Biology of the cell growth: Proliferating cells perform a series of coordinated actions collectively referred to as the cell cycle, processes that enables cells to grow and divide, to control or prevent growth when appropriate, to carry out the different stages of growth and division in the correct order, and to respond to DNA damage by arresting progression (Fuß, Dubitzky, Downes, & Kurth, 2005). The cell cycle governs the transition from quiescence (G0) to cell proliferation, and through its checkpoints, ensures the fidelity of the genetic transcript. It is the mechanism by which cells reproduce, and is typically divided into four phases. The periods associated with DNA synthesis (S phase) and mitosis (M phase) are separated by gaps of varying length called G1 and G2 (Schwartz & Shah, 2005). At the G1/S phase transition, cells pass a checkpoint, which controls entry into the S phase regulated by size. Likewise, in G2, a second checkpoint exists that ensures complete and accurate DNA replication has been completed before progressing to the M phase. At the end of the G2/M transition, the nucleus and cell divide, and the daughter cells start a new cycle (Qu, MacLellan, & Weiss, 2003).

The cell division cycle is controlled by a complex network of interacting proteins, including members of the cyclin and cyclin-dependent protein kinase (CDK) families (responsible for initiating DNA replication and mitosis), and the Anaphase Promoting Complex (APC). Successful progression through the cell cycle depends on precise, temporally ordered regulation of the functions of these proteins(Gérard, Tyson, Coudreuse, & Novák, 2015).

The cycle time between successive cell divisions in higher eukaryotes has been shown to depend on cell size, which under normal conditions is divided into two phases, corresponding to a sizer and timer. If the beginning cell size after the previous division is smaller than a critical size, the time required to grow to this critical size is called the sizer phase. When the cell grows to the critical size, or if the birth cell size exceeds it, the timerequired to complete division is called the timer phase, and is almost constant irrespective of the birth size. Checkpoints, cell size, and the sizer and timer phases are regulated by a signaling network of kinases and phosphatases (Qu et al., 2003). If requirements of cell size are not satisfied, then during successive division cycles, cells become progressively smaller or larger depending on which process is faster. This instability of cell size is not compatible with long-term perpetuation of life (Tyson & Novak, 2008). Also, when cells enter M phase prematurely and undergo unconditional "mitotic catastrophe", they divide before they have completed DNA replication. Hence, newborn cells do not receive complete copies of the genome and eventually die mitosis (Gérard et al., 2015).

Mathematical modeling of the cell cycle: To improve the understanding of the cell cycle regulatory network, many approaches includes mathematical modeling with systems biology technique in order to elucidate the emergent and dynamical properties of the system (Csikász-Nagy, Battogtokh, Chen, Novák, & Tyson, 2006; Csikász-Nagy, 2009; Fuß et al., 2005; Kapuy et al., 2009; Novák & Tyson, 2004; Tyson & Novak, 2008). Most of them explore observations in quantitative detail by considering the interactions between cell growth and the dynamics of the CDK regulatory system in yeast and mammalian cells. Recently, a minimal model in yeast was built, where they analyzed molecular interactions controlling the G1/S and G2/M transitions and conditions for the mitotic catastrophe in different cell lines. In light of this complexity, it is

surprising that in fission yeast, a minimal CDK network consisting of a single cyclin-CDK fusion protein could control DNA synthesis and mitosis (Gérard et al., 2015).

In this model by Gérard and collaborators, the alternation of S and M phases is consequence of oscillations of CDK:cyclin complexes, SPF (S-phase promoting factor) and MPF (M-phase promoting factor, or CDC13-L-CDC2). MPF activity can be regulated by reversible association with the CDK inhibitor Rum1, as well as by phosphorylation and dephosphorylation by the inhibitory kinase Wee1 and the activating phosphatase CDC25, respectively. MPF inhibits Rum1 and Wee1, while it activates CDC25. These regulatory interactions create mutual inhibitions between MPF and Rum1 and between MPF and Wee1, and a mutual activation loop between MPF and CDC25. Active MPF promotes its own degradation through a delayed negative feedback loop involving Slp1 and the. This negative feedback loop, which causes the destruction of MPF at the end of mitosis, is critical to generating sustained oscillations in MPF activity that drive repetitive cycles of DNA replication followed by mitosis (Gérard et al., 2015).

