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Qualitative Modelling of the Human Cell Cycle

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Abstract

The cell division cycle is the basis of all life and, therefore, one of the most interesting research fields in natural science. Recent findings suggest that the majority of the mechanisms involved in the regulation of the cell cycle are at least partially conserved from yeast to humans. In all organisms the main cell cycle regulators are the cyclin-dependent kinases (Cdks), which themselves are regulated by binding of their respective cyclin partners, post-translational changes, and their cellular localization. The exact functions of some of the proteins mainly involved in the regulation of the human cell cycle until now have been proved via detection of binding partners and regulatory interactions, but there is sparse information available only about the kinetics and parameters regulating these interactions. Therefore, first of all I developed a qualitative, i.e. Boolean, model to test the general behaviour resulting from the assumed network and its regulatory interactions. Second, this Boolean model was transcribed into an ordinary differential equations (ODE) system, to include gradual conformation changes and to enable a better temporal resolution. After an extense parameter adaptation by trial and error, the system was able to give the expected oscillating behaviour, at least for some cell cycle rounds. With the sensitivity analysis the influence of parameters involved in the regulation of protein synthesis on the behaviour of the whole network has been examined. Although, up to now, I have not applied this strategy to other networks, it can be assumed that it seems generally applicable for the modelling of regulatory networks without information about the kinetic and parameter data.

Zusammenfassung

Der Zellteilungszyklus im Allgemeinen ist die Grundlage allen Lebens, da durch ihn die Verdopplung des Erbmaterials ermöglicht wird. Dementsprechend ist seine Erforschung eines der interessantesten Gebiete der Naturwissenschaften. Es wurde gezeigt, dass die meisten Mechanismen, die an der Regulation des Zellzyklus beteiligt sind, zumindest teilweise von der Hefe bis zum Menschen konserviert sind. In allen Organismen sind die Hauptregulatoren des Zellzyklus die zyklinabhängigen Kinasen (Cdks), die wiederum durch Bindung ihrer spezifischen Zyklinpartner, durch posttranslationale Modifikationen und ihre zelluläre Lokalisierung reguliert werden. Die genaue Funktion einiger den menschlichen Zellzyklus regulierenden Proteine wurde experimentell bestimmt, aber über die Kinetiken und Parameter, die diese Reaktionen regulieren, sind kaum Informationen erhältlich. Daher wurde die generelle Strategie für die Entwicklung eines Modells des menschlichen Zellzyklus in zwei Schritte unterteilt. Zuerst habe ich, basierend auf Boole'scher Logik, ein qualitatives Modell entwickelt, mit dem das grundsätzliche Verhalten des regulatorischen Netzwerks, das den menschlichen Zellzyklus modelliert, getestet werden konnte. Im Anschluss daran wurde dieses Boole'sche Modell in ein Differenzialgleichungssystem (DGS) umgewandelt, um graduelle Konzentrationsveränderungen mit einzubeziehen und eine bessere zeitliche Auflösung zu ermöglichen. Nach einer zeitaufwendigen Parameteranpassung nach dem „trial-and-error"-Prinzip, zeigte das Netzwerk zumindest für drei Zellzyklusrunden das gewünschte oszillierende Verhalten, und mit einer anschließenden Sensitivitätsanalyse konnte der Einfluss der an der Regulation von Proteinsynthese beteiligten Parameter auf das Verhalten des Gesamtsystems getestet werden. Obwohl die entwickelte Strategie – d.h. die Entwicklung eines Boole'schen Modells, das dann in ein DGS umgewandelt wird – von mir bisher nicht für andere Netzwerke getestet wurde, kann zusammengefasst werden, dass sie generell für die Modellierung regulatorischer Netzwerke, ohne vorhandene Informationen über beschreibende Kinetiken und Parameter, anwendbar erscheint.

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Abbreviations

APC	anaphase promoting complex
ATP	adenosine triphosphate
CAK	cyclin-activating kinase
CC	cell cycle
Cdk	cyclin-dependent kinase
CKI	cyclin-dependent kinase inhibitor
DNA	desoxyribonucleic acid
ERK	extracellular signal-regulated kinase
HDAC	histone deacetylase
IDT	interdivision time
MDT	mass doubling time
MEK	mitogen-activated kinase kinase
MPF	M phase promoting factor/maturation promoting factor
mRNA	messenger ribonucleic acid
ODE	ordinary differential equations
Rb	retinoblastoma gene product
SCF (=SCF^{Skp2})	Skp-Cullin-F-box complex
TGF-β	transcription growth factor β
pX	phosphorylated form of a protein X
hypRb	hyperphosphorylated form of Rb
hyP	unknown number (at least four) of phosphate residues which are bound to pRb through cyclinE-Cdk2 complexes

1. Object of Work

This thesis describes the development of a computational model for the human cell cycle. The model is based on the sparse information available about the human cell cycle, but mainly on that about the mammalian and also the yeast cell cycle. To cope with the complexity of the cell cycle regulation, first, I developed a qualitative model and, second, a (semi-)quantitative model representing the essential features of cell cycle regulation, and especially its oscillating behaviour. Because of the huge number of proteins participating in cell cycle regulation, I had to decide which cell cycle compounds should be involved in the model, in which reactions these compounds interact with each other, and what kind of kinetic laws are able to describe my regulatory network. The chosen compounds and their interactions should be able to display the general behaviour of a cycling cell, without going to much into detail in order to keep the model's complexity manageable.

It was not an aim of this work to evaluate the model in practical experiments, but for future research it could be very interesting to test whether at least some of the assumptions and predictions, which were made in the model, are in agreement with the information reported in literature.

2. Keywords

Qualitative modelling, cell cycle, cyclins, cyclin-dependent kinases (Cdks), Cdk inhibitors (CKIs), phosphorylation/dephosphorylation, retinoblastoma protein (Rb), E2F family of transcription factors, checkpoints, ubiquitin-proteasome pathway, Ras-Raf-MEK-ERK pathway, cellular localization, Boolean formalization, differential equations, reaction kinetics, stoichiometry, parameter adaptation, sensitivity analysis.

3. Biological Background

The cell cycle consists of four general phases. These are (i) gap 1 (G1) phase, which is the interval between mitosis and DNA replication, (ii) synthesis (S) phase, in which the DNA replication takes place, (iii) gap 2 (G2) phase, during which growth and preparation for cell division occurs, and (iv) mitosis (M) phase, in which one cell with duplicated genome is divided into two daughter cells, each with one complete genome. Cells not progressing through the cell cycle are called quiescent cells and remain in the so-called gap 0 (G0) phase. To pass from G0 phase to G1 phase and S phase, respectively, growth factors and mitogens have to be available in the immediate environment of the cell. [1,2,3,4]

The passage through the cell cycle is mainly regulated by the cyclin-dependent kinases (Cdks) and their respective activating cyclins. To avoid uncontrolled cell growth, the so-called checkpoints – a complex network of additional regulatory mechanisms, which are substantial to ensuring the correct order of cell cycle events and the completion of one cell cycle before starting the next one – have to be passed. While the concentration of the Cdks remains more or less constant throughout the cell cycle, the cyclins are expressed and degraded periodically. Additionally to binding to their cyclin partners the Cdks are regulated by their cellular localization and post-translational modifications, mainly phosphorylation and dephosphorylation of the

Cdks themselves, of their bound cyclins or of both. Another mechanism presumably involved in the timing of the cell division cycle is the cell growth [87].

To mutate a normal cell into a cancer cell, several different mutations have to occur in the genes of proteins involved in cell cycle control, such as Rb, E2F, Cdks, or cyclins. Additionally, at least some of the events controlling the cell cycle must be deregulated in order to circumvent checkpoints and other control mechanisms. [4,5]

In the model presented, the respective overall Cdk concentrations remain constant throughout the cell cycle. Because of keeping the model's complexity reasonable and manageable, other regulating proteins, such as CKIs other than p27 (see 4.3.3. The CKIs), Cdc25 proteins or Wee1, the Polo-like kinases and the Aurora-related kinases, will not be discussed here. Cdc25 and Wee1 are antagonists in regulating the activity of cyclin-Cdk1 complexes, wherefore they change the phosphorylation state of Cdk1 [12,29]. Polo-like kinases and Aurora-related kinases are involved in cell cycle regulation by events occurring at the centrosomes, such as spindle assembly, centrosome separation, and chromosome segregation [3,91]. Also the cell growth will be neglected.

3.1 The Cell Cycle Phases

3.1.1 G0 Phase

Cells in G0 phase do not have growth factors and mitogens in their immediate environment, do not express cyclins, and show high concentrations of cell cycle inhibitors, such as p27. These cells are named quiescent cells and do not undergo cell division, but function in their regular role as components of an organism. [1,2,3,4]

3.1.2 G1 Phase

In presence of mitogenic signals and growth factors in the direct cell environment, the Ras-Raf-MEK-ERK kinase cascade activates the transcription of the cyclin D1 gene and, thus, allows the cell to pass from G0 to G1 phase [5,20]. It has been shown that at least Ras is also involved in the regulation of apoptosis [5]. The Ras-Raf-MEK-ERK pathway results in the nuclear translocation of phosphorylated ERK (pERK). There, pERK phosphorylates transcription factors involved in the transcriptional activation of cell cycle-regulated genes [5]. The D-type cyclins, the first cyclins expressed in the cell cycle, form complexes with Cdk4 and Cdk6 in the cytoplasm. These complexes after phosphorylation of the Cdk subunit mediated by CAK are transported into the nucleus [1], where they initially phosphorylate Rb and some of its related pocket proteins, resulting in the release of HDAC from the Rb/E2F complexes [55,60,72], and thus, in expression of cyclin E [25,49,52,72]. Cyclin E forms complexes with Cdk2 in the cytoplasm. In yeast, binding of Sic1, the homologue of p27 [102], to the cytoplasmic Clb5-Cdc28 complex, a yeast cyclin-Cdk complex active in late G1 phase, facilitates its transport to the nucleus [103]. In the nucleus the cyclin E-Cdk2 complexes pass their bound p27 to active cyclin D-Cdk4/6 complexes, leading to (i) the activation of cyclin E-Cdk2 complexes by an additional phosphorylation by the cyclin activating kinase (CAK) [1,7,9] and (ii), together with the phosphorylation of cyclin D, to the destruction of the cyclin D-Cdk4/6 complexes [1]. Cdk4/6 and the phosphorylated cyclin D (pCyclin D) are transported back to the

cytoplasm, where pCyclin D is degraded via the ubiquitin-proteasome pathway, mediated by SCF [1,22]. The active cyclin E-Cdk2 complex hyperphosphorylates Rb to split the DP-E2F-pRb complex, and thus, enables transcriptional activity of the released DP-E2F heterodimer [25,55,60,61]. Additionally, it is involved in inhibition of p27 gene expression via phosphorylation of transcription growth factor β (TGF-β). It also phosphorylates p27 [32,35] to initiate its degradation by the ubiquitin-proteasome pathway mediated by SCF and, thus, enables the cell to pass the G1/S transition. [1,2,3,4]

3.1.3 S Phase

After translocation of p27 from the nucleus the cell cycle irreversibly passes the G1/S checkpoint, also known as restriction point. E2F is involved in the transcriptional activation of a variety of cell cycle-regulated genes [49,52,65,72,78,86]. The transcription of cyclin A and – by passing of some additional regulatory steps, i.e. with a lag – also of the B-type cyclins is activated by the trimeric NF-Y and for the B-type cyclins by the coactivator p300 [16,116]. E2F also seems to be involved in regulating the transcription of cyclins A and B, because the cyclin A promotor as well as the cyclin B promotor are containing both positively- and negatively-acting E2F binding sites [16,54,86,115]. Degradation of the cyclin E-Cdk2 complex releases Cdk2, which is bound immediately by cyclin A to initiate DNA replication, to phosphorylate and, thus, inactivate the DP-E2F heterodimer, and to secure S phase progression. If both subunits of the E2F heterodimer become phosphorylated E2F is degraded via the ubiquitin-proteasome pathway [26,56,74], but it seems that an additional phosphorylation of E2F through cyclin A-pCdk1 complexes is important to indicate this degradation [56]. Phosphorylated cyclin E (pCyclin E) is transported to the cytoplasm where it is degraded by the ubiquitin-proteasome pathway mediated by SCF. [1,2,3,4]

3.1.4 G2 Phase

In the cytoplasm cyclin B and Cdk1 form complexes, in which the Cdk subunit is promptly phosphorylated twice [1,63,79,88]. The resulting inactive complexes accumulate in the cytoplasm until their activation via dephosphorylation of the inhibitory phosphorylation site and their transport to the nucleus where they regulate G2/M transition [71,75]. In case of DNA damage the cyclin B-Cdk1 complexes remain in or are transported back to the cytoplasm caused by inhibitory phosphorylation of Cdk1 mediated by Wee1 (G2/M checkpoint) [63,79,88]. In the meantime, cyclin A-Cdk2 complexes decompose and cyclin A binds to Cdk1 to form an inactive, on the Cdk subunit twofold phosphorylated, complex. This complex is activated via dephosphorylation of the inhibitory phosphorylation site of Cdk1 mediated by Wee1 [79]. The active cyclin A-pCdk1 complexes activate phosphorylation of a variety of cytoskeletal proteins and together with cyclin B-Cdk1 complexes they secure the G2/M phase transition [1,2,3].

3.1.5 M Phase

The cyclin A-Cdk1 complexes split and the phosphorylated cyclin A (pCyclin A) is translocated from the nucleus to be degraded by the ubiquitin-proteasome pathway mediated through APC/C [11]. The cyclin B-Cdk1 complexes, also known as MPF, are transported to the nucleus and activated, thus ensuring the progression through M phase and the correct completion of one cell cycle before starting the next one. Therefore, MPF seems to be involved in dephosphorylation of Rb, in regulation of spindle assembly and chromosome condensation, and in regulation of its own destruction [63,106]. Afterwards, similarly to the cyclin A-Cdk1 complexes, the cyclin B-Cdk1 complexes are disrupted and the phosphorylated cyclin B (pCyclin B) is transported to the cytoplasm and degraded via ubiquitination mediated by APC/C [11]. Additionally, in the M phase Rb is hypophosphorylated by a phosphatase called protein phosphatase 1 (PP1) [57] and, thus, it is able to complex with and inhibit E2F again.

3.2 The Checkpoints

The so-called checkpoints are time points in the cell cycle, whose transition is irreversible and, therefore, must be regulated carefully to avoid uncontrolled cell growth. The checkpoints respond to potential problems in cell cycle progression, such as not completely hyperphosphorylated Rb, DNA damage, delayed DNA replication, insufficient cell growth, or spindle defects by stabilizing an arrest state [1,2,3,87].

3.2.1 The G1/S Checkpoint

The G1/S checkpoint, also called the E2F/Rb restriction point or just restriction point, is situated in the late G1 phase. It ensures that early G1 gene expression is activated and that the initiation of DNA replication takes place correctly, which is not before the hyperphosphorylation of Rb, before the degradation of the cell cycle inhibitor p27, or in absence of mitogens and growth factors in the immediate environment of the cell. [1,2,3,40,87]

3.2.2 The G2/M Checkpoint

The G2/M checkpoint ensures the completion of DNA replication and the absence of DNA damages, before allowing the activation of the cyclin B-Cdk1 complexes and, thus, the G2/M transition [1,2,3,40,87].

3.2.3 The spindle Checkpoint

At the spindle checkpoint, also called the mitotic checkpoint, the cell checks whether the spindle assembly, the centrosome separation, and the chromosome segregation have been completed correctly, and probably whether the cell size is adequate. After

passage of the spindle checkpoint the cell is devided into two daughter cells, each with an entire copy of the genome [2,3,40,87].

3.3 Cyclins and Cdks

3.3.1 The Cyclins

The cyclins are a huge family of proteins from which at least one part (cyclin A, cyclin B, the D-type cyclins, cyclin E and cyclin H) is involved in the regulation of the cell division cycle. These cyclins, with exception of cyclin H, are periodically expressed and degraded throughout the cell cycle and, thus, enable an orderly progression through the cell cycle phases by binding to their Cdk partners [1,2,3]. Although, other findings suggest that the D-type cyclins are expressed continously throughout the cell cycle with a burst of new synthesis each time a cell enters G1 phase after the completion of M phase [1,25,82]. Post-translational events and the cellular localizations of the cyclins seem to play the main role in the regulation of Cdk activity [1,2,4,75]. Other cyclins are involved in the regulation of transcription and RNA splicing [31]. Although cyclin F is expressed and destroyed at almost the same time as cyclin A [16], it seems to be not involved essentially in regulation of cell cycle progression, because cyclin $F^{-/-}$ cells show only a reduced doubling time and a delay in cell cycle reentry from G0 phase [117].

The first cyclins expressed in the cell cycle are the D-type cyclins, cyclin D1, D2, and D3, which are expressed in early G1 phase and form complexes with Cdk4 and Cdk6 to enable G1 progression [1].

The next cell cycle cyclin is cyclin E, which is expressed in G1 phase, forms complexes with Cdk2, and enables passage of the restriction point and G1/S transition.

There are two existing A-type cyclins, cyclin A1 and A2, which are expressed in early S phase and also bind to Cdk2 in order to assure S phase progression [16]. Cyclin A1 seems to be mainly involved in regulation of early embryonic cell cycles, but to have similar functions as cyclin A2, also [39]. After its release from Cdk2, cyclin A binds to Cdk1, thus, providing G2 phase progression and G2/M transition [1,2,3].

The last expressed cell cycle cyclins are the B-type cyclins, cyclin B1 and B2. They are expressed throughout S phase [16] and form complexes with Cdk1, known as M phase or maturation promoting factor (MPF) as well. And, as the name implies, MPF regulates G2/M transition and M phase progression [1,2,4].

Cyclin H is not expressed periodically but stable and associates with Cdk2 and MAT1 to a complex, also known as cyclin activating kinase (CAK) [7,36,88]. CAK activates the different cyclin-Cdk complexes via phosphorylation of activatory phosphorylation sites of the Cdk subunits. Phosphorylation of the cyclin subunits leads to inhibition of the complex, disruption of the complex, and, depending on the phosphorylation site, cyclin degradation. All cyclins involved in cell cycle regulation are degraded by the ubiquitin-proteasome pathway [1,15,16,17,19,23]. The ubiquitination of cyclin D and cyclin E is mediated by the Skp-Cullin-F-box complex (SCF) [1,22], whereas that of cyclin A and B is mediated by the anaphase promoting complex (APC) [1,11,16,21].

3.3.2 The Cdks

The cyclin-dependent kinases (Cdks), also called the cdc2-like kinases named after its most famous member $p34^{cdc2}$ (known as Cdc2 or Cdk1, as will be referred to by now), are a big family of kinases, responsible for most of the main cell cycle events. They are involved in the inactivation of Rb, activation of E2F, correct DNA replication, spindle association, chromosome condensation, and phosphorylation of TGF-β, p27, the active E2F, and other proteins and transcription factors. In short, they are responsible for an orderly passage of the checkpoints and phase transitions through the regulation of cell cycle components. The Cdks themselves are regulated by binding of their respective cyclin partners and the cyclin dependent kinase inhibitors (CKIs), and through post-translational modifications, such as phosphorylation and dephosphorylation. In contrast to their binding partners, the cyclins, most Cdks are expressed continously throughout the cell cycle [25] and only Cdk1 seems to be expressed periodically [48,51,82,84]. Until now important functions in cell cycle regulation have been proved for Cdk1, Cdk2, Cdk4, Cdk6, and Cdk7. Cdk4 and Cdk6 are coworkers in regulating G1 phase, Cdk2 is active from late G1 until early G2 phase, and Cdk1 ensures cell cycle progression from the beginning of G2 phase until the end of M phase. It also seems likely that not only the activation but also the inactivation of the Cdks are important and precisely regulated events in cell cycle control. For example, it has been shown that inactivation of the MPF, i.e. of Cdk1 in complex with cyclin B, at the end of M phase, is essential for the completion of one cell cycle round [1,3,2,4,18]. Cdk7 complexes with cyclin H and MAT1 to build the Cdk-activating kinase (CAK), that is responsible for the activatory phosphorylations of all other cyclin-Cdk complexes involved in cell cycle regulation [7,36,88]. Also, it has been shown that CAK is a component of the human transcription factor TFIIH [13]. The Cdks in the following context always stand for Cdk1, Cdk2, Cdk4, and Cdk6, i.e. the Cdks involved in cell cycle regulation, with exception of Cdk7.

3.3.3 The CKIs

There are two families of Cdk inhibitors (CKIs), the Ink4 family and the Cip/Kip family, regulating the activity of cyclins, Cdks, and complexes of cyclins and Cdks. Thus, they are involved in cell cycle regulation, apoptosis, and, in case of deregulation, in the development of cancer [5].

The Ink4 family consists of four members, $p16^{Ink4A}$ (p16), $p15^{Ink4B}$ (p15), $p18^{Ink4C}$ (p18), and $p19^{Ink4D}$ (p19), which all form complexes with Cdk4, Cdk6, and the D-type cyclins to avoid their complex association and activation [5].

The Cip/Kip family consists of three members, $p21^{Cip1}$(p21), $p27^{Kip1}$(p27), and $p57^{Kip2}$ (p57), which interact with various cyclin-Cdk complexes, with cyclins A, E, D1, D2, and D3, and with the Cdks [5,9,10,101]. p21 and p27 do not only seem to have repressive functions, but also seem to be of importance for some key events in G1 phase [1,44,83]. It has been shown that the yeast CKI Sic1 and the mammalian CKI p27 are functional homologues with a structurally conserved inhibitory domain, inhibiting cyclin A-Cdk2 complexes via a multi-faceted mechanism involving disruption of the active site of Cdk2 and inhibition of the activatory phosphorylation of Cdk2 [102]. For the yeast system it has been proved that the p27 homologue Sic1 facilitates the transport of Clb5-Cdc28 complexes, the homologue of the cyclin E-Cdk2 complex, to the nucleus [103]. In murine fibroblasts p21 and p27 are essential

activators for cyclin D-dependent kinases [83]. For p27 another important function in regulation of self-renewal and differentiation in haematopoietic stem cells (HSCs) has been proved [6]. For detailed information about the expression of p27 see references [28,30].

The only CKI included in the model is p27. I adopted the yeast mechanism for the transport of cyclin E-Cdk2 complexes to the nucleus, wherefore cyclin E-Cdk2 complexes need to bind additionally to p27 to enable their nuclear translocation. For p27, binding to any cytoplasmic cyclin-Cdk complex only facilitates its transport to the nucleus, but is not necessary. A related nuclear transport of cyclin E-Cdk2 and p27 coincides with the finding, that in the nucleus cyclin E-Cdk2 complexes pass on their bound p27 to active cyclin D-pCdk4/6 complexes, thus, inhibiting cyclin D-pCdk4/6 and allowing activatory phosphorylation of cyclin E-Cdk2 by CAK [1,9,10]. Other findings suggest that p27 is necessary for nuclear transport of cyclin D-Cdk4/6 complexes [44,83]. The phosphorylation by active cyclin E-pCdk2 complexes, targeting p27 for degradation via the ubiquitin-proteasome pathway, is essential to allowing the cell to pass the restriction point, to driving the cell from G1 to S phase, and to the irreversible induction of DNA replication and cell division [9,10,26,27,32,35]. p27 expression rate is high in quiescent cells and must be inhibited for G1/S transition. This is mediated by inactivation of TGF-β [28,30]. Other findings suggest that p27 can be phosphorylated only in availability of high concentrations of active cyclin E-pCdk2 complexes, while it has to be bound to inactive cyclin E-Cdk2 complexes [10], but this mechanism is not included in this cell cycle model.

3.4 The Ubiquitin-Proteasome Pathway

The ubiquitin-proteasome pathway, one of the several mechanisms for protein degradation within cells, is an intracellular proteolytic system recognizing and destroying misfolded or damaged proteins, unassembled polypeptide chains, and short-lived regulatory proteins. Therefore ubiquitin, which was identified first by Schlesinger, et al. in 1976 [81], is activated by an ubiquitin-activating enzyme E1, then transferred to the ubiquitin-conjugating enzyme E2. Multiple ubiquitin molecules are covalently bound to the protein substrate via an enzymatic cascade, where the transfer of ubiquitin from E2 to the target protein is catalyzed by the ubiquitin ligase E3, either through direct binding of the ubiquitin molecule by E3 or through binding of E3 to E2, and thereby facilitating the ubiquitin transfer from E2 to the protein substrate. It can be suggested that binding of one ubiquitin molecule to the protein substrate is sufficient for its degradation in most cases. But the polyubiquitin chain enforces the degradation signal and, thus, accelerates degradation. This so-called poly-ubiquitination directs the protein to the 26S proteasome complex for degradation, where it is recognized and degraded. [1,4,33,34,58,59,80]

In the cell cycle a variety of cell cycle components is degraded via the ubiquitin-proteasome pathway to enable an orderly progression through the cell cycle and to reset the system for the next cell cycle circle [1,15,16,17,19,22,23,32,58,64]. The proteins included in the model and degraded via the ubiquitin-proteasome pathway are the cyclins A, B, D, and E, and the CKI p27. Cyclin D and p27 are degraded in late G1 phase, cyclin E in S phase, cyclin A in early M phase, and cyclin B in late M phase. Cyclin B destruction via the ubiquitin-proteasome pathway has been proven to be one of the key events controlling the completion of the cell cycle, the exit from M

phase [18]. At least for the mitotic cyclins, the destruction via the ubiquitin-proteasome pathway is highly conserved from yeast to humans [15]. Two structurally and functionally similar complexes, the Skp-Cullin-F-box (SCF) complex, active from late G1 until early G2 phase, and the anaphase-promoting complex (APC), also called cyclosome (APC/C), active from late G2 until the end of M phase [11], act as ubiquitin ligases (E3) in order to target specific cell cycle compounds for ubiquitination. Cyclin D, cyclin E, and p27, respectively, are degraded via targeting by the SCF complex, and cyclin A and B are targeted by APC (as will be referred to by now). SCF and APC belong to a family of E3 complexes containing a cullin subunit, a RINF-finger subunit and specialized subunits for substrate recognition and recruitment [11]. Although not all components of the larger APC are yet identified, it has been shown that the APC seems to be involved either directly or indirectly in regulation of sister chromatid separation, control of spindle function, regulation of the exit from mitosis via Cdk inactivation, and cytokinesis [11]. Target specifity of ubiquitination is provided by a variety of proteins that interact with the E3 complexes. For more detailed information about the ubiquitin-proteasome pathway, its substrates, the recognition mechanisms, and the subcellular localization of proteasomes see references [4,21,33,34,58,59,80].

In this cell cycle model the ubiquitin-proteasome pathway is described by the binding of a single ubiquitin protein to the particular component which should be degraded, and this binding is activated by SCF and APC, respectively. The over-all protein levels of ubiquitin, SCF, and APC remain constant throughout the cell cycle.

3.5 The E2F/Rb Complex [37,38,53,66]

The retinoblastoma gene product Rb and its related pocket proteins p107 and p130 function as cell cycle inhibitors and tumor suppressors. They all show high similarity in the so-called pocket region that is necessary for most of their interactions with other proteins. Depending on the phosphorylation state of the Rb family protein, it can bind to different proteins and, thus, regulate their activity. At least 12 phosphorylation sites have been identified for Rb, so far [60]. Rb-mediated regulation is achieved through direct protein protein interactions, wherefore an intact binding region of Rb is essential for its functions [37,42,53]. Deregulation of Rb is involved in the development of most human cancers [5].

One group of the most well analyzed and, therefore, best understood binding partners of the retinoblastoma family of proteins is the E2F family of transcription factors. They consists of at least eight members, six E2F and two DP proteins have been identified in mammals [49,67,85,92-96,112-114]. E2F was independently identified in two different laboratories [89,90]. Active E2F consists of one E2F and one DP subunit [25,41,49,50,54,67,85,90]. Therein, the E2F subunit seems to mediate the binding specifity [85], and is involved in the regulation of several cell cycle regulated genes, such as the ones encoding for cyclins A, B, and E, c-myc, Cdk1, and also E2F itself [49,52,54,72,78]. However, it seems that E2F-4 and E2F-5 are the only E2F family members involved in the activation of E2F gene expression [65]. E2F-6, the most recently discovered member of the E2F family, seems to repress E2F-dependent transcription [49,114]. It has been shown that the expression of E2F-1, E2F-2, and E2F-3 in a positive feedback loop increases E2F expression rates [65] and that expression of E2F can induce quiescent cells to enter S phase [76,77]. Rb binds preferentially to E2F-1, E2F-2, and E2F-3, while p107 and p130 preferentially bind to

E2F-4 and E2F-5 [25,65,74,76]. Until now, the binding specifity of E2F-6 regarding the Rb proteins has not been examined exactly. In the previous sentence, and in the following context interactions between Rb and E2F always symbolize interactions between a member of the Rb family of proteins and an active DP-E2F heterodimer.

In this model, only the interactions between Rb and the E2F proteins are included, but some of the functions that are normally fulfilled by E2F family members in complex with p107 and p130, respectively, have been taken over by the Rb-E2F complexes. This was assumed, because the members of the Rb family as well as the members of the E2F family are more or less activated and inactivated via the same mechanisms at the same moments of the cell cycle and thus the model complexity could be kept manageable. Therefore, the following text focuses on interactions between Rb and E2F and neglects interactions between p107 and E2F and between p130 and E2F.

In its hypo- and underphosphorylated form Rb, and also p107 and p130, are able to bind to E2F proteins and, thus, on the one hand inhibit the transcriptional activation of E2F-dependent genes, such as c-myc, cyclins A and B, the Cdk1 gene, and E2F itself [25,49,50,51,65,78,86], and on the other hand some Rb-E2F complexes function as active repressors for some other genes, like cyclin E or c-fos, for example [25,49,52,65,72,73,78,86].

In quiescent cells and early G1 phase Rb remains in its hypophosphorylated form and, therefore, in complex with the DP-E2F heterodimer and the histone deacetylase (HDAC). This complex functions as an active transcriptional repressor for cyclin E and other gene expression, and the initial phosphorylation of Rb through cyclin D-pCdk4/6 in early to mid G1 phase releases HDAC from the complex, thus avoiding the active repressive function of the E2F/Rb complex [1,25,55,60]. To complete inactivation of Rb and, thus, for the release of free active E2F heterodimers in mammalian cells, Rb must be hyperphosphorylated by cyclin E-pCdk2 in late G1 phase after the initial phosphorylation by cyclin D-Cdk4/6 [25,26,55,60,61,62]. Recent findings suggest that at least the cyclin A-Cdk2 additionally phosphorylates Rb in order to assure that Rb remains in its hyperphosphorylated form [62]. It could be proved that at least five of the twelve phosphorylation sites of Rb have to be phosphorylated to inactivate Rb functionally [61]. It has been shown also, that Cdk1 phosphorylates Rb on multiple, i.e. at least five, sites [62,97]. This suggests that all cyclin-Cdk complexes, involved in cell cycle regulation, cooperate with the aim to hyperphosphorylate Rb and keep it hyperphosphorylated throughout the cell cycle. For a detailed understanding of the binding mechanisms between E2F and Rb see [38].

The released active E2F heterodimer is regulated by phosphorylation and dephosphorylation, and is involved in the transcriptional activation of several cell cycle-regulated genes. This is achieved either by direct binding to the promotor of the gene or indirectly via interactions with other transcriptional cell cycle regulators [25,52,53]. Cyclin A-Cdk2 complexes interact with E2F through stable binding to the E2F subunit, leading to inactivation of E2F transcriptional activity at the end of S phase [39,56,65]. For degradation of E2F via the ubiquitin-proteasome pathway presumably both subunits have to be phosphorylated [26,65,74]. Until now it is not understood, which of the subunits of the E2F heterodimer has to be phosphorylated initially, in order to inactivate E2F transcriptional activity. While K. Helin discovered that a cyclin A-dependent kinase has to phosphorylate the DP subunit [65], the findings of R. Yang, et al. [39] and M. Xu, et al. [56] suggest a phosphorylation of the E2F subunit, because interactions between E2F-1 and cyclin A-Cdk2 *in vivo* are

independent of DP-1 [56]. Recent research suggests that not only cyclin A-Cdk2 complexes, but also cyclin A-Cdk1 complexes, interact with and phosphorylate E2F [74] and that cyclin A-Cdk2 complexes probably can phosphorylate the E2F heterodimer on more than one phosphorylation site [39,56]. All these findings share the common fact that the E2F subunit mediates the direct binding interaction between the E2F heterodimer and the regulating Cdks [39,56,65,85].

In late M phase hyperphosphorylated Rb becomes dephosphorylated by a phosphatase called PP1 [57]. The complete disappearance of cyclin B just before the dephosphorylation of Rb [57], and the finding that Cdk1 phosphorylates Rb on multiple sites [97] suggests a role of cyclin B or cyclin B-Cdk1 complexes in regulating the dephosphorylation of Rb, too. This probably is achieved by inhibition of the dephosphorylation until the correct completion of M phase.

It must be pointed out that Rb-association provides one element only, although probably the main one, of the processes regulating E2F activity and that E2F, in turn, is only one of several proteins that interact with Rb [49,78]. Inactivation of Rb and, thus, liberation of E2F is involved in the development of a variety of human cancers [66].

4. The Model

Based on literature information about the cell cycle, but not on kinetic data, I developed a model for the human cell cycle, allowing to simulate oscillating cell cycle behaviour. The model development was partitioned into one preliminary and two main steps. In the first main step a Boolean model (qualitative) was developed, in order to test the general behaviour of the modulated network. In the second main step this Boolean model was transcribed into an ordinary differential equations (ODE) model (quantitative) to enable inclusion of gradual concentration changes and a better temporal resolution of the model behaviour. Although it must be denoted that, because of the unavailability of parameter data, my ODE model is more semi-quantitative than purely quantitative.

In the preliminary step, I developed an animated scheme with Microsoft Powerpoint, showing the components I wanted to include in the model (see appendix A, 7.1, Figure 11) and their temporary order of activity. Based on this scheme, I designed a list of reactions (see appendix A, 7.2, Table2) describing the interactions between the model components, including activatory and inhibitory relations. All stoichiometric coefficients n_{ij}, describing the proportions the corresponding metabolite i is involved in the corresponding reaction j, can be summarized in a matrix, the so-called stoichiometric matrix N (see 5.2.1 & appendix B, 8.1). In a stoichiometric matrix N the rows i represent the converted substances and the columns j the respective reactions, where the positive coefficients stand for production and the negative coefficients for consumption of the respective network component i in the respective reaction j. One condition for simulating (cell cycle) oscillations is that the stoichiometric coefficients of each model component summarized over all reactions, i.e. over its corresponding row in the stoichiometric matrix, had to be zero. Thereby, it is guaranteed that all components between two cell cycle rounds can reconstitute their initial state in case of the Boolean model or their initial concentration in case of the ODE model, respectively. This means every protein and complex that is built up during one cell cycle round is also degraded or split off again in the same round and vice versa. The involvement of activators and inhibitors

in the regulatory interactions, which cannot be seen in the stoichiometric matrix, are noted in the activation matrix (see appendix B, 8.2). With the Boolean model (see 4.3. The Boolean model & appendix A, 7.7, Tables 1 & 2) I tested whether the developed network and its assumed regulatory interactions give the expected behaviour, i.e. whether an oscillating behaviour is possible in principle. The time-dependent simulation of the Boolean model is displayed in the Boolean matrix (see appendix B, 8.3). Based on the matrices and the list of reactions the Boolean model, then, was transcribed into an ODE model (see 4.2.3 The ODE model & appendix A, 7.5, Figure 12) generated in CellDesigner 3.1 in SBML format. After definition of the reaction kinetics a parameter adaptation was performed to evaluate the oscillating behaviour, suggested through the Boolean matrix. Finally, a sensitivity analysis was performed for the parameters of some selected reactions in order to test the influence of these reactions on the general cell cycle behaviour of my ODE model.

The addition and separation of phosphate is noted in the reactions and the Powerpoint scheme, but excluded in all matrices, and in the ODE model only the bound phosphate residues are displayed. Therefore, phosphate concentration was not measured in the model simulations and, according to this, not displayed in the figures. All matrices, including the time-dependent simulation of the Boolean model, were generated with Microsoft Excel 2003.

4.1 Qualitative Modeling

The aim of qualitative modelling is to predict the behaviour of dynamical systems, such as cellular regulatory networks – i.e. the cell cycle – in absence of detailed, quantitative information on parameter values and functional relations [45, 46]. In case of the human cell cycle, there is information in literature about most of the functional relations involved in cell cycle regulation available, but neither kinetic, nor parameter, nor concentrational data.

4.1.1 The Boolean Model

A Boolean model is a discrete system, representing the modelled regulatory network, in this case the human cell cycle, as interconnected elements, having two possible states of activation only, 1 (or active) and 0 (or inactive) [109]. The conditions for the activity of the elements of the network are described in Boolean terms, i.e. the Boolean term describes the state of a cell cycle component at a time point (t+1) in dependence of the states of all compounds, regulatorily related to the considered component, one or also two arbitrary time steps before (at time point (t) or also (t-1)). This means the Boolean term, or the Boolean condition, displays the dependence on the activity or inactivity of other components of the regulated network. The Boolean conditions for this model (see appendix A, 7.3, Table 3) are displayed in form of "if-conditions", giving back 1 to symbolize activity at time point (t+1), if the condition is satisfied, and 0 to symbolize inactivity at time point (t+1), if the condition is false.

The time-dependent simulation of this Boolean model is displayed in the Boolean matrix (see appendix B, 8.3), i.e. the availability or activity, respectively, of each cell cycle compound, respective to the simulation time, can be seen in the Boolean matrix. This facilitated presentation of the basic behaviour of a network was used to ensure, whether the network and its assumed regulating interactions are able to produce the

expected oscillating behaviour, or whether compounds have to be included/excluded or interactions have to be redefined.

My Boolean model was developed with Microsoft Excel 2003 and has an appearance similar to the stoichiometric and the activation matrix (rows = compounds; columns = arbitrary time steps).

Two columns of initial states (see appendix A, 7.4, table 4) were necessary to develop a Boolean condition for each compound and, thereby, enabling oscillating behaviour of the regulatory network. The Boolean conditions were developed by means of the list of reactions (see appendix A, 7.2, table 2) and logic combination, such as, if two cell cycle compounds build a complex and if else one of these two compounds is activated before the other, than the first one has to stay active until the other one becomes activated, to ensure the complex building. Reference [24] acted as an example for the development of the Boolean formalization terms.

To obtain oscillating behaviour for the regulatory network without inclusion of further compounds, I had to include an inactivation of the mitogen-receptor complex after the initialisation of the cell cycle round when cyclin D is successfully transcribed. At the end of mitosis the destruction of cyclin B, the last cyclin active in the cell cycle, reactivates the mitogen-receptor complex in order to enable mitogenic signalling for the next cell cycle round. In reality mitogens and growth factors have to be available in the direct environment of the cell at least until the completion of G1 phase, if not for the whole cell cycle, and, if these signals disappear before the restriction point, the cell will not initiate DNA replication and, therefore, is arrested in G1 phase.

As can be seen in the Boolean matrix (see appendix B, 8.3), it is theoretically possible to create oscillations for the developed network model of cell cycle progression in humans with no additional compounds or reactions. For more information about the network behaviour, the parameter adaptation and the sensitivity analysis with the ODE model have to serve.