Manipulating the cell cycle as anti-cancer strategy: The therapeutic value of targeting members of regulator molecules of the cell cycle has been intensively studied. The search for synthetic inhibitors of protein kinases and phosphatases as anticancer drugs has been investigated by the successful approval of a number of molecules (Lapenna & Giordano, 2009). Some of the most popular targets of the cell cycle are CDKs with specific inhibitors. The selective inhibition of CDK inhibits proliferation and induces apoptosis in tumour cells. This enzyme is frequently overexpressed, especially in carcinomas, and its deregulation is probably involved in neoplastic transformation and tumorigenesis. Because this, selective CDK inhibition may be an attractive anticancer therapy strategy (Fischer & Gianella-Borradori, 2005). In the same way, the CDC25 phosphatase has been reported as potential oncogene, being overexpressed in more than ten types of human cancer. A number of potent CDC25 inhibitors have been synthesized or isolated from natural product extracts, and although many of these exhibit selectivity against other dual-specificity phosphatases (Sakaue-Sawano, Kobayashi, Ohtawa, & Miyawaki, 2011).

Also, the combination of those inhibitors of cell cycle regulators with standard cytotoxic agents is emerging as an alternative approach to anticancer therapy (Schwartz & Shah, 2005). This

approach exploits the cell cycle perturbations of malignancy and it lets to increase the therapeutic index and enhance the effects of anti-tumor activity by synergism (Spina et al., 2013).

The aim of the study was to give an interdisciplinary strategy for teaching the cell cycle and systems of differential equations simulating the effect of five hypothetical anti-cancer candidates (based on plant extracts) with known inhibitory activity against CDK (called PDC-01, 02 and 03) or CDC25 phosphatase (called PDC-04 and 05) on the cell mass using a minimal model of the cell cycle.

MATERIALS AND METHODS

Context of implementation

The implementation of interdisciplinary teaching by modeling was done in the course of Differential Equations for Life Sciences at the University of Costa Rica, which is offered to students of Pharmacy, Science Teaching, Biology and Biosystems Engineering.

Synthetic data source

Five hypothetical plant compounds were assumed as inhibitors of enzymes of the cell cycle regulation. The components PDC-01 (constant of inhibition Ki = 110.00 nM), PDC-02 (Ki = 240.50 nM) and PDC-03 (Ki = 120.76 nM) had shown that they are selective inhibitors of cyclin dependent kinases, meanswhile the PDC-04 (Ki = 200.12 nM) and PDC-05 (Ki = 105.76 nM) had shown that they are selective inhibitors of phosphatase CDC25.

Topology, kinetics and computational approach

Based on the original topology of Gérard and collaborators (2015), there were included two points of regulation of the cell cycle by the compounds, each per kind of inhibition. Those new steps of reaction were also included in their mathematical model (EDO-based) with 4 new parameters: Drug1 and kdrug1 for compounds who inhibit CDK, and Drug2 and kdrug2 for compounds who inhibit CDC25. In order to simulate the effect of the compounds in the cell

mass, the mathematical model was run on MATLAB with the incorporation of different values for Drug and kdrug. Drug1 and Drug2 represented the concentration of the potential drug (in this case the compound concentration varying between 0.025, 0.050, 0.075 and 0.100 mM); kdrug1 and kdrug2 represented the constant of inhibition (Ki) for each compound. The best conditions per compound were selected considering the minimal concentration of the compound with the best effect on the cell mass increment. The measurement of the cell mass was made by area under the curve.

In silico double perturbation

In order to evaluate potential synergic effect between the 2 kinds of inhibitors (CDK or CDC25 inhibitors), the best conditions per compound were tested between the groups (PDC-01, 02 and 03 against PDC-04 and 05). The expected mass was compared with the obtained in the simulation, considering an additive effect; doble perturbation mass increment must be equal to sum of the individual mass increment if there were no interaction between the compounds. A change in the expected area means an interaction between the compounds. If the area of the model is less than expected, there is an antagonism (effect is reduced); if the area of the model is larger than expected, there is a synergism (effect is enhanced).

RESULTS

In Figure 1 the topology of the model is shown. The modification, considering the previous model (Gérard et al., 2015), is about 2 points. First at all, is assumed that Drug1 inhibit directly the CDK (Cdc2-Cdc13 or MPF), shown mathematically as kSMPF*Mass/(1+kdrug1*Drug1*MPF) in the first reaction of the model (see Figure 2 for the ODE). The second point is the inhibition of CDC25, assumed as kCDC25*MPFp/(1+kdrug2*Drug2*Cdc25), again in the first reaction of the model (see Figure 2).

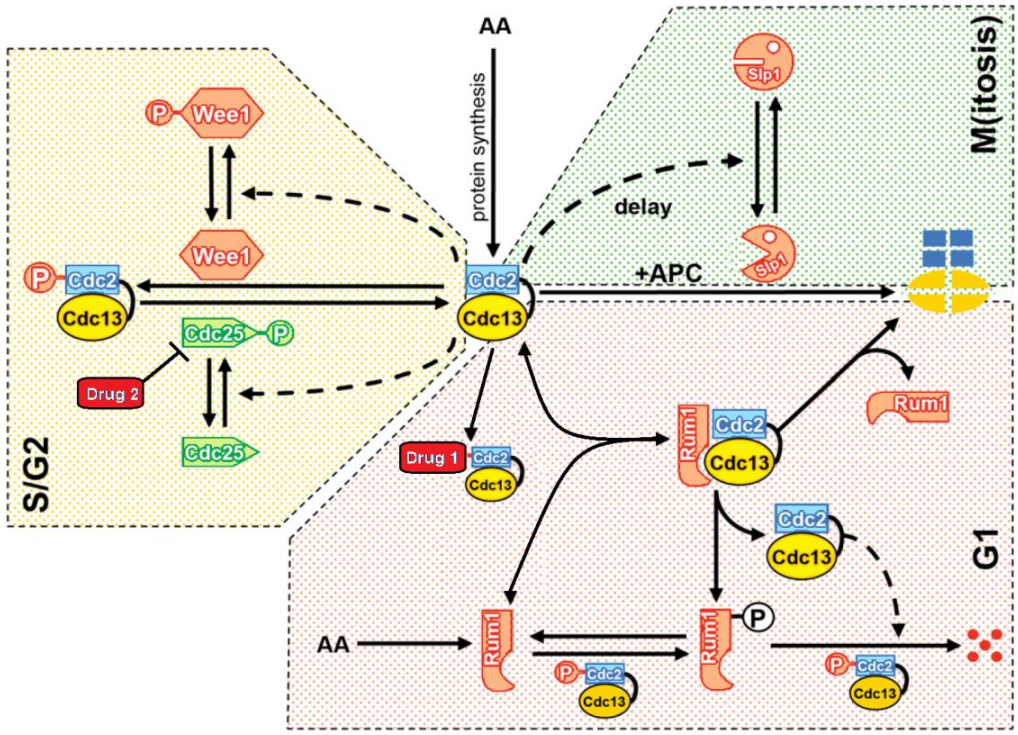

Figure 1 Topology of the cell cycle model with inhibitors of CDK (Drug 1) and CDC25 (Drug 2). Modified of the Gérard and collaborators model (2015).

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% ODEs
y = [
%MPF
kSMPF*Mass/(1+kdrug1*Drug1*MPF)-kWEE1*MPF+kCDC25*MPFp/(1+kdrug2*Drug2*Cdc25)-(kD1CYC+kD2CYC*Slp1A)*MPF
-kASS*Rum1*MPF+(kDISS+kDRUM1+kIRUM1)*MPFRum1+kDX*CCP*MPFRum1;
%MPFp
kWEE1*MPF-kCDC25*MPFp-(kD1CYC+kD2CYC*Slp1A)*MPFp;
%Slp1A
k1SLP1*IEA*Slp1/(J1SLP1+Slp1)-V2SLP1*Slp1A/(J2SLP1+Slp1A);
%IEA
k1IE*(MPF+a*MPFp)*IE/(J1IE+IE)-V2IE*IEA/(J2IE+IEA);
%MPFRum1
kASS*Rum1*MPF-(kDISS+kDRUM1+kIRUM1+kDMPFRUM1)*MPFRum1-kDX*CCP*MPFRum1;
%Rum1
VSRUM1-kASS*Rum1*MPF+(kDISS+kDMPFRUM1)*MPFRum1-k12RUM1*MPFp*Rum1+kARUM1*Rum1p-kDRUM1*Rum1-kDX*CCP*Rum1;
%Rum1p
kIRUM1*MPFRum1+k12RUM1*MPFp*Rum1-kARUM1*Rum1p-kDRUM1P*(MPF+a*MPFp)*Rum1p-kDRUM1*Rum1p+kDX*CCP*Rum1
+kDX*CCP*MPFRum1-kDX*CCP*Rum1p;
%Wee1
VWEE1*Wee1p/(J1WEE1+Wee1p)-kWEE1*(MPF+a*MPFp)*Wee1/(J2WEE1+Wee1);
%Cdc25p
kCDC25*(MPF+a*MPFp)*Cdc25/(J1CDC25+Cdc25)-VCDC25*Cdc25p/(J2CDC25+Cdc25p);
%Mass
m*Mass
] ;
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Figure 2 System of differential equations for modeling the cell cycle. Modified of the Gérard and collaborators model (2015).