4.2 Quantitative Modelling

4.2.1 Time-Dependent Variations of Protein Concentrations

The time-dependent variation of the concentration S_m of a metabolite m of the cell cycle model depends on its synthesis and on how much m is released from complexes with other components (including through dephosphorylation), i.e. on its generation on the one hand, and on its degradation and on how often m is bound to a complex with other components (including through phosphorylation), i.e. on its consumption on the other hand. This can be displayed by a differential equation of the following form:

$$\frac{dS_{metab}}{dt} = \text{generation}(m) - \text{consumption}(m)$$

In steady states no time-dependent variation of the concentration exists, i.e. the same number of the metabolite, being generated, must be consumed again. The steady state of a metabolite is described by:

$$\frac{dS_{metab}}{dt} = 0$$

For a regulatory network, as in this case the human cell cycle, the set of differential equations, which describes the time-dependent concentration variations for all network components, can describe the behaviour of the whole network. The stoichiometric matrix N includes the stoichiometric coefficients n_{ij} describing the proportions, with which the corresponding metabolite i is involved in the corresponding reaction j. With N it is possible to write the system's equation, describing the behaviour of the whole network in the following concise form:

$$\frac{dS}{dt} = Nv$$

Where S stands for the vector of metabolite concentrations $S=(S_1,\ldots,S_q)^T$, N is the stoichiometric matrix $N=\{n_{ij}\}$ with i=1,…,q and j=1,…,r, and v is the vector of reaction rates $v=(v_1,\ldots,v_r)^T$. Metabolite concentrations and reaction rates are parameter-dependent, that means S=S(p) and v=(S,p), with $p=(p_1,\ldots,p_m)^T$ being the vector of parameters. Therefore, the steady state of the whole system can be described by:

$$\frac{dS}{dt} = 0 \qquad \text{or} \qquad Nv(S,p) = 0$$

The complete set of differential equations describing the dynamics of the ODE model for the human cell cycle can be seen in appendix A, 7.7, tables 6 & 7.

4.2.2 Reaction Kinetics

To simulate the model, I used a system of differential equations, based on the Hill kinetic:

$$v = \frac{V_{max} \cdot S_m^n}{K_{0.5}^n + S_m^n}$$

S_m := concentration of m
V_{max} := maximal velocity
$K_{0.5}$:= substrate concentration of m such that $v=V_{max}/2$
n := Hill coefficient

To include the modifications of activators and inhibitors, I combined the Hill kinetics with the Monod-Wyman-Changeux model [43]. Thus, I received simplified modification terms for activation and inhibition, from which I deducted the following reaction kinetics for reactions with one (positive or negative) modifier. The equations for reactions including more than one modifier can be received via combination of the different described terms expanding the original kinetic.

Hill equation with one positive modifier (activator) for a reaction that can take place without the activator:

$$v = \frac{V_{max} \cdot S_m^n}{K_{0.5}^n + S_m^n} \cdot (1 + K_{a0.5} \cdot S_a)^{n_a}$$

a := activator
S_a := concentration of a
$K_{a0.5}$:= substrate concentration of a such that $v=V_{max}/2$
n_a := Hill coefficient of a

Altered Hill equation with one positive modifier (activator) for a reaction that only can take place in availability of the activator:

$$v = \frac{V_{max} \cdot S_m^n}{K_{0.5}^n + S_m^n} \cdot (K_{a0.5} \cdot S_a)^{n_a}$$

Altered Hill equation with one negative modifier (inhibitor):

$$v = \frac{V_{max} \cdot S_m^n}{(K_{0.5}^n + S_m^n)} \cdot \frac{1}{(1 + K_{i0.5} \cdot S_i)^{n_i}}$$

i := inhibitor
S_i := concentration of i
$K_{i0.5}$:= substrate concentration of i such that $v=V_{max}/2$
n_i := Hill coefficient of i

Altered Hill equation for complex building:

$$v = V_{max} \cdot \frac{S_{mA}^n}{K_{0.5}^n + S_{mA}^n} \cdot \frac{S_{mB}^n}{K_{0.5}^n + S_{mB}^n}$$

mA := metabolite A
mB := metabolite B

4.2.3 The ODE Model

The Boolean model was transcribed into an ODE model in order to include gradual conformation changes, to obtain a better temporal resolution as well as a graphical diagram of the model components and their regulating interactions. The ODE model was implemented in CellDesigner 3.1 in SBML format (see appendix A, 7.5, figure 12) and all ODEs can be seen in appendix A, 7.7, table 7.
This ODE model shows a highly simplified version of the human cell cycle. It focuses on the Ras-Raf-MEK-ERK pathway, the cyclin-Cdk activities and their regulation, the Rb-E2F complex, and the ubiquitin-dependent degradation of cell cycle components.

To keep the model complexity manageable, all cell cycle reactions are considered as irreversible, although most of the cell cycle reactions are reversible in reality.

Because of the sparse information available about the human cell cycle, I have included some unknown reactions and activatory and inhibitory relations or reduced some complicated mechanisms.

The retinoblastoma gene family consists of at least three members, the retinoblastoma gene product (Rb) and the related pocket proteins p107 and p130, but in the model they are treated as just one protein, Rb. Similarly, I performed for the E2F family of transcription factors consisting of two subfamilies, the E2F and the DP subfamily, where eight members, E2F-1, E2F-2, E2F-3, E2F-4, E2F-5, and E2F-6 and DP-1 and DP-2, have been identified in mammals so far [49,67,85,92-96,112-114]. Active E2F consists of a heterodimer with one E2F subunit and one DP subunit [25,41,49,54,90]. In the model, the whole E2F subfamily is lumped together to E2F and the DP subfamily is grouped to DP. Normally, E2F-1, E2F-2, and E2F-3 bind preferably to Rb, whereas E2F-4 and E2F-5 prefer p107 and p130 as their binding partners [25,74,76], but in the model all these interactions are treated as interactions between the heterodimer DP-E2F and variably phosphorylated forms of Rb. The HDAC family, from which at least two proteins (HDAC-1 and HDAC-2) have been identified so far, is reduced to HDAC. ERK1 and ERK2, both activated by the Ras-Raf-MEK-ERK signalling cascade [20], are lumped to ERK, such as MEK1 and MEK 2 are grouped to MEK.

To enable oscillations, the mitogen-receptor complex is inactivated by the cytoplasmic cyclin D-pCdk4/6 complex and activated again by ubiquitin-pCyclin B complexes at the end of M phase. This does not happen in reality, where mitogens and growth factors have to be available in the direct environment of the cell at least until the irreversible passage of the restriction point [1,40]. The finding that cyclin D seems to be expressed continuously throughout the cell cycle, with a burst of new synthesized cyclin D at the beginning of each new cell cycle round [1,25,82], also suggests that the mitogen-receptor complexes stay active throughout the whole cell cycle. In order to regenerate the component concentrations for the next cell cycle round, I included a second mechanism to inactivate and activate the mitogen-receptor complex, this way producing a delay in initialising the next cell cycle round. In this mechanism the inactivation is realized dissociation of the mitogen-receptor complex into inactive receptor and in mitogen, mediated by the cytoplasmic cyclin D-pCdk4/6 complex. The reactivation is delayed by the assumption that the inactive receptor has to be activated before it can associate again with the mitogen and, thus, allowing the new activation of the Ras-Raf-MEK-ERK signaling cascade.

The regulation of the cyclin-Cdk complexes through phosphorylation in the model is only mediated by CAK, which is a complex of cyclin H, Cdk2 and MAT1, identified in a number of eukaryotic cells [7,36,88], and also shown to be a component of the human transcription factor TFIIH [13]. In reality, there exists a complex network for the regulation of phosphorylation events on cyclin-Cdk complexes. Until now, beside the regulation through cyclins, CKIs, and CAK at least some other kinases and phosphatases, for example the phosphatase Cdc25 and the kinase Wee1 [12,29] or the Myt kinase [8], are mainly involved in the regulation of cyclin-Cdk complexes. Wee1 mediates an inhibitory phosphorylation of Cdk1 in complex with cyclin A as well as with cyclin B and Cdc25 functions as the antagonist of Wee1 [29]. Human Myt1 kinase preferentially phosphorylates Cdk1, but on a site different from the one used by human Wee1 [8].

Because in the model diffusion, half life, and additional regulatory proteins, involved in regulating the localization of cell cycle components, are not included, I had to rename some components in order to enable an orderly progression through the

cell cycle. Cdk1, complexing with cyclin A in the nucleus, and Cdk1, complexing with cyclin B in the cytoplasm, had to be considered as two different proteins. Nuclear Cdk1, complexing with cyclin A, is named nuclear pCdk1 to distinguish it from nuclear Cdk1, which is released from cyclin B-pCdk1 complexes and afterwards transported back to the cytoplasm to be available for complex building with cyclin B in the next cell cycle round. The cyclin A released from cyclin A-pCdk2 complexes is named p_xCyclin A, to distinguish it from nuclear cyclin A, complexing with Cdk2, and from phosphorylated cyclin A (pCyclin A), that with phosphorylation has become a target for degradation via the ubiquitin-proteasome pathway. These changes in terminology – referring to nuclear cyclin A and Cdk1 – explain why CAK activates association of nuclear p_xCyclin A and pCdk1 to cyclin A-ppCdk1, although Cdk1 in reality becomes phosphorylated after complex building with cyclin A. Additionally, the nuclear Cdk2, which is released from cyclin A-pCdk2 complexes and afterwards is transported back to the cytoplasm to enable complex building with cyclin E in the next cell cycle round, is named pCdk2 to distinguish it from the Cdk2 released from cyclin E-pCdk2 complexes.

Such simplifications are doubtful because, normally, different proteins, even when closely related, have at least in parts different functions and, therefore, they should be treated as different compounds of the cell cycle. But in consideration of the limitation of modelling, I had to compromise on model complexity and accuracy of the represented regulatory network.

Cell Cycle Initiation

The initiation of the cell division cycle includes more than one signalling pathway [20], but this model focusses on and, thus, only includes a simplified version of the Ras-Raf-MEK-ERK signalling cascade [20], which is activated by the mitogen-receptor complex and results in the successive phosphorylation of ERK and, therefore, in its transport into the nucleus [20]. In the model phosphorylated ERK (pERK) in the nucleus directly activates the transcription of cyclin D. In mammalian cells the signalling cascade is regulated by a variety of other factors, for example, the 14-3-3 proteins. Nuclear pERK is involved in transcriptional activation via phosphorylation and, thus, targeting of transcription factors regulating gene expression [20,98-100]. At least Ras is also involved in the regulation of apoptosis [5].

G1 Phase

After activation of cyclin D gene expression through pERK, cyclin D forms complexes with Cdk4 and Cdk6 in the cytoplasm. After phosphorylation mediated by cytoplasmic CAK, these complexes inactivate the mitogen-receptor complex, either by activation of a direct state transition to an inactive mitogen-receptor complex or by inactivation of the receptor complex, resulting in dissociation of the mitogen-receptor complex into inactive receptor and mitogen. Thereafter, cyclin D-pCdk4/6 complexes are transported into the nucleus. This nuclear transport is inhibited by cytoplasmic Cdk4/6 to enable a fast accumulation of cyclin D-pCdk4/6 complexes in the nucleus. Cyclin D-pCdk4/6 in the nucleus initially phosphorylates Rb, resulting in the release of HDAC from the Rb-E2F complex. In reality, this leads to elimination of the active repressive function of HDAC-DP-E2F-Rb complexes in regulating expression of cyclin E and other genes [49,52,55,60,72]. In the model, this is displayed through an essential activatory regulation of the cyclin E gene expression by the DP-E2F-pRb complex. Additionally, the nuclear cyclin D-pCdk4/6 complex mediates the

dephosphorylation of nuclear pERK to stop further expression of cyclin D, in the model.

As for the human cell cycle the mechanism of the transport of cyclin E-Cdk2 complexes to the nucleus is not clear, I took over the yeast mechanism [103] for my model. This also correlates with the findings that p27 has not only repressive functions, but is also a necessary factor for some key events in the mammalian cell cycle [67] and that inactive cyclin E-Cdk2 complexes pass their bound p27 to active cyclin D-Cdk4/6 complexes resulting in disruption of the cyclin D-Cdk4/6 complexes [1]. The released Cdk4/6 and the phosphorylated cyclin D (pCyclin D) are transported back to the cytoplasm, where pCyclin D is degraded by the ubiquitin-proteasome pathway [1,22].

As established above, cyclin E, after the activation of cyclin E gene expression through DP-E2F-pRB, binds to Cdk2 in the cytoplasm and, after additional binding of p27 these complexes are transported into the nucleus. Nuclear cyclin E-cdk2-p27 complexes pass their bound p27 to active cyclin D-pCdk4/6 complexes, resulting in the dissociation of the cyclin D-pCdk4/6 complexes via initiation of cyclin D phosphorylation. Then Cdk4/6 and pCyclin D are transported back to the cytoplasm, where pCyclin D is degraded via ubiquitination, mediated by SCF. The nuclear cyclin E-Cdk2 complex, after its release of p27-mediated inhibition, is activated through phosphorylation, mediated by CAK [9].

G1/S Transition

The active cyclin E-pCdk2 complex enables the cell to pass the restriction point through (i) hyperphosphorylation of Rb, (ii) targeting of p27 for degradation via phosphorylation, and (iii) phosphorylation and, thus, inactivation of the transcription growth factor β (TGF-β). In accordance to the information reported in literature, phosphorylated p27 (Pp27) is transported out of the nucleus, and degraded after ubiquitination, mediated by SCF [14,17,22,23,]. The phosphorylation of TGF-β leads to inhibition of p27 gene expression by avoiding the activating function of TGF-β in p27 gene expression [28,30]. Hyperphosphorylation of Rb leads to the release of free active DP-E2F heterodimers from DP-E2F-pRb complexes and, thus, allows transcriptional activity of E2F [12,38,50,54,72,78,86]. This leads to the activation of cyclin A transcription in the model.

S Phase

After the onset of the S phase, the cyclin E-pCdk2 complex is split off following phosphorylation of cyclin E and the phosphorylated cyclin E (pCyclin E) is transported to the cytoplasm, where it is degraded by the ubiquitin-proteasome pathway, mediated by SCF [1,17,22]. The dissociation of the cyclin E-pCdk2 complex is inhibited by nuclear p27, in order to display the restriction point and secure an orderly G1/S transition. The transport of pCyclin E to the nucleus is supplementarily activated by the remaining nuclear Cyclin E-pCdk2 complexes, as suggested by reference [1]. The released Cdk2 complexes with cyclin A, meanwhile accumulated in the nucleus [75], to regulate DNA replication and to phosphorylate the active DP-E2F heterodimer in order to change its transcriptional activity.

Phosphorylation of one subunit, in case of this model the E2F subunit, of the active E2F heterodimer by Cdk2 in complex with cyclin A, initially targets the active E2F heterodimer for degradation [39] and seems to be important for the completion of S phase [65]. Until now, it is not examined in detail whether cyclin A in complex with Cdk1 is involved in targeting E2F for degradation, but both cyclin A-containing

complexes seem to interact with and phosphorylate the E2F heterodimer [62,97]. If there are no other regulatory changes occurring in E2F activity, the transcription of cyclin A and B must be activated at the same time and, accordingly, only different expression rates and the different binding partners can regulate their different times of activity. Probably, another mechanism – not identified until now – is involved in the switch of transcriptional activity of E2F from the cyclin A to the cyclin B gene promotor.

In the model phosphorylation of DP-E2F by cyclin A-pCdk2 leads to activation of cyclin B expression and not to degradation of E2F.

S/G2 Transition

At the end of S phase cyclin A-pCdk2 complexes divide, and, in the model, release pCdk2 (in reality Cdk2) to distinguish it from tha Cdk2 released from complexes with cyclin E. pCdk2 immediately is transported back to the cytoplasm, where it is dephosphorylated, to make it available for association with cyclin E in the next cell cycle round.

G2 Phase

After its release from the cyclin A-pCdk2 complex, phosphorylated cyclin A (termed p_xCyclin A) remains in the nucleus and complexes with pCdk1. This association is activated in presence of CAK, which normally phosphorylates Cdk1 on the activating phosphorylation site only [79]. This complex building, activated by CAK, results in an inactive twice phosphorylated cyclin A-Cdk1 complex in the model, because of the neglect of other regulatory mechanisms, namely regulation of the phosphorylation state of Cdk1 by Cdc25 and Wee1. This complex is named cyclin A-ppCdk1 and is dephosphorylated once in the next reaction. The active cyclin A-pCdk1 complex phosphorylates the second subunit of the DP-pE2F heterodimer, normally resulting in its degradation, but in the model it only inactivates cyclin B gene expression, and makes DP-E2F available for complex building with HDAC and hypophosphorylated Rb at the end of M phase.

Reversible activation and inactivation of cyclin A-pCdk1, for example in response to DNA damage, in reality is furthermore achieved by changing the phosphorylation state of the inhibitory phosphorylation site of Cdk1 mediated by antagonistic activity of the phosphatase Cdc25 and the kinase Wee1 [63,71,79]. But in the model these two regulators are not included.

In reality, cyclin B forms complexes with phosphorylated Cdk1 in the cytoplasm. This promptly entailes inhibitory phosphorylation of Cdk1 by Cdc25 and an additional activatory phosphorylation of Cdk1 by CAK [1,63,71,75,79,88]. Because of the exclusion of Cdc25 and Wee1 from the model, CAK exclusively mediates complex building of cyclin B and Cdk1 via a double phosphorylation of Cdk1. The twice phosphorylated, inactive complexes accumulate in the cytoplasm until the end of G2 phase.

G2/M Transition

To enable an oscillating cell cycle model without additional compounds, I had to include some arbitrary additional regulatory relations between the nuclear cyclin A-pCdk1 and the different cyclin B-Cdk1 complexes.

At the end of G2 phase, cyclin B-ppCdk1 complexes are transported to the nucleus abruptly. This is catalyzed by nuclear cyclin A-pCdk1 complexes, which have accumulated in the meantime. The nuclear cyclin B-ppCdk1 complexes, in turn, are

essential activators of the dissociation of the cyclin A-pCdk1 complex into phosphorylated cyclin A (pCyclin A) and pCdk1. This results in the transport of pCyclinA to the cytoplasm, where it is degraded via the ubiquitin-proteasome pathway, mediated by APC, and in the new accumulation of pCdk1 in the nucleus for the next cell cycle round.

Usually, Cdc25 and Wee1 – through their antagonistic activity – regulate the phosphorylation state of the inhibitory phosphorylation site of Cdk1 in complex with cyclin B in the nucleus, too. Thus, they secure an orderly G2/M transition and M phase progression via controlling correct DNA replication, correct chromosome condensation, and spindle assembly [63,71,75,79].

As Cdc25 and Wee1 regulate Cdk1 in complex with cyclin B the same way as in complex with cyclin A, the reversible regulation of cyclin B-pCdk1 complexes is not included in the model, as in case of cyclin A-pCk1 complexes. The activating dephosphorylation of the nuclear cyclin B-ppCdk1 complex is inhibited by remaining nuclear cyclin A-pCdk1 complexes to enable a fast activation of cyclin B-pCdk1 at the onset of M phase. The active cyclin B-pCdk1 complex is also known as MPF, but in the model and, therefore, in all reactions and matrices, it is always named cyclin B-pCdk1.

In early *Xenopus* embryos the homologue of human cyclin B is the only newly synthesized protein required to induce MPF activity [18], and it has been shown that the onset of M phase is regulated by a universal control mechanism common to all eukaryotic cells [71].

M Phase

Because of the important functions in regulating the exit from M phase proven for MPF and the degradation of cyclin B [18,69], the active cyclin B-pCdk1 complex in my model achieved some functions in regulating the events occurring at the end of M phase.

Even with an expanded literature search no information could be found about the complex formation of HDAC-DP-E2F-Rb, although there is a lot of information available about how the complex disruption, caused by Rb phosphorylation, is achieved, in order to enable subsequent activation of the transcription factor E2F [26]. To allow a complete oscillating model of the cell cycle, I assumed that association of the HDAC-DP-E2F-Rb complex is initialized following dephosphorylation of the hyperphosphorylated Rb (hypRb) and takes place at the end of M phase. Usually, Rb is dephosphorylated in late M phase, too, but this dephosphorylation is mediated by PP1 [57]. In the model, this dephosphorylation is mediated by the active cyclin B-pCdk1 complex just before its inactivation by degradation of cyclin B, because it has been shown that cyclin B dissappears just before the onset of Rb dephosphorylation [57]. This could denote that PP1 activity is inhibited or antagonized by active cyclin B-pCdk complexes. This is also suggested by the finding that Cdk1 phosphorylates Rb on multiple sites [97]. Additionally, it has been shown that the active DP-E2F heterodimer is targeted for degradation via the ubiquitin-proteasome pathway [26,56,74] by phosphorylation of both, the DP and the E2F subunit, by cyclin A-pCdk2, and probably cyclin A-pCdk1 complexes. But because the mechanisms for the regulation of E2F transcription are not completely understood until now, the pDP-pE2F complexes are not degraded, but used directly for the association of the HDAC-DP-E2F-Rb complexes in this model. Thus, the HDAC-DP-E2F-Rb complex is available at the start of the G1 phase of the next cell cycle round.

Likewise, I modelled the transcription growth factor TGF-β. TGF-β is phosphorylated at the end of G1 phase in order to enable the inactivation of p27 gene expression [28,30] and must be dephosphorylated at the end of mitosis to make p27 available for the next cell division cycle. The active cyclin B-Cdk1 complexes take over this function in the model, although it must be denoted that, in reality, this dephosphorylation could not be derived from direct interaction, but would have to include other components not integrated in this model. Additionally, the cyclin B-pCdk1 complex activates the transport of nuclear ERK back to the cytoplasm to make it available for the next cell cycle round.

M/G1 Transition

For correct timing of the M phase onset, the activation of the MPF is as important as its inactivation for the exit from mitosis. At the end of M phase, phosphorylation of cyclin B leads to destruction of the active cyclin B-pCdk1 complex. The phosphorylated cyclin B (pCyclin B) is transported to the cytoplasm, where it is degraded via the ubiquitin-proteasome pathway, mediated by APC, as has been shown by [1,17,18,19,21,64,75]. It has been reported in literature that inactivation of cyclin B destruction leads to remaining active MPF and, thus, to induction of M phase arrest [18,69].

For the destruction of the cyclin B-pCdk1 complex within phosphorylation of cyclin B, the activating HDAC-DP-E2F-Rb complex must be build up again and the inhibiting pTGF-β has to be dephosphorylated. These regulatory relations for the dissociation of the cyclin B-pCdk1 complex were included to symbolize the fact that the cyclin B-pCdk1 complex induces – with a delay – its own degradation [63,106,107], and to ensure complete dephosphorylation of Rb and TGF-β. Cdk1, which cannot be phosphorylated in absence of cyclin B [79], is transported to the cytoplasm, to make it available for complex formation with cyclin B in the next cell cycle round. pCyclin B is transported out of the nucleus as well and is degraded in the cytoplasm via the ubiquitin-proteasome pathway, mediated by APC [16].

To activate the next cell cycle round the mitogen-receptor complex must be activated again at the end of M phase. Therefore, the ubiquitin-pCyclin B complex either directly activates the inactive mitogen-receptor complex or it activates the inactive receptor to enable new docking of the mitogen to the receptor.

In the ODE model version the parameter adaptation and the sensitivity analysis were performed with, the reactivation of the mitogen-receptor complex includes this delay. Therefore, the inactivation of the mitogen-receptor complex is achieved via inactivation of the receptor, avoiding the association of the mitogen and the receptor. For new complex building the inactive receptor has to be activated again to enable association with the mitogen.

4.3 Parameter Adaptation

Because of the sparse kinetic data available concerning the human cell cycle, for the kinetic simulations an extensive parameter adaptation had to be carried out for the ODE model. For each reaction x, I defined an initial rx_V_{max} value, an initial rx_$K_{0.5}$ value, and an initial rx_n value, according to the kinetics of the ODE model (see 5.2.2). For reactions including modifiers, the additional initial parameters rx_$K_{a0.5}$ and rx_n_a for activation and rx_$K_{i0.5}$ and rx_n_i for inhibition have been defined.

The initial parameters were:
global $V_{max} = 1$
global $K_{0.5} = K_{a0.5} = K_{i0.5} = 0.5$
global $n = n_a = n_i = 4$

a and i stand for activator and inhibitor, respectively. To distinguish between the parameters of the different reactions each parameter was named after its corresponding reaction (for example V_{max} of reaction 7 is named r7_V_{max}).
Additionally, for the simulations I had to appoint the initial concentrations for the ODE model compounds (see appendix A, table 5). For lack of experimental data, they were chosen freely and considered in arbitrary units.

Because the targets for parameter optimization, essential for the programs used in our group, could not be defined, I performed the parameter adaptation by trial and error.

First, I changed the initial parameters until the model compounds were activated in the right order and certain compounds accumulated in consistency with the reality, i.e. either in the nucleus – like for example cyclin A – or in the cytoplasm – like for example the cyclin B-ppCdk1 complex. This was realized to ensure the possibility of simulating an oscillating cell cycle model with the defined reactions. For this, I changed the maximal reaction velocity of reaction 75a (r75a_V_{max}) or 75b (r75b_V_{max}), respectively, to zero, to avoid the reactivation of the mitogen-receptor complex, thus only observing one cell cycle round.

When the concentrational changes displayed the expected behaviour for one cell cycle round, I allowed reactivation of the mitogen-receptor complex in order to enable the simulation of more than one cell cycle round. Afterwards again I changed the parameters by trial and error until at least similar concentration courses for at least three consecutive cell cycle rounds occurred. The resulting parameters can be seen in appendix A, 7.8, table 8.

Because of limitation of time, the parameter adaptation was aborted at that point, though an ongoing parameter adaptation could have advanced the oscillating behaviour of the model.
Although it is known, for at least some human cell types, how much time a full cycle round needs, the time in these model simulations is for simplification – like the compound concentrations – observed in arbitrary units, too.

4.4 Sensitivity Analysis

The influence on the cell cycle progression of parameters of some cell cycle limiting reactions, for example of the gene expressions or the transcriptions of the cyclins, was tested with the sensitivity analysis. The parameters x resulting from the parameter adaptation by trial and error were varied to 0.1x, 0.5x, 2x, and 10x to identify their importance.

The cyclins and the CKI p27 are the only network components newly synthesized in each cell cycle round. With the sensitivity analysis I focused on their expression rates, their transcription rates, and – with respect to the model characteristics – on the transport of their mRNAs to the cytoplasm, i.e. the ribosomes. Because of missing data about the timing of these reactions, I could not distinguish between the mRNA transport to the cytoplasm and the transcription of the mRNA at the ribosome.

5. Simulation Results

5.1 Parameter Adaptation

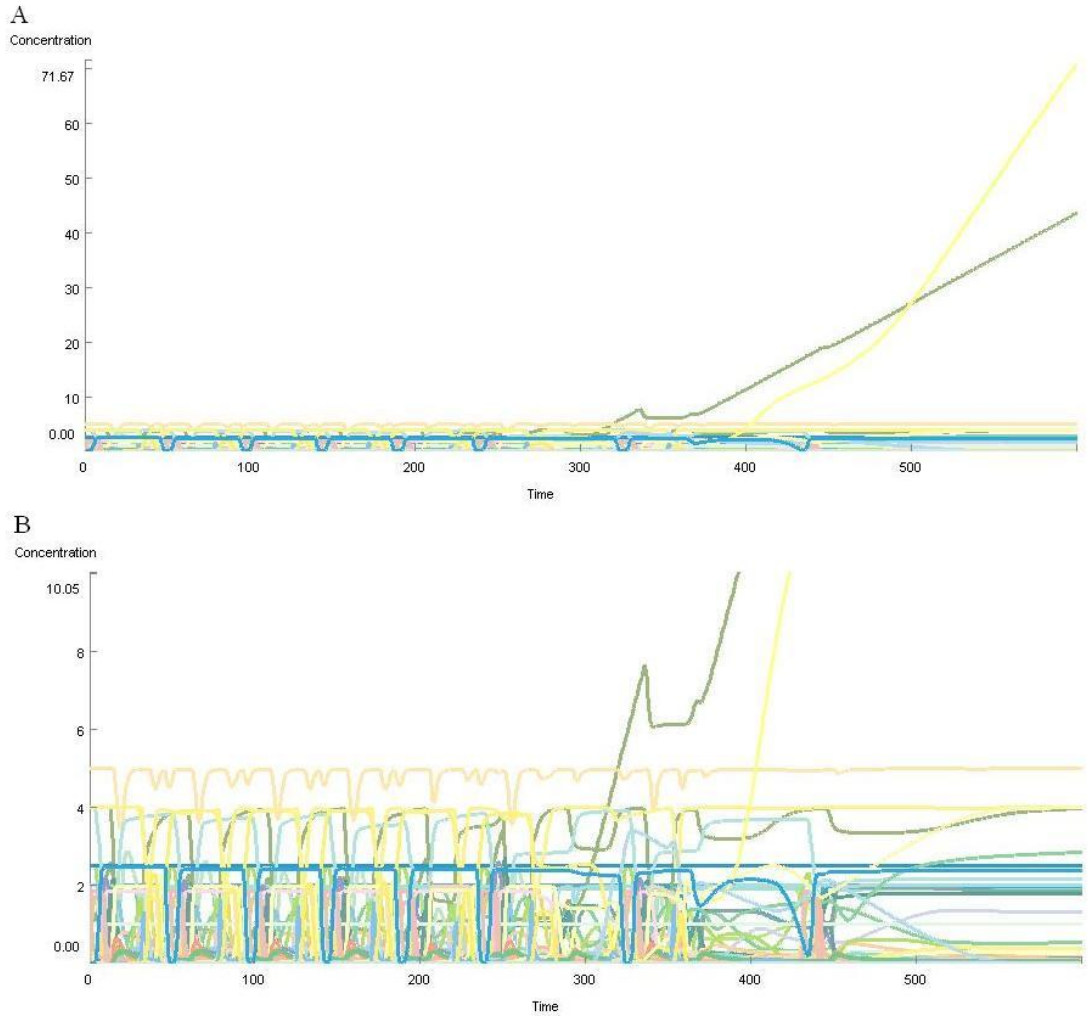

Figure 1: Concentration courses of all ODE model components after the parameter adaptation; A: overview; B: cutout until a maximal concentration of 10.05; concentration and time are displayed in arbitrary units

With the parameter adaptation by trial and error it was possible to simulate, at least for some cell cycle circles, oscillating behaviour of the cell cycle model (see figure 1). Even though, several compounds, until now, do not show the right behaviour. The time-dependent changes of all model compound concentrations of the ODE model resulting from the parameter adaptation can be seen for 150 arbitrary time steps in appendix A, 7.10, table 10. In figure 2A, the concentration courses show similar curves for the first three cell cycle rounds. But, also, it can be seen that there are some concentrations with their maximum and minimum decreasing and increasing, respectively, from one cell cycle round to the next, and that some compounds do not reach their initial concentrations before the next cell cycle round is started. Therefore, it must be denoted that with the parameters resulting from the parameter adaptation it is not yet possible to simulate real oscillating behaviour not converging to a steady state for the mayority of the model components.

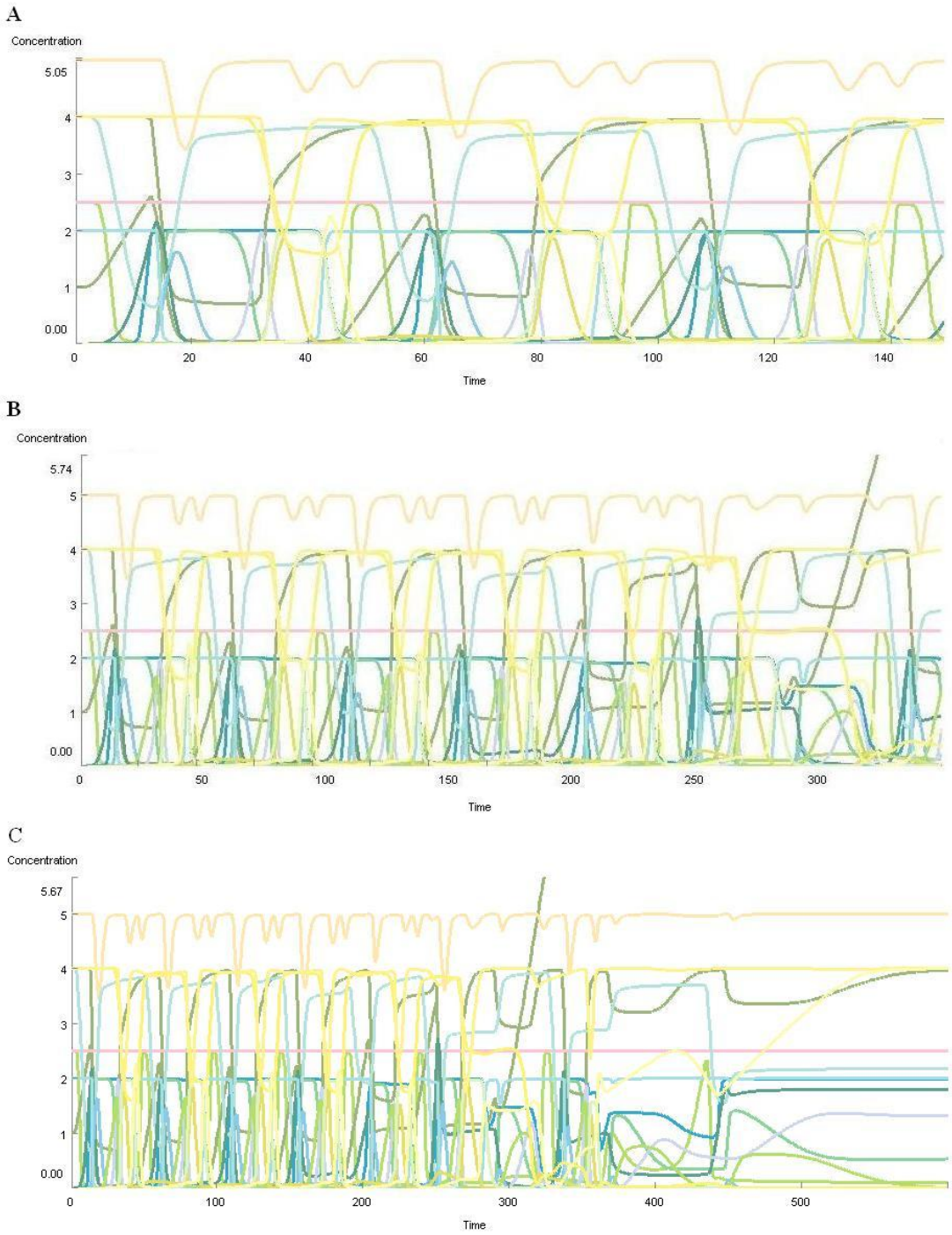

Figure 2: Concentration courses of some selected important cell cycle components, which are significant for the behaviour of the simulated network, in dependence of time; A: for the first three simulated cell cycle rounds; B: for 350 time steps; C: for 600 time steps; concentrations and time are displayed in arbitrary units

In figure 2B, in the fourth cell cycle round the simulations begin to go wrong, when the Cdk4/6 return transport to the cytoplasm is clearly limited (see figure 2B: light blue line with an initial concentration of 4). In the fifth round, less Cdk4/6 and Cdk2 associate in their respective cyclin-Cdk complexes and the cytoplasmic p27 is not fully transported to the nucleus, therefore beginning to accumulate in the cytoplasm (see figure 2B: dark green line with an initial concentration of 1). Additionally, not only the Cdk4/6 (see figure 2B: light blue line with an initial concentration of 4), as in

the first rounds, but as well Cdk2 (see figure 2B: dark green line with an initial concentration of 4), is not completely transported back to the cytoplasm. At the latest, after 250 arbitrary time steps (approximately at the beginning of the sixth cell cycle round) the concentration courses show highly diverging behaviour in comparison to the first three cell cycle rounds. After approximately 300 time steps, cytoplasmic p27 (see figure 2B) and, with a little delay, cytoplasmic cyclin B (not displayed in figure 2) accumulate infinitely. In reality, this would result in G1 arrest, actuated by high concentrations of nuclear p27. Because in the model, not conform to the reality, cytoplasmic p27 can only be transported into the nucleus after binding to cyclin E-Cdk2 complexes, p27 accumulates in the cytoplasm (see figure 2B & 2C), and after approximately 600 time steps all compounds of the simulated cell cycle network reach a steady state, with exception of p27 and cyclin B, which accumulate in the cytoplasm (see figures 1A & 2C).

The behaviour of Cdks and cyclins is displayed in figure 3A and B, respectively; in both subfigures, 3A and 3B, ubiquitin, the active mitogen-receptor complex, and SCF or APC, respectively, are displayed for easier comparison of the concentration changes. As it can be seen in figure 3A, the Cdks – with exception of Cdk4/6 – nearly completely reach their initial concentrations before starting the next cell cycle round until at least the fifth round. Afterwards, the concentration of cytoplasmic Cdk1 goes to 0.00, while cytoplasmic Cdk4/6 reaches a steady state concentration of ~2.1803. Nuclear pCdk1 and cytoplasmic Cdk2 concentrations have almost gone back to their initial concentration values of 4.00, after 600 time steps.

In figure 3B concerning the cyclins, nuclear cyclin A starts to accumulate in the first cell cycle round and its concentration continuously increases from one cell cycle round to the next. After 600 simulated arbitrary time steps, the concentration still increases about 0.0017 arbitrary concentration units per arbitrary time step. The other cyclins, through all cell cycle rounds, are – except for a small rest concentration – fully assembled in their corresponding complexes regulating the cell cycle progression, and after 600 simulated time steps cyclins D and E concentration values nearly decrease to 0.00. Cytoplasmic cyclin B only, after completion of the fifth cell cycle circle, rapidly accumulates, and after 600 simulated time steps nearly reaches an arbitrary concentration of 71.

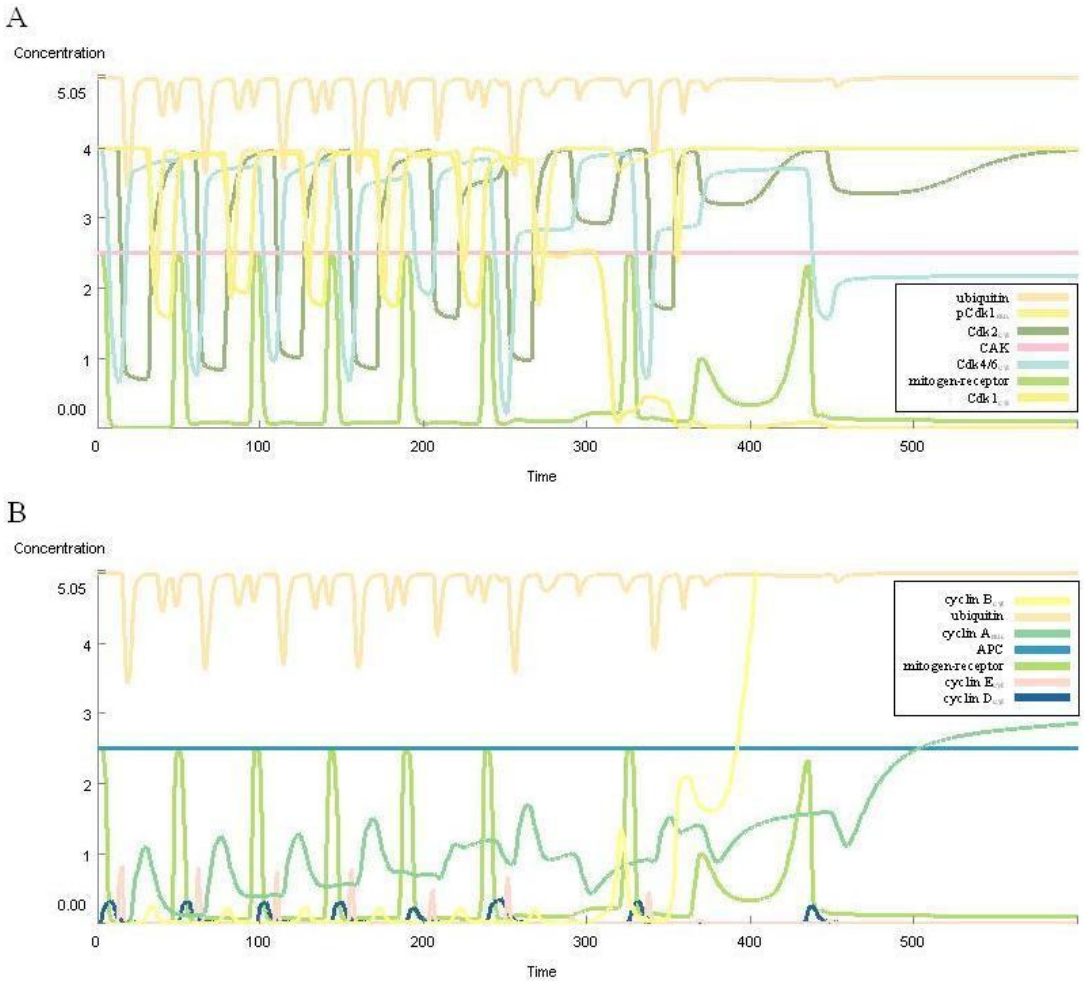

Figure 3: Concentration courses of A: the Cdks, and B: the cyclins depending on the time; ubiquitin, the mitogen-receptor complex, and CAK or APC, respectively are displayed for a better possibility of comparison of the concentration changes; concentration and time are displayed in arbitrary units

To get a better survey of the concentration changes during the cell cycle oscillations, I extracted the minimal and maximal concentration values for different simulation times and afterwards plotted the minimal and maximal concentrations of all compounds included in the ODE model in figure 4. To keep the figure concise the components were assigned to the numbers on the x-axis, as can be seen in table 1. Figure 4A shows maximal and minimal concentrations of the ODE model components, when the behaviour of the regulatory network is simulated for 150 arbitrary time steps, which is the time span the model is able to show almost normal cell cycle oscillations for; figure 4B and 4C display them after 600 simulated arbitrary time steps, i.e. for the same time window the results of parameter changes in the sensitivity analysis were occupied for, but they show differences in the observed maximal concentration. This was necessary, because of the, relatively, high maximal concentrations of cytoplasmic p27 and cyclin B after 600 time steps, all other concentration values could not be observed in detail. To keep the different figures comparable, minimal and maximal concentrations of cytoplasmic p27 and cyclin B for figure 4C were set to 0.00. Therefore, the numbers on the x-axis, corresponding to the different model components, do not change from one figure to another. The values were extracted from the CellDesigner simulation output file with MATLAB 6.1 and

also plotted with MATLAB 6.1. The code of the MATLAB file minmax.m can be seen in appendix A, 7.11.1.