In Figure 3, there is a comparison between the compound and the concentrations tested. In all the cases, the no-presence of the compound (Drug1=kdrug1=Drug2=kdrug2=0) represented a no-change in the cell mass (remains as the control). In the other cases, always there was an increment in the cell mass, being proportional to the concentrations for PDC-01, 02 and 03. However, the increment of the cell mass by PDC-04 and 05 remains almost the same though the different concentrations.

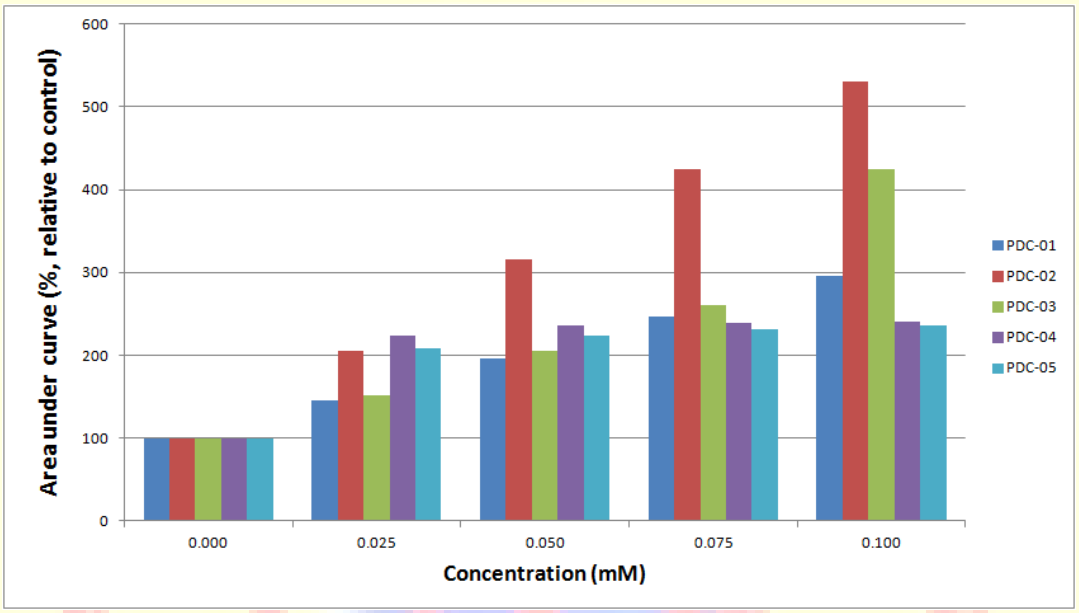
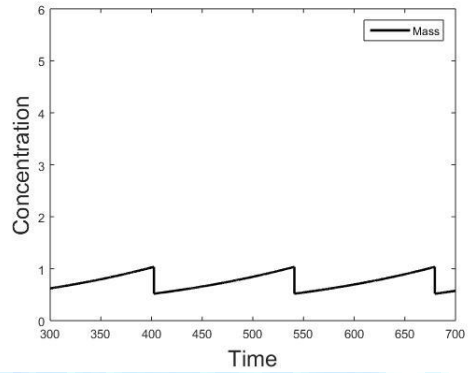


Figure 3 Increment of the cell mass (area under the curve relative to control, y axis) considering different concentrations of the compounds (x axis). The power of inhibition was included by the Ki value of each compound.

Because this, the best concentrations for CDK inhibitors were 0.100 mM and 0.025 mM for CDC inhibitors. The most efficient component was PDC-01 with the best increment (more than 500% in comparison with control). Also, PDC-02 and PDC-03 become always more efficient than CDC25 inhibitors in the most efficient conditions. PDC-04 and 05 had the same effect in the cell mass, being PDC-04 slightly better. The behavior of the cell mass in each of the most efficient conditions is shown in Figure 4. The behavior of the MPF, FPT, Wee1, Rum1t and S1P1A species with the PDC-01 and PDC-04 compounds are shown in the Figure 5. For the other

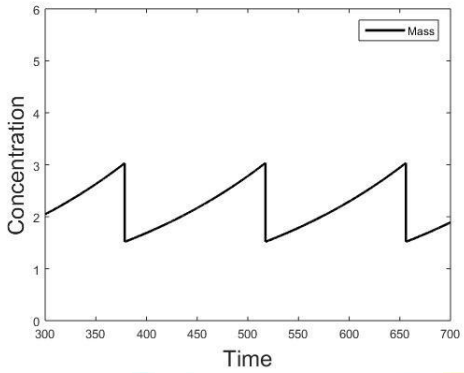
compounds, the behavior was very similar to the same kind of inhibitor shown here. The main changes were for PDC-01 and others CDK inhibitors, with a very different kinetic of the species, in contrast with PDC-04 and 05, which keep the same kinetics for most of the species but with increased levels in mass.

Control



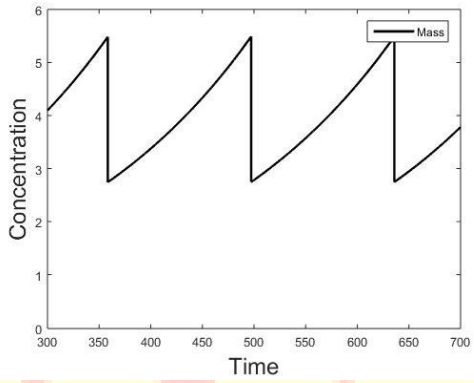
(kdrug1=Drug1=kdrug2=Drug2=0)

PDC-01 0.100 mM



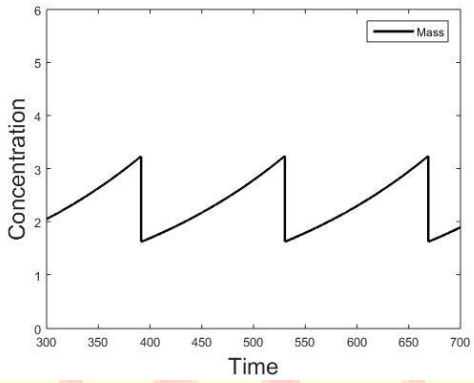
(Kdrug1=110.0, Drug1=0.100)

PDC-02 0.100 mM



(Kdrug1=240.50, Drug1=0.100)

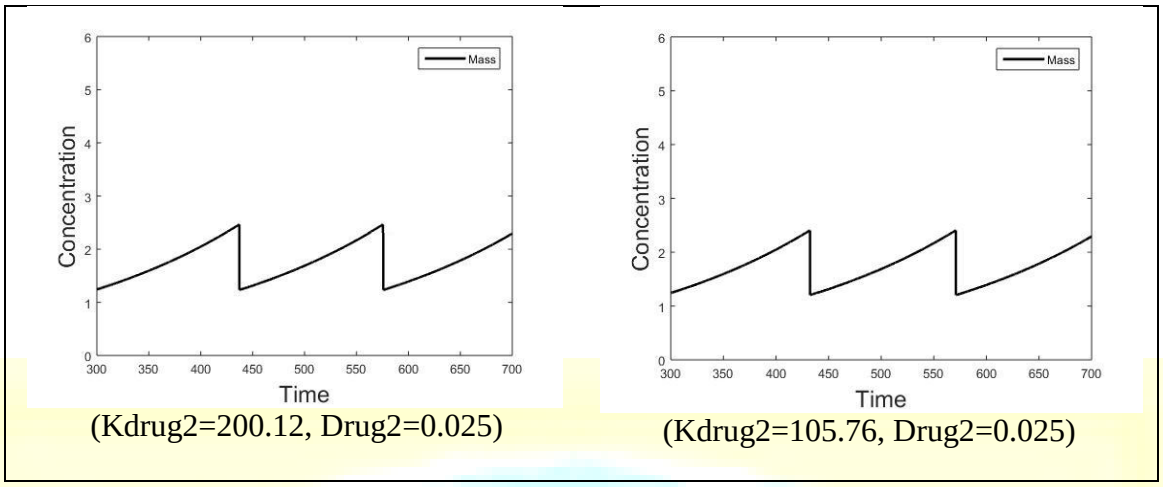
PDC-03 0.100 mM



(Kdrug1=120.76, Drug1=0.100)