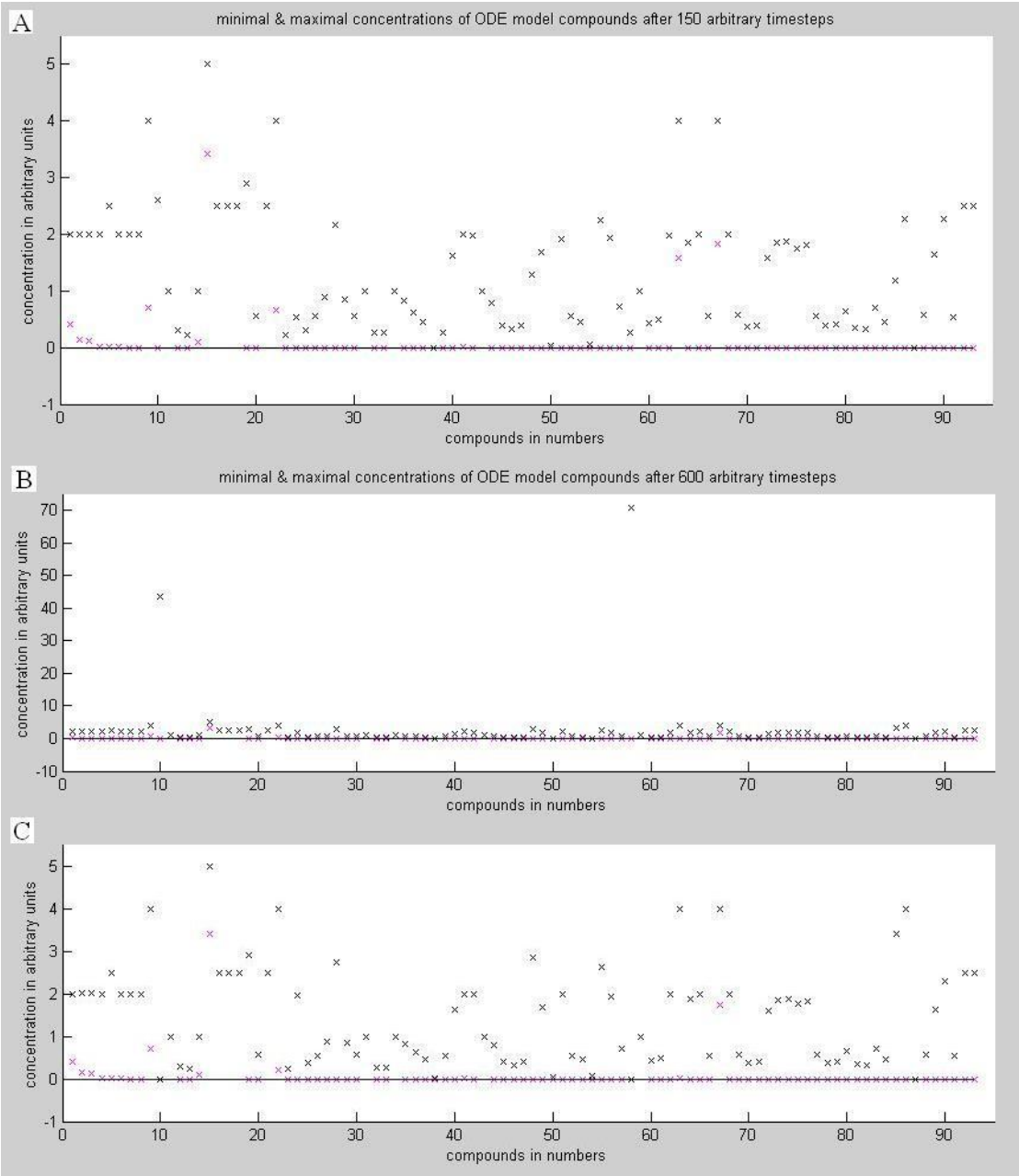

Figure 4: Minimal and maximal concentrations of all ODE model components for different simulation times; A: after 150 arbitrary time steps, B: after 600 arbitrary time steps, C: after 600 arbitrary time steps, but the minimal and maximal concentration values for cytoplasmic p27 and cyclin B are set to zero to enable better observation of the other values; the ODE model compounds corresponding to the numbers on the x-axis can be seen in table 1

To analyze the concentration changes between the different consecutive cell cycle circles in detail, I ascertained the length of the first three cell cycle rounds from the simulation output of the ODE model. The cell cycle rounds shorten from 49 arbitrary time steps in the first round, over 48 time steps in the second, to 46 time steps in the third round. This can be explained by the incomplete reset of the compound concentrations between two cell cycle rounds, resulting in small rest concentrations of some model components, which remain for the next round. Therefore, the necessary

concentration thresholds for the activation of some reactions can be reached faster in the next cell cycle circle.

With the information on the cell cycle length I extracted the maximal and minimal concentration values corresponding to the first three cell cycle rounds, with MATLAB 6.1 and plotted them afterwards, as can be seen in figure 5. Figure 5A shows the maximal and minimal values of all ODE model components in the first cell cycle round, figure 5B in the second, and figure 5C in third. As in case of figure 4, the ODE model components, corresponding to the numbers on the x-axis in figure 5, are displayed in table 1. For easier comparison the values additionally are displayed in appendix A, 7.9, table 9. All concentration values for 150 simulated time steps can be seen in appendix A, 7.10, table10. A detailed analysis of the concentration changes could be used for former parameter adaptation. The code of the MATLAB file compareMins.m can be seen in appendix A, 7.11.2.

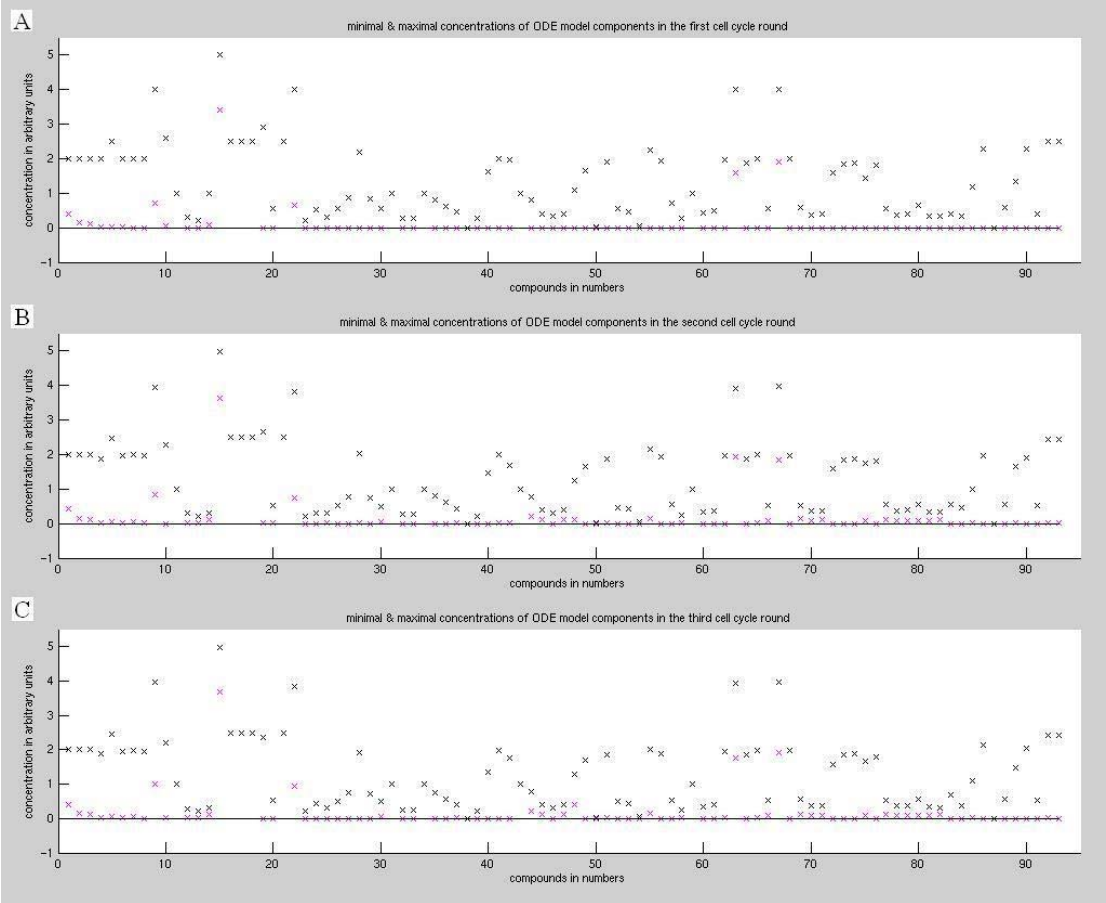

Figure 5: Minimal (x) and maximal (x) concentration values for the first three cell cycle circles; A: first cell cycle round (time steps 1-49); B: second cell cycle round (time steps 50-97); C: third cell cycle round (time steps 98-143); the ODE model compounds corresponding to the numbers on the x-axis can be seen in table 1

1 Ras_{cyt}	25 $CyclinD_{cyt}$	49 $(CyclinA\text{-}pCdk2)_{nuc}$	73 $pRaf_{cyt}$
2 Raf_{cyt}	26 $(ubiquitin\text{-}pCyclinD)_{cyt}$	50 $(CyclinA\text{-}Cdk2)_{nuc}$	74 $pMEK_{cyt}$
3 MEK_{cyt}	27 $(CyclinD\text{-}pCdk4/6\text{-}p27)_{nuc}$	51 $(CyclinA\text{-}pCdk1)_{nuc}$	75 $pERK_{cyt}$
4 ERK_{cyt}	28 $(CyclinD\text{-}pCdk4/6)_{nuc}$	52 $(ubiquitin\text{-}pCyclinA)_{cyt}$	76 $pERK_{nuc}$
5 mitogen-receptor	29 $mRNA(CyclinE)_{nuc}$	53 $(ubiquitin\text{-}pCyclinB)_{cyt}$	77 $pCyclinD_{nuc}$
6 $(HDAC\text{-}DP\text{-}E2F\text{-}Rb)_{nuc}$	30 $mRNA(CyclinE)_{cyt}$	54 $(CyclinD\text{-}Cdk4/6)_{cyt}$	78 $pCyclinD_{cyt}$
7 $HDAC_{nuc}$	31 CyclinEgene	55 $(CyclinD\text{-}pCdk4/6)_{cyt}$	79 $Pp27_{cyt}$
8 $(DP\text{-}E2F)_{nuc}$	32 $mRNA(CyclinD)_{nuc}$	56 $(DP\text{-}E2F\text{-}pRb)_{nuc}$	80 $Pp27_{nuc}$
9 $Cdk2_{cyt}$	33 $mRNA(CyclinD)_{cyt}$	57 $(ubiquitin\text{-}Pp27)_{cyt}$	81 $pCyclinE_{cyt}$
10 $p27_{cyt}$	34 CyclinDgene	58 $CyclinB_{cyt}$	82 $pCyclinE_{nuc}$
11 p27gene	35 $CyclinE_{cyt}$	59 CyclinBgene	83 $pCdk2_{nuc}$
12 $mRNA(p27)_{nuc}$	36 $(CyclinE\text{-}Cdk2)_{cyt}$	60 $mRNA(CyclinB)_{nuc}$	84 $pCdk2_{cyt}$
13 $mRNA(p27)_{cyt}$	37 $(CyclinE\text{-}Cdk2\text{-}p27)_{cyt}$	61 $mRNA(CyclinB)_{cyt}$	85 $(CyclinB\text{-}ppCdk1)_{cyt}$
14 $p27_{nuc}$	38 $(CyclinE\text{-}Cdk2)_{nuc}$	62 $(pDP\text{-}pE2F)_{nuc}$	86 $(CyclinB\text{-}pCdk1)_{nuc}$
15 $ubiquitin_{cyt}$	39 $(CyclinE\text{-}Cdk2\text{-}p27)_{nuc}$	63 $Cdk1_{cyt}$	87 inact-mitogen-receptor
16 SCF_{cyt}	40 $(CyclinE\text{-}pCdk2)_{nuc}$	64 ERK_{nuc}	88 $(CyclinA\text{-}ppCdk1)_{nuc}$
17 CAK_{nuc}	41 $TGF\text{-}\beta_{nuc}$	65 $pTGF\text{-}\beta_{nuc}$	89 $p_xCyclinA_{nuc}$
18 CAK_{cyt}	42 $(DP\text{-}pE2F)_{nuc}$	66 $pCyclinB_{nuc}$	90 $(CyclinB\text{-}ppCdk1)_{nuc}$
19 $Cdk2_{nuc}$	43 CyclinAgene	67 $pCdk1_{nuc}$	91 receptor
20 $Cdk1_{nuc}$	44 $mRNA(CyclinA)_{nuc}$	68 $hypRb_{nuc}$	92 mitogen
21 APC_{cyt}	45 $mRNA(CyclinA)_{cyt}$	69 $pCyclinA_{nuc}$	93 inact-receptor
22 $Cdk4/6_{cyt}$	46 $(ubiquitin\text{-}pCyclinE)_{cyt}$	70 $pCyclinB_{cyt}$	
23 $Cdk4/6_{nuc}$	47 $CyclinA_{cyt}$	71 $pCyclinA_{cyt}$	
24 Rb_{nuc}	48 $CyclinA_{nuc}$	72 $pRas_{cyt}$	

Table 1: ODE model components and their corresponding numbers on the x-axis' of figures 4 and 5

5.2 Sensitivity Analysis

In the sensitivity analysis, I tested the influence of the parameters involved in the regulation of the reactions involved in the synthesis of model compounds, such as p27 and the cyclins. Because the kinetics of protein synthesis in the human cell cycle are unknown, I changed the parameters of gene expression, i.e. transcription, transport of the nuclear mRNA to the cytoplasm, i.e. to the ribosome, and of translation of these mRNAs into proteins.

In figure 1, the behaviour of all compound concentrations, resulting from the parameter adaptation by trial and error, can be seen. The adaptation results were used as the starting point for the sensitivity analysis. It must be denoted that, therefore, the sensitivity analysis is depending on not completely oscillating behaviour of the examined system.

With the sensitivity analysis I was able to show that all reactions involved in protein synthesis have essential functions in regulating the cell cycle progression. It must be denoted that, where the Hill coefficient n of any of the reactions tested on its influence on the cell cycle progression is decreased below 1.00, there was no simulation at all or only rudimental cell cycle progression possible. This can be explained with the involvement of the parameter n in the reaction kinetics (see 5.1.2). There is no simulation possible at all ($0 \leq t_{max} \leq 12$), when the differential equations system becomes unsolvable because of the value changes of n, i.e. in the reactions not including a modifier, such as mRNA transport to the cytoplasm and translation of the mRNA into the protein. After a value change of n only rudimental cell cycle progression can be noticed, if one or two modifiers are included in the reaction, i.e. for all gene transcriptions. Because half life of the newly synthesized proteins of the

ODE model is not included in the model, newly synthesized proteins, which are not included in their corresponding cyclin-Cdk complexes, accumulate and cannot be degraded. Therefore, the whole system can never reach a steady state, because there will be at least one protein, whose gene expression is active at each possible time point of the cell cycle. For each newly synthesized protein, an illustrating figure, showing the effect of one parameter change on the behaviour of the cyclins and p27, and of another one on the behaviour of the Cdks and p27, is included. In these figures, the observed concentration area will be restricted in order to enable the consideration of not only the proteins accumulating in each case but also the important concentration changes. For comparison with the network behaviour after the parameter adaptation see figure 3. Because of limitation of time in this work, the control coefficients have not been computed so far, though it would enable a better analysis of the consequences of parameter changes on the concentration courses of different model components.

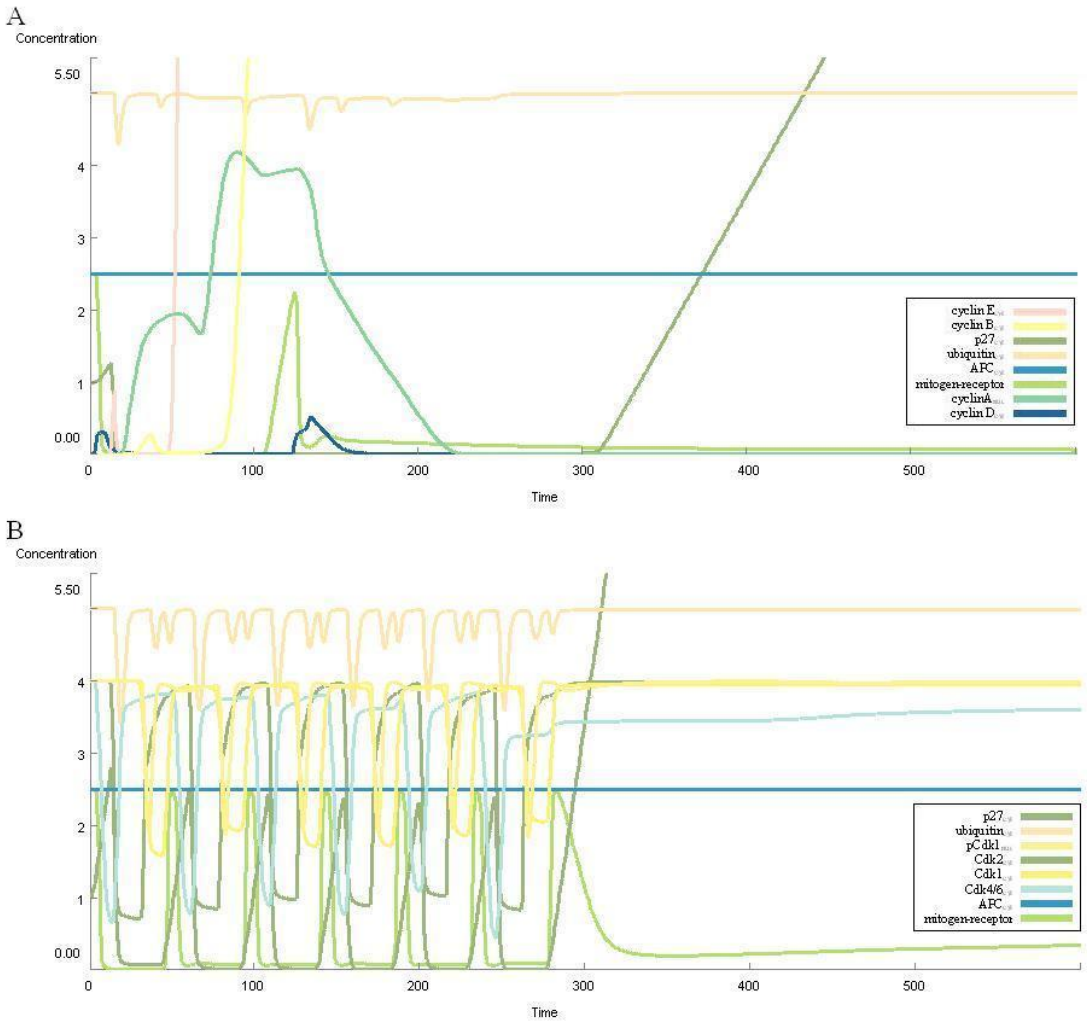

Figure 6: Effects of parameter changes on the concentration courses of ODE model components; A: Concentration courses of the cyclins after increasing r0_ns from 4 to 8 (p27 gene expression); B: Concentration courses of the Cdks after decreasing r2_k_{50} from 0.5 to 0.05 (transcription of mRNA(p27)); concentration courses of ubiquitin, APC, and the mitogen-receptor complex are displayed for better comparison of the value changes during the simulation; concentration and time are displayed in arbitrary units

Changing Parameters Involved in the Regulation of p27 Synthesis

Expression of the p27 gene is activated essentially by the active DP-E2F heterodimer, wherefore the parameters regulating this activation ($r0\_k_{a50}$ = 0.3525 and $r0\_n_a$ = 4.00) should be limiting for the reaction rate. The sensitivity analysis showed that decreasing $r0\_k_{a50}$ and increasing $r0\_n_a$ completely inhibit cell cycle progression (see figure 6A). Increasing $r0\_k_{a50}$ and decreasing $r0\_ n_a$ only result in less completed cell cycle rounds and reaching the steady state earlier for all model components, with exception of cyclin B and E in case of changing $r0\_k_{a50}$, and with exception of cyclin B or cyclin E depending on the increase of $r0\_n_a$. If the maximal velocity of p27 gene transcription ($r0\_V_{max}$ = 0.71) is decreased to 0.7, cell cycle progression is disrupted subsequently after the fourth cell cycle round, and if it is decreased below the half of its original value, there is no correct cell cycle progression at all possible, while p27 and cyclin B still accumulate in the cytoplasm. If the maximal velocities of the mRNA(p27) transport to the cytoplasm ($r1\_V_{max}$ = 2.00) and of the translation of the cytoplasmic mRNA(p27) to p27 protein ($r2\_V_{max}$ = 1.00) are decreased, cell cycle progression is decelerated in G1 phase and the steady state, at the latest, is reached after the fourth cell cycle round, except for p27. If $r1\_V_{max}$ and $r2\_V_{max}$ are increased, the oscillating behaviour of the whole network seems to be enhanced, i.e. after six akin cell cycle rounds, all model components, with exception of p27, reach a steady state. Analogous behaviour can be observed, if the k_{50} parameters of all three reactions, involved in p27 protein synthesis, are decreased, i.e. after six akin cell cycle rounds the oscillating behaviour reaches a steady state, except for p27 (see figure 6B). If the k_{50} value of p27 gene expression ($r0\_k_{50}$ = 0.50) is multiplied by two, the system showed chaotic behaviour but seems to complete one cell cycle round followed by a steady state of all model components, with exception of p27 and cyclin B, which accumulate in the cytoplasm. If $r0\_k_{50}$ is multiplied by ten, cell cycle progression is completely inhibited, the system components reach a steady state, and only cyclin E accumulates in the cytoplasm. If $r1\_k_{50}$ and $r2\_k_{50}$ are doubled, only four cell cycle rounds can be completed before the network compounds, with exception of p27, reach a steady state. If they are increased tenfold, only one chaotic cell cycle round can be completed before reaching the steady state. If the n value of p27 gene expression (r0_n = 4.00) is increased, all ODE model components, with exception of p27, reach a steady state after six akin cell cycle rounds. This means that the behaviour of the whole model seems to have improved. Increasing the values of n in cytoplasmic transport of the mRNA and translation of mRNA(p27) (r1_n = 2.00; r2_n = 2.00) impairs the general oscillating behaviour, so the modelled cell cycle network can complete a maximum of four cell cycle rounds before reaching the steady state, with exception of p27.

Especially the $r0\_V_{max}$ value seems to be rate limiting for p27 synthesis, but, in general, it can be concluded that p27 protein synthesis is rate limiting for the cell cycle progression of the simulated network, because p27 is necessary for the transport of cyclin E-Cdk2 complexes to the nucleus.

Changing Parameters Involved in the Regulation of Cyclin D Synthesis

Cyclin D gene expression needs activation by nuclear pERK, implying an important role for the parameters regulating the activation of this reaction ($r11\_k_{a50}$ = 0.50, $r11\_n_a$ = 4.00). Decreasing as well as increasing one of these two parameters results in poor cell cycle progression or none at all before the network components, with exception of p27, reach a steady state. After reducing $r11\_n_a$ below 1, there was no simulation possible at all, because of an unsolvable differential equations system.

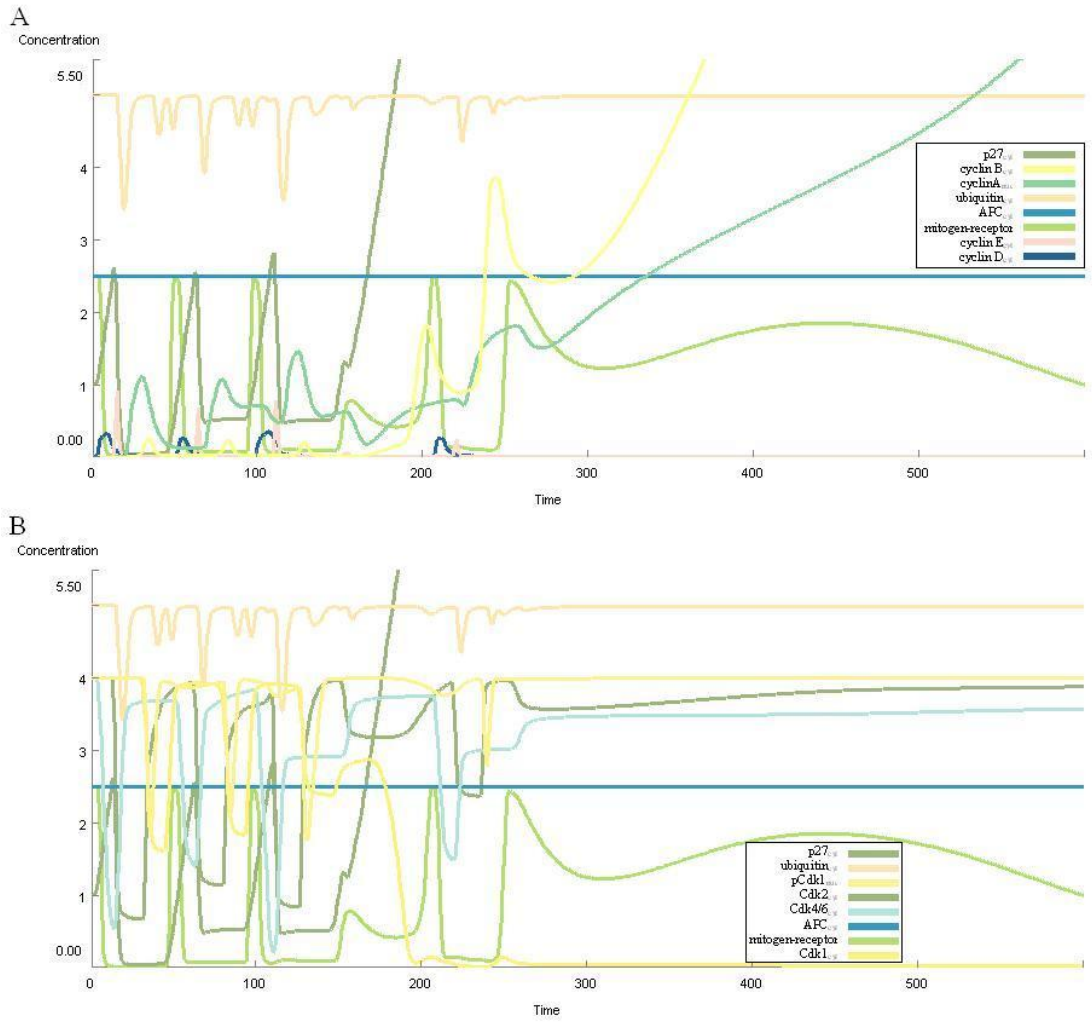

Figure 7: Effects of parameter changes on the concentration courses of ODE model components; A: Concentration courses of the cyclins after decreasing r12_ V_{max} from 2.50 to 1.25 (cytoplasmic transport of mRNA(cyclin D)); B: Concentration courses of the Cdks after increasing r11_V_{max} from 1.01 to 2.02 (cyclin D gene expression); concentration courses of ubiquitin, APC, and the mitogen-receptor complex are displayed for better comparison of the value changes during the simulation; concentration and time are displayed in arbitrary units

Increasing and decreasing the maximal velocity of cyclin D gene expression (r11_V_{max} = 1.01) seems to change the oscillating behaviour of the regulated network in a similar manner. Thereby, small changes (0.5* r11_V_{max}; 2* r11_V_{max}) allow just one correct completed cell cycle round, followed by chaotic behaviour and a steady state for all ODE model compounds, with exception of p27 and cyclin B, which accumulate in the cytoplasm. Bigger changes (0.1* r11_V_{max}; 10* r11_V_{max}) inhibit cell cycle progression completely and the system only shows chaotic behaviour before reaching the steady state, except for p27, (see figure 7B) and, in case of highly increasing r11_V_{max}, cyclin B. Changing the maximal velocities of the transport of mRNA(cyclin D) to the cytoplasm (r12_V_{max} = 2.50) and the translation of mRNA(cyclin D) into cyclin D (r13_V_{max} = 2.50) inhibits cell cycle progression in a similar manner, but not as strong as does changing r11_V_{max}. Additionally to cytoplasmic p27 and cyclin B partially cyclin A does not reach a steady state either, but accumulates in the nucleus (see figure 7A). Increasing the k_{50} values of all three reactions involved in cyclin D protein synthesis has an inhibitory effect on the cell

cycle progression stronger than decreasing them, but both debases the oscillating network behaviour perceptibly. Changing the k_{50} values of the reactions involved in cyclin D synthesis (r11_ k_{50} = 0.50; r12_ k_{50} = 0.50; r13_ k_{50} = 0.50) results – if at all – in two completed cell cycle rounds before reaching the steady state, with exception of p27 and in parts cyclin A or cyclin B. Reducing the Hill coefficient n of cyclin D gene expression (r11_n = 2.00) inhibits cell cycle progression after the second cell cycle round at the latest, when the system compounds, with exception of cytoplasmic p27, and in case of small changes, nuclear cyclin A, reach a steady state. Increasing r11_n only allows one completed cell cycle round before reaching the steady state, with exception of p27. If the Hill coefficients n of the other two reactions involved in cyclin D synthesis (r12_n = 2.00; r13_n = 2.00) are decreased to 1.00, the system's behaviour is inhibited twice as strong as if they are increased, but in all cases the general network behaviour – compared to that after the parameter adaptation – worsened.

Either the whole system depends in greater consequence on cyclin D synthesis than on p27 synthesis or in general the parameters involved in cyclin D synthesis regulation are better adapted than those involved in p27 synthesis, because small changes in parameter values, in general, have a greater negative consequence on the behaviour of the whole system.

Changing Parameters Involved in the Regulation of Cyclin E Synthesis

Cyclin E gene expression essentially is activated through the DP-E2F-pRb complex after the initial phosphorylation of Rb and inhibited by active nuclear cyclin E-pCdk2 complexes. If the parameters regulating the activation of cyclin E gene expression (r20_k_{a50} = 0.525; r20_n_a = 4.00) are increased, cell cycle progression is inhibited and the regulated network components, with exception of p27 in case of changing r20_n_a, reach a steady state faster than with unchanged parameters. If r20_k_{a50} is increased, additionally to p27, cyclins B and E, and for bigger changes even nuclear mRNA(cyclin E) do not reach a steady state. Already a small decrease of r20_k_{a50} results in chaotic oscillating behaviour followed by a steady state, with exception of p27. Greater changes completely inhibit cell cycle progression, which means after some concentration changes the system compounds, with exception of p27, reach a steady state. Reducing r20_n_a to its half worsens the general oscillating behaviour, while reducing it to one tenth results in an unsolvable differential equations system. Changing the parameters regulating the inhibition assures two correctly completed cell cycle rounds at the most before all model components, with exception of p27, and in case of increased parameters, cyclin B, reach a steady state (see figure 8B). An increase as well as a decrease of the maximal velocity of cyclin E gene expression results in a strong inhibition of the oscillating network behaviour, i.e. in less completed cell cycle rounds, followed by a steady state, except for p27, cyclin B, and cyclin A or E, respectively, depending on the direction of the value change. Decreasing the maximal velocities of the transport of mRNA(cyclin E) to the cytoplasm (r21_V_{max} = 2.00) and the translation of mRNA(cyclin E) (r22_V_{max} = 2.00) results in chaotic courses of compound concentrations, followed by a steady state for all ODE model components, with exception of p27, while increasing them inhibits cell cycle progression after the second cell cycle round at the latest. Changing the k_{50} value of cyclin E gene expression (r20_k_{50} = 0.50) causes that the system components, after maximal two completed cell cycle rounds, reach a steady state, with exception of p27 in case of decreasing, and additionally cyclin A or B, respectively, in case of increasing r20_ k_{50}. If the k_{50} values of mRNA transport to the

cytoplasm (r21_ k_{50} = 0.40) and of mRNA translation (r22_ k_{50} = 0.40) are decreased, the regulatory network compounds, with exception of p27, reach a steady state after completion of one slow cell cycle round. If r21_ k_{50} and r22_ k_{50} are increased the steady state is reached, with exception of p27 and, in case of the mRNA transport, cyclin B, after one cell cycle round and some additional chaotic concentration changes (see figure 8A). Changing the Hill coefficient n of cyclin E gene expression (r20_n = 4.00) in either direction inhibits cell cycle progression after one completed cell cycle round, while changing the Hill coefficients of mRNA transport (r21_n = 2.00) and mRNA translation (r22_n = 4.00) results in a maximum of three completed cell cycle rounds. Afterwards, all cell cycle components, with exception of p27, reach a steady state.

Similar to cyclin D synthesis, the parameters involved in cyclin E synthesis seem to be adapted quite well and are rate-limiting for the cell cycle progression, because small parameter changes in either direction already debase the oscillating behaviour of the simulated network.

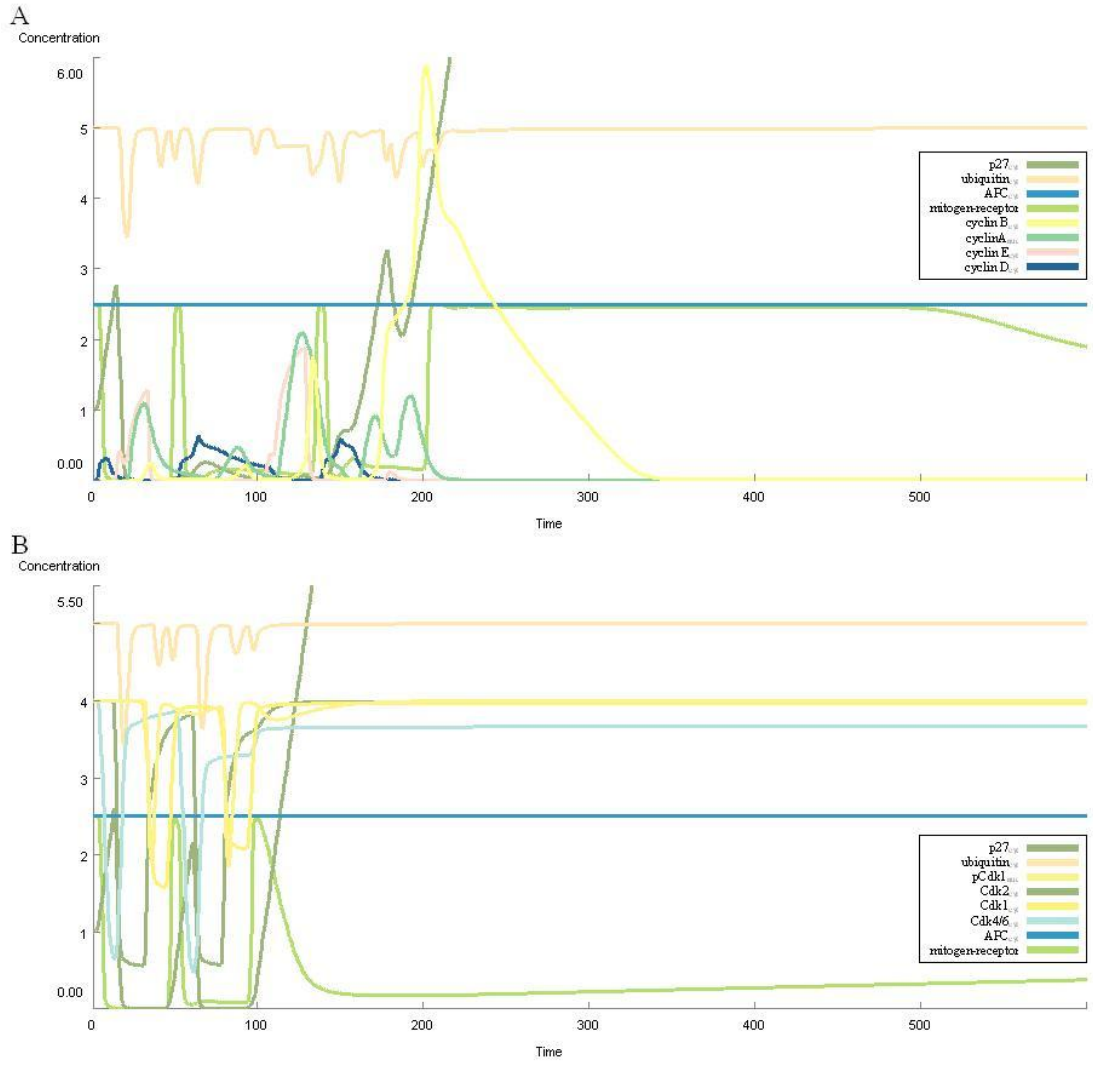

Figure 8: Effects of parameter changes on the concentration courses of ODE model components; A: Concentration courses of the cyclins after increasing r21_ k_{50} from 0.40 to 4.00 (cytoplasmic transport of mRNA(cyclin E)); B: Concentration courses of the Cdks after decreasing r20_n_i from 2.00 to 1.00 (cyclin E gene expression); concentration courses of ubiquitin, APC, and the mitogen-receptor complex are displayed for better comparison of the value changes during the simulation; concentration and time are displayed in arbitrary units

Changing Parameters Involved in the Regulation of Cyclin A Synthesis

Cyclin A gene expression essentially is activated by the active DP-E2F heterodimer after its release from Rb inhibition. Changing the parameters regulating this activation ($r39\_k_{a50}$ = 0.50 and $r39\_n_a$ = 4.00) has a great influence on the behaviour of the whole system. Increasing one of these two parameters results in less completed cell cycle rounds, after which the components of the regulatory network, with exception of p27 and different additional compounds like cyclin A and mRNA(cyclin A), in case of increasing $r39\_k_{a50}$ (see figure 9A), and cyclin B, in case of increasing $r39\_n_a$, reach a steady state. Decreasing $r39\_k_{a50}$ produces chaotic or no oscillating behaviour. In case of very small $r39\_k_{a50}$ values the whole network reaches a steady state approximately after G1 phase. If $r39\_n_a$ is decreased below 1.00, there is no simulation possible at all, because the differential equations system becomes unsolvable, while reducing $r39\_n_a$ to 2.00 inhibits cell cycle progression after the third round, after which the system compounds, with exception of p27, reach a steady state. If the maximal velocity of cyclin A gene expression ($r39\_V_{max}$ = 0.345) is decreased, the system shows abnormal oscillating behaviour, switching to a steady state, except for p27 and cyclin B. If $r39\_V_{max}$ is increased, the system shows oscillations similar to the cell cycle for four rounds, followed by a steady state, with exception of p27, cyclin A, and in case of a big increase, additionally the mRNA(cyclin A). Changing the maximal velocities of mRNA(cyclin A) transport to the cytoplasm ($r40\_V_{max}$ =1.00) and of transcription of mRNA(cyclin A) into cyclin A protein ($r41\_V_{max}$ =1.00) has no effect on the system's behaviour as strong as has changing $r39\_V_{max}$, but both results in less completed cell cycle rounds than when simulating the system with the parameters found with the parameter adaptation (see figure 9B). If the k_{50} value of cyclin A gene expression ($r39\_k_{50}$ = 0.65) is decreased or doubled, the simulated network is able to complete four cell cycle rounds before, with exception of cytoplasmic p27, all model components reach a steady state. If $r39\_k_{50}$ is increased tenfold, the whole system reaches a steady state without former oscillations. Changing the k_{50} value of mRNA(cyclin A) transport ($r40\_k_{50}$ = 1.00) results in three completed cell cycle rounds at the most, followed by a steady state, with exception of p27 and cyclin A or B respectively, depending on the direction of the parameter change. Changes of $r41\_k_{50}$ (= 0.50) result in similar, but not as strong cell cycle inhibition and a steady state, with exception of p27 and cyclin B. The Hill coefficient n of cyclin A gene expression (r39_n = 4.00) seems to be rate-limiting, and thus very important for the behaviour of the whole system, because small changes in either direction already result in less completed cell cycle rounds, followed by a steady state for the system compounds, with exception of p27. Reducing the Hill coefficients of mRNA(cyclin A) transport (r40_n = 4.00) and transcription (r41_n = 4.00) to the half of their original value, allows four completed cell cycle rounds before reaching the steady state, while increasing them diminishes the number of completed cell cycle rounds with a linear effect. Finally, the system components, with exception of p27, and, additionally, in case of tenfold increase of r41_n cyclins A and B, reach a steady state.