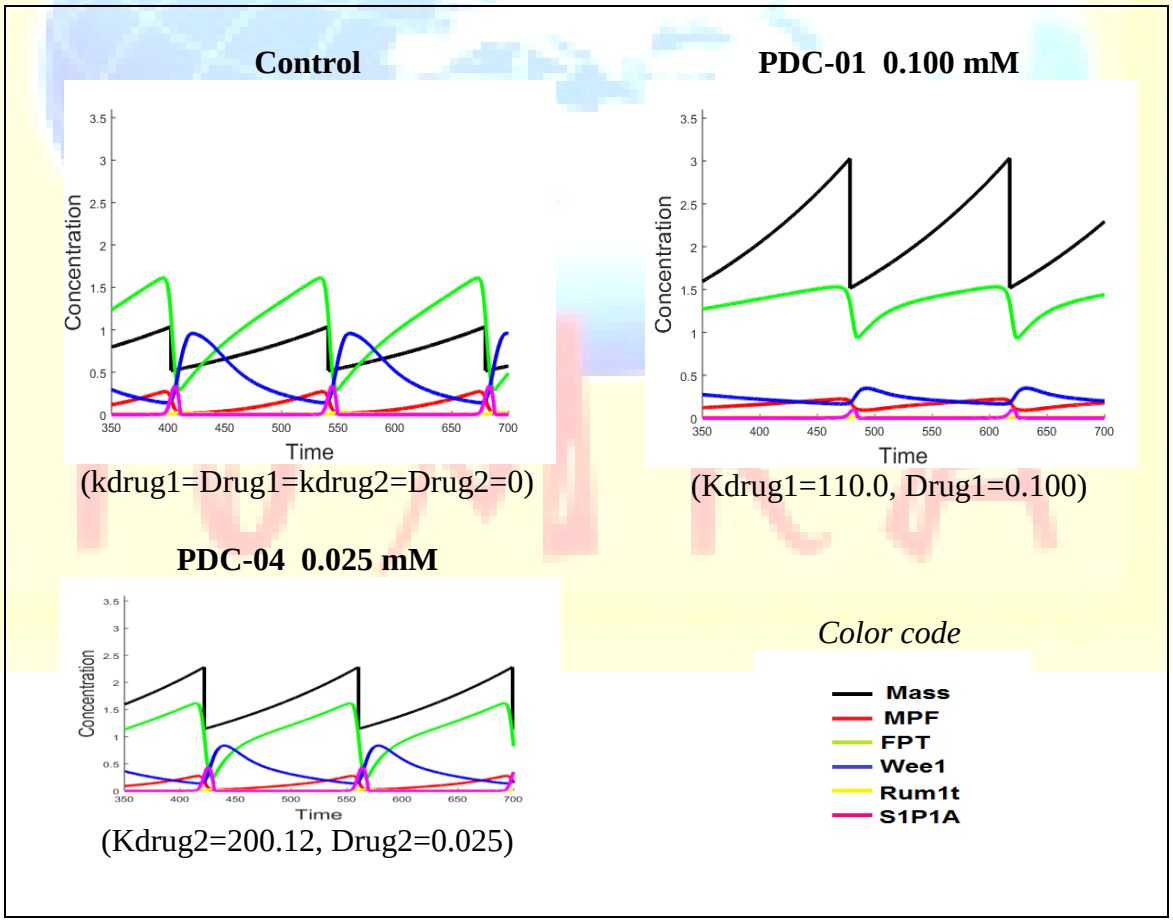
PDC-04 0.025 mM

PDC-05 0.025 mM



(Kdrug2=200.12, Drug2=0.025) (Kdrug2=105.76, Drug2=0.025)

Figure 4 Simulations of the cell mass changes with the best conditions per compound. The conditions for simulating are specified under each graph. Not considered parameters were always 0.



(kdrug1=Drug1=kdrug2=Drug2=0) (Kdrug1=110.0, Drug1=0.100)

(Kdrug2=200.12, Drug2=0.025)

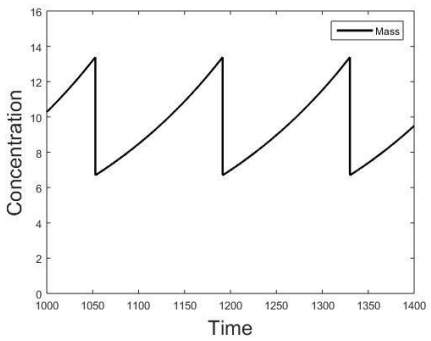
Figure 5 Simulations of the cell mass, MPF, FPT, Wee1, Rum1t and S1P1A changes with the best compounds per kind of inhibitor (PDC-01 and PDC-04).

Table 1 Modeled and expected area under the curve (respect 100% control) for double perturbations between CDK inhibitors and CDC25 inhibitors.

Compounds	PDC-04 (0,025 mM)		PDC-05 (0,025 mM)	
	Model	Expected	Model	Expected
PDC-01 (0,100 mM)	758.82	419.61	721.57	403.92
PDC-02 (0,100 mM)	1376.47	654.90	1311.76	639.22
PDC-03 (0,100 mM)	807.84	549.02	770.59	533.33

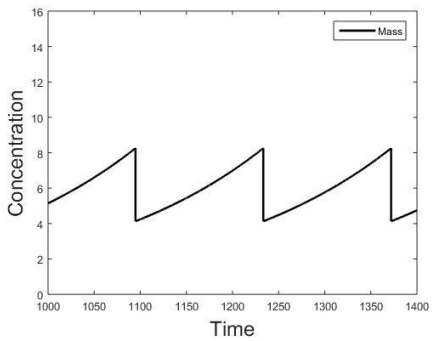
In order to evaluate potential synergic effect between the 2 kinds of inhibitors (CDK or CDC25 inhibitors), a double perturbation, considering the best conditions per compound, were tested. The area under the curve in the model (giving the respective values to Drug1, kdrug1, Drug2 and kdrug2) was quantified, and then it was compared with the sum of the areas of the individual perturbations. The modeled and expected values are shown in Table 1. Because area under the curve in the model was always higher than the expected, so, the different double perturbation always shows a synergism. PDC-02/PDC-04 and PDC-02/PDC-05 represented the best double perturbation for increasing the cell mass. In Figure 6 there is shown the behavior of the PDC-02/PDC-05 and PDC-03/PDC-04 perturbations.

PDC-02 (0.100 mM) + PDC-05 (0.025 mM)



(Kdrug1=240.50, Drug1=0.100, Kdrug2=105.76, Drug2=0.025)

PDC-03 (0.100 mM) + PDC-04 (0.025 mM)



(Kdrug1=120.73, Drug1=0.100, Kdrug2=200.12, Drug2=0.025)

Figure 6 Simulations of double perturbation and their effect on cell mass for PDC-02/PDC-05 and PDC-03/PDC-04.

DISCUSSION

The interdisciplinary knowledge makes the teaching-learning process to reach high levels of significance in education, including university level. Therefore, it is required that the teacher and the student acquire and assume different functions to the more traditional methods in response to this paradigm shift in education (Belando-Montoro, 2014). Although the academic exercise was performed with a hypothetical data, it allowed the students to appreciate the potential and usefulness of the mathematical formulation in solving problems in their academic area.

The experience of the implementation of the modeling of the cell cycle in the course of differential equations began modifying the existing topology, mathematical description using a system of differential equations, simulations with and without changes and predictions of system behavior.

In the context of the model of cell cycle and normal proliferating cells, the DNA damage checkpoint is in place to prevent erroneous DNA from being replicated before progression through mitosis (Lapenna & Giordano, 2009). However, tumor cells are unable to stop at predetermined points of the cell cycle because of loss of checkpoint integrity. This can be due to inactivation of critical inhibitors of the cell cycle or to overexpression of molecules that regulate it positively (Schwartz & Shah, 2005). This point is particularly interesting, because if a cell attempts a second mitotic division before its chromosomes have been fully replicated, the daughter cells will inherit broken, incomplete or unbalanced chromosomes, which is almost always lethal (Tyson & Novak, 2008). As in the introduction was mentioned, the premature entrance to M phase can end in mitotic catastrophe with an uncompleted or aberrant genome with the eventual cell death (Gérard et al., 2015). So, accelerating the pass to M phase can be used as strategy for induce cell death.

For this purpose, mathematical modeling and nonlinear dynamics have been essential tools. Using the model by Gérard et al. (2015), a minimal CDK network consisting of an autonomous

monomolecular cyclin-CDK fusion protein, a simulation of the effect of 5 plant extracts with known inhibitory activity against CDK (PDC-01, 02 and 03) or CDC25 phosphatase (PDC-04 and 05) on the cell mass was made. In used model, to create a role for cell size in the regulation of CDK activities, it assumes that the rates of synthesis of cyclins proportional to cell mass, cell mass increases exponentially and that cell mass is exactly halved at division. The important features are that ‘‘mass’’ increases monotonically as the cell grows (driving the control system through bifurcations that govern events of the cell cycle) and that mass decreases abruptly at cell division (Csikász-Nagy et al., 2006). The MATLAB script was used for making modifications and then run the conditions given by the compounds (concentrations and constant of inhibition Ki). These modifications are shown graphically in Figure 1 and algebraically in the system of EDO (Figure 2), and basically it was the introduction of 2 steps of inhibition, one for the compound which inhibits CDK (called Drug 1 and kdrug1) and another one for the inhibitors of CDC25 (Drug2 and kdrug2).