As for cyclins D and E, all parameter changes undertaken in reactions involved in cyclin A synthesis had negative consequences on the general behaviour of the simulated network, i.e. fewer cell cycle rounds are completed and sometimes, additional to p27, some other components do not converge to a steady state. Thus, cyclin A synthesis is rate limiting for cell cycle progression.

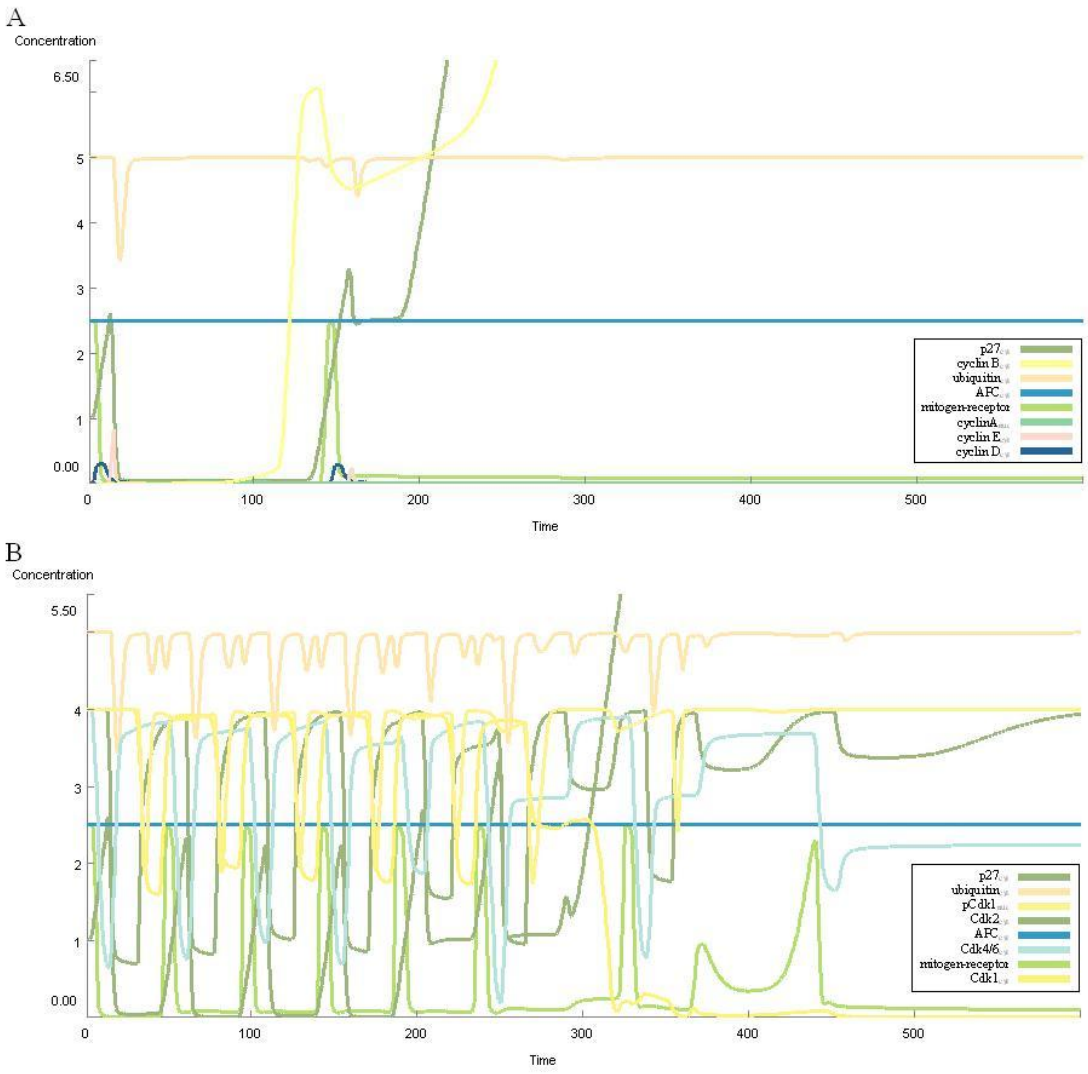

Figure 9: Effects of parameter changes on the concentration courses of ODE model components; A: Concentration courses of the cyclins after decreasing r39_ ka_{50} from 0.50 to 0.25 (cyclin A gene expression); B: Concentration courses of the Cdks after increasing r41_V_{max} from 1.00 to 10.00 (transcription of mRNA(cyclin A)); concentration courses of ubiquitin, APC, and the mitogen-receptor complex are displayed for better comparison of the value changes during the simulation; concentration and time are displayed in arbitrary units

Changing Parameters Involved in the Regulation of Cyclin B Synthesis

DP-pE2F phosphorylated by cyclin A-pCdk2 essentially activates cyclin B gene transcription. The parameters regulating this activation (r50_k_{a50} = 0.50 and r50_n_a = 1.00), therefore, are supposed to have important influence on the behaviour of the simulated network. Decreasing r50_k_{a50} results in a strong inhibition of cell cycle progression, i.e. only for small value changes at the most one cell cycle round can be completed before the system components, with exception of p27 and cyclin B, reach a steady state, while for larger changes there is no oscillation at all and the whole system switches into a steady state. Increasing r50_k_{a50} results in oscillations similar to those of cell cycle, followed by a steady state, with exception of p27. If r50_n_a is reduced, there is no simulation possible at all, while increasing it inhibits cell cycle oscillation at the latest after two completed cell cycle rounds. A small decrease of the maximal velocity of cyclin B gene expression (r50_V_{max} = 0.70) already has a strong inhibitory effect on the cell cycle progression (see figure 10A). Reducing it to a tenth

of its original value inhibits cell cycle progression completely, which happens approximately after G2 phase.

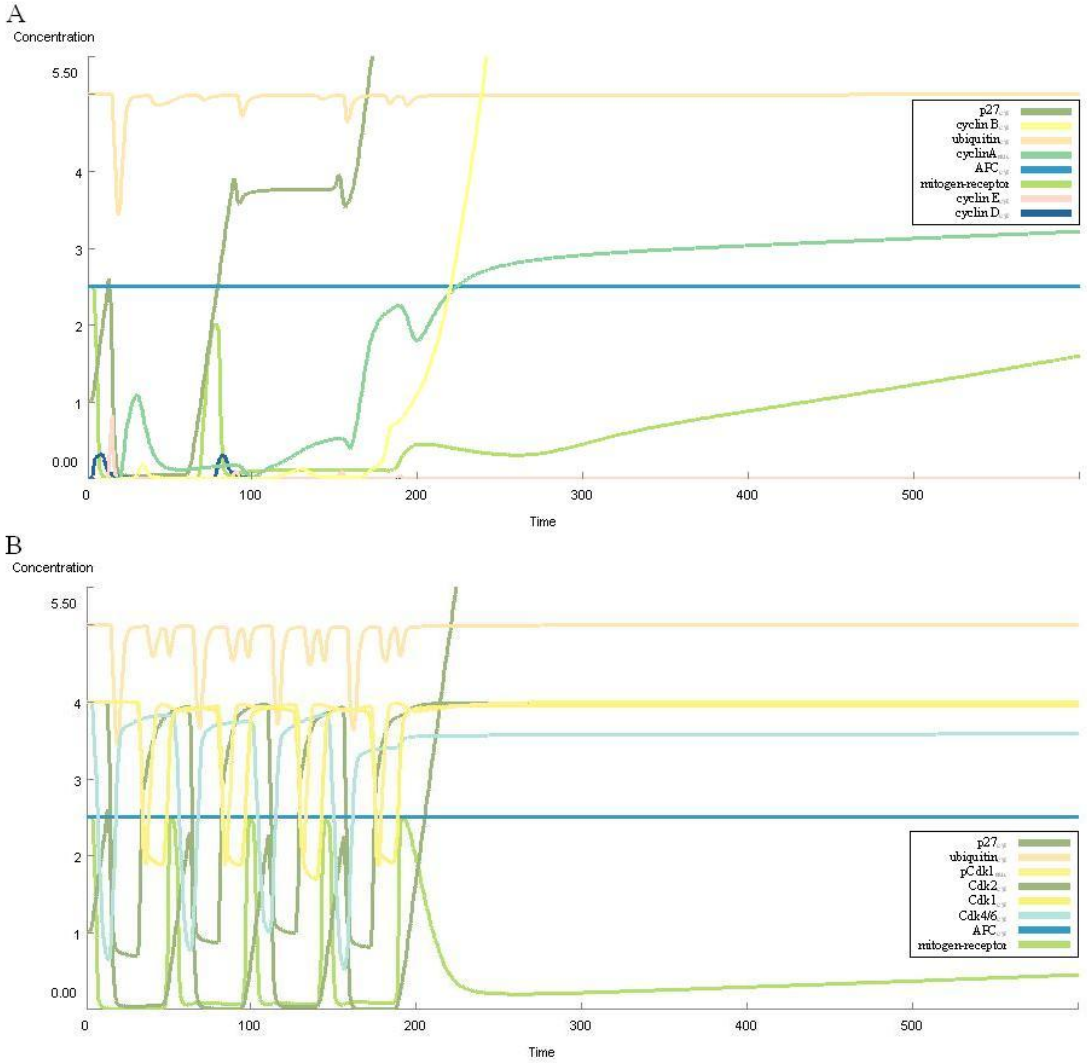

Figure 10: Effects of parameter changes on the concentration courses of ODE model components; A: Concentration courses of the cyclins after decreasing r50_ V_{max} from 0.70 to 0.35 (cyclin B gene expression); B: concentration courses of the Cdks after increasing r55_n from 1.00 to 10.00 (transcription of mRNA(cyclin B)); Concentration courses of ubiquitin, APC, and the mitogen-receptor complex are displayed for better comparison of the value changes during the simulation; concentration and time are displayed in arbitrary units

Increasing r50_V_{max} also reduces the number of completed cell cycle rounds, but not as much as it does the decrease. p27 and cyclin B accumulate in the cytoplasm, while all other model components reach a steady state. Increasing the maximal velocities of mRNA(cyclin B) transport to the cytoplasm (r54_V_{max} = 2.00) and of mRNA(cyclin B) translation (r55_V_{max} = 1.00) and reducing them to one half, does not seem to have any noteworthy effect on the network behaviour. Decreasing them to a tenth inhibits cell cycle progression after two completed cell cycle rounds and only p27 does not reach a steady state. If the k_{50} value of cyclin B gene expression (r50_k_{50} = 0.50) is decreased the system compounds, with exception of p27, reach a steady state after four completed cell cycle rounds. Its increase strongly inhibits cell cycle oscillation and with a tenfold bigger k_{50} value the system reaches the steady state approximately after the first G2 phase. Changing the k_{50} values of mRNA transport and transcription (r54_k_{50} = 1.00 and r55_k_{50} = 0.50) barely has an effect on cell cycle progression and,

as after parameter adaptation, p27 and cyclin B do not reach a steady state. Reducing the Hill coefficient n of cyclin B gene transcription (r50_n = 4.00) strongly inhibits cell cycle progression and allows two completed cell cycle rounds at the most before the network converges to a steady state, with exception of p27. If r50_n is increased, the steady state is reached after four completed cell cycle rounds. If the Hill coefficients of mRNA(cyclin B) transport and translation (r54_n = 1.00 and r55_n = 1.00) are decreased, the differential equations system becomes unsolvable, while a small increase does not seem to have any detectable effect on the network behaviour, and a tenfold increase inhibits cell cycle progression after the fourth completed cell cycle round (see figure 10B).

Changing the parameters involved in cyclin B synthesis, in general has negative effects on the oscillating behaviour of the simulated network, too. Therefore, it can be suggested that the reactions involved in cyclin B synthesis and its regulating parameters are rate-limiting for the cell cycle progression of the modelled network.

Summarizing, it can be concluded: All reactions involved in the synthesis of one of the five model compounds newly synthesized in each cell cycle round can almost completely inhibit the desired behaviour of the ODE model of the human cell cycle, i.e. especially these reactions are limiting for the cell cycle progression. The five transcription rates clearly have the greatest influence on cell cycle behaviour.

6. Discussion and Perspectives

The primary goal, creating a semi-quantitative ODE model of the human cell cycle which is able to show oscillating behaviour and, additionally, has properties – already proved by experiments – was completely fulfilled, as the parameter adaptation by trial and error has shown. But it must be denoted that, up to now, the simulation of the ODE model shows oscillating compound concentrations, which are similar, but not really identical, from one cell cycle round to the next and which converge to a steady state, with exception of some proteins, which are expressed continuously. Therefore, it is a primary goal for the future to enhance the parameter adaptation until better oscillating behaviour of the system can be achieved.

Additionally, the control coefficients, omitted here because of limitation of time in this work, should be computed. Afterwards, it would be possible to enlarge the sensitivity analysis because, until now, the results of the sensitivity analysis only give an approximate overview of the importance of the parameters regulating the reactions involved in protein synthesis in this model. The effects of parameter changes and, also, the effects of changing more than one parameter at a time on the behaviour of individual model components or even of the whole system could be computed and analyzed with the help of the control coefficients. To enhance the general behaviour of the network, additional compounds and reversible reactions could be added. Especially the Cdk1 regulators Wee1 and Cdc25 could prove interesting insights into the regulation of the Cdk1 activity. The inclusion of half life, at least for the proteins newly synthesized in each cell cycle round, might result in improved behaviour of the modelled cell cycle network, too. And in order to get a better grasp of the properties of this model a detailed analysis of concentration course and fluxes of the time-dependent simulation could be accomplished.

In general, the developed model gives a survey of the cyclin-Cdk activities at the different phases of the cell cycle and the involvement of the different Rb/E2F

complexes, the CKI p27, and the ubiquitin-proteasome pathway in cell cycle regulation. Because of the unavailability of kinetic data, the human cell cycle gives way to many different possibilities for research. Therefore, one of the main goals when improving this ODE model should be to develop a model displaying well the actual state of information, but fittable against experimental data, that might be available in the future.

Csikász-Nagy and coworkers use bifurcation theory to examine a generic model of eukaryotic cell cycle controls, in order to detect similarities and differences in the dynamical regulation of cell cycle regulation in yeasts, frog eggs, and mammalian cells [87]. The main regulator of cell cycle progression in their model is cell growth, while otherwise the model focuses on cyclin-Cdk interactions, their functions and regulation, comparable to my model, and additionally includes Wee1 and Cdc25. To analyze the influence of cell growth on phase transitions they employed bifurcation diagrams, where the stable steady states correspond to the arrest states in G1, G2, and M phase, and the phase transitions are identified by SNIPER bifurcation points identifying critical cell sizes for leaving an arrest state [87]. (SNIPER bifurcations are resistant properties of nonlinear control systems with both positive and negative feedback and they are very active in achieving a balance between the interdivision time (IDT), i.e. the time the cell needs to progress through one cell cycle round, and mass doubling time (MDT), i.e. the overall cell growth. [87]) Once my model will have been enhanced until it shows real oscillating behaviour, it would be very interesting to examine whether the cell growth can be included and, also, whether with bifurcation theory my model could be analyzed in further detail.

K.C. Chen, et al. developed a molecular model of the budding yeast cell cycle. There they showed that the budding yeast division cycle consists, as predicted by K. Nasmyth [111], of two stable steady states, the G1 and the S/M, which are discontinued through a “Start” transition from G1 to S/M and a “Finish” transition from S/M to G1 [108]. In this model, influence of cell growth and division are involved again, and the checkpoints are symbolized by three “target” variables, ORI (initiation of DNA synthesis), BUD (budding), and SPN (spindle association) [108]. But one of the most interesting characteristics of their model is the mechanism regulating phosphorylation and dephosphorylation events: They use the Goldbetter-Koshland function for ultrasensitive switches [110] to model sigmoidal behaviour. With help of the Goldbetter-Koshland function it is possible to achieve additional sensitivity in biological control, equivalent to that of allosteric proteins with high Hill coefficients, because it functions as an amplification of the response to a stimulus when the modifying enzymes operate outside of first-order kinetics [110]. The modelling of the checkpoints seems very interesting, because it results in a delay before the next cell cycle phase is activated. If additional thresholds – perhaps independent of protein concentrations but only regulated by an ascertained time period, displaying the necessary time for DNA replication, spindle association, chromosome condensation, or even cell growth – have to be reached the network could be able to reach steady states symbolizing the different cell cycle phases. Perhaps, it could be interesting as well to test whether the general network behaviour is advanced, if, for example, phosphorylation and dephosphorylation events were not modelled with the Hill kinetic, as has been done until now, but with the Goldbetter-Koshland function or a similar sigmoidal function.

The used strategy of model development (first: creation of a Boolean model, in order to test whether the expected oscillating behaviour with the included proteins and their respective regulatory interactions is possible at all and, second: transcription of

the Boolean model into an ODE model to include gradual conformation changes and to enable a better temporal resolution of the simulated behaviour) was very successful. Therefore, missing components and reactions could be included in the model before starting the parameter adaptation, and when the Boolean model was showing the expected oscillations and the transcription into the ODE model has been fulfilled only the correct parameters had to be found until the ODE model showed oscillating behaviour, too. When additional compounds have to be included in the model their influence on the general behaviour can be tested first in the Boolean model, and afterwards can be taken over for the ODE model. Although, up to now, this strategy was not applied for other models, I suppose that it can be used for the development of qualitative models for regulatory networks, in general. For example, L. Mendoza and I. Xenarios [109] developed a standardized method for generating qualitative models of regulatory networks. This method is divided into two steps: First, they develop a discrete and second, a continuous system for each network they want to model, which makes their strategy comparable to mine. Additionally, they showed that steady states found with the discrete system hint to the steady states of the continuous system, missing only steady states with a relatively small basin of attraction [109]. In the future, the possibility of trying to generate a model of my cell cycle network with the equations developed by Mendoza and Xenarios [109] would be very interesting. If this is achieved, the resulting behaviour can be analyzed and compared to that resulting from the ODE model presented in this thesis.

7. Appendix A

7.1 Powerpoint Scheme

This scheme was developed in order to obtain a general idea of the compounds I wanted to include in my model of the human cell cycle. Because some mechanisms, for example the Ras-Raf-MEK-ERK signaling cascade, are displayed facilitated, not all reactions of the later ODE model are displayed in this scheme.

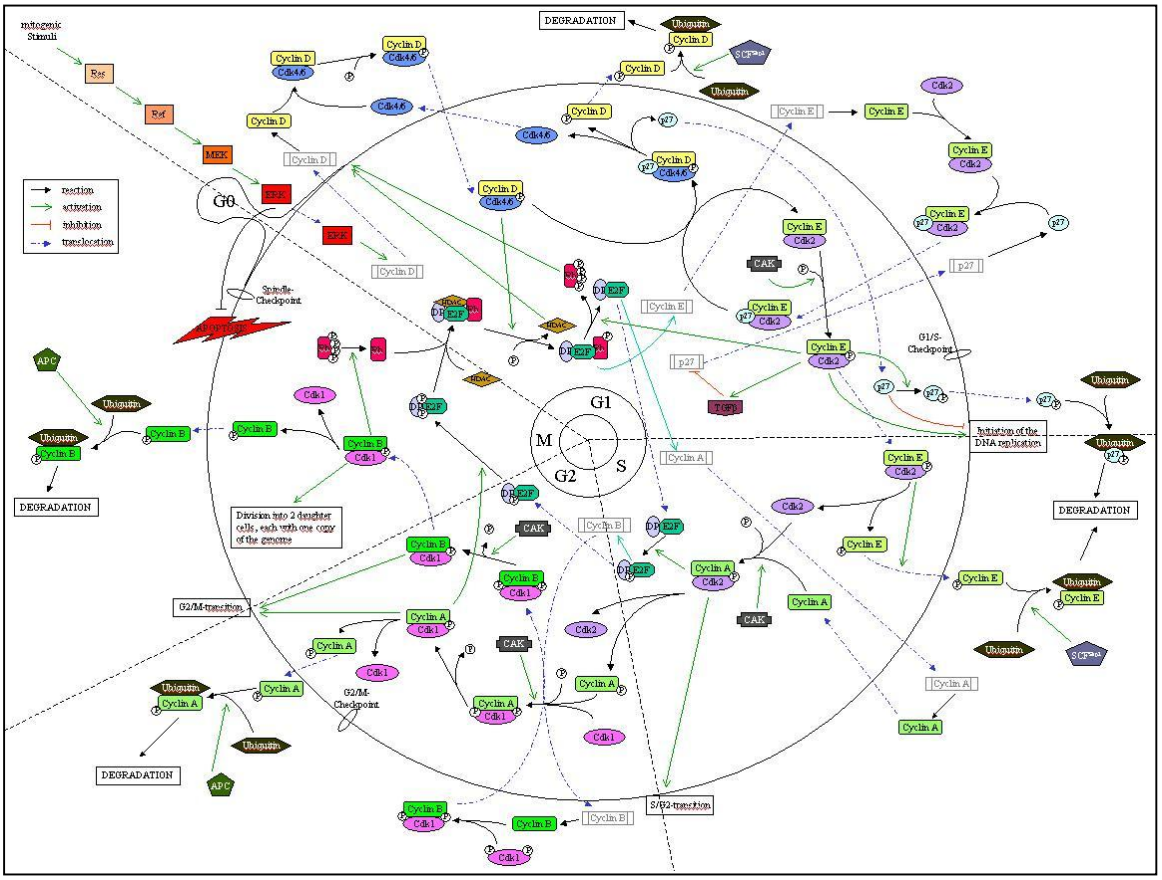

Figure 11: Initial cell cycle scheme, showing all compounds included in the ODE model; developed with Microsoft Powerpoint

7.2 Reactions

$r_0 = \text{TGF-}\beta_{nuc} + \text{p27gene}_{nuc} \rightarrow \text{TGF-}\beta_{nuc} + \text{mRNA(p27)}_{nuc}$
$r_1 = \text{mRNA(p27)}_{nuc} \rightarrow \text{mRNA(p27)}_{cyt}$
$r_2 = \text{mRNA(p27)}_{cyt} \rightarrow \text{p27}_{cyt}$
$r_3 = \text{mitogen-receptor} + \text{Ras}_{cyt} + P \rightarrow \text{mitogen-receptor} + \text{pRas}_{cyt}$
$r_4 = \text{pRas}_{cyt} + \text{Raf}_{cyt} + P \rightarrow \text{pRas}_{cyt} + \text{pRaf}_{cyt}$
$r_5 = \text{pRaf}_{cyt} + \text{MEK}_{cyt} + P \rightarrow \text{pRaf}_{cyt} + \text{pMEK}_{cyt}$
$r_6 = \text{pRas}_{cyt} \rightarrow \text{Ras}_{cyt} + P$
$r_7 = \text{pRaf}_{cyt} \rightarrow \text{Raf}_{cyt} + P$
$r_8 = \text{pMEK}_{cyt} \rightarrow \text{MEK}_{cyt} + P$
$r_9 = \text{pMEK}_{cyt} + \text{ERK}_{cyt} + P \rightarrow \text{pMEK}_{cyt} + \text{pERK}_{cyt}$

r_{10} = $pERK_{cyt}$ → $pERK_{nuc}$

r_{11} = $pERK_{nuc}$ + CyclinD-gene → $pERK_{nuc}$ + CyclinD-gene + $mRNA(CyclinD)_{nuc}$

r_{12} = $mRNA(CyclinD)_{nuc}$ → $mRNA(CyclinD)_{cyt}$

r_{13} = $mRNA(CyclinD)_{cyt}$ → $CyclinD_{cyt}$

r_{14} = $CyclinD_{cyt}$ + $Cdk4/6_{cyt}$ → $(CyclinD\text{-}Cdk4/6)_{cyt}$

r_{15} = CAK_{cyt} + $(CyclinD/Cdk4/6)_{cyt}$ + P → CAK_{cyt} + $(CyclinD\text{-}pCdk4/6)_{cyt}$

r_{16} = $(CyclinD\text{-}pCdk4/6)_{cyt}$ + $Cdk4/6_{cyt}$ → $(CyclinD\text{-}pCdk4/6)_{nuc}$ + $Cdk4/6_{cyt}$

r_{17} = $(CyclinD\text{-}pCdk4/6)_{nuc}$ + $(HDAC\text{-}DP\text{-}E2F\text{-}Rb)_{nuc}$ + P → $(CyclinD\text{-}pCdk4/6)_{nuc}$ + $HDAC_{nuc}$ + $(DP\text{-}E2F\text{-}pRb)_{nuc}$

r_{18} = $(CyclinD\text{-}pCdk4/6)_{nuc}$ + $pERK_{nuc}$ → $(CyclinD\text{-}pCdk4/6)_{nuc}$ + ERK_{nuc} + P

r_{19} = $(CyclinB\text{-}pCdk1)_{nuc}$ + ERK_{nuc} → $(CyclinB\text{-}pCdk1)_{nuc}$ + ERK_{cyt}

r_{20} = $(DP\text{-}E2F\text{-}pRb)_{nuc}$ + CyclinE-gene + $(CyclinE\text{-}pCdk2)_{nuc}$ → $(DP\text{-}E2F\text{-}pRb)_{nuc}$ + CyclinE-gene + $mRNA(CyclinE)_{nuc}$ + $(CyclinE\text{-}pCdk2)_{nuc}$

r_{21} = $mRNA(CyclinE)_{nuc}$ → $mRNA(CyclinE)_{cyt}$

r_{22} = $mRNA(CyclinE)_{cyt}$ → $CyclinE_{cyt}$

r_{23} = $CyclinE_{cyt}$ + $Cdk2_{cyt}$ → $(CyclinE\text{-}Cdk2)_{cyt}$

r_{24} = $(CyclinE\text{-}Cdk2)_{cyt}$ + $p27_{cyt}$ → $(CyclinE\text{-}Cdk2\text{-}p27)_{cyt}$

r_{25} = $(CyclinE\text{-}Cdk2\text{-}p27)_{cyt}$ → $(CyclinE\text{-}Cdk2\text{-}p27)_{nuc}$

r_{26} = $(CyclinE\text{-}Cdk2\text{-}p27)_{nuc}$ + $(CyclinD\text{-}pCdk4/6)_{nuc}$ → $(CyclinE\text{-}Cdk2)_{nuc}$ + $(CyclinD\text{-}pCdk4/6\text{-}p27)_{nuc}$

r_{27} = $(CyclinD\text{-}pCdk4/6\text{-}p27)_{nuc}$ → $Cdk4/6_{nuc}$ + $pCyclinD_{nuc}$ + $p27_{nuc}$

r_{28} = $Cdk4/6_{nuc}$ → $Cdk4/6_{cyt}$

r_{29} = $pCyclinD_{nuc}$ → $pCyclinD_{cyt}$

r_{30} = SCF_{cyt} + $pCyclinD_{cyt}$ + $ubiquitin_{cyt}$ → SCF_{cyt} + $(ubiquitin\text{-}pCyclinD)_{cyt}$

r_{31} = $(ubiquitin\text{-}pCyclinD)_{cyt}$ → DEGRADATION(CyclinD) + $ubiquitin_{cyt}$ + P

r_{32} = CAK_{nuc} + $(CyclinE\text{-}Cdk2)_{nuc}$ + P → CAK_{nuc} + $(CyclinE\text{-}pCdk2)_{nuc}$

r_{33} = $(CyclinE\text{-}pCdk2)_{nuc}$ + $(DP\text{-}E2F\text{-}pRb)_{nuc}$ + hyP → $(CyclinE\text{-}pCdk2)_{nuc}$ + $(DP\text{-}E2F)_{nuc}$ + $hypRb_{nuc}$

r_{34} = $(CyclinE\text{-}pCdk2)_{nuc}$ + $TGF\text{-}\beta_{nuc}$ + P → $(CyclinE\text{-}pCdk2)_{nuc}$ + $pTGF\text{-}\beta_{nuc}$

r_{35} = $(CyclinE\text{-}pCdk2)_{nuc}$ + $p27_{nuc}$ + P → $(CyclinE\text{-}pCdk2)_{nuc}$ + $Pp27_{nuc}$

r_{36} = $Pp27_{nuc}$ → $Pp27_{cyt}$

r_{37} = SCF_{cyt} + $Pp27_{cyt}$ + $ubiquitin_{cyt}$ → SCF_{cyt} + $(ubiquitin\text{-}Pp27)_{cyt}$

r_{38} = $(ubiquitin\text{-}Pp27)_{cyt}$ → DEGRADATION(p27) + $ubiquitin_{cyt}$ + P

r_{39} = $(DP/E2F)_{nuc}$ + CyclinA-gene → $(DP/E2F)_{nuc}$ + CyclinA-gene + $mRNA(CyclinA)_{nuc}$

r_{40} = $mRNA(CyclinA)_{nuc}$ → $mRNA(CyclinA)_{cyt}$

r_{41} = $mRNA(CyclinA)_{cyt}$ → $CyclinA_{cyt}$

r_{42} = $CyclinA_{cyt}$ → $CyclinA_{nuc}$

r_{43} = $(CyclinE\text{-}pCdk2)_{nuc}$ + $p27_{nuc}$ → $pCyclinE_{nuc}$ + $Cdk2_{nuc}$ + $p27_{nuc}$

r_{44} = $(CyclinE\text{-}pCdk2)_{nuc}$ + $pCyclinE_{nuc}$ → $(CyclinE\text{-}pCdk2)_{nuc}$ + $pCyclinE_{cyt}$

r_{45} = SCF_{cyt} + $pCyclinE_{cyt}$ + $ubiquitin_{cyt}$ → SCF_{cyt} + $(ubiquitin\text{-}pCyclinE)_{cyt}$

r_{46} = $(ubiquitin\text{-}pCyclinE)_{cyt}$ → DEGRADATION(CyclinE) + $ubiquitin_{cyt}$ + P

r_{47} = $CyclinA_{nuc}$ + $Cdk2_{nuc}$ + $(CyclinE\text{-}pCdk2)_{nuc}$ → $(CyclinA\text{-}Cdk2)_{nuc}$ + $(CyclinE\text{-}pCdk2)_{nuc}$

r_{48} = CAK_{nuc} + $(CyclinA\text{-}Cdk2)_{nuc}$ + P → CAK_{nuc} + $(CyclinA\text{-}pCdk2)_{nuc}$

r_{49} = $(CyclinA\text{-}pCdk2)_{nuc}$ + $(DP\text{-}E2F)_{nuc}$ + P → $(CyclinA\text{-}pCdk2)_{nuc}$ + $(DP\text{-}pE2F)_{nuc}$

r_{50} = $(DP\text{-}pE2F)_{nuc}$ + CyclinB-gene → $(DP\text{-}pE2F)_{nuc}$ + CyclinB-gene + $mRNA(CyclinB)_{nuc}$

r_{51} = $(CyclinA\text{-}pCdk2)_{nuc}$ + P → $p_xCyclinA_{nuc}$ + $pCdk2_{nuc}$

r_{52} = $pCdk2_{nuc}$ → $pCdk2_{cyt}$

r_{53} = $pCdk2_{cyt}$ → $Cdk2_{cyt}$ + P

r_{54} = $mRNA(CyclinB)_{nuc}$ → $mRNA(CyclinB)_{cyt}$
r_{55} = $mRNA(CyclinB)_{cyt}$ → $CyclinB_{cyt}$
r_{56} = CAK_{cyt} + $CyclinB_{cyt}$ + $Cdk1_{cyt}$ → CAK_{cyt} + $(CyclinB\text{-}ppCdk1)_{cyt}$
r_{57} = $(CyclinA\text{-}pCdk1)_{nuc}$ + $(CyclinB\text{-}ppCdk1)_{cyt}$ → $(CyclinA\text{-}pCdk1)_{nuc}$ + $(CyclinB\text{-}ppCdk1)_{nuc}$
r_{58} = CAK_{nuc} + $p_xCyclinA_{nuc}$ + $pCdk1_{nuc}$ → CAK_{nuc} + $(CyclinA\text{-}ppCdk1)_{nuc}$
r_{59} = $(CyclinA\text{-}ppCdk1)_{nuc}$ → $(CyclinA\text{-}pCdk1)_{nuc}$ + P
r_{60} = $(CyclinB\text{-}ppCdk1)_{nuc}$ + $(CyclinA\text{-}pCdk1)_{nuc}$ → $(CyclinB\text{-}pCdk1)_{nuc}$ + $(CyclinA\text{-}pCdk1)_{nuc}$
r_{61} = $(CyclinB\text{-}ppCdk1)_{nuc}$ + $(CyclinA\text{-}pCdk1)_{nuc}$ + P → $(CyclinB\text{-}ppCdk1)_{nuc}$ + $pCyclinA_{nuc}$ + $pCdk1_{nuc}$
r_{62} = $pCyclinA_{nuc}$ → $pCyclinA_{cyt}$
r_{63} = APC_{cyt} + $pCyclinA_{cyt}$ + $ubiquitin_{cyt}$ → APC_{cyt} + $(ubiquitin\text{-}pCyclinA)_{cyt}$
r_{64} = $(ubiquitin\text{-}pCyclinA)_{cyt}$ → DEGRADATION(CyclinA) + $ubiquitin_{cyt}$ + P
r_{65} = $(CyclinA\text{-}pCdk1)_{nuc}$ + $(DP\text{-}pE2F)_{nuc}$ + P → $(CyclinA\text{-}pCdk1)_{nuc}$ + $(pDP\text{-}pE2F)_{nuc}$
r_{66} = $(CyclinB\text{-}pCdk1)_{nuc}$ + $hypRb_{nuc}$ → $(CyclinB\text{-}pCdk1)_{nuc}$ + Rb_{nuc} + hyP
r_{67} = $(CyclinB\text{-}pCdk1)_{nuc}$ + $pTGF\text{-}\beta_{nuc}$ → $(CyclinB\text{-}pCdk1)_{nuc}$ + $TGF\text{-}\beta_{nuc}$ + P
r_{68} = Rb_{nuc} + $HDAC_{nuc}$ + $(pDP\text{-}pE2F)_{nuc}$ → $(HDAC\text{-}DP\text{-}E2F\text{-}Rb)_{nuc}$ + 2P
r_{69} = $(CyclinB\text{-}pCdk1)_{nuc}$ + $pTGF\text{-}\beta_{nuc}(inhibitor)$ → $pCyclinB_{nuc}$ + $Cdk1_{nuc}$ + $pTGF\text{-}\beta_{nuc}(inhibitor)$
r_{70} = $Cdk1_{nuc}$ → $Cdk1_{cyt}$
r_{71} = $pCyclinB_{nuc}$ + $(CyclinB\text{-}pCdk1)_{nuc}$ → $pCyclinB_{cyt}$ + $(CyclinB\text{-}pCdk1)_{nuc}$
r_{72} = APC_{cyt} + $pCyclinB_{cyt}$ + $ubiquitin_{cyt}$ → APC_{cyt} + $(ubiquitin\text{-}pCyclinB)_{cyt}$
r_{73} = $(ubiquitin\text{-}pCyclinB)_{cyt}$ → DEGRADATION(CyclinB) + $ubiquitin_{cyt}$ + P
r_{74a} = $(CyclinD\text{-}pCdk4o6)_{cyt}$ + mitogen-receptor → $(CyclinD\text{-}pCdk4o6)_{cyt}$ + inact-mitogen-receptor
r_{75a} = $(ubiquitin\text{-}pCyclinB)_{cyt}$ + inact-mitogen-receptor → $(ubiquitin\text{-}pCyclinD)_{cyt}$ + mitogen-receptor
r_{74b} = $(CyclinD\text{-}pCdk4o6)_{cyt}$ + mitogen-receptor → $(CyclinD\text{-}pCdk4o6)_{cyt}$ + mitogen + inact-receptor
r_{75b} = $(ubiquitin\text{-}pCyclinB)_{cyt}$ + inact-receptor → $(ubiquitin\text{-}pCyclinD)_{cyt}$ + receptor
r_{76} = receptor + mitogen → mitogen-receptor

Table 2: Reactions included in the ODE model ; activators are highlighted in green, inhibitors in pink, and reaction which are not based on literature information and included in the model only to reset the system between two cell cycle rounds, in orange

7.3 Boolean Conditions

The Boolean conditions were used to build up the Boolean matrix (see appendix B 8.3). As one can see in table 3 there are two different mitogen-receptor complexes, mitogen-receptor1 and 2. After the first part of the parameter adaptation (one cell cycle round) I included a delay in reactivation of the mitogen receptor complex, i.e. I changed the way it is inhibited from simply inactivating the complex to a dissociation of the mitogen from the receptor via an inactivation of the receptor mediated by nuclear pERK. In the ODE model the inactivation is mediated by cytoplasmic cyclin D-pCdk4/6 complexes (see appendix A, 7.5, figure 12 & 7.2, table 2). Reactivation of the inactive receptor, as in case of the inactive mitogen-receptor complex, is mediated by the ubiquitin-pCyclin B complex and enables new docking of the mitogen to the receptor. If the dependency of Ras and pRas are switched from mitogen-receptor1

complex to mitogen-receptor2 complex, the second cell cycle round in the Boolean matrix is delayed for one arbitrary time step, but the general behaviour of the regulated network is the same.