When simulation was done assuming the absence of any compound (Drug1=Drug2=0), the cell mass remains as the control. With the inhibitors of CDK there was a proportional increment in the cell mass according to the concentrations of PDC-01, 02 and 03 (Figure 3). PDC-02 represented the higher change in the cell mass, including the CDC25 inhibitors cases, being the more efficient compound which drive mitotic catastrophe. In the other hand, PDC-04 and 05 cause an increment of the cell mass almost constant though the different concentrations of the compounds, being quite better the case of PDC-04. Based on the rate of increment, the best concentrations of the compounds were defined as 0.100 mM for the CDK inhibitors, meanwhile it was 0.025 mM for the CDC25 inhibitors. The change in the mass of those cases was shown in Figure 4. In this context of inhibition by compounds, the cell divides at a larger cell size than control, but always maintains the same cycle time of 139 units of time.

The simulations with the plants extracts provide a mechanistic explanation for physiological consequence of inhibition of CDK and CDC25, were the cell size through all the cycle remains higher than control. In all those cases, the abrupt increment of cell mass cannot let a adequate DNA replication and therefore cells divide with catastrophic consequences, as previously reported (Gérard et al., 2015).

This approach is particularly relevant, because targeted tumor therapy uses computational model predictions to select the most effective medication and to reduce the overall costs of a therapy. Computer simulations can help linking observations to hypotheses by reproducing the expected behavior from a theoretical model, and of course, extrapolating from a given state of the cell or its components to subsequent states, as example the prediction of anti-cancer drug response (Fuß et al., 2005).

The key features of this complex pathway, such as emergent properties, can be understood through the analysis of the model's dynamical behaviors using numerical simulations (Alfieri, Merelli, Mosca, & Milanesi, 2007). The use of mathematical models provide powerful tools for managing the complexity of the cell cycle control system and of other signaling networks (Sible & Tyson, 2007). This let to study the behaviors of the system as a whole and infer the emergent properties of the system, which cannot be achieved individually.

About the behavior of other species of the model, the effect of CDK inhibitors is clearly stronger than the CDC25 inhibitors. The PDC-04 and 05 compounds have changes only in the kinetics of the cell mass. For PDC-01, 02 and 03 and because MPF activity can be regulated by Rum1, Wee1 and phosphatase CDC25, the changes caused by the inhibitors could be seen in the simulation. Also, as mentioned before, MPF inhibits Rum1 and Wee1 and it activates CDC25, creating mutual inhibitions between MPF and Rum1 and between MPF and Wee1, and a mutual activation loop between MPF and CDC25.

When CDK is inhibited by PDC-01 (Figure 5), 02 and 03 (not shown), the kinetics is meanly changed for Wee1 and S1P1A, where there is a reduction of the global levels but keeping the oscillations as the control case. The effect about this is that the oscillations for FPT and MPF are less abrupt for the PCD-01, 02 and 03 compounds, driving uncontrolled repetitive cycles of DNA replication and cell mass increment followed by mitosis with aberrant composition (Gérard et al., 2015).

Respect Rum1, which is present during the G1 phase of the cell cycle and inhibits CDC2/cyclin kinase activity until the critical mass required to pass Start is achieved (Blanco, Prada, &

Moreno, 2000), there is no important change in its values between the perturbations, single or doubles ones.

Because different studies have shown a synergy between the mechanisms of CDK inhibitors and chemotherapies (Fischer & Gianella-Borradori, 2005), the analysis of double perturbations in the model of the cell cycle has sense. The combinations of the components of the study, CDK inhibitors (PDC-01, PDC-02 and PDC-03) with the CDC25 inhibitors (PDC-04 and PDC-05), offers a frame for developing strategies of maximize the therapeutic effect by attacking 2 points of the cell cycle model. The double perturbations PDC-02/PDC-04 and PDC-02/PDC-05 represented the best ones for increasing the cell mass, suggesting potential applications of drugs with those mechanism of action for regulate the cell cycle by increasing the cell mass and letting the cell get into mitotic catastrophe.

Potentially, this information can be used for creation of novel drug for anticancer therapy or combination strategies, which remains a challenge for scientists. This approach marks a frame for manipulate the cell destiny, particularly of interest in cancer.

CONCLUSION

The practical scenario for understanding the cell cycle, its regulation and the possible effects of their manipulation, the combination of biology concepts with a system of differential equations allowed to highlight the power of modeling, natural look in the future professional work of the students. The introduction of models and the use of specialized software manage a connection to a language more suited to their interests and develop skills for interpreting, determine the suitability of the models and their implications to make predictions. These strategies may be considered for other courses of differential equations or be adapted in other as calculus, numerical analysis or higher mathematics. Thus, the link of systems of differential equations with different problems of the academic areas students is a motivational axis to consider in the teaching-learning process in mathematics.

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