mitogen-receptor1(t+1)	IF (mitogen-receptor1(t) AND NOT($pERK_{nuc}$(t))) OR (($ubiquitin\text{-}pCyclinB)_{cyt}$(t) AND inact-mitogen-receptor(t))
inact-mitogen-receptor(t+1)	IF (mitogen-receptor1(t) AND $pERK_{nuc}$(t)) OR (NOT(($ubiquitin\text{-}pCyclinB)_{cyt}$(t)) AND inact-mitogen-receptor(t))
mitogen-receptor2(t+1)	IF (mitogen-receptor2(t) AND NOT($pERK_{nuc}$(t))) OR (mitogen(t) AND receptor(t))
inact-receptor(t+1)	IF (mitogen-receptor2(t) AND $pERK_{nuc}$(t)) OR (NOT(($ubiquitin\text{-}pCyclinB)_{cyt}$(t)) AND inact-receptor(t))
receptor(t+1)	IF (($ubiquitin\text{-}pCyclinB)_{cyt}$(t)) AND inact-receptor(t))
mitogen(t+1)	IF (mitogen-receptor2(t) AND $pERK_{nuc}$(t)) OR (mitogen(t) AND NOT(receptor(t)))
Ras_{cyt}(t+1)	IF (NOT(mitogen-receptor(t) AND Ras_{cyt}(t)) OR $pRas_{cyt}$(t)
$pRas_{cyt}$(t+1)	IF mitogen-receptor(t) AND Ras_{cyt}(t)
Raf_{cyt}(t+1)	IF (NOT($pRas_{cyt}$(t) AND Raf_{cyt}(t)) OR $pRaf_{cyt}$(t)
$pRaf_{cyt}$(t+1)	IF $pRas_{cyt}$(t) AND Raf_{cyt}(t)
MEK_{cyt}(t+1)	IF (NOT($pRaf_{cyt}$(t) AND MEK_{cyt}(t)) OR $pMEK_{cyt}$(t)
$pMEK_{cyt}$(t+1)	IF $pRaf_{cyt}$(t) AND MEK_{cyt}(t)
ERK_{cyt}(t+1)	IF (NOT($pMEK_{cyt}$(t) AND Ras_{cyt}(t)) OR $pRas_{cyt}$(t)
ERK_{nuc}(t+1)	IF $pERK_{nuc}$(t-1) AND $pERK_{nuc}$(t)
$pERK_{cyt}$(t+1)	IF $pMEK_{cyt}$(t) AND ERK_{cyt}(t)
$pERK_{nuc}$(t+1)	IF $pERK_{cyt}$(t) OR (NOT($pERK_{nuc}$(t-1) AND $pERK_{nuc}$(t))
SCF_{cyt}(t+1)	IF SCF_{cyt}(t)
APC_{cyt}(t+1)	IF APC_{cyt}(t)
CAK_{nuc}(t+1)	IF CAK_{nuc}(t)
CAK_{cyt}(t+1)	IF CAK_{cyt}(t)
$CyclinA_{cyt}$(t+1)	IF $mRNA(CyclinA)_{cyt}$(t)
$CyclinA_{nuc}$(t+1)	IF $CyclinA_{cyt}$(t)
$CyclinB_{cyt}$(t+1)	IF $mRNA(CyclinB)_{cyt}$(t)
$CyclinD_{cyt}$(t+1)	IF $mRNA(CyclinD)_{cyt}$(t)
$CyclinE_{cyt}$(t+1)	IF $mRNA(CyclinE)_{cyt}$(t)
$mRNA(CyclinA)_{nuc}$(t+1)	IF NOT($(DP\text{-}E2F)_{nuc}$(t-1)) AND $(DP\text{-}E2F)_{nuc}$(t)
$mRNA(CyclinA)_{cyt}$(t+1)	IF $mRNA(CyclinA)_{nuc}$(t)
$mRNA(CyclinB)_{nuc}$(t+1)	IF NOT($(pDP\text{-}E2F)_{nuc}$(t-1)) AND $(pDP\text{-}E2F)_{nuc}$(t)
$mRNA(CyclinB)_{cyt}$(t+1)	IF $mRNA(CyclinB)_{nuc}$(t)
$mRNA(CyclinD)_{nuc}$(t+1)	IF NOT($pERK_{nuc}$(t-1)) AND $pERK_{nuc}$(t)
$mRNA(CyclinD)_{cyt}$(t+1)	IF $mRNA(CyclinD)_{nuc}$(t)
$mRNA(CyclinE)_{nuc}$(t+1)	IF NOT($(DP\text{-}E2F\text{-}pRb)_{nuc}$(t-1)) AND $(DP\text{-}E2F\text{-}pRb)_{nuc}$(t)
$mRNA(CyclinE)_{cyt}$(t+1)	IF $mRNA(CyclinE)_{nuc}$(t)

$mRNA(p27)_{nuc}(t+1)$	IF $((mRNA(p27)_{nuc}(t-1))$ AND $TGF\text{-}\beta_{nuc}(t))$ OR $(NOT(mRNA(p27)_{nuc}(t-1))$ AND $NOT(pTGF\text{-}\beta_{nuc}(t)))$
$mRNA(p27)_{cyt}(t+1)$	IF $mRNA(p27)_{nuc}(t)$
$pCyclinA_{cyt}(t+1)$	IF $pCyclinA_{nuc}(t)$
$pCyclinA_{nuc}(t+1)$	IF $(CyclinA\text{-}pCdk1)_{nuc}(t)$ AND $(CyclinB\text{-}pCdk1)_{nuc}(t)$
$p_xCyclinA_{nuc}(t+1)$	IF $(pDP\text{-}E2F)_{nuc}(t)$ AND $(CyclinA\text{-}pCdk2)_{nuc}(t)$
$pCyclinB_{cyt}(t+1)$	IF $pCyclinB_{nuc}(t)$
$pCyclinB_{nuc}(t+1)$	IF $(CyclinB\text{-}pCdk1)_{cyt}(t)$ AND $(HDAC\text{-}DP\text{-}E2F\text{-}Rb)_{nuc}(t)$
$pCyclinD_{cyt}(t+1)$	IF $pCyclinD_{nuc}(t)$
$pCyclinD_{nuc}(t+1)$	IF $(CyclinD\text{-}pCdk4/6)_{nuc}(t)$
$pCyclinE_{cyt}(t+1)$	IF $pCyclinE_{nuc}(t)$
$pCyclinE_{nuc}(t+1)$	IF $Pp27_{nuc}(t)$ AND $(CyclinA\text{-}pCdk2)_{nuc}(t)$
$Cdk1_{cyt}(t+1)$	IF $(Cdk1_{cyt}(t)$ AND $NOT(CyclinB_{cyt}(t)))$ OR $Cdk1_{nuc}(t)$
$Cdk1_{nuc}(t+1)$	IF $(CyclinB\text{-}pCdk1)_{cyt}(t)$ AND $(HDAC\text{-}DP\text{-}E2F\text{-}Rb)_{nuc}(t)$
$pCdk1_{nuc}(t+1)$	IF $(NOT(p_xCyclinA_{nuc}(t))$ AND $pCdk1_{nuc}(t))$ OR $((CyclinA\text{-}pCdk1)_{nuc}(t)$ AND $(CyclinB\text{-}ppCdk1)_{nuc}(t))$
$Cdk2_{cyt}(t+1)$	IF $(NOT(CyclinE_{cyt}(t))$ AND $Cdk2_{cyt}(t))$ OR $pCdk2_{cyt}(t)$
$pCdk2_{cyt}(t+1)$	IF $pCdk2_{nuc}(t)$
$Cdk2_{nuc}(t+1)$	IF $(Pp27_{nuc}(t)$ AND $(CyclinE\text{-}pCdk2)_{nuc}(t))$ OR $(NOT(CyclinA_{nuc}(t))$ AND $Cdk2_{nuc}(t))$
$pCdk2_{nuc}(t+1)$	IF $(DP\text{-}pE2F)_{nuc}(t)$ AND $(CyclinA\text{-}pCdk2)_{nuc}(t)$
$Cdk4/6_{cyt}(t+1)$	IF $(NOT(CyclinD_{cyt}(t))$ AND $Cdk4/6_{cyt}(t))$ OR $Cdk4/6_{nuc}(t)$
$Cdk4/6_{nuc}(t+1)$	IF $(CyclinD\text{-}pCdk4/6\text{-}p27)_{nuc}(t)$
$Rb_{nuc}(t+1)$	IF $hypRb_{nuc}(t)$ AND $(CyclinB\text{-}pCdk1)_{cyt}(t)$
$hypRb_{nuc}(t+1)$	IF $((DP\text{-}E2F\text{-}pRb)_{nuc}(t)$ AND $(CyclinE\text{-}pCdk2)_{nuc}(t))$ OR $(hypRb_{nuc}(t)$ AND $NOT((CyclinB\text{-}pCdk1)_{cyt}(t)))$
$(DP\text{-}E2F)_{nuc}(t+1)$	IF $((DP\text{-}E2F\text{-}pRb)_{nuc}(t)$ AND $(CyclinE\text{-}pCdk2)_{nuc}(t))$ OR $((DP\text{-}E2F)_{nuc}(t)$ AND $NOT((CyclinA\text{-}pCdk2)_{nuc}(t)))$
$(DP\text{-}pE2F)_{nuc}(t+1)$	IF $((DP\text{-}E2F)_{nuc}(t)$ AND $(CyclinA\text{-}pCdk2)_{nuc}(t))$ OR $((DP\text{-}pE2F)_{nuc}(t)$ AND $NOT((CyclinA\text{-}pCdk1)_{nuc}(t)))$
$(pDP\text{-}pE2F)_{nuc}(t+1)$	IF $((DP\text{-}pE2F)_{nuc}(t)$ AND $(CyclinA\text{-}pCdk1)_{nuc}(t))$ OR $((pDP\text{-}pE2F)_{nuc}(t)$ AND $NOT((Rb)_{nuc}(t)))$
$(DP\text{-}E2F\text{-}pRb)_{nuc}(t+1)$	IF $((HDAC\text{-}DP\text{-}E2F\text{-}pRb)_{nuc}(t)$ AND $(CyclinD\text{-}pCdk4/6)_{nuc}(t))$ OR $((DP\text{-}E2F\text{-}pRb)_{nuc}(t)$ AND $NOT((CyclinE\text{-}pCdk2)_{nuc}(t)))$
$HDAC_{nuc}(t+1)$	IF $((HDAC\text{-}DP\text{-}E2F\text{-}pRb)_{nuc}(t)$ AND $(CyclinD\text{-}pCdk4/6)_{nuc}(t))$ OR $(HDAC_{nuc}(t)$ AND $(NOT(Rb_{nuc}(t))$ OR $(pDP\text{-}pE2F)_{nuc}(t)))$
$(HDAC\text{-}DP\text{-}E2F\text{-}pRb)_{nuc}(t+1)$	IF $((HDAC\text{-}DP\text{-}E2F\text{-}pRb)_{nuc}(t)$ AND $NOT((CyclinD\text{-}pCdk4/6)_{nuc}(t)))$ OR $(Rb_{nuc}(t)$ AND $(pDP\text{-}pE2F)_{nuc}(t)$ AND $HDAC_{nuc}(t))$
$p27_{cyt}(t+1)$	IF $mRNA(p27)_{cyt}(t)$

$p27_{nuc}(t+1)$	IF $(CyclinD\text{-}pCdk4/6\text{-}p27)_{nuc}(t)$ OR ($p27_{nuc}(t)$ AND NOT($(CyclinE\text{-}pCdk2)_{nuc}(t)$))
$Pp27_{cyt}(t+1)$	IF $Pp27_{nuc}(t)$
$Pp27_{nuc}(t+1)$	IF $p27_{nuc}(t)$ AND $(CyclinE\text{-}pCdk2)_{nuc}(t)$
$TGF\text{-}\beta_{nuc}(t+1)$	IF ($TGF\text{-}\beta_{nuc}(t)$ AND NOT($(CyclinE\text{-}pCdk2)_{nuc}(t)$)) OR ($pTGF\text{-}\beta_{nuc}(t)$ AND $(CyclinB\text{-}pCdk1)_{cyt}(t)$)
$pTGF\text{-}\beta_{nuc}(t+1)$	IF ($TGF\text{-}\beta_{nuc}(t)$ AND $(CyclinE\text{-}pCdk2)_{nuc}(t)$) OR ($pTGF\text{-}\beta_{nuc}(t)$ AND NOT($(CyclinB\text{-}pCdk1)_{cyt}(t)$))
$ubiquitin_{cyt}(t+1)$	IF ($ubiquitin_{cyt}(t)$ AND NOT($pCyclinA_{cyt}(t)$) AND NOT($pCyclinB_{cyt}(t)$) AND NOT($pCyclinD_{cyt}(t)$) AND NOT($pCyclinE_{cyt}(t)$) AND NOT($Pp27_{cyt}(t)$)) OR $(ubiquitin\text{-}pCyclinA)_{cyt}(t)$ OR $(ubiquitin\text{-}pCyclinB)_{cyt}(t)$ OR $(ubiquitin\text{-}pCyclinD)_{cyt}(t)$ OR $(ubiquitin\text{-}pCyclinE)_{cyt}(t)$ OR $(ubiquitin\text{-}Pp27)_{cyt}(t)$
$(CyclinA\text{-}pCdk1)_{nuc}(t+1)$	IF $(CyclinA\text{-}ppCdk1)_{nuc}(t)$ OR ($(CyclinA\text{-}pCdk1)_{nuc}(t)$ AND NOT($(CyclinB\text{-}ppCdk1)_{nuc}(t)$))
$(CyclinA\text{-}ppCdk1)_{nuc}(t+1)$	IF $p_xCyclinA_{nuc}(t)$ AND $pCdk1_{nuc}(t)$
$(CyclinA\text{-}Cdk2)_{nuc}(t+1)$	IF ($CyclinA_{nuc}(t)$ AND $Cdk2_{nuc}(t)$) OR (NOT($(CyclinA\text{-}Cdk2)_{nuc}(t\text{-}1)$) AND $(CyclinA\text{-}Cdk2)_{nuc}(t)$)
$(CyclinA\text{-}pCdk2)_{nuc}(t+1)$	IF $(CyclinA\text{-}Cdk2)_{nuc}(t)$
$(CyclinB\text{-}pCdk1)_{nuc}(t+1)$	IF ($(CyclinB\text{-}ppCdk1)_{nuc}(t)$ AND NOT($(CyclinA\text{-}pCdk1)_{nuc}(t)$)) OR ($(CyclinB\text{-}pCdk1)_{nuc}(t)$ AND NOT ($(HDAC\text{-}DP\text{-}E2F\text{-}Rb)_{nuc}(t)$))
$(CyclinB\text{-}ppCdk1)_{nuc}(t+1)$	IF ($(CyclinB\text{-}ppCdk1)_{cyt}(t)$ AND $(CyclinA\text{-}pCdk1)_{nuc}(t)$) OR ($(CyclinB\text{-}ppCdk1)_{nuc}(t)$ AND $(CyclinA\text{-}pCdk1)_{nuc}(t)$)
$(CyclinB\text{-}ppCdk1)_{cyt}(t+1)$	IF ($CyclinB_{cyt}(t)$ AND $Cdk1_{cyt}(t)$) OR ($(CyclinB\text{-}ppCdk1)_{cyt}(t)$ AND NOT($(CyclinA\text{-}pCdk1)_{nuc}(t)$))
$(CyclinD\text{-}Cdk4/6)_{cyt}(t+1)$	IF $CyclinD_{cyt}(t)$ AND $Cdk4/6_{cyt}(t)$
$(CyclinD\text{-}pCdk4/6)_{cyt}(t+1)$	IF $(CyclinD\text{-}Cdk4/6)_{cyt}(t)$
$(CyclinD\text{-}pCdk4/6)_{nuc}(t+1)$	IF ($(CyclinD\text{-}pCdk4/6)_{cyt}(t)$ AND NOT$(Cdk4/6)_{cyt}(t)$) OR ($(CyclinD\text{-}pCdk4/6)_{nuc}(t)$ AND NOT($(CyclinE\text{-}Cdk2\text{-}p27)_{nuc}(t)$))
$(CyclinD\text{-}pCdk4/6\text{-}p27)_{nuc}(t+1)$	IF $(CyclinD\text{-}pCdk4/6)_{nuc}(t)$ AND $(CyclinE\text{-}Cdk2\text{-}p27)_{nuc}(t)$
$(CyclinE\text{-}Cdk2)_{cyt}(t+1)$	IF $CyclinE_{cyt}(t)$ AND $Cdk2_{cyt}(t)$
$(CyclinE\text{-}Cdk2)_{nuc}(t+1)$	IF $(CyclinD\text{-}pCdk4/6)_{nuc}(t)$ AND $(CyclinE\text{-}Cdk2\text{-}p27)_{nuc}(t)$
$(CyclinE\text{-}Cdk2\text{-}p27)_{cyt}(t+1)$	IF $p27_{cyt}(t)$ AND $(CyclinE\text{-}Cdk2)_{cyt}(t)$
$(CyclinE\text{-}Cdk2\text{-}p27)_{nuc}(t+1)$	IF $(CyclinE\text{-}Cdk2\text{-}p27)_{cyt}(t)$
$(CyclinE\text{-}pCdk2)_{nuc}(t+1)$	IF $(CyclinE\text{-}Cdk2)_{nuc}(t)$ OR ($(CyclinE\text{-}Cdk2)_{nuc}(t)$ AND NOT($Pp27_{cyt}(t)$))
$(ubiquitin\text{-}pCyclinA)_{cyt}(t+1)$	IF $pCyclinA_{cyt}(t)$ AND $ubiquitin_{cyt}(t)$
$(ubiquitin\text{-}pCyclinB)_{cyt}(t+1)$	IF $pCyclinB_{cyt}(t)$ AND $ubiquitin_{cyt}(t)$
$(ubiquitin\text{-}pCyclinD)_{cyt}(t+1)$	IF $pCyclinD_{cyt}(t)$ AND $ubiquitin_{cyt}(t)$
$(ubiquitin\text{-}pCyclinE)_{cyt}(t+1)$	IF $pCyclinE_{cyt}(t)$ AND $ubiquitin_{cyt}(t)$
$(ubiquitin\text{-}Pp27)_{cyt}(t+1)$	IF $Pp27_{cyt}(t)$ AND $ubiquitin_{cyt}(t)$

Table 3: Boolean conditions, with which the Boolean matrix was built up

7.4 Initial States of the Boolean Matrix

To enable time-dependent simulation of the Boolean model two columns of initial activity states had to be defined for each component of the Boolean model. To symbolize the high concentration of p27 in quiescent cells the states of nuclear and cytoplasmic mRNA(p27) were set to 1.

compound	t = 0	t = 1	compound	t = 0	t = 1	compound	t = 0	t = 1
mitogen-receptor1	0	1	$mRNA(CyclinD)_{cyt}$	0	0	$(HDAC\text{-}DP\text{-}E2F\text{-}Rb)_{nuc}$	1	1
inact-mitogen-receptor	0	0	$mRNA(CyclinE)_{nuc}$	0	0	$p27_{cyt}$	0	0
mitogen-receptor2	0	1	$mRNA(CyclinE)_{cyt}$	0	0	$p27_{nuc}$	0	0
inact-receptor	0	0	$mRNA(p27)_{nuc}$	1	1	$Pp27_{cyt}$	0	0
receptor	0	0	$mRNA(p27)_{cyt}$	0	1	$Pp27_{nuc}$	0	0
mitogen	0	0	$pCyclinA_{cyt}$	0	0	$TGF\text{-}\beta_{nuc}$	1	1
Ras_{cyt}	1	1	$pCyclinA_{nuc}$	0	0	$pTGF\text{-}\beta_{nuc}$	0	0
$pRas_{cyt}$	0	0	$p_xCyclinA_{nuc}$	0	0	$ubiquitin_{cyt}$	1	1
Raf_{cyt}	1	1	$pCyclinB_{cyt}$	0	0	$(CyclinA\text{-}pCdk1)_{nuc}$	0	0
$pRaf_{cyt}$	0	0	$pCyclinB_{nuc}$	0	0	$(CyclinA\text{-}ppCdk1)_{nuc}$	0	0
MEK_{cyt}	1	1	$pCyclinD_{cyt}$	0	0	$(CyclinA\text{-}Cdk2)_{nuc}$	0	0
$pMEK_{cyt}$	0	0	$pCyclinD_{nuc}$	0	0	$(CyclinA\text{-}pCdk2)_{nuc}$	0	0
ERK_{cyt}	1	1	$pCyclinE_{cyt}$	0	0	$(CyclinB\text{-}ppCdk1)_{nuc}$	0	0
ERK_{nuc}	0	0	$pCyclinE_{nuc}$	0	0	$(CyclinB\text{-}pCdk1)_{nuc}$	0	0
$pERK_{cyt}$	0	0	$Cdk1_{cyt}$	1	1	$(CyclinB\text{-}ppCdk1)_{cyt}$	0	0
$pERK_{nuc}$	0	0	$Cdk1_{nuc}$	0	0	$(CyclinD\text{-}Cdk4/6)_{cyt}$	0	0
SCF_{cyt}	1	1	$pCdk1_{nuc}$	1	1	$(CyclinD\text{-}pCdk4/6)_{cyt}$	0	0
APC_{cyt}	1	1	$Cdk2_{cyt}$	1	1	$(CyclinD\text{-}pCdk4/6)_{nuc}$	0	0
CAK_{nuc}	1	1	$pCdk2_{cyt}$	0	0	$(CyclinD\text{-}pCdk4/6\text{-}p27)_{nuc}$	0	0
CAK_{cyt}	1	1	$Cdk2_{nuc}$	0	0	$(CyclinE\text{-}Cdk2)_{cyt}$	0	0
$CyclinA_{cyt}$	0	0	$pCdk2_{nuc}$	0	0	$(CyclinE\text{-}Cdk2)_{nuc}$	0	0
$CyclinA_{nuc}$	0	0	$Cdk4/6_{cyt}$	1	1	$(CyclinE\text{-}Cdk2\text{-}p27)_{cyt}$	0	0
$CyclinB_{cyt}$	0	0	$Cdk4/6_{nuc}$	0	0	$(CyclinE\text{-}Cdk2\text{-}p27)_{nuc}$	0	0
$CyclinD_{cyt}$	0	0	Rb_{nuc}	0	0	$(CyclinE\text{-}pCdk2)_{nuc}$	0	0
$CyclinE_{cyt}$	0	0	$hypRb_{nuc}$	0	0	$(ubiquitin\text{-}pCyclinA)_{cyt}$	0	0
$mRNA(CyclinA)_{nuc}$	0	0	$(DP\text{-}E2F)_{nuc}$	0	0	$(ubiquitin\text{-}pCyclinB)_{cyt}$	0	0
$mRNA(CyclinA)_{cyt}$	0	0	$(pDP\text{-}E2F)_{nuc}$	0	0	$(ubiquitin\text{-}pCyclinD)_{cyt}$	0	0
$mRNA(CyclinB)_{nuc}$	0	0	$(pDP\text{-}pE2F)_{nuc}$	0	0	$(ubiquitin\text{-}pCyclinE)_{cyt}$	0	0
$mRNA(CyclinB)_{cyt}$	0	0	$(DP\text{-}E2F\text{-}pRb)_{nuc}$	0	0	$(ubiquitin\text{-}Pp27)_{cyt}$	0	0
$mRNA(CyclinD)_{nuc}$	0	0	$HDAC_{nuc}$	0	0			

Table 4: Initial states of the components of the Boolean model for the time-dependent simulation

7.5 The ODE Model

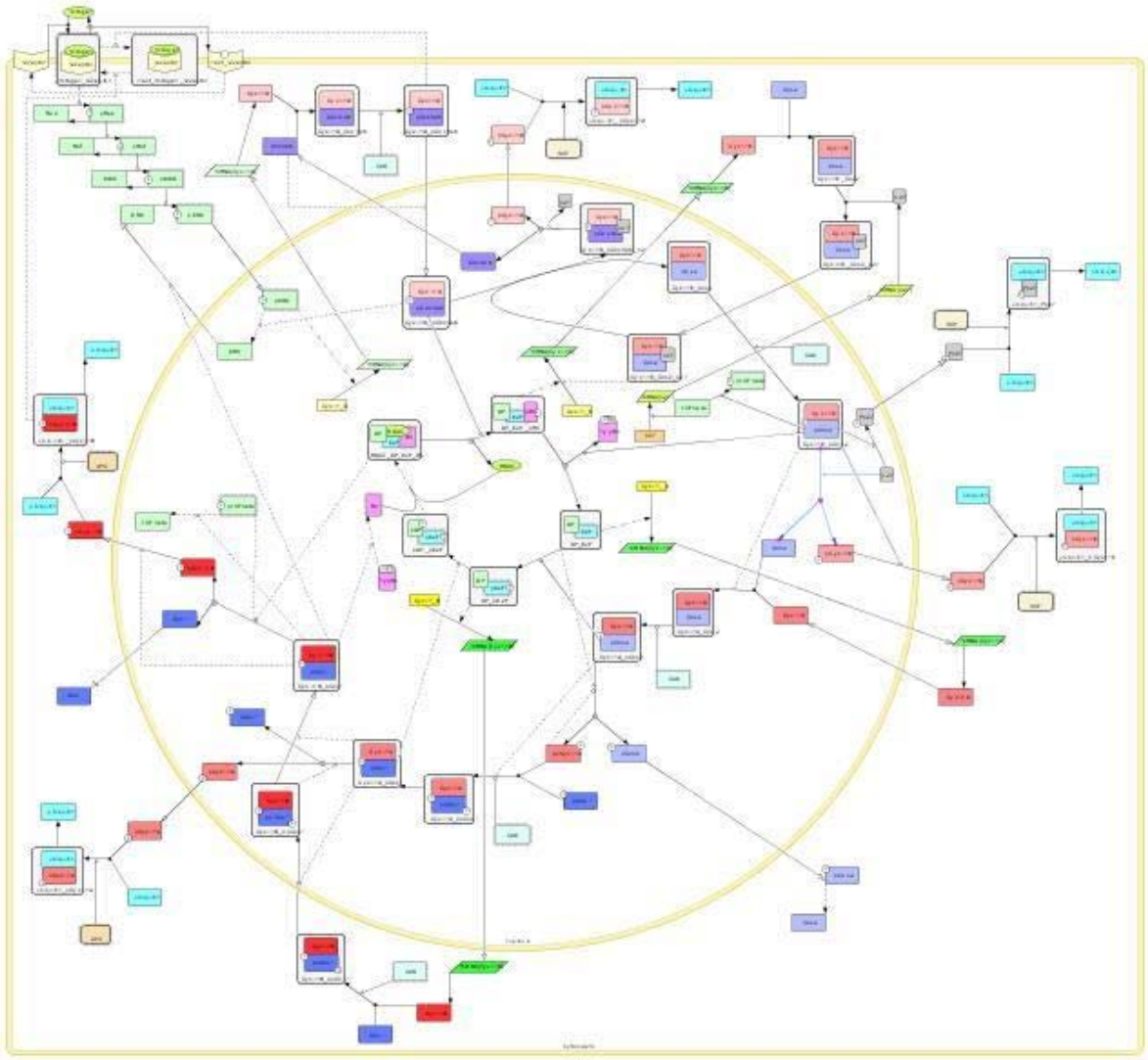

Figure 12: Snapshot of the ODE model designed with CellDesigner 3.1

7.6 Initial Concentrations of the ODE Model Compounds

To symbolize the high protein levels of p27 in quiescent cells the initial concentrations of nuclear and cytoplasmic p27 were set to 1 in the ODE model, while the initial concentrations of nuclear and cytoplasmic mRNA(p27) remained 0, although when active TGF-β is available the p27 gene expression, usually, is active in quiescent cells, too. In the Boolean model, the active p27 gene expression is symbolized via active states of nuclear and cytoplasmic mRNA(p27), but the ODE model results in a better general network behaviour when the initial activity is switched from the mRNAs(p27) to the p27 proteins.

compound	initial concentration	constant?	compound	initial concentration	constant?
mitogen-receptor	2,50	FALSE	$pCdk2_{cyt}$	0,00	FALSE
inact-mitogen-receptor	0,00	FALSE	$Cdk2_{nuc}$	0,00	FALSE
receptor	0,00	FALSE	$pCdk2_{nuc}$	0,00	FALSE
inact-receptor	0,00	FALSE	$Cdk4/6_{cyt}$	4,00	FALSE
mitogen	0,00	FALSE	$Cdk4/6_{nuc}$	0,00	FALSE
Ras_{cyt}	2,00	FALSE	Rb_{nuc}	0,00	FALSE
$pRas_{cyt}$	0,00	FALSE	$hypRb_{nuc}$	0,00	FALSE
Raf_{cyt}	2,00	FALSE	$(DP\text{-}E2F)_{nuc}$	0,00	FALSE
$pRaf_{cyt}$	0,00	FALSE	$(pDP\text{-}E2F)_{nuc}$	0,00	FALSE
MEK_{cyt}	2,00	FALSE	$(pDP\text{-}pE2F)_{nuc}$	0,00	FALSE
$pMEK_{cyt}$	0,00	FALSE	$(DP\text{-}E2F\text{-}pRb)_{nuc}$	0,00	FALSE
ERK_{cyt}	2,00	FALSE	$HDAC_{nuc}$	0,00	FALSE
ERK_{nuc}	0,00	FALSE	$(HDAC\text{-}DP\text{-}E2F\text{-}Rb)_{nuc}$	2,00	FALSE
$pERK_{cyt}$	0,00	FALSE	$p27_{cyt}$	1,00	FALSE
$pERK_{nuc}$	0,00	FALSE	$p27_{nuc}$	1,00	FALSE
SCF_{nuc}	2,50	TRUE	$Pp27_{cyt}$	0,00	FALSE
APC_{nuc}	2,50	TRUE	$Pp27_{nuc}$	0,00	FALSE
CAK_{nuc}	2,50	TRUE	$TGF\text{-}\beta_{nuc}$	2,00	FALSE
CAK_{cyt}	2,50	TRUE	$pTGF\text{-}\beta_{nuc}$	0,00	FALSE
$CyclinA_{cyt}$	0,00	FALSE	$ubiquitin_{cyt}$	5,00	FALSE
$CyclinA_{nuc}$	0,00	FALSE	$(CyclinA\text{-}pCdk1)_{nuc}$	0,00	FALSE
$CyclinB_{cyt}$	0,00	FALSE	$(CyclinA\text{-}ppCdk1)_{nuc}$	0,00	FALSE
$CyclinD_{cyt}$	0,00	FALSE	$(CyclinA\text{-}Cdk2)_{nuc}$	0,00	FALSE
$CyclinE_{cyt}$	0,00	FALSE	$(CyclinA\text{-}pCdk2)_{nuc}$	0,00	FALSE
$mRNA(CyclinA)_{nuc}$	0,00	FALSE	$(CyclinB\text{-}ppCdk1)_{nuc}$	0,00	FALSE
$mRNA(CyclinA)_{cyt}$	0,00	FALSE	$(CyclinB\text{-}pCdk1)_{nuc}$	0,00	FALSE
$mRNA(CyclinB)_{nuc}$	0,00	FALSE	$(CyclinB\text{-}ppCdk1)_{cyt}$	0,00	FALSE
$mRNA(CyclinB)_{cyt}$	0,00	FALSE	$(CyclinD\text{-}Cdk4/6)_{cyt}$	0,00	FALSE
$mRNA(CyclinD)_{nuc}$	0,00	FALSE	$(CyclinD\text{-}pCdk4/6)_{cyt}$	0,00	FALSE
$mRNA(CyclinD)_{cyt}$	0,00	FALSE	$(CyclinD\text{-}pCdk4/6)_{nuc}$	0,00	FALSE
$mRNA(CyclinE)_{nuc}$	0,00	FALSE	$(CyclinD\text{-}pCdk4/6\text{-}p27)_{nuc}$	0,00	FALSE
$mRNA(CyclinE)_{cyt}$	0,00	FALSE	$(CyclinE\text{-}Cdk2)_{cyt}$	0,00	FALSE
$mRNA(p27)_{nuc}$	0,00	FALSE	$(CyclinE\text{-}Cdk2)_{nuc}$	0,00	FALSE
$mRNA(p27)_{cyt}$	0,00	FALSE	$(CyclinE\text{-}Cdk2\text{-}p27)_{cyt}$	0,00	FALSE
$pCyclinA_{cyt}$	0,00	FALSE	$(CyclinE\text{-}Cdk2\text{-}p27)_{nuc}$	0,00	FALSE
$pCyclinA_{nuc}$	0,00	FALSE	$(CyclinE\text{-}pCdk2)_{nuc}$	0,00	FALSE
$p_xCyclinA_{nuc}$	0,00	FALSE	$(ubiquitin\text{-}pCyclinA)_{cyt}$	0,00	FALSE
$pCyclinB_{cyt}$	0,00	FALSE	$(ubiquitin\text{-}pCyclinB)_{cyt}$	0,00	FALSE
$pCyclinB_{nuc}$	0,00	FALSE	$(ubiquitin\text{-}pCyclinD)_{cyt}$	0,00	FALSE
$pCyclinD_{cyt}$	0,00	FALSE	$(ubiquitin\text{-}pCyclinE)_{cyt}$	0,00	FALSE
$pCyclinD_{nuc}$	0,00	FALSE	$(ubiquitin\text{-}Pp27)_{cyt}$	0,00	FALSE
$pCyclinE_{cyt}$	0,00	FALSE	cyclin A-gene	1,00	TRUE
$pCyclinE_{nuc}$	0,00	FALSE	cyclin B-gene	1,00	TRUE
$Cdk1_{cyt}$	4,00	FALSE	cyclin D-gene	1,00	TRUE
$Cdk1_{nuc}$	0,00	FALSE	cyclin E-gene	1,00	TRUE
$pCdk1_{nuc}$	4,00	FALSE	p27-gene	1,00	TRUE
$Cdk2_{cyt}$	4,00	FALSE			

Table 5: Initial concentrations of the compounds of the ODE model

7.7 Time-Dependent Variations of Model Component Concentrations

7.7.1 Differential Equations for the Total Protein Concentrations of the ODE Model

$$\frac{d(Ras_{tot})}{dt} = 0$$

$$Ras_{tot} = Ras_{cyt} + pRas_{cyt}$$

$$\frac{d(Raf_{tot})}{dt} = 0$$

$$Raf_{tot} = Raf_{cyt} + pRaf_{cyt}$$

$$\frac{d(MEK_{tot})}{dt} = 0$$

$$MEK_{tot} = MEK_{cyt} + pMEK_{cyt}$$

$$\frac{d(ERK_{tot})}{dt} = 0$$

$$ERK_{tot} = ERK_{cyt} + pERK_{cyt} + ERK_{nuc} + pERK_{nuc}$$

$$\frac{d(CAK_{tot})}{dt} = \frac{d(CAK_{cyt})}{dt} = \frac{d(CAK_{nuc})}{dt} = 0$$

$$CAK_{tot} = CAK_{nuc} + CAK_{cyt}$$

$$\frac{d(Cdk1_{tot})}{dt} = 0$$

$$Cdk1_{tot} = Cdk1_{nuc} + Cdk1_{cyt} + pCdk1_{nuc} + (CyclinA\text{-}pCdk1)_{nuc} + (CyclinA\text{-}ppCdk1)_{nuc} + (CyclinB\text{-}pCdk1)_{nuc} + (CyclinB\text{-}pCdk1)_{cyt} + (CyclinB\text{-}ppCdk1)_{cyt}$$

$$\frac{d(Cdk2_{tot})}{dt} = 0$$

$$Cdk2_{tot} = Cdk2_{cyt} + Cdk2_{nuc} + pCdk2_{cyt} + pCdk2_{nuc} + (CyclinA\text{-}Cdk2)_{nuc} + (CyclinA\text{-}pCdk2)_{nuc} + (CyclinE\text{-}Cdk2)_{cyt} + (CyclinE\text{-}Cdk2)_{nuc} + (CyclinE\text{-}Cdk2\text{-}p27)_{cyt} + (CyclinE\text{-}Cdk2\text{-}p27)_{nuc} + (CyclinE\text{-}pCdk2)_{nuc}$$

$$\frac{d(Cdk4/6_{tot})}{dt} = 0$$

$$Cdk4/6_{tot} = Cdk4/6_{nuc} + Cdk4/6_{cyt} + (CyclinD\text{-}Cdk4/6)_{cyt} + (CyclinD\text{-}pCdk4/6)_{cyt} + (CyclinD\text{-}pCdk4/6)_{nuc} + (Cyclind\text{-}pCdk4/6)_{nuc} + (CyclinD\text{-}pCd4/6\text{-}p27)_{nuc}$$

$$\frac{d(Rb_{tot})}{dt} = 0$$

$$Rb_{tot} = Rb_{nuc} + hypRb_{nuc} + (DP\text{-}E2F\text{-}pRb)_{nuc} + (HDAC\text{-}DP\text{-}E2F\text{-}Rb)_{nuc}$$

$$\frac{d(\text{DP-E2F}_{tot})}{dt} = 0$$

$$d(\text{DP-E2F}_{tot}) = d(\text{DP-pE2F}_{nuc}) = d(\text{pDP-pE2F}_{nuc}) = d(\text{DP-E2F-pRb}_{nuc}) = d(\text{HDAC-DP-E2F-Rb}_{nuc})$$

$$\frac{d(\text{HDAC}_{tot})}{dt} = 0$$

$$\text{HDAC}_{tot} = \text{HDAC}_{nuc} + (\text{HDAC-DP-E2F-Rb})_{nuc}$$

$$\frac{d(\text{TGF}-\beta_{tot})}{dt} = 0$$

$$\text{TGF-}\beta_{tot} = \text{TGF-}\beta_{nuc} + \text{pTGF-}\beta_{nuc}$$

$$\frac{d(\text{ubiquitin}_{tot})}{dt} = 0$$

$$\text{ubiquitin}_{tot} = \text{ubiquitin}_{cyt} + (\text{ubiquitin-pCyclinA})_{cyt} + (\text{ubiquitin-pCyclinB})_{cyt} + (\text{ubiquitin-pCyclinD})_{cyt} + (\text{ubiquitin-pCyclinE})_{cyt} + (\text{ubiquitin-Pp27})_{cyt}$$

Table 6: Differential equations for total protein concentrations of the ODE model

7.7.2 Differential Equations for all ODE Model Components

$$\frac{d(\text{mitogen-receptor1})}{dt} = -v74a + v75a$$

$$\frac{d(\text{inact-mitogen-receptor})}{dt} = v74a - v75a$$

$$\frac{d(\text{mitogen-receptor2})}{dt} = -v74b + v76$$

$$\frac{d(\text{inact-receptor})}{dt} = v74b - v75b$$

$$\frac{d(\text{receptor})}{dt} = v75b - v76$$

$$\frac{d(\text{mitogen})}{dt} = v74b - v76$$

$$\frac{d(\text{Ras}_{cyt})}{dt} = -v3 + v6$$

$$\frac{d(\text{pRas}_{cyt})}{dt} = v3 - v6$$

$$\frac{d(\text{Raf}_{cyt})}{dt} = -v4 + v7$$

$$\frac{d(\text{pRaf}_{cyt})}{dt} = v4 - v7$$

$$\frac{d(\text{MEK}_{cyt})}{dt} = -v5 + v8$$

$$\frac{d(\text{pMEK}_{cyt})}{dt} = v5 - v8$$

$$\frac{d(\text{ERK}_{cyt})}{dt} = -v9 + v19$$

$$\frac{d(\text{ERK}_{nuc})}{dt} = v18 - v19$$

$$\frac{d(\text{pERK}_{cyt})}{dt} = v9 - v10$$

$$\frac{d(\text{pERK}_{nuc})}{dt} = v10 - v18$$

$$\frac{d(\text{SCF})}{dt} = 0$$

$$\frac{d(\text{APC})}{dt} = 0$$

$$\frac{d(\text{CAK}_{nuc})}{dt} = 0$$

$$\frac{d(\text{CAK}_{cyt})}{dt} = 0$$

$$\frac{d(\text{CyclinA}_{cyt})}{dt} = v41 - v42$$
$$\frac{d(\text{CyclinA}_{nuc})}{dt} = v42 - v47$$
$$\frac{d(\text{CyclinB}_{cyt})}{dt} = v55 - v56$$
$$\frac{d(\text{CyclinD}_{cyt})}{dt} = v13 - v14$$
$$\frac{d(\text{CyclinE}_{cyt})}{dt} = v22 - v23$$
$$\frac{d(\text{mRNA[CyclinA]}_{nuc})}{dt} = v39 - v40$$
$$\frac{d(\text{mRNA[CyclinA]}_{cyt})}{dt} = v40 - v41$$
$$\frac{d(\text{mRNA[CyclinB]}_{nuc})}{dt} = v50 - v54$$
$$\frac{d(\text{mRNA[CyclinB]}_{cyt})}{dt} = v54 - v55$$
$$\frac{d(\text{mRNA[CyclinD]}_{nuc})}{dt} = v11 - v12$$
$$\frac{d(\text{mRNA[CyclinD]}_{cyt})}{dt} = v12 - v13$$
$$\frac{d(\text{mRNA[CyclinE]}_{nuc})}{dt} = v20 - v21$$
$$\frac{d(\text{mRNA[CyclinE]}_{cyt})}{dt} = v21 - v22$$
$$\frac{d(\text{mRNA[p27]}_{nuc})}{dt} = v0 - v1$$
$$\frac{d(\text{mRNA[p27]}_{cyr})}{dt} = v1 - v2$$
$$\frac{d(\text{pCyclinA}_{cyt})}{dt} = v62 - v63$$
$$\frac{d(\text{pCyclinA}_{nuc})}{dt} = v61 - v62$$
$$\frac{d(\text{p}_x\text{CyclinA}_{nuc})}{dt} = v51 - v58$$
$$\frac{d(\text{pCyclinB}_{cyt})}{dt} = v71 - v72$$
$$\frac{d(\text{pCyclinB}_{nuc})}{dt} = v69 - v71$$
$$\frac{d(\text{pCyclinD}_{cyt})}{dt} = v29 - v30$$
$$\frac{d(\text{pCyclinD}_{nuc})}{dt} = v27 - v29$$
$$\frac{d(\text{pCyclinE}_{cyt})}{dt} = v44 - v45$$
$$\frac{d(\text{pCyclinE}_{nuc})}{dt} = v43 - v44$$
$$\frac{d(\text{Cdk1}_{cyt})}{dt} = -v56 + v70$$
$$\frac{d(\text{Cdk1}_{nuc})}{dt} = v69 - v70$$
$$\frac{d(\text{pCdk1}_{nuc})}{dt} = -v58 + v61$$
$$\frac{d(\text{Cdk2}_{cyt})}{dt} = -v23 + v53$$
$$\frac{d(\text{pCdk2}_{cyt})}{dt} = v52 - v53$$
$$\frac{d(\text{Cdk2}_{nuc})}{dt} = v43 - v47$$
$$\frac{d(\text{pCdk2}_{nuc})}{dt} = v51 + v52$$
$$\frac{d(\text{Cdk4/6}_{cyt})}{dt} = -v14 + v28$$
$$\frac{d(\text{Cdk4/6}_{nuc})}{dt} = v27 + v28$$
$$\frac{d(\text{Rb}_{nuc})}{dt} = v66 - v68$$
$$\frac{d(\text{hypRb}_{nuc})}{dt} = v33 - v66$$
$$\frac{d(\text{DP-E2F}_{nuc})}{dt} = v33 - v49$$
$$\frac{d(\text{DP-pE2F}_{nuc})}{dt} = v49 - v65$$
$$\frac{d(\text{pDP-pE2F}_{nuc})}{dt} = v65 - v68$$
$$\frac{d(\text{DP-E2F-pRb}_{nuc})}{dt} = v17 - v33$$
$$\frac{d(\text{HDAC}_{nuc})}{dt} = v17 + v68$$
$$\frac{d(\text{HDAC-DP-E2F-Rb}_{nuc})}{dt} = -v17 - v68$$
$$\frac{d(\text{p27}_{cyt})}{dt} = v2 - v24$$
$$\frac{d(\text{p27}_{nuc})}{dt} = v27 - v35$$

$$\frac{d(Pp27_{cyt})}{dt} = v36 - v37$$
$$\frac{d(Pp27_{nuc})}{dt} = v35 - v36$$
$$\frac{d(TGF\text{-}\beta)}{dt} = -v34 + v67$$
$$\frac{d(pTGF\text{-}\beta)}{dt} = v34 - v67$$
$$\frac{d(CyclinA\text{-}pCdk1_{nuc})}{dt} = v59 - v61$$
$$\frac{d(CyclinA\text{-}ppCdk1_{nuc})}{dt} = v58 - v59$$
$$\frac{d(CyclinA\text{-}pCdk2_{nuc})}{dt} = v47 - v48$$
$$\frac{d(CyclinA\text{-}ppCdk2_{nuc})}{dt} = v48 - v51$$
$$\frac{d(CyclinB\text{-}ppCdk1_{nuc})}{dt} = v57 - v60$$
$$\frac{d(CyclinB\text{-}pCdk1_{nuc})}{dt} = v60 - v69$$
$$\frac{d(CyclinB\text{-}ppCdk1_{cyt})}{dt} = v56 - v57$$
$$\frac{d(CyclinD\text{-}Cdk4/6_{cyt})}{dt} = v14 - v15$$
$$\frac{d(CyclinD\text{-}pCdk4/6_{cyt})}{dt} = v15 - v16$$
$$\frac{d(CyclinD\text{-}pCdk4/6_{nuc})}{dt} = v16 - v26$$
$$\frac{d(CyclinD\text{-}pCdk4/6\text{-}p27_{nuc})}{dt} = v26 - v27$$
$$\frac{d(CyclinE\text{-}Cdk2_{cyt})}{dt} = v23 - v24$$
$$\frac{d(CyclinE\text{-}Cdk2_{nuc})}{dt} = v26 - v32$$
$$\frac{d(CyclinE\text{-}Cdk2\text{-}p27_{cyt})}{dt} = v24 - v25$$
$$\frac{d(CyclinE\text{-}Cdk2\text{-}p27_{nuc})}{dt} = v25 - v26$$
$$\frac{d(CyclinE\text{-}pCdk2_{nuc})}{dt} = v32 - v43$$
$$\frac{d(ubiquitin\text{-}pCyclinA_{cyt})}{dt} = v63 - v64$$
$$\frac{d(ubiquitin\text{-}pCyclinB_{cyt})}{dt} = v72 - v73$$
$$\frac{d(ubiquitin\text{-}pCyclinD_{cyt})}{dt} = v30 - v31$$
$$\frac{d(ubiquitin\text{-}pCyclinE_{cyt})}{dt} = v45 - v46$$
$$\frac{d(ubiquitin\text{-}Pp27_{cyt})}{dt} = v37 - v38$$

$$\frac{d(ubiquitin_{cyt})}{dt} = -v30 + v31 - v37 + v38 - v45 + v46 - v63 + v64 - v72 + v73$$

Table 7: Differential equations for all ODE model components

7.8 Parameters of the ODEs Resulting From the Parameter Adaptation by Trial and Error

reaction	Vmax	k50	n	ka50	na	ki50	ni
r0	0,71	0,5	4	0,3525	4		
r1	2	1	2				
r2	1	0,5	2				
r3	1	0,5	4	0,5	4		
r4	1	0,5	4	2	4		
r5	1	0,5	4	2	4		
r6	1	0,5	1				
r7	1	0,5	1				
r8	1	0,5	1				
r9	1	0,5	4	2	4		
r10	1	0,5	4				
r11	1,01	0,5	2	0,5	4		
r12	2,5	0,5	2				
r13	2,5	0,5	2				
r14	2	0,5	2				
r15	2	0,5	1	0,5	4		
r16	1	0,5	2			0,3	4
r17	1	0,5	2	0,75	6		
r18	1	0,5	4	2	4		
r19	2	0,4	1	2	4		
r20	1,95	0,5	4	0,525	4	2	2
r21	2	0,4	2				
r22	2	0,4	4				
r23	2	0,4	1				
r24	2	0,4	1				
r25	2	0,5	2				
r26	1,25	0,1	1				
r27	1	0,5	1				
r28	2	0,5	1				
r29	1	0,5	4				
r30	1	0,5	4	0,5	4		
r31	1	0,5	1				
r32	2	0,45	1	2	4		
r33	2,6	0,25	2	1,5	1		
r34	3,5	0,35	3	2	4		
r35	1	0,5	2	3	1		
r36	1	0,5	4				
r37	1	0,5	4	0,5	4		
r38	1	0,5	1				
r39	0,345	0,65	4	0,5	4		
r40	1	1	4				
r41	1	0,5	4				
r42	1	0,5	4				
r43	1	0,5	1			4	1
r44	1	0,5	4	0,5	4		
r45	1	0,5	4	0,5	4		
r46	1	0,5	1				
r47	0,4	0,5	1			2	2
r48	1,5	0,5	1	0,5	4		
r49	2,15	0,1	1	0,5	4		
r50	0,7	0,5	4	0,5	1		
r51	1,6	0,25	1	0,55	2	4	4
r52	2	0,25	2				
r53	2	0,25	2				
r54	2	1	1				
r55	1	0,5	1				
r56	1	0,5	2	0,5	4		
r57	0,03	0,25	1	0,78	4		
r58	1	0,3	2	0,4	4	4	1
r59	2	1	1				
r60	1,5	0,4	1			3,5	4
r61	0,03	0,5	1	0,6	4		
r62	1	0,5	4				
r63	1	0,5	4	0,5	4		
r64	1	0,5	1				
r65	1	0,5	2	2,5	1,1		
r66	1,5	0,5	1	0,5	4		
r67	2,5	0,5	2	0,6	4		
r68	2,5	0,3	1				
r69	1	0,5	1	1	4	0,5	4
r70	1	0,5	2				
r71	1	0,5	4			0,5	4
r72	1	0,5	4	0,5	4		
r73	1	0,5	1				
r74	0	0,5	2	1	1		
r75	0	0,5	4	2,2	1		
r76	1,5	0,5	2	1	1		
r77	3	0,1	1	2,5	1		
r78	2,5	0,25	1				

Table 8: Parameters resulting from the parameter adaptation by trial and error

7.9 Minimal and Maximal Concentrations of the Three Cell Cycle Rounds of the ODE Model After the Parameter Adaptation

	cell cycle round 1; timesteps 1 - 49				cell cycle round 2; timesteps 50 - 97				cell cycle round 3; timesteps 98 - 147			
	min	time	max	time	min	time	max	time	min	time	max	time
Ras_{cyt}	0,41014	3	2	0	0,418	50	2	92	0,41931	98	2	138
Raf_{cyt}	0,14841	3	2	46	0,14915	50	2	94	0,14926	98	2	140
MEK_{cyt}	0,1274	3	2	47	0,12745	50	2	95	0,12745	98	2	141
ERK_{cyt}	0,023498	28	2	0	0,023644	60	1,883	95	0,023666	107	1,8818	141
mitogen-receptor	0,0075133	45	2,5	1	0,062861	59	2,4704	49	0,062502	107	2,4681	97
$(HDAC\text{-}DP\text{-}E2F\text{-}Rb)_{nuc}$	0,0069052	29	2	4	0,010954	63	1,9638	56	0,016447	111	1,9529	104
$HDAC_{nuc}$	0	1	1,9931	30	0,036236	56	1,989	63	0,047053	104	1,9836	111
$(DP\text{-}E2F)_{nuc}$	0	8	1,9911	23	0,0053367	79	1,9751	70	0,0053576	97	1,9566	117
$Cdk2_{cyt}$	0,69698	31	4	12	0,83474	77	3,9378	60	1,0074	125	3,9618	107
$p27_{cyt}$	0,043831	26	2,607	13	0,0024865	91	2,2789	60	0,014839	137	2,214	108
p27 gene	1	48	1	48	1	96	1	96	1	142	1	142
$mRNA(p27)_{nuc}$	0	0	0,29994	13	0,01729	90	0,29576	61	0,018123	136	0,29331	108
$mRNA(p27)_{cyt}$	0	0	0,22232	13	0,017041	90	0,21893	61	0,018147	136	0,21694	109
$p27_{nuc}$	0,093788	22	1	12	0,11457	70	0,30704	62	0,10789	117	0,31829	110
$ubiquitin_{cyt}$	3,4117	19	5	14	3,6173	66	4,9876	62	3,6718	114	4,9879	109
SCF_{cyt}	2,5	48	2,5	48	2,5	96	2,5	96	2,5	142	2,5	142
CAK_{nuc}	2,5	48	2,5	48	2,5	96	2,5	96	2,5	142	2,5	142
CAK_{cyt}	2,5	48	2,5	48	2,5	96	2,5	96	2,5	142	2,5	142
$Cdk2_{nuc}$	0	8	2,8967	23	0,024333	95	2,647	70	0,0047969	108	2,3558	117
$Cdk1_{nuc}$	0	16	0,55913	47	0,0067375	90	0,51015	95	0,0069012	136	0,54	141
APC_{cyt}	2,5	48	2,5	48	2,5	96	2,5	96	2,5	142	2,5	142
$Cdk4/6_{cyt}$	0,65633	14	4	1	0,74302	61	3,8298	50	0,94943	109	3,8288	142
$Cdk4/6_{nuc}$	0	8	0,22182	17	0,00015883	60	0,21696	65	0,00023363	108	0,20285	112
Rb_{nuc}	0	18	0,52795	44	1,46E-06	81	0,3188	92	1,01E-06	128	0,43311	138
$CyclinD_{cyt}$	0	0	0,31464	9	0,0064402	49	0,31038	56	0,0063354	97	0,29913	103
$(ubiquitin\text{-}pCyclinD)_{cyt}$	0	12	0,55281	19	0,0014139	61	0,52111	66	0,0019101	109	0,49852	114
$(CyclinD\text{-}pCdk4/6\text{-}p27)_{nuc}$	0	8	0,88143	17	0,00031437	60	0,7795	64	0,00045931	108	0,75821	112
$(CyclinD\text{-}pCdk4/6)_{nuc}$	0	0	2,1721	14	0,024725	49	2,0301	61	0,0020227	130	1,9233	109
$mRNA(CyclinE)_{nuc}$	0	2	0,84229	14	0,0018436	58	0,73936	61	0,0018252	106	0,71531	109
$mRNA(CyclinE)_{cyt}$	0	3	0,56518	14	0,048708	59	0,49283	61	0,048541	107	0,50295	109
CyclinE gene	1	48	1	48	1	96	1	96	1	142	1	142
$mRNA(CyclinD)_{nuc}$	0	0	0,26154	8	0,0025236	96	0,2589	55	0,0026047	142	0,25228	102
$mRNA(CyclinD)_{cyt}$	0	0	0,26158	8	0,0040649	49	0,25818	55	0,0042138	142	0,25143	102
CyclinD gene	1	48	1	48	1	96	1	96	1	142	1	142
$CyclinE_{cyt}$	0	5	0,81993	15	9,76E-05	59	0,80233	62	9,60E-05	107	0,74332	110
$(CyclinE\text{-}Cdk2)_{cyt}$	0	5	0,61219	15	0,00010647	59	0,62987	63	0,00010527	107	0,57386	111
$(CyclinE\text{-}Cdk2\text{-}p27)_{cyt}$	0	5	0,45023	15	0,0087669	60	0,44161	63	0,010856	107	0,41868	111
$(CyclinE\text{-}Cdk2)_{nuc}$	0	8	0,00030366	16	2,22E-07	60	0,00029062	63	3,32E-07	108	0,00028544	111
$(CyclinE\text{-}Cdk2\text{-}p27)_{nuc}$	0	8	0,26919	16	5,23E-05	60	0,22213	63	7,84E-05	108	0,22341	111
$(CyclinE\text{-}pCdk2)_{nuc}$	0	8	1,6178	18	0,00061399	60	1,4671	65	0,00093952	108	1,3465	113
$TGF\text{-}\beta_{nuc}$	0,0043704	29	2	13	0,0057756	69	1,9871	50	0,0066302	117	1,9838	142
$(DP\text{-}pE2F)_{nuc}$	0	15	1,9826	32	0,008936	70	1,6725	78	0,0087928	116	1,7479	126
CyclinA gene	1	48	1	48	1	96	1	96	1	142	1	142
$mRNA(CyclinA)_{nuc}$	0	11	0,79677	24	0,21664	62	0,78779	71	0,21447	110	0,77733	118
$mRNA(CyclinA)_{cyt}$	0	12	0,39835	25	0,12096	62	0,39379	71	0,11909	110	0,38861	119
$(ubiquitin\text{-}pCyclinE)_{cyt}$	0	12	0,32697	20	0,0014397	61	0,30745	67	0,0019422	109	0,29431	114
$CyclinA_{cyt}$	0	13	0,39829	25	0,13013	63	0,39377	72	0,12821	111	0,38846	119
$CyclinA_{nuc}$	0	14	1,0894	30	0,12249	56	1,2534	76	0,39686	99	1,2805	123
$(CyclinA\text{-}pCdk2)_{nuc}$	0	14	1,6594	31	0,00070181	61	1,6543	78	0,00032833	108	1,6882	125

	cell cycle round 1; timesteps 1 - 49				cell cycle round 2; timesteps 50 - 97				cell cycle round 3; timesteps 98 - 147			
	min	time	max	time	min	time	max	time	min	time	max	time
$(CyclinA\text{-}Cdk2)_{nuc}$	0	14	0,030345	28	0,00048616	65	0,031491	74	0,00023948	108	0,030416	121
$(CyclinA\text{-}pCdk1)_{nuc}$	0	14	1,9078	36	0,018542	90	1,8744	82	0,015285	137	1,846	130
$(ubiquitin\text{-}pCyclinA)_{cyt}$	0	19	0,5523	40	0,0027213	80	0,45594	86	0,0018312	127	0,49854	134
$(ubiquitin\text{-}pCyclinB)_{cyt}$	0	25	0,45109	48	0,00069573	92	0,43584	49	0,00070393	138	0,44686	142
$(CyclinD\text{-}Cdk4/6)_{cyt}$	0	0	0,060552	8	3,36E-05	49	0,058934	55	3,24E-05	97	0,056717	103
$(CyclinD\text{-}pCdk4/6)_{cyt}$	0	0	2,2438	10	0,14215	50	2,142	57	0,14071	8	2,0262	105
$(DP\text{-}E2F\text{-}pRb)_{nuc}$	0	1	1,9372	13	0,0019469	54	1,9333	61	0,0022956	101	1,8877	109
$(ubiquitin\text{-}Pp27)_{cyt}$	0	12	0,71465	19	0,0010035	61	0,55195	66	0,0011359	109	0,53031	114
$CyclinB_{cyt}$	0	15	0,25779	34	0,017698	71	0,23314	80	0,017463	118	0,23989	128
CyclinB gene	1	48	1	48	1	96	1	96	1	142	1	142
$mRNA(CyclinB)_{nuc}$	0	15	0,42484	33	0,0014744	70	0,33279	79	0,0014506	117	0,35172	126
$mRNA(CyclinB)_{cyt}$	0	15	0,49921	34	0,0014802	70	0,37925	80	0,0014535	117	0,41793	127
$(pDP\text{-}pE2F)_{nuc}$	0	16	1,9742	41	0,00032921	72	1,9547	88	0,013808	119	1,9613	134
$Cdk1_{cyt}$	1,5824	44	4	22	1,934	91	3,927	62	1,7563	138	3,9371	109
ERK_{nuc}	0	0	1,8598	29	7,33E-08	91	1,8586	66	2,19E-14	137	1,8581	113
$pTGF\text{-}\beta_{nuc}$	0	11	1,9956	29	0,01286	50	1,9942	69	0,016229	142	1,9934	117
$pCyclinB_{nuc}$	0	16	0,55161	47	0,082421	90	0,51725	95	0,082577	137	0,53786	141
$pCdk1_{nuc}$	1,894	36	4	20	1,8404	82	3,9712	93	1,9258	129	3,9707	139
$hypRb_{nuc}$	0	8	1,9911	40	0,0004749	49	1,9701	77	0,0047305	142	1,9791	126
$pCyclinA_{nuc}$	0	14	0,57804	38	0,13211	78	0,52551	85	0,11822	126	0,56017	132
$pCyclinB_{cyt}$	0	19	0,37524	47	0,077094	91	0,36441	95	0,07761	138	0,37164	141
$pCyclinA_{cyt}$	0	16	0,38769	39	0,10845	79	0,36738	85	0,098306	127	0,37867	132
$pRas_{cyt}$	0	0	1,5899	3	9,28E-07	92	1,582	50	7,67E-07	138	1,5807	98
$pRaf_{cyt}$	0	0	1,8516	3	5,99E-24	93	1,8508	50	2,73E-24	139	1,8507	98
$pMEK_{cyt}$	0	0	1,8726	3	1,34E-31	94	1,8726	50	3,12E-30	140	1,8725	98
$pERK_{cyt}$	0	0	1,4428	1	0,077763	95	1,754	96	0,078718	141	1,6687	142
$pERK_{nuc}$	0	0	1,8052	7	0,00067315	62	1,7985	55	0,00075311	109	1,7805	102
$pCyclinD_{nuc}$	0	8	0,56122	18	0,10363	60	0,55481	65	0,11536	108	0,54008	113
$pCyclinD_{cyt}$	0	11	0,38164	18	0,091719	61	0,37782	65	0,099069	109	0,37406	113
$Pp27_{cyt}$	0	11	0,40777	16	0,084261	61	0,38339	65	0,087051	109	0,37889	113
$Pp27_{nuc}$	0	8	0,64798	16	0,094269	60	0,56844	65	0,10183	108	0,55801	112
$pCyclinE_{cyt}$	0	11	0,34057	18	0,092122	61	0,33615	65	0,099441	109	0,33273	113
$pCyclinE_{nuc}$	0	8	0,32577	22	0,1041	60	0,31981	69	0,11613	108	0,31875	117
$pCdk2_{nuc}$	0	14	0,39101	32	0,0026631	74	0,55275	79	0,0026655	121	0,6985	126
$pCdk2_{cyt}$	0	14	0,32676	33	0,0032308	76	0,45897	79	0,0031996	123	0,36672	126
$(CyclinB\text{-}ppCdk1)_{cyt}$	0	16	1,1801	35	0,017819	85	1,006	81	0,02316	119	1,1103	128
$(CyclinB\text{-}pCdk1)_{nuc}$	0	16	2,2788	44	0,001637	57	1,9537	92	0,0011862	104	2,13	138
inact-mitogen-receptor	0	48	0	48	0	96	0	96	0	142	0	142
$(CyclinA\text{-}ppCdk1)_{nuc}$	0	14	0,57537	34	5,64E-05	76	0,54081	80	5,51E-05	123	0,56298	128
$p_xCyclinA_{nuc}$	0	14	1,3305	33	0,0074479	72	1,6388	79	0,0072331	119	1,4733	126
$(CyclinB\text{-}ppCdk1)_{nuc}$	0	16	2,2805	39	0,001231	94	1,8957	86	0,0014198	121	2,0577	133
receptor	0	25	0,38973	47	0,00049974	92	0,51784	95	0,00050824	138	0,53377	141
mitogen	0	0	2,4925	45	0,029645	49	2,4371	59	0,031885	97	2,4375	107
inact-receptor	0	0	2,4925	45	0,0067905	49	2,4327	59	0,0075993	142	2,4337	107

Table 9: Minimal and maximal concentrations of all ODE model components in the three consecutive cell cycle rounds, which the ODE model completed after the parameter adaptation; the ODE model components are noted in the same order as in figures 4 & 5, and in table 2

7.10 Concentration Values of all ODE Model Components for the First 150 Simulated Time Steps

species	Ras_{cyt}	Raf_{cyt}	MEK_{cyt}	ERK_{cyt}	mitogen-receptor	$(DP\text{-}E2F)_{nuc}$	$Cdk2_{cyt}$	$p27_{cyt}$	$p27_{nuc}$	$HDAC_{nuc}$
t										
0	2	2	2	2	2,5	0	4	1	1	0
1	0,485641229	0,158625766	0,128315496	0,060753507	2,5	0	4	1,00015033	1	0
2	0,410516886	0,148458632	0,127400604	0,04159158	2,5	0	4	1,010022682	1	7,75E-145
3	0,41013517	0,14841032	0,127396356	0,034990595	2,499833217	0	4	1,065849141	1	4,32E-51
4	0,417606419	0,149006887	0,127431865	0,031244327	2,446463494	0	4	1,176034305	1	4,01E-23
5	0,507198708	0,157175286	0,127954861	0,028717253	2,043733778	0	4	1,317900678	1	7,25E-14
6	0,900718489	0,207929462	0,131333131	0,026854894	1,127595188	0	4	1,473814291	1	7,68E-10
7	1,488551005	0,423067695	0,148003192	0,025420949	0,250445402	0	4	1,635381017	1	1,86E-07
8	1,855717335	1,014812575	0,229135392	0,024343523	0,080441676	0	4	1,799134073	1	1,07E-05
9	1,975202162	1,583153452	0,510018677	0,023689133	0,04224162	6,10E-275	4	1,963716265	1	3,21E-04
10	1,996497922	1,894786812	1,141590391	0,023510108	0,027271922	7,84E-185	4	2,128609373	1	0,006964643
11	1,999523162	1,98301312	1,667263853	0,023497692	0,020060239	6,16E-105	4	2,293618225	1	0,104353255
12	1,999935411	1,997632864	1,924651366	0,023497509	0,016232363	1,34E-40	4	2,458669949	1	0,901775916
13	1,999991257	1,99967833	1,988415658	0,023497509	0,014039091	5,34E-06	3,94487744	2,606996381	0,999999317	1,937246658
14	1,999998816	1,999956442	1,998400607	0,023497509	0,012735621	0,157531309	3,091196418	2,23711454	0,95841518	1,987007195
15	1,999999839	1,999994105	1,999782946	0,023497509	0,011952619	1,623134348	1,931714555	1,494285923	0,491541684	1,992412252
16	1,999999978	1,999999202	1,999970614	0,023497509	0,011448064	1,975520306	1,085110074	0,728290468	0,233398655	1,993065282
17	1,999999997	1,999999892	1,999996023	0,023497509	0,011078237	1,986244909	0,833998606	0,262983334	0,198769397	1,993094645
18	1,999999999	1,999999985	1,999999462	0,023497509	0,010776274	1,989077773	0,784421669	0,114642114	0,186597552	1,993094775
19	2	1,999999998	1,999999927	0,023497509	0,010513009	1,990167711	0,762363575	0,072747469	0,173694087	1,993094775
20	2	2	1,99999999	0,023497509	0,010275374	1,990675713	0,74807676	0,05754227	0,142656837	1,993094775
21	2	2	1,999999999	0,023497509	0,010057375	1,990927553	0,737738445	0,050688987	0,108783084	1,993094775
22	2	2	2	0,023497509	0,009856104	1,991044252	0,729803184	0,047192728	0,093787734	1,993094775
23	2	2	2	0,023497509	0,009669745	1,991084958	0,723462919	0,045325426	0,094678876	1,993094775
24	2	2	2	0,023497509	0,009496816	1,990915767	0,718245065	0,044357174	0,103192543	1,993094775
25	2	2	2	0,023497509	0,009336007	1,988870854	0,713852214	0,043926588	0,114131589	1,993094775
26	2	2	2	0,023497509	0,009186142	1,97779883	0,710086665	0,043831436	0,125227513	1,993094775
27	2	2	2	0,023497509	0,009046175	1,939140762	0,706811228	0,043948019	0,135701093	1,993094775
28	2	2	2	0,023497509	0,008915172	1,836562164	0,70392735	0,044196065	0,145344222	1,993094775
29	2	2	2	0,023497509	0,008792303	1,610604298	0,701362205	0,044521669	0,154144137	1,993094775
30	2	2	2	0,023497509	0,00867683	1,178403083	0,699060775	0,044888105	0,162150242	1,993094775
31	2	2	2	0,023497538	0,008568096	0,464034586	0,696982218	0,045270377	0,169428626	1,993094775
32	2	2	2	0,023499345	0,008465515	0,0064778	0,860317902	0,045651032	0,176046514	1,993094775
33	2	2	2	0,023518489	0,008368565	0,005550729	2,240209217	0,045990717	0,182066875	1,993094747
34	2	2	2	0,023556473	0,008276777	0,005552462	2,733098746	0,046302823	0,187546628	1,993094628
35	2	2	2	0,023600401	0,008189733	0,005554108	2,894616105	0,046608991	0,192535625	1,993094503
36	2	2	2	0,023646817	0,008107059	0,005555668	3,036113967	0,046902461	0,197075981	1,993094372
37	2	2	2	0,023695083	0,008028414	0,005557142	3,165161814	0,047177739	0,201201535	1,993094235
38	2	2	2	0,023746672	0,007953496	0,005558529	3,279277415	0,047432235	0,204936687	1,993094091
39	2	2	2	0,023813347	0,007882029	0,005559824	3,378176101	0,047665149	0,208294431	1,993093913
40	2	2	2	0,024167695	0,007813765	0,005561019	3,462848949	0,04787673	0,211273921	1,993093235
41	2	2	2	0,113950441	0,007748478	0,005562103	3,534766617	0,048067815	0,213859341	1,992963981
42	2	2	2	1,883304212	0,007685964	0,005563057	3,595577852	0,048239556	0,216025363	1,970608514
43	2	2	2	1,883304215	0,007626038	0,005563867	3,646926858	0,048396161	0,21775721	1,632105312
44	2	2	2	1,883304223	0,00756853	0,005564526	3,690332569	0,04945654	0,219083274	0,780794473
45	2	2	2	1,883304243	0,007513321	0,00556505	3,727125251	0,064272057	0,220090658	0,263876036
46	1,999999986	2	2	1,883304286	0,047963536	0,005565469	3,758431183	0,123730283	0,220898394	0,133752344
47	1,995454519	2	2	1,88330437	0,893913868	0,005565823	3,785187878	0,232149475	0,221615925	0,09203635
48	1,53533562	1,947353831	1,999997656	1,883304471	2,316346396	0,005566142	3,808170822	0,36983576	0,222300966	0,072671727
49	0,457288541	0,154287085	0,127900967	0,054625672	2,470354627	0,005566437	3,828019868	0,520966985	0,222952284	0,061536639
50	0,417995775	0,149153097	0,127447803	0,040043245	2,467158911	0,005566713	3,845260048	0,67765522	0,223556829	0,054267659
51	0,420642292	0,1493773	0,12746166	0,034191869	2,451744943	0,005566968	3,860317967	0,836550735	0,224113568	0,049117822
52	0,443051808	0,15132453	0,127584793	0,03073045	2,32961916	0,005567206	3,87353779	0,996313568	0,224632261	0,045256794
53	0,593764216	0,166111128	0,128539841	0,02834917	1,79731629	0,005567434	3,885197155	1,156421343	0,225141361	0,042239959
54	1,10282928	0,250834254	0,134364995	0,026577153	0,781724672	0,005567652	3,895521709	1,316672915	0,225619793	0,039807759
55	1,640049349	0,579618576	0,162937517	0,025216319	0,184160411	0,005567854	3,904697104	1,476991048	0,226047403	0,037803295
56	1,915481561	1,222371183	0,285924665	0,024238183	0,097807052	0,005568048	3,912876203	1,637345796	0,226440673	0,036236373
57	1,986806569	1,716918424	0,699171029	0,023736276	0,07485945	0,005568416	3,920184834	1,797725172	0,226810448	0,037138014
58	1,998172819	1,940130858	1,338299288	0,023647544	0,065681053	0,005581801	3,926727896	1,958124009	0,227161118	0,069865785
59	1,999751497	1,991029356	1,782330342	0,023643626	0,062861368	0,006220453	3,932594067	2,118539763	0,227494925	0,378316702
60	1,99996593	1,998767021	1,958129672	0,023643603	0,063393954	0,008399086	3,937768978	2,278950371	0,227813594	1,681879973
61	1,999994907	1,999832778	1,993913068	0,023643727	0,06094981	0,02069387	3,56255826	2,246044926	0,231419343	1,968645065
62	1,999998701	1,999977362	1,99916752	0,023644404	0,070647354	0,596691128	2,513216412	1,654730472	0,307036589	1,987242538
63	1,999999	1,999996936	1,999887174	0,02364659	0,076312693	1,915639195	1,477602259	0,904267831	0,278996326	1,989046011
64	1,999998767	1,999999585	1,999984728	0,023651906	0,081604865	1,965395344	1,013417572	0,329049908	0,222772983	1,988555797
65	1,999998472	1,999999944	1,999997933	0,023662732	0,085551275	1,971651233	0,926818592	0,108295244	0,200285453	1,988026011
66	1,999998234	1,999999992	1,99999972	0,023682225	0,087941594	1,973611242	0,899370646	0,050742392	0,187983543	1,987635658
67	1,999998093	1,999999999	1,999999962	0,023714309	0,088999638	1,974435484	0,883421043	0,032326786	0,162189639	1,987341601
68	1,999998044	2	1,999999995	0,023763634	0,0891026	1,974832867	0,872454709	0,024123563	0,130667748	1,987113748
69	1,99999806	2	1,999999999	0,023835533	0,088614007	1,975020827	0,864315236	0,019415068	0,114645151	1,986932533
70	1,999998116	2	2	0,023936005	0,087802923	1,975054798	0,857967352	0,016254923	0,114572003	1,98678489
71	1,99999819	2	2	0,02407169	0,086839236	1,974476813	0,852838976	0,013934086	0,122925804	1,986661615

72	1,999998271	2	2	0,024249864	0,085822565	1,969969702	0,848585636	0,012135896	0,133811695	1,98655306
73	1,999998351	2	2	0,024478453	0,084809061	1,949565318	0,84498624	0,010693863	0,144306065	1,986424875
74	1,999998426	2	2	0,024766249	0,083829083	1,885118171	0,841891641	0,009509338	0,153455007	1,986027859
75	1,999998496	2	2	0,025124417	0,082897896	1,725610227	0,839197475	0,008518746	0,161161729	1,983974586
76	1,999998561	2	2	0,0255746	0,082022004	1,393750636	0,836829666	0,007678628	0,167609928	1,978180507
77	1,999998619	2	2	0,026184244	0,081202891	0,796047096	0,834741333	0,006957967	0,173034062	1,973403257
78	1,999998672	2	2	0,027179015	0,080439232	0,044649993	0,834978947	0,006333898	0,177642585	1,972453136
79	1,999998719	2	2	0,029130715	0,079728204	0,005336736	1,79453824	0,005787844	0,181601406	1,972391746
80	1,999998763	2	2	0,032039055	0,079066266	0,005338295	2,793403644	0,005305488	0,185038041	1,972381987
81	1,999998802	2	2	0,035196824	0,07844962	0,005339689	2,988499722	0,004880075	0,188049741	1,972372924
82	1,999998838	2	2	0,038431768	0,077874472	0,005340944	3,135856486	0,004503014	0,190710683	1,972363744
83	1,999998871	2	2	0,041709512	0,077337184	0,00534208	3,269500415	0,004166841	0,193078612	1,972354439
84	1,999998901	2	2	0,04503931	0,076834328	0,005343114	3,387565365	0,003865634	0,1951993	1,972344995
85	1,999998928	2	2	0,048491311	0,076362715	0,005344058	3,488766202	0,003594609	0,197109472	1,972335249
86	1,999998954	2	2	0,052381708	0,075919493	0,005344924	3,573778944	0,003349834	0,198838907	1,972324485
87	1,999998977	2	2	0,058968936	0,075502118	0,005345721	3,644068125	0,00312803	0,200412004	1,972307971
88	1,999998999	2	2	0,11699015	0,075108303	0,005346457	3,701435067	0,002926435	0,201848947	1,972197933
89	1,999999019	2	2	1,861827692	0,074735972	0,005347139	3,747778783	0,002742703	0,203166578	1,967124629
90	1,999999038	2	2	1,882555191	0,074383222	0,005347772	3,784932163	0,002574846	0,204379065	1,851119672
91	1,999999056	2	2	1,88263388	0,074048358	0,005348361	3,814560532	0,002486423	0,205498433	1,31624273
92	1,999999072	2	2	1,882725753	0,073745858	0,005348912	3,838113117	0,005361703	0,206538849	0,611299172
93	1,999999046	2	2	1,882831405	0,076592935	0,00534946	3,856812319	0,028444222	0,207618701	0,248138187
94	1,999904541	2	2	1,882946102	0,35608628	0,005350268	3,871670003	0,090912597	0,209587149	0,138770545
95	1,948327925	1,999994422	2	1,88304558	1,510698615	0,005352023	3,883550809	0,195215755	0,214161792	0,099737301
96	0,944564426	0,301823676	0,159059861	0,121051311	2,460039777	0,005354788	3,893312227	0,331384739	0,220294083	0,081171879
97	0,422936268	0,149776615	0,127502142	0,046501262	2,468114795	0,005357633	3,901850878	0,481863163	0,22511722	0,070429887
98	0,419307982	0,149262924	0,127454445	0,037224544	2,45947325	0,005359956	3,909881596	0,637078346	0,228150209	0,063403816
99	0,426584433	0,149899065	0,127495271	0,032612911	2,419839421	0,005361708	3,91772103	0,793934904	0,230096906	0,058428107
100	0,481993867	0,15489722	0,127814803	0,029674678	2,160318741	0,005363023	3,9253261	0,951417682	0,231490124	0,054705131
101	0,768648025	0,187546811	0,129956141	0,027575839	1,410069352	0,005364037	3,932499545	1,109152297	0,232588972	0,05180589
102	1,356708682	0,34169514	0,141259413	0,025984864	0,41646278	0,005364844	3,939064443	1,266995397	0,233490654	0,049483937
103	1,791874707	0,850326777	0,198286792	0,024775575	0,132060641	0,005365516	3,944929817	1,424891583	0,234246166	0,047650239
104	1,960529957	1,462907017	0,404095294	0,023981117	0,085208458	0,005366272	3,950083197	1,582819081	0,234894921	0,047052933
105	1,994284388	1,844175651	0,98171965	0,023693987	0,06983605	0,005371451	3,954562517	1,740768953	0,235463498	0,057108784
106	1,999218301	1,972728708	1,559998973	0,023666055	0,064056758	0,005578644	3,958431537	1,898737177	0,235969418	0,151041509
107	1,999893646	1,996132373	1,885759704	0,023665417	0,062501617	0,007833548	3,961762929	2,056721632	0,236425089	0,668523816
108	1,999985185	1,999473065	1,981284471	0,023665422	0,063205757	0,011473287	3,961599912	2,214018577	0,236840019	1,811361169
109	1,999997526	1,999928622	1,997384244	0,023665496	0,065504405	0,053425321	3,408568367	2,060930066	0,248357943	1,96749974
110	1,999999096	1,999990339	1,999644392	0,023665836	0,069136557	0,88880536	2,334274401	1,422487209	0,318295163	1,982407602
111	1,999999157	1,999998692	1,999951844	0,023666851	0,073337731	1,921846663	1,436114487	0,706664963	0,265797639	1,983553577
112	1,999998995	1,999999823	1,999993482	0,023669231	0,07703307	1,949079614	1,146230678	0,248463286	0,218177229	1,983078754
113	1,999998824	1,999999976	1,999999118	0,023673999	0,07963918	1,953882164	1,091794765	0,099502135	0,200306825	1,982686686
114	1,999998701	1,999999997	1,999999881	0,023682559	0,081088335	1,955500895	1,068515268	0,057750653	0,182998831	1,982409983
115	1,999998638	2	1,999999984	0,023696729	0,081592372	1,956193063	1,053931518	0,042256558	0,14664085	1,982212762
116	1,999998626	2	1,999999998	0,023718771	0,081455712	1,956506994	1,043650475	0,03465445	0,116210542	1,982071142
117	1,999998647	2	2	0,023751421	0,080950715	1,956598207	1,035911208	0,030132739	0,107888659	1,98196892
118	1,999998686	2	2	0,023797916	0,080262195	1,956175038	1,02981983	0,027096025	0,113909763	1,981894863
119	1,999998733	2	2	0,023862016	0,079499155	1,952678597	1,02486801	0,024894857	0,125948195	1,981841051
120	1,999998781	2	2	0,023948038	0,078722319	1,936257614	1,020743337	0,0232175	0,139443435	1,981801772
121	1,999998827	2	2	0,024060974	0,077964161	1,883107031	1,017242195	0,021894091	0,152495083	1,981772483
122	1,999998871	2	2	0,024207168	0,077240993	1,749879836	1,014225869	0,020822851	0,164466766	1,981748008
123	1,999998911	2	2	0,024397992	0,076559955	1,470905028	1,011597345	0,019938336	0,17522409	1,981722869
124	1,999998948	2	2	0,024666834	0,075923048	0,963909806	1,009291378	0,019196166	0,184814547	1,981702998
125	1,999998982	2	2	0,025129297	0,075329467	0,207529302	1,007363764	0,018564997	0,193344096	1,98169539
126	1,999999012	2	2	0,026132505	0,074776945	0,006396026	1,52871863	0,018020674	0,200930888	1,981692127
127	1,99999904	2	2	0,027968072	0,07426254	0,006398391	2,811669399	0,017537707	0,207688336	1,981686915
128	1,999999065	2	2	0,030110877	0,073783076	0,006402615	3,064469577	0,017112471	0,213719386	1,981680626
129	1,999999089	2	2	0,032335283	0,073335397	0,006406615	3,205645842	0,016738897	0,219115076	1,981674307
130	1,99999911	2	2	0,034598702	0,072916499	0,006410401	3,331607862	0,016407839	0,223954859	1,981667881
131	1,999999129	2	2	0,036901201	0,072523586	0,006413983	3,443183389	0,016111926	0,228307555	1,98166135
132	1,999999148	2	2	0,039296847	0,072154065	0,006417371	3,538725179	0,015845356	0,232232482	1,981654593
133	1,999999164	2	2	0,042141725	0,071805615	0,006420574	3,61870646	0,015603492	0,235780568	1,981646846
134	1,99999918	2	2	0,050737347	0,071476226	0,006423601	3,684530313	0,015382576	0,238995367	1,981628225
135	1,999999195	2	2	0,511910877	0,071164149	0,006426461	3,737989507	0,015179528	0,241913917	1,980861643
136	1,999999208	2	2	1,881808787	0,070867808	0,006429162	3,78100478	0,014991803	0,24456743	1,933131076
137	1,999999221	2	2	1,881808787	0,070585737	0,006431711	3,815441228	0,0148312	0,246981768	1,500487053
138	1,999999233	2	2	1,881808787	0,070321751	0,006434111	3,84298621	0,016364551	0,24917768	0,693875595
139	1,999999228	2	2	1,881808787	0,071556081	0,006436367	3,865086518	0,0357212	0,251171385	0,250781165
140	1,999956401	2	2	1,881808787	0,296766873	0,006438481	3,882932938	0,101312178	0,252980857	0,132526975
141	1,961918922	1,999998436	2	1,881808787	1,416207558	0,006440466	3,897476036	0,212893136	0,254637404	0,092814102
142	1,040599988	0,529886687	0,2830439	0,269563932	2,450392045	0,006442333	3,909459284	0,351757125	0,256161869	0,074060739
143	0,425697444	0,150109403	0,127530193	0,047485602	2,466209422	0,006444079	3,919457833	0,502882936	0,257538502	0,063190885
144	0,419333388	0,149269243	0,127455109	0,037620939	2,460084083	0,006445685	3,927911797	0,658914598	0,258743922	0,056062008
145	0,425029125	0,149763846	0,127486672	0,032844807	2,428359192	0,006447133	3,935151391	0,816869266	0,259770383	0,050997312
146	0,472982893	0,154048128	0,127759666	0,02983294	2,19510598	0,00644849	3,941418448	0,975580695	0,260809329	0,047194072
147	0,73794147	0,183333127	0,129672947	0,027693056	1,463861817	0,006449852	3,946892761	1,134596395	0,261876926	0,044220176
148	1,32397856	0,32621481	0,140038489	0,026075185	0,442165274	0,006450848	3,951728987	1,29374186	0,262237336	0,041822306
149	1,774439202	0,811740304	0,192263362	0,024842586	0,135072008	0,006451525	3,956035187	1,452949749	0,262405627	0,039848879
150	1,95609651	1,432662396	0,383950532	0,024020449	0,086354988	0,006452067	3,959844133	1,612193701	0,262614223	0,038393323
144	0,419333388	0,149269243	0,127455109	0,037620939	2,460084083	1,943937992	0,056062008	0,006445685	3,927911797	0,658914598
145	0,425029125	0,149763846	0,127486672	0,032844807	2,428359192	1,949002688	0,050997312	0,006447133	3,935151391	0,816869266
146	0,472982893	0,154048128	0,127759666	0,02983294	2,19510598	1,952805928	0,047194072	0,00644849	3,941418448	0,975580695
147	0,73794147	0,183333127	0,129672947	0,027693056	1,463861817	1,955779824	0,044220176	0,006449852	3,946892761	1,134596395
148	1,32397856	0,32621481	0,140038489	0,026075185	0,442165274	1,958177694	0,041822306	0,006450848	3,951728987	1,29374186
149	1,774439202	0,811740304	0,192263362	0,024842586	0,135072008	1,960151121	0,039848879	0,006451525	3,956035187	1,452949749
150	1,95609651	1,432662396	0,383950532	0,024020449	0,086354988	1,961606677	0,038393323	0,006452067	3,959844133	1,612193701

t	species	p27 gene	(HDAC-DP-E2F-Rb)$_{nuc}$	mRNA(p27)$_{nuc}$	mRNA(p27)$_{cyt}$	ubiquitin$_{cyt}$	SCF$_{cyt}$	CAK$_{nuc}$	CAK$_{cyt}$	Cdk2$_{nuc}$	Cdk1$_{nuc}$	APC$_{cyt}$	Cdk4/6$_{cyt}$	Cdk4/6$_{nuc}$
0	1	2	0	0	5	2.5	2.5	2.5	0	0	2.5	4	0
1	1	2	0.149225914	0.015700494	5	2.5	2.5	2.5	0	0	2.5	4	0
2	1	2	0.23737621	0.082754583	5	2.5	2.5	2.5	0	0	2.5	4	0
3	1	2	0.276025068	0.153356004	5	2.5	2.5	2.5	0	0	2.5	3.997862734	0
4	1	2	0.29107 4622	0.193198025	5	2.5	2.5	2.5	0	0	2.5	3.852922089	0
5	1	2	0.296689875	0.210793136	5	2.5	2.5	2.5	0	0	2.5	3.469376742	0
6	1	1.999999999	0.298753179	0.217892957	5	2.5	2.5	2.5	0	0	2.5	2.999766846	0
7	1	1.999999814	0.299507144	0.220649004	5	2.5	2.5	2.5	0	0	2.5	2.495620455	0
8	1	1.999989341	0.299782102	0.221697728	5	2.5	2.5	2.5	0	0	2.5	1.972527856	0
9	1	1.999679353	0.299882301	0.222092075	5	2.5	2.5	2.5	7.35E-268	0	2.5	1.449141105	3.46E-267
10	1	1.993035357	0.299918805	0.2222392	5	2.5	2.5	2.5	1.24E-182	0	2.5	1.012478642	6.33E-182
11	1	1.895646745	0.299932103	0.222293787	5	2.5	2.5	2.5	4.85E-105	0	2.5	0.798248758	2.45E-104
12	1	1.098224084	0.299936947	0.222313957	5	2.5	2.5	2.5	1.60E-41	0	2.5	0.706565134	7.98E-41
13	1	0.062753342	0.299938712	0.222321387	5	2.5	2.5	2.5	5.56E-07	0	2.5	0.658558886	2.32E-06
14	1	0.012992805	0.299869401	0.222319548	5	2.5	2.5	2.5	0.014131745	0	2.5	0.656334837	0.029031243
15	1	0.007587748	0.23896887	0.209220894	4.983868815	2.5	2.5	2.5	0.127058283	0	2.5	0.885736574	0.116474019
16	1	0.006934718	0.163683384	0.162678715	4.544580771	2.5	2.5	2.5	0.421198441	0	2.5	1.333664832	0.183023319
17	1	0.006905355	0.123921969	0.126267588	3.944349812	2.5	2.5	2.5	0.821564994	2.68E-258	2.5	1.901745463	0.221824554
18	1	0.006905225	0.099549816	0.101732903	3.547445523	2.5	2.5	2.5	1.255985964	2.68E-152	2.5	2.515130313	0.221558187
19	1	0.006905225	0.083133771	0.084790765	3.411739188	2.5	2.5	2.5	1.689442565	3.93E-92	2.5	3.072368759	0.163179257
20	1	0.006905225	0.071734187	0.072563025	3.589428247	2.5	2.5	2.5	2.113751284	1.34E-60	2.5	3.447275611	0.074454325
21	1	0.006905225	0.062468218	0.063374806	4.011857635	2.5	2.5	2.5	2.509555184	4.43E-44	2.5	3.600782748	0.02120429
22	1	0.006905225	0.055551778	0.056236248	4.420584029	2.5	2.5	2.5	2.797437781	9.64E-35	2.5	3.645269808	0.007168512
23	1	0.006905225	0.050010795	0.050537245	4.679445345	2.5	2.5	2.5	2.896695391	9.74E-29	2.5	3.663845144	0.004485594
24	1	0.006905225	0.045472848	0.045885045	4.822666444	2.5	2.5	2.5	2.829199639	1.95E-24	2.5	3.677494598	0.003844134
25	1	0.006905225	0.041688621	0.042016685	4.897148537	2.5	2.5	2.5	2.679735806	3.16E-21	2.5	3.689833515	0.003544316
26	1	0.006905225	0.038484989	0.038749974	4.933614927	2.5	2.5	2.5	2.499901918	8.98E-19	2.5	3.701441241	0.003312642
27	1	0.006905225	0.035738013	0.035954898	4.952117792	2.5	2.5	2.5	2.308308373	7.57E-17	2.5	3.712421096	0.003104643
28	1	0.006905225	0.033356651	0.033536283	4.962532313	2.5	2.5	2.5	2.111533157	2.68E-15	2.5	3.722805741	0.00291212
29	1	0.006905225	0.031272531	0.0314229	4.969048422	2.5	2.5	2.5	1.913030045	4.85E-14	2.5	3.732619456	0.002732831
30	1	0.006905225	0.029433316	0.029560399	4.973477756	2.5	2.5	2.5	1.715961701	4.73E-13	2.5	3.741886857	0.002565584
31	1	0.006905225	0.027798263	0.0279066	4.976679666	2.5	2.5	2.5	1.523883405	2.49E-12	2.5	3.750633275	0.002409381
32	1	0.006905225	0.026335189	0.026428272	4.979710636	2.5	2.5	2.5	1.340352589	7.63E-12	2.5	3.758888391	0.002263236
33	1	0.006905253	0.025018332	0.02509888	4.981015455	2.5	2.5	2.5	1.168320692	1.57E-11	2.5	3.766662909	0.002126123
34	1	0.006905372	0.023826827	0.023896984	4.982563918	2.5	2.5	2.5	1.009976548	2.48E-11	2.5	3.77399258	0.001996957
35	1	0.006905497	0.022743599	0.02280507	4.983852262	2.5	2.5	2.5	0.866826093	3.41E-11	2.5	3.780892263	0.001874367
36	1	0.006905628	0.021754535	0.021808692	4.984947573	2.5	2.5	2.5	0.739718778	4.34E-11	2.5	3.78737671	0.001756672
37	1	0.006905765	0.020847875	0.020895383	4.985811526	2.5	2.5	2.5	0.628820775	5.28E-11	2.5	3.793454403	0.001641749
38	1	0.006905909	0.020013735	0.020056397	4.74867686	2.5	2.5	2.5	0.533638677	6.23E-11	2.5	3.799124959	0.001526707
39	1	0.006906087	0.019243753	0.019281871	4.521742842	2.5	2.5	2.5	0.453052156	7.21E-11	2.5	3.804375146	0.001407511
40	1	0.006906765	0.018530803	0.018564999	4.43585642	2.5	2.5	2.5	0.385511005	8.36E-11	2.5	3.809173623	0.001278775
41	1	0.007036019	0.017868776	0.017899569	4.526617226	2.5	2.5	2.5	0.329212992	1.00E-10	2.5	3.813466297	0.001134468
42	1	0.029391486	0.017252806	0.017280235	4.713214258	2.5	2.5	2.5	0.282308034	1.11E-10	2.5	3.817178988	9.71E-04
43	1	0.367894688	0.032773661	0.0168958	4.85977581	2.5	2.5	2.5	0.243069717	5.68E-05	2.5	3.820240446	7.95E-04
44	1	1.219205527	0.15108176	0.03364784	4.927443637	2.5	2.5	2.5	0.210025169	0.029619093	2.5	3.82263191	6.26E-04
45	1	1.736123964	0.233520167	0.093380449	4.952588644	2.5	2.5	2.5	0.182017725	0.256385109	2.5	3.824431505	4.90E-04
46	1	1.866247656	0.271426122	0.155183197	4.90951239	2.5	2.5	2.5	0.158179634	0.464119901	2.5	3.82580084	4.00E-04
47	1	1.90796365	0.286609823	0.191167694	4.666828759	2.5	2.5	2.5	0.137851561	0.559127208	2.5	3.826925872	3.55E-04
48	1	1.927328273	0.292368358	0.207650787	4.523731027	2.5	2.5	2.5	0.120486526	0.541293817	2.5	3.827944745	3.33E-04
49	1	1.938463361	0.294507183	0.214500721	4.543000858	2.5	2.5	2.5	0.105587509	0.369553938	2.5	3.828901423	3.13E-04
50	1	1.945732341	0.295296398	0.217222063	4.72499499	2.5	2.5	2.5	0.092723585	0.193813838	2.5	3.829781916	2.91E-04
51	1	1.950882178	0.295586988	0.218277445	4.878866709	2.5	2.5	2.5	0.081550046	0.118226953	2.5	3.817670361	2.69E-04
52	1	1.954743206	0.295693901	0.218680811	4.94344808	2.5	2.5	2.5	0.071801561	0.085206973	2.5	3.602914954	2.53E-04
53	1	1.957760041	0.295733224	0.218833492	4.965119906	2.5	2.5	2.5	0.063290446	0.068032339	2.5	3.191322647	2.48E-04
54	1	1.960192241	0.295747685	0.218890892	4.973663716	2.5	2.5	2.5	0.055829237	0.057919884	2.5	2.713268913	2.31E-04
55	1	1.962196705	0.295753004	0.218912363	4.978117973	2.5	2.5	2.5	0.049241525	0.051460128	2.5	2.206236612	2.10E-04
56	1	1.963763627	0.295755496	0.218920364	4.980945707	2.5	2.5	2.5	0.043415381	0.047087172	2.5	1.689340442	1.95E-04
57	1	1.962861986	0.295755679	0.218923338	4.98294371	2.5	2.5	2.5	0.038264863	0.043984633	2.5	1.219016073	1.84E-04
58	1	1.930134215	0.295755943	0.21892444	4.984444706	2.5	2.5	2.5	0.033714487	0.041644778	2.5	0.944383501	1.74E-04
59	1	1.621683298	0.295756041	0.218924848	4.985622023	2.5	2.5	2.5	0.029696982	0.03932789	2.5	0.830014594	1.66E-04
60	1	1.318120027	0.295756076	0.218924999	4.986595575	2.5	2.5	2.5	0.026152821	0.035023111	2.5	0.774021378	1.59E-04
61	1	1.031354935	0.295756085	0.218925054	4.987459575	2.5	2.5	2.5	0.02567306	0.03073649	2.5	0.743015888	0.003312783
62	1	0.012757462	0.291367842	0.218438352	4.987639677	2.5	2.5	2.5	0.123514472	0.027381363	2.5	0.836729738	0.071379825
63	1	0.010953989	0.201464881	0.188967354	4.895236245	2.5	2.5	2.5	0.358316662	0.024685015	2.5	1.185217193	0.149894459
64	1	0.011444203	0.144781486	0.145628362	4.327960515	2.5	2.5	2.5	0.697737289	0.022471127	2.5	1.695873644	0.200789775
65	1	0.011973989	0.112677875	0.114888457	3.855495972	2.5	2.5	2.5	1.096519805	0.020621044	2.5	2.282699183	0.216960528
66	1	0.012364342	0.092129317	0.0940068	3.617348504	2.5	2.5	2.5	1.505111968	0.01905202	2.5	2.849974858	0.176576474
67	1	0.012658399	0.077881255	0.07929772	3.675252218	2.5	2.5	2.5	1.900074049	0.017704604	2.5	3.271873235	0.095099704
68	1	0.012886252	0.067435265	0.068485403	4.001756387	2.5	2.5	2.5	2.26243934	0.016534992	2.5	3.483006943	0.034675821
69	1	0.013067467	0.059447285	0.060237546	4.378014554	2.5	2.5	2.5	2.535086266	0.015510199	2.5	3.562736477	0.013492523
70	1	0.01321511	0.05314816	0.053751268	4.639727606	2.5	2.5	2.5	2.646994383	0.014604919	2.5	3.598518555	0.007557357
71	1	0.013338385	0.048053284	0.048521707	4.790749212	2.5	2.5	2.5	2.595570756	0.013799411	2.5	3.62080644	0.005406675
72	1	0.01344694	0.043848059	0.044218006	4.873557468	2.5	2.5	2.5	2.448306594	0.013078054	2.5	3.637427624	0.004274059
73	1	0.013575125	0.040318521	0.040615207	4.916856189	2.5	2.5	2.5	2.261798242	0.012428324	2.5	3.650725446	0.003511509
74	1	0.013972141	0.037314139	0.037555391	4.939879053	2.5	2.5	2.5	2.06092764	0.011840062	2.5	3.661661927	0.002935027
75	1	0.016025414	0.034725954	0.034924587	4.953181831	2.5	2.5	2.5	1.855195308	0.011304943	2.5	3.670776643	0.002479884

76	1	0,021819493	0,032473171	0,032638553	4,961648515	2,5	2,5	2,5	1,649369612	0,010816082	2,5	3,678448629	0,002116262
77	1	0,026596743	0,030494617	0,030633707	4,967488821	2,5	2,5	2,5	1,447332256	0,010367733	2,5	3,684971664	0,001824521
78	1	0,027546864	0,02874313	0,028861177	4,971768205	2,5	2,5	2,5	1,252911667	0,009955061	2,5	3,690576365	0,001588913
79	1	0,027608254	0,027181772	0,027282786	4,975045558	2,5	2,5	2,5	1,069544627	0,009573971	2,5	3,695441509	0,001396721
80	1	0,027618013	0,025781196	0,025868285	4,977595903	2,5	2,5	2,5	0,899973567	0,009220974	2,5	3,69970481	0,001238206
81	1	0,027627076	0,024517798	0,024593394	4,97939952	2,5	2,5	2,5	0,746248588	0,008893074	2,5	3,703472665	0,001105846
82	1	0,027636256	0,023372376	0,023438407	4,979291155	2,5	2,5	2,5	0,609742974	0,008587688	2,5	3,706827183	9,94E-04
83	1	0,027645561	0,02232915	0,022387157	4,945324305	2,5	2,5	2,5	0,491107087	0,008302573	2,5	3,709832773	8,98E-04
84	1	0,027655005	0,021375033	0,02142626	4,768584126	2,5	2,5	2,5	0,390226666	0,008035777	2,5	3,712541029	8,16E-04
85	1	0,027664751	0,02049908	0,02054454	4,609447273	2,5	2,5	2,5	0,306253855	0,007785591	2,5	3,714993824	7,45E-04
86	1	0,027675515	0,019692067	0,019732593	4,532686112	2,5	2,5	2,5	0,237738317	0,007550509	2,5	3,717225486	6,82E-04
87	1	0,027692029	0,018946167	0,018982445	4,543379249	2,5	2,5	2,5	0,182834756	0,007329205	2,5	3,719264418	6,27E-04
88	1	0,027802067	0,018254693	0,018287295	4,635522583	2,5	2,5	2,5	0,139530793	0,007120502	2,5	3,721134329	5,79E-04
89	1	0,032875371	0,017611902	0,017641306	4,765789968	2,5	2,5	2,5	0,105840962	0,006923356	2,5	3,722855173	5,36E-04
90	1	0,148880328	0,017289581	0,017041318	4,872606309	2,5	2,5	2,5	0,079938625	0,006737539	2,5	3,72444387	4,98E-04
91	1	0,68375727	0,07953127	0,019184322	4,930613246	2,5	2,5	2,5	0,060225378	0,008215762	2,5	3,725914875	4,63E-04
92	1	1,388700828	0,18793645	0,053230863	4,955885652	2,5	2,5	2,5	0,045356214	0,076055277	2,5	3,727283074	4,35E-04
93	1	1,751861813	0,249395963	0,118494186	4,963025328	2,5	2,5	2,5	0,034320175	0,293022718	2,5	3,728647361	4,75E-04
94	1	1,861229455	0,276301037	0,170075507	4,824250637	2,5	2,5	2,5	0,026985958	0,454835399	2,5	3,730854148	9,40E-04
95	1	1,900262699	0,286922832	0,197039817	4,643580614	2,5	2,5	2,5	0,024333084	0,510151501	2,5	3,736376914	0,002047823
96	1	1,918828121	0,290937209	0,208931949	4,577662435	2,5	2,5	2,5	0,025092889	0,434211309	2,5	3,745625094	0,002570202
97	1	1,929570113	0,292431777	0,213807573	4,67917165	2,5	2,5	2,5	0,025721645	0,251808961	2,5	3,754840408	0,002129883
98	1	1,936596184	0,292985788	0,215736127	4,840233954	2,5	2,5	2,5	0,02469431	0,141804898	2,5	3,761565422	0,001522727
99	1	1,941571893	0,29319084	0,216483776	4,928280892	2,5	2,5	2,5	0,022371856	0,095039428	2,5	3,705263677	0,001090175
100	1	1,945294869	0,293266693	0,216769994	4,959964784	2,5	2,5	2,5	0,019488779	0,072067317	2,5	3,39662536	8,20E-04
101	1	1,94819411	0,293294747	0,216878634	4,971532469	2,5	2,5	2,5	0,016581375	0,058984345	2,5	2,958961125	6,48E-04
102	1	1,950516063	0,293305122	0,216919619	4,976930824	2,5	2,5	2,5	0,013914916	0,050771316	2,5	2,477435016	5,27E-04
103	1	1,952349761	0,293308958	0,216935012	4,980117992	2,5	2,5	2,5	0,011590373	0,045276115	2,5	1,98092305	4,38E-04
104	1	1,952947067	0,293310377	0,216940773	4,982296783	2,5	2,5	2,5	0,009630485	0,041432296	2,5	1,513669558	3,73E-04
105	1	1,942891216	0,293310902	0,216942924	4,98391926	2,5	2,5	2,5	0,008014781	0,038641675	2,5	1,199470259	3,24E-04
106	1	1,848958491	0,293311096	0,216943725	4,985195401	2,5	2,5	2,5	0,006701924	0,036455923	2,5	1,063641901	2,87E-04
107	1	1,331476184	0,293311168	0,216944023	4,986241818	2,5	2,5	2,5	0,005644478	0,034042246	2,5	1,000275091	2,57E-04
108	1	0,188638831	0,293311194	0,216944133	4,987142442	2,5	2,5	2,5	0,004796944	0,030306404	2,5	0,964936318	2,34E-04
109	1	0,03250026	0,293310717	0,216944151	4,987943154	2,5	2,5	2,5	0,013303462	0,027039392	2,5	0,949415755	0,010372731
110	1	0,017592398	0,279052351	0,215046308	4,986104587	2,5	2,5	2,5	0,137731807	0,024406586	2,5	1,099086241	0,088152854
111	1	0,016446423	0,186200224	0,178460876	4,793434881	2,5	2,5	2,5	0,387546226	0,022240073	2,5	1,488504438	0,16029301
112	1	0,016921246	0,136594173	0,137888075	4,21661095	2,5	2,5	2,5	0,73442052	0,020426244	2,5	2,016759511	0,202852222
113	1	0,017313314	0,107619667	0,109718813	3,813532516	2,5	2,5	2,5	1,126020869	0,018885576	2,5	2,595645412	0,202705665
114	1	0,017590017	0,088706987	0,090441452	3,671843728	2,5	2,5	2,5	1,515644708	0,017560754	2,5	3,111598738	0,141891334
115	1	0,017787238	0,075416043	0,076724164	3,851404539	2,5	2,5	2,5	1,882820398	0,016409434	2,5	3,430407823	0,056449435
116	1	0,017928858	0,065574045	0,066550932	4,231728823	2,5	2,5	2,5	2,189742111	0,015399656	2,5	3,546138703	0,01617864
117	1	0,01803108	0,057996705	0,058734146	4,557776269	2,5	2,5	2,5	2,355826918	0,014506852	2,5	3,583943368	0,00722389
118	1	0,018105137	0,051984922	0,052550743	4,751603034	2,5	2,5	2,5	2,345358077	0,013711824	2,5	3,605305161	0,005436624
119	1	0,018158949	0,047099912	0,047541504	4,855394826	2,5	2,5	2,5	2,218426825	0,012999353	2,5	3,623130062	0,00486813
120	1	0,018198228	0,043052574	0,043402826	4,908287121	2,5	2,5	2,5	2,044281936	0,012357222	2,5	3,639560521	0,004511014
121	1	0,018227517	0,039644772	0,039926724	4,935138344	2,5	2,5	2,5	1,855164495	0,011775511	2,5	3,654961049	0,004205339
122	1	0,018251992	0,036736211	0,036966245	4,949774976	2,5	2,5	2,5	1,662473746	0,011246079	2,5	3,669423013	0,003925151
123	1	0,018277131	0,03422479	0,034414746	4,958593811	2,5	2,5	2,5	1,470985467	0,010762184	2,5	3,682999149	0,003665449
124	1	0,018297002	0,032034447	0,032193019	4,964408137	2,5	2,5	2,5	1,284053532	0,010318196	2,5	3,695738317	0,003424528
125	1	0,01830461	0,03010736	0,030241037	4,968523552	2,5	2,5	2,5	1,104928903	0,009909377	2,5	3,707689537	0,003201194
126	1	0,018307873	0,028398796	0,028512486	4,971601652	2,5	2,5	2,5	0,936629776	0,009531707	2,5	3,718901568	0,002994322
127	1	0,018313085	0,026873604	0,026971075	4,973994614	2,5	2,5	2,5	0,781625268	0,009181759	2,5	3,729422074	0,0028028
128	1	0,018319374	0,025503785	0,025587964	4,975829101	2,5	2,5	2,5	0,641777648	0,008856589	2,5	3,739296955	0,002625524
129	1	0,018325693	0,024266762	0,024339947	4,976841485	2,5	2,5	2,5	0,518344688	0,008553657	2,5	3,748569828	0,002461394
130	1	0,018332119	0,023144127	0,023208143	4,968769367	2,5	2,5	2,5	0,411929648	0,008270756	2,5	3,757281692	0,002309341
131	1	0,01833865	0,022120721	0,022177032	4,833010672	2,5	2,5	2,5	0,322425421	0,008005966	2,5	3,765470749	0,002168332
132	1	0,018345407	0,021183952	0,021233741	4,619807198	2,5	2,5	2,5	0,249017281	0,0077576	2,5	3,77317228	0,00203736
133	1	0,018353154	0,020323268	0,020367502	4,488317158	2,5	2,5	2,5	0,19027902	0,007524177	2,5	3,780418534	0,001915436
134	1	0,018371775	0,019529766	0,019569238	4,486041809	2,5	2,5	2,5	0,144354785	0,007304388	2,5	3,787238621	0,001801574
135	1	0,019138357	0,018795877	0,018831246	4,614567468	2,5	2,5	2,5	0,109183802	0,007097073	2,5	3,793658341	0,001694763
136	1	0,066868924	0,018123054	0,018146987	4,78219489	2,5	2,5	2,5	0,082713753	0,00690122	2,5	3,799699904	0,001593926
137	1	0,499512947	0,050890104	0,018226834	4,892604949	2,5	2,5	2,5	0,063061921	0,007014926	2,5	3,805381458	0,001497853
138	1	1,306124405	0,167733874	0,041750891	4,939806951	2,5	2,5	2,5	0,048608294	0,051614056	2,5	3,810716326	0,001405118
139	1	1,749218835	0,240889086	0,10459218	4,955772476	2,5	2,5	2,5	0,038027433	0,2777748	2,5	3,815712332	0,00131441
140	1	1,867473025	0,273740328	0,162082056	4,829126049	2,5	2,5	2,5	0,030282438	0,464229446	2,5	3,820377668	0,001228079
141	1	1,907185898	0,286805716	0,193940879	4,626555073	2,5	2,5	2,5	0,024602667	0,540001254	2,5	3,824742561	0,001153269
142	1	1,925939261	0,291751286	0,208289351	4,529407744	2,5	2,5	2,5	0,020418014	0,491246815	2,5	3,828845087	0,00108348
143	1	1,936809115	0,293589844	0,214218044	4,601724551	2,5	2,5	2,5	0,01727668	0,30288139	2,5	3,832670502	0,00100305
144	1	1,943937992	0,294269643	0,216569501	4,785478533	2,5	2,5	2,5	0,014828067	0,163244446	2,5	3,836028929	9,08E-04
145	1	1,949002688	0,294520531	0,217481502	4,905703359	2,5	2,5	2,5	0,012825582	0,105165793	2,5	3,786954304	8,05E-04
146	1	1,952805928	0,29461306	0,217830387	4,951140256	2,5	2,5	2,5	0,011285168	0,078205515	2,5	3,485660017	8,27E-04
147	1	1,955779824	0,294647176	0,217962628	4,966864814	2,5	2,5	2,5	0,010230477	0,063477961	2,5	3,045776232	7,51E-04
148	1	1,958177694	0,294659753	0,218012426	4,973699175	2,5	2,5	2,5	0,008757779	0,054497753	2,5	2,556765868	4,23E-04
149	1	1,960151121	0,29466439	0,218031088	4,977589444	2,5	2,5	2,5	0,007133384	0,048609539	2,5	2,043188213	2,96E-04
150	1	1,961606677	0,294666099	0,218038056	4,980224006	2,5	2,5	2,5	0,00573076	0,044545902	2,5	1,524090198	2,53E-04

species	Rb_{nuc}	$CyclinD_{cyt}$	$(ubiquitin\text{-}pCyclinD)_{cyt}$	$(CyclinD\text{-}pCdk4/6\text{-}p27)_{nuc}$	$(CyclinD\text{-}pCdk4/6)_{nuc}$	$mRNA(CyclinE)_{nuc}$	$mRNA(CyclinE)_{cyt}$	CyclinE gene	$mRNA(CyclinD)_{nuc}$	$mRNA(CyclinD)_{cyt}$
t										
0	0	0	0	0	0	0	0	1	0	0
1	0	4,09E-16	0	0	1,68E-69	0	0	1	3,08E-04	4,33E-08
2	0	2,16E-05	0	0	3,12E-24	0	0	1	0,059038724	0,005428104
3	0	0,046708154	0	0	1,19E-08	2,40E-205	0	1	0,192006038	0,135487364
4	0	0,210320815	0	0	4,47E-04	4,39E-93	4,93E-187	1	0,23099435	0,218965305
5	0	0,269782093	0	0	0,013328906	7,65E-56	7,33E-112	1	0,245581693	0,241295993
6	0	0,290306781	0	0	0,056021172	1,77E-39	7,35E-79	1	0,254101266	0,251609122
7	0	0,302612824	0	0	0,13113324	9,10E-30	2,89E-59	1	0,259893037	0,258224843
8	0	0,312700291	0	0	0,247862503	1,22E-22	6,45E-45	1	0,261539795	0,261577519
9	0	0,314638632	0	1,21E-265	0,428108304	1,14E-16	6,32E-33	1	0,235885799	0,248104565
10	0	0,25223942	0	5,40E-180	0,704148177	2,77E-11	4,04E-22	1	0,101288765	0,152666225
11	0	0,158909696	0	1,82E-102	1,074182782	1,65E-06	1,68E-12	1	0,050836378	0,082218457
12	0	0,111598296	0	4,94E-39	1,492427142	0,011936739	1,14E-04	1	0,033780668	0,054901943
13	0	0,085937249	4,84E-94	3,35E-05	1,925531446	0,579196482	0,390075003	1	0,025272502	0,041064569
14	0	0,069885298	8,52E-21	0,116189535	2,17214976	0,842293708	0,56517887	1	0,020182312	0,032769951
15	0	0,057087958	9,98E-06	0,423433285	1,858694004	0,1679311	0,322780961	1	0,0167969	0,027255593
16	0	0,046222198	0,073319703	0,715387334	1,230493266	0,056324519	0,190375204	1	0,014383286	0,023327374
17	0	0,038213237	0,310499718	0,881431992	0,546937433	0,033211776	0,15132467	1	0,012575783	0,020387961
18	0	0,032509925	0,479491658	0,705219323	0,155866923	0,02350225	0,130947527	1	0,01117165	0,018106092
19	0	0,028344167	0,552807148	0,345737377	0,042340601	0,018176586	0,117874001	1	0,010049463	0,016283463
20	9,24E-199	0,025188525	0,479517918	0,109203808	0,009805435	0,01481595	0,108545141	1	0,009132076	0,014794173
21	4,71E-134	0,022716369	0,292329524	0,028297914	0,004315689	0,012503068	0,101440399	1	0,008368126	0,013554463
22	1,74E-97	0,020722678	0,131919012	0,011653271	0,003355397	0,010814339	0,095785804	1	0,0077221	0,012506459
23	5,89E-74	0,01907501	0,056704567	0,008478617	0,002978559	0,009527278	0,091139911	1	0,007168654	0,01160889
24	3,43E-57	0,017686013	0,030160992	0,007551442	0,002758577	0,008513867	0,087229858	1	0,006689222	0,010831538
25	1,02E-44	0,016496226	0,020203516	0,007009956	0,002609622	0,007695248	0,083876561	1	0,006269891	0,010151766
26	3,09E-35	0,015463707	0,015508873	0,0065579	0,002503042	0,007020199	0,080956885	1	0,005900027	0,009552287
27	7,91E-28	0,014557909	0,012795392	0,006145743	0,002426539	0,006454004	0,07838295	1	0,005571368	0,009019669
28	6,76E-22	0,013755974	0,011009868	0,005763355	0,002374253	0,005972304	0,076090103	1	0,005277392	0,008543316
29	3,89E-17	0,013040401	0,009735572	0,005407253	0,002343507	0,005557502	0,074029553	1	0,005012885	0,008114761
30	1,87E-13	0,01239753	0,008773177	0,005075189	0,002333555	0,005196568	0,07216368	1	0,00477363	0,007727152
31	8,21E-11	0,011816512	0,008014232	0,004765134	0,002345125	0,00487965	0,070462939	1	0,004556175	0,007374889
32	5,20E-09	0,011288613	0,007394664	0,004475044	0,002380344	0,004599161	0,068903749	1	0,004357674	0,007053348
33	3,10E-08	0,010806707	0,006874412	0,004202802	0,002442868	0,004349161	0,06746703	1	0,004175751	0,006758678
34	2,02E-08	0,010364914	0,006427336	0,003946114	0,002538168	0,004124936	0,066137144	1	0,004008415	0,006487646
35	2,05E-08	0,009958338	0,006035754	0,003702024	0,002674977	0,003922696	0,06490114	1	0,00385398	0,006237518
36	2,13E-08	0,009582861	0,005687296	0,003466966	0,00286663	0,003739358	0,063748179	1	0,003711011	0,006005964
37	2,22E-08	0,009234995	0,005372998	0,003236356	0,003133127	0,003572391	0,062669115	1	0,003578277	0,005790991
38	2,43E-08	0,008911762	0,005086045	0,00300389	0,003504693	0,003419697	0,061656165	1	0,003454718	0,005590879
39	3,62E-08	0,008610605	0,004821076	0,0027608	0,004026868	0,003279519	0,060702655	1	0,003339417	0,005404139
40	3,66E-07	0,008329312	0,004573641	0,002495637	0,004766215	0,003150381	0,059802831	1	0,003231572	0,005229474
41	1,28E-04	0,008065961	0,004339652	0,002196538	0,00581205	0,003031027	0,058951695	1	0,003130484	0,005065749
42	0,014560036	0,007818876	0,00411515	0,001859568	0,007262224	0,002920386	0,058144882	1	0,003035539	0,004911969
43	0,180568397	0,007586581	0,003896479	0,001503454	0,009178635	0,002817538	0,057378564	1	0,002946193	0,004767255
44	0,527954635	0,00736778	0,003681019	0,001174953	0,011527532	0,002721687	0,056649364	1	0,002861968	0,004630827
45	0,256893893	0,007161323	0,003468081	9,23E-04	0,014169602	0,002632142	0,05595429	1	0,002782436	0,004501995
46	0,131065734	0,006966188	0,003259256	7,68E-04	0,016920772	0,002548302	0,055290681	1	0,002707216	0,004380141
47	0,089597211	0,006781462	0,00305768	6,96E-04	0,019622555	0,002469638	0,054656162	1	0,002635967	0,004264714
48	0,07024867	0,006606331	0,00286682	6,57E-04	0,022216928	0,002395685	0,054048602	1	0,002568385	0,004155218
49	0,059113783	0,006440166	0,002689087	6,15E-04	0,024725496	0,002326032	0,053466086	1	0,00439082	0,004064918
50	0,051844804	0,006904338	0,002525301	5,70E-04	0,02716803	0,002260314	0,052906886	1	0,096764502	0,022929149
51	0,046694966	0,092977207	0,002375081	5,29E-04	0,029610678	0,002198208	0,05236944	1	0,205479617	0,16613506
52	0,042833938	0,232075044	0,002237541	5,02E-04	0,036434234	0,002139424	0,051852326	1	0,235091174	0,226152011
53	0,039817101	0,276204696	0,002111732	4,92E-04	0,065293	0,002083701	0,051354255	1	0,24770995	0,244019441
54	0,037384736	0,293863309	0,00199679	4,51E-04	0,124729323	0,002030808	0,050874048	1	0,255332886	0,25313276
55	0,035374713	0,305313236	0,001891626	4,12E-04	0,220086772	0,001980533	0,050410628	1	0,258901049	0,258183068
56	0,033679088	0,310382883	0,00179509	3,84E-04	0,366711924	0,001932687	0,049963008	1	0,2461157	0,252447456
57	0,032200021	0,275039895	0,001706231	3,63E-04	0,59112495	0,001887099	0,04953028	1	0,142523805	0,188615801
58	0,030562681	0,174857616	0,001624274	3,44E-04	0,905396142	0,001843644	0,049111609	1	0,059945623	0,096105813
59	0,027199166	0,117219874	0,001548552	3,28E-04	1,274129191	0,002057177	0,048707647	1	0,037604706	0,061035271
60	0,02273216	0,08741647	0,001478477	3,14E-04	1,663786408	0,191902999	0,094779439	1	0,027358709	0,04444207
61	0,019791779	0,069698376	0,0014139	0,018026008	2,030139016	0,739357808	0,49283199	1	0,02149245	0,034895387
62	0,018037237	0,057484275	0,001704461	0,255999911	1,960643711	0,432310996	0,482399092	1	0,017695113	0,028713184
63	0,016914695	0,047335491	0,050825962	0,555841041	1,462027634	0,085396288	0,229720906	1	0,015037109	0,024388175
64	0,016156334	0,039352683	0,254008888	0,77950179	0,802289397	0,041775531	0,166845945	1	0,013072871	0,021194224
65	0,015621794	0,033477686	0,425148622	0,737785124	0,306866003	0,027511599	0,139764157	1	0,011562265	0,018739464
66	0,01523148	0,029138485	0,521111917	0,414180082	0,140259763	0,020489948	0,123753278	1	0,010364471	0,016794101
67	0,014937514	0,025843138	0,48840742	0,156364816	0,080991683	0,016318978	0,11283374	1	0,009391474	0,015214565
68	0,014709801	0,023263083	0,330424729	0,051045932	0,05345403	0,013557284	0,104753237	1	0,008585435	0,013906573
69	0,01452879	0,021186089	0,165960824	0,022050854	0,039708065	0,011594362	0,098448723	1	0,007906789	0,012805662
70	0,014381433	0,019473251	0,07525262	0,013645785	0,033070486	0,010127644	0,093343852	1	0,007327551	0,011866272
71	0,014258543	0,018032338	0,039579354	0,010172754	0,030436978	0,008990175	0,089095166	1	0,006827375	0,01105529
72	0,014150494	0,016800463	0,025648335	0,008157466	0,030272065	0,008082319	0,08548339	1	0,006391111	0,010348074
73	0,014022958	0,015733299	0,019024116	0,006736919	0,031767371	0,007340946	0,082360984	1	0,006007247	0,009725906
74	0,013626759	0,01479861	0,01516134	0,005644165	0,034435364	0,006724118	0,079624476	1	0,00566688	0,009174317
75	0,011574503	0,01397231	0,012582426	0,004777689	0,03792944	0,006202892	0,077198826	1	0,005363013	0,008681941

76	0,005781703	0,013235987	0,010714404	0,004085398	0,041981737	0,005756644	0,075028081	1	0,005090077	0,008239729
77	0,001006184	0,012575291	0,009289678	0,003529869	0,046386186	0,005370283	0,073069539	1	0,004843578	0,007840387
78	5,89E-05	0,011978843	0,008164371	0,003080607	0,050989546	0,005032515	0,071289957	1	0,004619854	0,007477969
79	3,04E-06	0,011437495	0,007252941	0,002713327	0,055681034	0,004734715	0,069663008	1	0,00441589	0,00714758
80	1,55E-06	0,010943791	0,006500582	0,00240969	0,060381434	0,004470187	0,068167528	1	0,004229179	0,006845155
81	1,46E-06	0,010491591	0,005870126	0,002155393	0,065035717	0,00423365	0,066786278	1	0,004057623	0,006567287
82	1,48E-06	0,010075785	0,005335246	0,001939842	0,069606521	0,004020885	0,065505055	1	0,003899449	0,006311103
83	1,49E-06	0,009692084	0,00487665	0,001755413	0,074068355	0,00382848	0,064312029	1	0,003753151	0,006074159
84	1,52E-06	0,009336856	0,00447982	0,001596328	0,078404323	0,003653646	0,06319726	1	0,003617442	0,005854367
85	1,60E-06	0,009007006	0,004133681	0,001458089	0,082603877	0,003494082	0,062152322	1	0,003491213	0,005649929
86	1,91E-06	0,008699877	0,003829631	0,001337156	0,086661126	0,003347871	0,061170017	1	0,003373505	0,005459292
87	4,16E-06	0,008413176	0,003560847	0,001230718	0,090573585	0,003213404	0,060244157	1	0,003263485	0,005281103
88	5,99E-05	0,008144912	0,003321859	0,001136518	0,094341234	0,003089322	0,059369383	1	0,003160424	0,005114183
89	0,003217681	0,007893345	0,003108228	0,001052728	0,097965829	0,002974465	0,058541031	1	0,003063683	0,004957495
90	0,055196189	0,007656951	0,002916328	9,78E-04	0,101450376	0,002867842	0,057755017	1	0,002972699	0,004810126
91	0,236296124	0,007434389	0,002743181	9,11E-04	0,104798664	0,002768598	0,057007748	1	0,002886974	0,004671271
92	0,318799799	0,00722447	0,002586332	8,61E-04	0,107998732	0,002675993	0,056296049	1	0,002806065	0,004540211
93	0,187202579	0,007026139	0,002443895	0,00102846	0,110705684	0,002589382	0,055617101	1	0,002729578	0,004416308
94	0,105797001	0,006838458	0,002316513	0,002319945	0,11081979	0,002508202	0,05496839	1	0,002657161	0,004298993
95	0,069634532	0,006660578	0,002215288	0,00465574	0,105738213	0,002431957	0,05434767	1	0,002588499	0,004187754
96	0,051177339	0,006491736	0,00216479	0,005127745	0,099190798	0,00236021	0,053752922	1	0,002523604	0,00408213
97	0,040435508	0,006335448	0,002177055	0,003955128	0,095102212	0,002292575	0,053182327	1	0,018684431	0,004411098
98	0,033409321	0,015897803	0,002232169	0,002786113	0,093293628	0,002228709	0,052634244	1	0,155309504	0,075201645
99	0,028433504	0,161644825	0,002297056	0,00201306	0,093390492	0,002168304	0,052107183	1	0,21965278	0,198919909
100	0,024710383	0,253728695	0,002346994	0,001536767	0,105031963	0,002111087	0,051599792	1	0,238868738	0,233160175
101	0,021810498	0,281720815	0,002370546	0,001227219	0,145170532	0,002056812	0,051110838	1	0,248283166	0,245586582
102	0,019481895	0,294619586	0,002365919	0,001002372	0,218254094	0,002005258	0,050639195	1	0,252283234	0,251433702
103	0,017566077	0,299129258	0,002336254	8,38E-04	0,332456849	0,001956225	0,050183832	1	0,243329406	0,247721179
104	0,015950108	0,275583968	0,002286652	7,18E-04	0,505014505	0,001909533	0,049743803	1	0,177627039	0,20623296
105	0,014470931	0,185203461	0,002222556	6,28E-04	0,748788679	0,001865018	0,049318238	1	0,069798603	0,10982014
106	0,012498079	0,119682427	0,002148874	5,57E-04	1,042183298	0,001825193	0,048906351	1	0,041300239	0,066793312
107	0,009223284	0,086565543	0,002069619	5,01E-04	1,356825847	0,005148828	0,048540764	1	0,029269882	0,047489013
108	0,006069188	0,067586987	0,001987873	4,59E-04	1,676213163	0,32085994	0,21596653	1	0,022656032	0,036763972
109	0,004046961	0,055400636	0,001910129	0,047190171	1,923331626	0,715314419	0,50295905	1	0,018476898	0,02997234
110	0,002778994	0,046590765	0,003385549	0,312433224	1,686016922	0,269289406	0,391326436	1	0,01559816	0,025293082
111	0,001946336	0,03946771	0,092386074	0,59530198	1,114423644	0,068532521	0,207423871	1	0,013494965	0,021875523
112	0,001381159	0,03386427	0,292509234	0,75821167	0,479707375	0,03718074	0,158664819	1	0,011891271	0,01927075
113	9,89E-04	0,029566604	0,442402378	0,602728563	0,111993427	0,025430924	0,1352497	1	0,010628094	0,017219927
114	7,12E-04	0,026242473	0,498522621	0,276450958	0,016533185	0,019311002	0,120788425	1	0,009607425	0,015563456
115	5,15E-04	0,023617567	0,408459852	0,07791841	0,004983378	0,015561655	0,110691226	1	0,008765564	0,014197631
116	3,73E-04	0,021497806	0,231235543	0,023220724	0,003682057	0,013030216	0,103108652	1	0,00805932	0,013052155
117	2,71E-04	0,019748481	0,102546283	0,012823897	0,003234064	0,011206579	0,097132799	1	0,007458372	0,012077699
118	1,97E-04	0,018276824	0,047644075	0,010550351	0,002973884	0,009830454	0,092258487	1	0,006940811	0,011238633
119	1,44E-04	0,017018858	0,028056524	0,009618755	0,002784267	0,008755189	0,088179036	1	0,006490409	0,010508577
120	1,05E-04	0,015929367	0,020145247	0,008936768	0,002632839	0,007891876	0,084695914	1	0,006094895	0,009867586
121	7,57E-05	0,01497543	0,016140864	0,008331344	0,002506997	0,007183487	0,081674082	1	0,005744812	0,009300299
122	5,16E-05	0,014132429	0,013713608	0,007773374	0,002400564	0,006591764	0,079018006	1	0,005432761	0,008794697
123	2,70E-05	0,013381533	0,0120611	0,0072563	0,002310083	0,006090085	0,076657908	1	0,005152864	0,008341237
124	7,90E-06	0,012708052	0,010845674	0,006777127	0,002233469	0,005659353	0,074541449	1	0,004900396	0,00793225
125	1,61E-06	0,012100336	0,009900006	0,00633342	0,002169436	0,005285516	0,072628482	1	0,004671516	0,007561499
126	1,20E-06	0,01154901	0,009131793	0,005922824	0,002117212	0,004958	0,070887617	1	0,004463066	0,007223861
127	1,21E-06	0,011046437	0,008486455	0,005543021	0,002076384	0,004668699	0,0692939	1	0,00427243	0,006915091
128	1,01E-06	0,010586321	0,007930094	0,005191711	0,002046857	0,004411295	0,067827206	1	0,004097418	0,006631639
129	1,02E-06	0,010163425	0,007440814	0,004866626	0,002028898	0,004180788	0,066471092	1	0,003936186	0,006370512
130	1,03E-06	0,009773351	0,007003965	0,00456558	0,002023121	0,003973172	0,065211977	1	0,003787171	0,006129175
131	1,05E-06	0,009412379	0,006609388	0,004286462	0,002030531	0,003785199	0,064038524	1	0,003649034	0,005905459
132	1,11E-06	0,009077334	0,006249827	0,00402722	0,002052629	0,003614207	0,062941183	1	0,003520629	0,005697503
133	1,47E-06	0,008765494	0,005920018	0,003785839	0,002091572	0,003457996	0,061911849	1	0,003400963	0,005503698
134	7,33E-06	0,00847451	0,005615926	0,003560303	0,002150411	0,003314727	0,060943582	1	0,003289174	0,005322649
135	5,91E-04	0,008202341	0,005334325	0,003348534	0,002233443	0,003182857	0,060030406	1	0,00318451	0,005153135
136	0,027124563	0,007947205	0,00507252	0,003148302	0,002346745	0,003061077	0,059167142	1	0,003086313	0,004994089
137	0,218172366	0,007707544	0,004828237	0,002957072	0,002498985	0,002948272	0,058349274	1	0,002994002	0,004844571
138	0,43310659	0,007481982	0,004599545	0,002771845	0,002702569	0,002843486	0,057572841	1	0,002907064	0,00470375
139	0,229422227	0,007269304	0,00438472	0,002590496	0,002972772	0,002745892	0,056834359	1	0,002825045	0,004570889
140	0,124094642	0,007068433	0,004182156	0,002421105	0,003309128	0,002654774	0,056130741	1	0,002747539	0,004445331
141	0,085484109	0,006878406	0,00399059	0,002276849	0,003677806	0,00256951	0,055459246	1	0,002674186	0,004326491
142	0,066786876	0,006698365	0,003809468	0,002134696	0,004085605	0,002489551	0,054817428	1	0,002604666	0,004213844
143	0,055917347	0,006530139	0,003638283	0,001965779	0,004605914	0,002414419	0,054203098	1	0,01501798	0,004373888
144	0,04878847	0,013404854	0,003475751	0,001767821	0,005314682	0,002343688	0,053614288	1	0,148779795	0,066170559
145	0,043723773	0,153998058	0,003319904	0,001569225	0,00668412	0,002276984	0,053049223	1	0,219504483	0,196626936
146	0,039920534	0,253207734	0,003169355	0,001721267	0,017374048	0,002213971	0,0525063	1	0,240287053	0,234113722
147	0,036946637	0,28348804	0,003027343	0,001331784	0,05483105	0,002154352	0,051984064	1	0,250735208	0,247683051
148	0,034548627	0,298245172	0,002892647	7,37E-04	0,124707493	0,002097859	0,051481192	1	0,25747975	0,255530415
149	0,032567732	0,309213472	0,002755876	5,60E-04	0,234058953	0,002044254	0,050996478	1	0,260237925	0,25984311
150	0,030897213	0,313233755	0,002615947	4,92E-04	0,402466472	0,00199332	0,050528821	1	0,241026308	0,250358506

species	CyclinD gene	$CyclinE_{cyt}$	$(CyclinE\text{-}Cdk2)_{cyt}$	$(CyclinE\text{-}Cdk2\text{-}p27)_{cyt}$	$(CyclinE\text{-}Cdk2)_{nuc}$	$(CyclinE\text{-}Cdk2\text{-}p27)_{nuc}$	$(CyclinE\text{-}pCdk2)_{nuc}$	$TGF\text{-}\beta_{nuc}$	$(DP\text{-}pE2F)_{nuc}$	CyclinA gene	$mRNA(CyclinA)_{nuc}$
t											
0	1	0	0	0	0	0	0	2	0	1	0
1	1	0	0	0	0	0	0	2	0	1	0
2	1	0	0	0	0	0	0	2	0	1	0
3	1	0	0	0	0	0	0	2	0	1	0
4	1	0	0	0	0	0	0	2	0	1	0
5	1	0	0	0	0	0	0	2	0	1	0
6	1	2.6565783909	1.176783574E	4.6704624E-3	0	0	0	2	0	1	0
7	1	1,25E-234	8,21E-236	4,92E-237	0	0	0	2	0	1	0
8	1	2,91E-177	1,95E-178	1,25E-179	0	0	0	2	0	1	0
9	1	2,55E-129	1,75E-130	1,15E-131	2,91E-267	9,59E-265	1,21E-265	2	0	1	0
10	1	2,13E-86	9,88E-88	4,44E-89	3,09E-181	8,33E-179	5,14E-180	2	0	1	0
11	1	7,45E-48	4,02E-49	2,14E-50	9,17E-104	2,35E-101	1,75E-102	2	0	1	0
12	1	2,00E-16	1,36E-17	9,26E-19	2,07E-40	5,13E-38	4,80E-39	2	0	1	6,42E-164
13	1	0,112306717	0,038381449	0,016635444	2,95E-07	6,95E-05	3,53E-05	2	0	1	1,43E-25
14	1	0,666417023	0,35710763	0,317385262	1,64E-04	0,061876865	0,15813765	1,99702812	0	1	6,78E-07
15	1	0,819927793	0,612191531	0,450228294	2,79E-04	0,187646421	0,690882195	0,133122737	0	1	0,020952844
16	1	0,217398526	0,570972674	0,432864069	3,04E-04	0,269194783	1,2203563	0,019419043	1,81E-218	1	0,267581228
17	1	0,028450337	0,280604465	0,284077301	2,42E-04	0,173778828	1,605734146	0,008441694	1,02E-114	1	0,520827106
18	1	0,008960068	0,132933343	0,162968666	8,62E-05	0,045840394	1,617763747	0,005468644	5,29E-62	1	0,682020164
19	1	0,005301165	0,07973861	0,107396947	3,10E-05	0,030176797	1,330850381	0,004641799	3,18E-33	1	0,753604201
20	1	0,003703845	0,054800585	0,080198887	1,18E-05	0,041389024	0,961590701	0,004418759	6,46E-19	1	0,781088628
21	1	0,002783155	0,040223746	0,064594145	6,84E-06	0,058081896	0,583152162	0,004374966	6,69E-12	1	0,791234536
22	1	0,002191217	0,03060775	0,054436086	5,93E-06	0,06829685	0,277794945	0,004370596	2,83E-08	1	0,794947353
23	1	0,001783907	0,023840726	0,047205431	5,48E-06	0,072818346	0,104002531	0,004370425	5,39E-06	1	0,796303607
24	1	0,001489517	0,018900182	0,041730542	5,13E-06	0,073725029	0,037356946	0,004370422	1,91E-04	1	0,796773247
25	1	0,001268581	0,01520986	0,037404174	4,80E-06	0,072348061	0,017483816	0,004370422	0,002241769	1	0,796589299
26	1	0,001097757	0,012409914	0,033881702	4,51E-06	0,069510165	0,011847782	0,004370422	0,013317245	1	0,794249638
27	1	9,62E-04	0,010259887	0,030951983	4,23E-06	0,065738568	0,010068827	0,004370422	0,051977947	1	0,784666528
28	1	8,53E-04	0,008591858	0,02847695	3,97E-06	0,061383523	0,009323032	0,004370422	0,154558838	1	0,757762452
29	1	7,63E-04	0,007285193	0,026361169	3,73E-06	0,056684228	0,008857189	0,004370422	0,380518368	1	0,701910908
30	1	6,88E-04	0,006251668	0,024535529	3,50E-06	0,051807305	0,008468056	0,004370422	0,812719219	1	0,617516053
31	1	6,25E-04	0,005426028	0,02294803	3,29E-06	0,046870466	0,008100863	0,004370423	1,527082354	1	0,532034368
32	1	5,58E-04	0,004772396	0,021559015	3,09E-06	0,041957861	0,007741558	0,004370444	1,982622405	1	0,472850492
33	1	4,04E-04	0,004305745	0,020361283	2,91E-06	0,037133986	0,007387039	0,004370665	1,759217944	1	0,432760354
34	1	3,50E-04	0,003832588	0,01930306	2,73E-06	0,032449493	0,007036641	0,004371105	0,502139278	1	0,403253549
35	1	3,22E-04	0,003430666	0,018343291	2,56E-06	0,027934053	0,00668904	0,004371613	0,067631004	1	0,380301044
36	1	2,97E-04	0,003099305	0,017474326	2,40E-06	0,023613252	0,006341476	0,004372151	0,028183354	1	0,361742031
37	1	2,76E-04	0,002822322	0,016688478	2,23E-06	0,019515562	0,005989038	0,004372709	0,017562592	1	0,346301147
38	1	2,57E-04	0,002587561	0,015976952	2,06E-06	0,015676158	0,005623539	0,004373307	0,013619779	1	0,33317055
39	1	2,41E-04	0,002386178	0,015331085	1,89E-06	0,012142459	0,005232226	0,004374079	0,01201822	1	0,321810081
40	1	2,26E-04	0,002211618	0,014742921	1,69E-06	0,008980417	0,004797075	0,004378181	0,011424843	1	0,311842794
41	1	2,13E-04	0,002058928	0,014205405	1,46E-06	0,006276801	0,004297468	0,005422135	0,011260855	1	0,302996378
42	1	2,01E-04	0,0019243	0,013712391	1,21E-06	0,004125438	0,003721954	0,154653487	0,011228065	1	0,295068412
43	1	1,90E-04	0,001804757	0,013258576	9,53E-07	0,002583153	0,003091692	1,704310128	0,011213922	1	0,287904778
44	1	1,80E-04	0,001694699	0,012842507	7,37E-07	0,001610615	0,002475838	1,967765499	0,011197575	1	0,281385711
45	1	1,72E-04	0,001522996	0,012524648	5,90E-07	0,001067466	0,001962199	1,983707275	0,011177682	1	0,275416495
46	1	1,63E-04	0,001091188	0,012467968	5,13E-07	7,94E-04	0,001605304	1,98661302	0,011152709	1	0,269921068
47	1	1,56E-04	5,93E-04	0,012442825	4,83E-07	6,59E-04	0,001404193	1,987100949	0,011117567	1	0,264837521
48	1	1,49E-04	3,41E-04	0,012168868	4,58E-07	5,64E-04	0,001293411	1,987139172	0,011067314	1	0,260114862
49	1	1,42E-04	2,48E-04	0,011773901	4,26E-07	4,80E-04	0,001205296	1,987139657	0,010999446	1	0,255710644
50	1	1,36E-04	2,06E-04	0,01137572	3,94E-07	4,12E-04	0,001119649	1,987139657	0,010915131	1	0,251589197
51	1	1,31E-04	1,81E-04	0,011004945	3,66E-07	3,58E-04	0,001039079	1,987139657	0,010817748	1	0,247720285
52	1	1,26E-04	1,64E-04	0,010665082	3,58E-07	2,98E-04	9,79E-04	1,987139657	0,01071076	1	0,244078081
53	1	1,21E-04	1,51E-04	0,010354032	3,45E-07	1,94E-04	9,51E-04	1,987139657	0,010597111	1	0,240640366
54	1	1,16E-04	1,40E-04	0,010068675	3,08E-07	1,24E-04	8,87E-04	1,987139657	0,010479226	1	0,237387902
55	1	1,12E-04	1,31E-04	0,009805927	2,85E-07	9,21E-05	8,16E-04	1,987139657	0,010359073	1	0,234303932
56	1	1,08E-04	1,24E-04	0,009563019	2,68E-07	7,58E-05	7,58E-04	1,987139657	0,010238232	1	0,231373781
57	1	1,04E-04	1,17E-04	0,009337544	2,54E-07	6,60E-05	7,13E-04	1,987139657	0,010117957	1	0,22858453
58	1	1,01E-04	1,12E-04	0,009127438	2,42E-07	5,97E-05	6,75E-04	1,987139657	0,009999232	1	0,225924755
59	1	9,76E-05	1,06E-04	0,008930938	2,31E-07	5,54E-05	6,42E-04	1,987139657	0,009882819	1	0,22338431
60	1	3,82E-04	1,69E-04	0,008766876	2,22E-07	5,23E-05	6,14E-04	1,987139657	0,009769312	1	0,220954146
61	1	0,370610527	0,186747918	0,166522132	4,95E-05	0,013082885	0,020277012	1,987139276	0,009659187	1	0,218626162
62	1	0,802334049	0,488544616	0,392422176	2,31E-04	0,117351471	0,339463049	1,870969479	0,009552836	1	0,216638901
63	1	0,419947333	0,629874127	0,441614332	2,91E-04	0,222133131	0,843302828	0,053805249	0,009450828	1	0,315182895
64	1	0,059517656	0,421559294	0,336525372	2,69E-04	0,20410977	1,298173705	0,015334525	0,009353863	1	0,542450727
65	1	0,012209624	0,226614864	0,193405359	1,27E-04	0,059707975	1,467138358	0,008181016	0,009262317	1	0,685323752
66	1	0,006219106	0,156654846	0,120857508	4,47E-05	0,020469956	1,265025252	0,006371453	0,009176266	1	0,748720234
67	1	0,004122376	0,126469337	0,087439274	2,29E-05	0,012806716	0,949862379	0,005894907	0,009095631	1	0,77339292
68	1	0,003003149	0,108966615	0,06956609	1,43E-05	0,010059019	0,616244541	0,005789062	0,009020415	1	0,782659274
69	1	0,002314283	0,096981201	0,058528361	1,02E-05	0,008630753	0,327839817	0,005775709	0,008953023	1	0,786118216
70	1	0,001854516	0,088067007	0,050935335	7,80E-06	0,007496018	0,141628923	0,005775991	0,008935988	1	0,787404998
71	1	0,001529716	0,08113269	0,045302292	6,28E-06	0,006358087	0,056141234	0,005777535	0,009481721	1	0,787789817
72	1	0,001290261	0,07558466	0,040900943	5,19E-06	0,005217914	0,025363487	0,005779597	0,013911026	1	0,78710254
73	1	0,001107744	0,071056587	0,037335656	4,34E-06	0,004169641	0,014795999	0,005782244	0,033974191	1	0,782593045
74	1	9,65E-04	0,067304088	0,034371773	3,67E-06	0,003288347	0,010661299	0,005785576	0,095959452	1	0,766628709
75	1	8,51E-04	0,064155736	0,031859633	3,13E-06	0,002594416	0,008594102	0,005789723	0,240971284	1	0,726738371

76	1	7,57E-04	0,061487004	0,029698076	2,70E-06	0,00206735	0,007280588	0,005794935	0,523582667	1	0,654600203
77	1	6,80E-04	0,059205019	0,027815522	2,34E-06	0,001671643	0,00631161	0,005801994	1,030602829	1	0,565209425
78	1	6,15E-04	0,057239138	0,026159462	2,06E-06	0,001373347	0,005543602	0,005813513	1,672501282	1	0,494422977
79	1	4,86E-04	0,055607447	0,024691415	1,82E-06	0,001145797	0,004914175	0,005836116	1,544929885	1	0,447833015
80	1	3,97E-04	0,054159322	0,023380985	1,63E-06	9,70E-04	0,004389149	0,005869806	0,680000836	1	0,414575569
81	1	3,60E-04	0,052850313	0,022200642	1,46E-06	8,31E-04	0,003945412	0,005906396	0,091169614	1	0,389230367
82	1	3,31E-04	0,05169601	0,021131958	1,32E-06	7,20E-04	0,003566165	0,005943892	0,033238687	1	0,369033956
83	1	3,05E-04	0,050676003	0,020160183	1,20E-06	6,30E-04	0,003239216	0,005981896	0,019139228	1	0,352413204
84	1	2,83E-04	0,049771391	0,019272851	1,09E-06	5,55E-04	0,002955293	0,006020515	0,013988219	1	0,338398226
85	1	2,64E-04	0,048966535	0,018459443	1,00E-06	4,94E-04	0,002707121	0,006060565	0,011692622	1	0,326353935
86	1	2,47E-04	0,048248422	0,017711082	9,19E-07	4,42E-04	0,002488901	0,006105717	0,01058955	1	0,315844465
87	1	2,32E-04	0,04760613	0,017020245	8,48E-07	3,98E-04	0,002295968	0,006182207	0,010084945	1	0,306559187
88	1	2,18E-04	0,047030411	0,016380527	7,85E-07	3,60E-04	0,002124534	0,006858116	0,009889473	1	0,298269782
89	1	2,06E-04	0,046513389	0,015786442	7,28E-07	3,28E-04	0,0019715	0,040393837	0,009831124	1	0,290804058
90	1	1,95E-04	0,046048315	0,015233272	6,77E-07	3,00E-04	0,001834312	0,709499119	0,00981331	1	0,284029289
91	1	1,84E-04	0,045624014	0,014722108	6,32E-07	2,75E-04	0,001710922	1,894237596	0,0098004	1	0,277841241
92	1	1,75E-04	0,044790295	0,014668278	6,14E-07	2,63E-04	0,001612624	1,9656635	0,009787033	1	0,27215672
93	1	1,67E-04	0,039129196	0,019005239	9,22E-07	3,92E-04	0,001787029	1,976923615	0,009773823	1	0,266908376
94	1	1,59E-04	0,022759057	0,031118747	2,45E-06	0,001044867	0,003488772	1,979249273	0,009759044	1	0,262041001
95	1	1,52E-04	0,006952893	0,037605544	3,96E-06	0,001744127	0,007153579	1,97955381	0,009740343	1	0,257508833
96	1	1,45E-04	0,001269348	0,033582712	3,40E-06	0,001541277	0,008957685	1,979565426	0,00971622	1	0,253273565
97	1	1,39E-04	3,29E-04	0,027701417	2,35E-06	0,001081363	0,007943824	1,979565152	0,009686289	1	0,249302837
98	1	1,33E-04	2,12E-04	0,023289391	1,65E-06	7,64E-04	0,006129219	1,979565011	0,009650994	1	0,245569095
99	1	1,28E-04	1,81E-04	0,020166431	1,23E-06	5,68E-04	0,004581405	1,979564964	0,009610939	1	0,242048702
100	1	1,23E-04	1,63E-04	0,017877165	9,69E-07	4,22E-04	0,00348166	1,97956495	0,009566687	1	0,238721245
101	1	1,18E-04	1,50E-04	0,016135619	7,87E-07	2,96E-04	0,002731338	1,979564944	0,009518868	1	0,235568988
102	1	1,14E-04	1,39E-04	0,014770554	6,51E-07	2,12E-04	0,002196627	1,979564942	0,009468216	1	0,232576432
103	1	1,10E-04	1,30E-04	0,013674467	5,53E-07	1,60E-04	0,001810317	1,979564941	0,009415519	1	0,229729961
104	1	1,06E-04	1,23E-04	0,012776649	4,79E-07	1,28E-04	0,001528893	1,979564941	0,009361545	1	0,227017558
105	1	1,03E-04	1,16E-04	0,012028762	4,23E-07	1,07E-04	0,001319618	1,979564941	0,009306995	1	0,224428568
106	1	9,92E-05	1,10E-04	0,011396698	3,78E-07	9,22E-05	0,001160022	1,979564941	0,009252474	1	0,221953506
107	1	9,60E-05	1,05E-04	0,010855759	3,42E-07	8,18E-05	0,001035413	1,979564941	0,009198482	1	0,21958389
108	1	0,009320003	0,002426234	0,011081509	3,32E-07	7,84E-05	9,40E-04	1,97956494	0,009145428	1	0,217312114
109	1	0,453144502	0,246817211	0,229840031	9,44E-05	0,028334522	0,054858322	1,979535385	0,009093639	1	0,215131342
110	1	0,743316389	0,527082159	0,407654181	2,46E-04	0,138006628	0,430741184	1,617938538	0,00904337	1	0,214470295
111	1	0,241154661	0,573863038	0,418676507	2,85E-04	0,223408276	0,927304516	0,039650985	0,008994887	1	0,355852819
112	1	0,029675636	0,317072381	0,286447284	2,30E-04	0,160482151	1,315324569	0,01372841	0,008948511	1	0,56611691
113	1	0,009035519	0,166772514	0,16621615	8,53E-05	0,0559503	1,346465221	0,00832093	0,008904474	1	0,6900137
114	1	0,005227494	0,111220214	0,109991342	2,33E-05	0,057253971	1,080768416	0,006983957	0,008862975	1	0,744124532
115	1	0,003577834	0,084214091	0,082608716	9,97E-06	0,087471695	0,733988281	0,006679592	0,008824549	1	0,765272151
116	1	0,002649	0,067639601	0,067013732	8,22E-06	0,105950134	0,41144394	0,006633269	0,008792818	1	0,773277401
117	1	0,002063363	0,05610889	0,056920611	7,52E-06	0,114181276	0,183384322	0,006630187	0,008804819	1	0,77627756
118	1	0,001666254	0,047524536	0,049765488	6,99E-06	0,116439028	0,071412019	0,006630613	0,009247033	1	0,777326051
119	1	0,001382456	0,040867633	0,044362795	6,52E-06	0,1151739	0,031424932	0,006631352	0,012719502	1	0,777090446
120	1	0,001171369	0,035561783	0,040099584	6,09E-06	0,111783125	0,018987651	0,006632348	0,029005273	1	0,773685049
121	1	0,001009345	0,031246715	0,036627621	5,69E-06	0,107101657	0,014999377	0,006633655	0,081185929	1	0,76086601
122	1	8,82E-04	0,027681802	0,033733093	5,32E-06	0,101651993	0,013462459	0,006635348	0,208374956	1	0,727630183
123	1	7,79E-04	0,024698713	0,031276228	4,97E-06	0,095772667	0,012635456	0,006637557	0,464495154	1	0,664596308
124	1	6,95E-04	0,022175602	0,029160956	4,65E-06	0,08968815	0,012014483	0,006640669	0,92519787	1	0,579840735
125	1	6,26E-04	0,020021903	0,02731855	4,35E-06	0,083549247	0,011454268	0,006646023	1,622770347	1	0,505067054
126	1	5,34E-04	0,018199993	0,025699446	4,07E-06	0,077457788	0,010915336	0,006657639	1,747922476	1	0,45506572
127	1	4,26E-04	0,016641713	0,024271574	3,82E-06	0,071484038	0,010389501	0,006678895	1,210237733	1	0,419910898
128	1	3,82E-04	0,015231887	0,022994665	3,58E-06	0,065674202	0,009877289	0,006703713	0,17229798	1	0,39338563
129	1	3,50E-04	0,013991977	0,021843092	3,36E-06	0,060055437	0,009381013	0,006729482	0,044869338	1	0,37239624
130	1	3,22E-04	0,012900727	0,020800415	3,15E-06	0,054644375	0,008902771	0,006755708	0,022939092	1	0,355211838
131	1	2,98E-04	0,011935671	0,019852743	2,96E-06	0,049450669	0,008443928	0,006782393	0,015828921	1	0,34077882
132	1	2,77E-04	0,011078354	0,018988195	2,79E-06	0,044479068	0,008005041	0,006810164	0,012977568	1	0,328414012
133	1	2,59E-04	0,010313624	0,018196652	2,62E-06	0,039731075	0,007585924	0,006843151	0,011772758	1	0,317652157
134	1	2,42E-04	0,009628914	0,017469502	2,47E-06	0,035206326	0,007185712	0,006942873	0,011322498	1	0,308163753
135	1	2,28E-04	0,009013713	0,016799398	2,32E-06	0,030903795	0,006802875	0,012440677	0,011197924	1	0,299707862
136	1	2,15E-04	0,008459168	0,016180047	2,18E-06	0,02682297	0,00643516	0,312839892	0,011171328	1	0,292103562
137	1	2,03E-04	0,007957622	0,015606188	2,05E-06	0,022965125	0,00607943	1,830201193	0,011157905	1	0,285211913
138	1	1,92E-04	0,00746627	0,015107597	1,92E-06	0,019336763	0,005731412	1,967241982	0,011143228	1	0,278924149
139	1	1,82E-04	0,006435657	0,015174788	1,79E-06	0,015994486	0,005387273	1,98072795	0,011127643	1	0,273153698
140	1	1,73E-04	0,003830488	0,016586845	1,68E-06	0,013177668	0,005056668	1,983358141	0,01110963	1	0,267830646
141	1	1,65E-04	0,001364399	0,017460633	1,58E-06	0,011006816	0,004762818	1,983749436	0,011085878	1	0,262897808
142	1	1,57E-04	4,70E-04	0,016725466	1,48E-06	0,009113006	0,004483097	1,983771099	0,011053899	1	0,258307875
143	1	1,50E-04	2,76E-04	0,015535496	1,34E-06	0,00727355	0,004168486	1,983771206	0,011012944	1	0,25402131
144	1	1,44E-04	2,21E-04	0,014461041	1,19E-06	0,005542615	0,003800682	1,983771192	0,010964157	1	0,250004769
145	1	1,38E-04	1,93E-04	0,013560384	1,08E-06	0,00399313	0,003407959	1,983771182	0,010909412	1	0,246229898
146	1	1,32E-04	1,74E-04	0,012803824	1,33E-06	0,002029795	0,003471828	1,983771175	0,010850387	1	0,242672405
147	1	1,27E-04	1,59E-04	0,012161051	6,53E-07	4,11E-04	0,003040065	1,983771168	0,01078844	1	0,23931134
148	1	1,22E-04	1,48E-04	0,01160853	4,17E-07	1,67E-04	0,001998954	1,983771165	0,010724645	1	0,236128513
149	1	1,17E-04	1,38E-04	0,011128367	3,68E-07	1,17E-04	0,001441481	1,983771165	0,010659843	1	0,233108049
150	1	1,13E-04	1,30E-04	0,010706882	3,36E-07	9,34E-05	0,001164203	1,983771165	0,010594734	1	0,230236014

t ~ species	mRNA(CyclinA)$_{cyt}$	(ubiquitin-pCyclinE)$_{cyt}$	CyclinA$_{cyt}$	CyclinA$_{nuc}$	(CyclinA-pCdk2)$_{nuc}$	(CyclinA-Cdk2)$_{nuc}$	(CyclinA-pCdk1)$_{nuc}$	(ubiquitin-pCyclinA)$_{cyt}$	(ubiquitin-pCyclinB)$_{cyt}$	(CyclinD-Cdk4/6)$_{cyt}$
0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0	1,29E-32
2	0	0	0	0	0	0	0	0	0	9,74E-11
3	0	0	0	0	0	0	0	0	0	0,001002426
4	0	0	0	0	0	0	0	0	0	0,028562944
5	0	0	0	0	0	0	0	0	0	0,04842128
6	0	0	0	0	0	0	0	0	0	0,055285511
7	0	0	0	0	0	0	0	0	0	0,058685963
8	0	0	0	0	0	0	0	0	0	0,060551631
9	0	0	0	0	0	0	0	0	0	0,058773024
10	0	0	0	0	0	0	0	0	0	0,039586873
11	0	0	0	0	0	0	0	0	0	0,015380982
12	0	0	0	0	0	0	0	0	0	0,007052753
13	1,47E-102	6,51E-105	0	0	0	0	0	0	0	0,003962696
14	3,14E-27	4,86E-30	8,05E-108	0	0	0	0	0	0	0,002580542
15	7,56E-09	1,23E-11	5,07E-34	3,15E-135	5,29E-141	2,48E-139	1,91E-295	0	0	0,002052086
16	0,001004167	0,003081325	7,63E-13	6,54E-50	1,91E-54	2,21E-53	5,42E-121	0	0	0,001575552
17	0,030266222	0,15120141	1,38E-06	1,48E-24	1,60E-28	8,80E-28	5,55E-68	0	0	0,001151746
18	0,15307984	0,276638809	0,001722884	6,75E-12	2,45E-15	7,44E-15	1,14E-40	0	0	8,55E-04
19	0,31109568	0,320804916	0,058861147	1,97E-05	3,26E-08	5,06E-08	2,36E-25	0	0	6,57E-04
20	0,375475865	0,326974402	0,24129025	0,012737828	1,03E-04	7,77E-05	3,04E-17	1,70E-304	0	5,20E-04
21	0,391773518	0,312049695	0,362554144	0,145967369	0,004902625	0,001743456	7,46E-13	3,72E-230	0	4,23E-04
22	0,396307604	0,266893089	0,390786698	0,362024121	0,03448471	0,007116176	2,12E-10	1,89E-186	0	3,51E-04
23	0,397758455	0,18966277	0,396528925	0,550673088	0,115932	0,015967428	6,37E-09	6,97E-159	0	2,97E-04
24	0,398255465	0,112099471	0,397921427	0,686979839	0,257111111	0,023553426	5,49E-08	1,81E-140	0	2,55E-04
25	0,398350668	0,061802678	0,398293174	0,790633553	0,436238443	0,02740683	2,28E-07	1,62E-127	0	2,22E-04
26	0,397764766	0,036422313	0,398088959	0,879223337	0,632741379	0,029129619	6,22E-07	5,76E-118	4,57E-290	1,95E-04
27	0,394856042	0,024166731	0,396400605	0,959056932	0,837206869	0,029968897	1,32E-06	1,40E-110	1,03E-258	1,73E-04
28	0,385841533	0,017762458	0,390510138	1,028382455	1,045499952	0,030345276	2,40E-06	1,25E-104	2,24E-233	1,54E-04
29	0,365612877	0,014033416	0,37605096	1,077221945	1,254849566	0,030318185	4,05E-06	1,19E-99	7,09E-213	1,38E-04
30	0,33279678	0,011649415	0,350436123	1,089404189	1,462121013	0,029812609	6,82E-06	2,71E-95	1,14E-196	1,25E-04
31	0,295730701	0,010011251	0,318352805	1,054835907	1,659429827	0,028759973	1,62E-05	3,94E-91	1,88E-184	1,13E-04
32	0,26535739	0,008820917	0,288731446	0,981356285	1,076802222	0,027198766	0,009676284	3,46E-67	7,21E-176	1,03E-04
33	0,243124014	0,007916492	0,265305057	0,886391415	0,010188864	0,025246658	0,299053225	2,54E-36	5,47E-170	9,48E-05
34	0,226446479	0,007203573	0,24718597	0,784176112	0,015320017	0,02302236	0,953533793	9,53E-24	5,04E-166	8,72E-05
35	0,21341649	0,00662399	0,232873586	0,683628581	0,02068723	0,020630466	1,600565567	4,26E-16	3,33E-163	8,05E-05
36	0,202878438	0,006140245	0,221257687	0,590004766	0,020698615	0,018172527	1,907837496	1,39E-08	4,82E-161	7,45E-05
37	0,194119859	0,005727209	0,211597348	0,506190481	0,018413215	0,015749823	1,700650743	0,007781103	2,69E-159	6,92E-05
38	0,186681565	0,005367373	0,203397471	0,433437179	0,015894512	0,013456084	1,176584545	0,238055213	7,83E-158	6,44E-05
39	0,180254397	0,005048146	0,196318825	0,371834287	0,013525198	0,011365977	0,63973833	0,4657367	1,44E-156	6,01E-05
40	0,174622108	0,004760121	0,190122067	0,320685673	0,011405875	0,009526043	0,249215467	0,552301493	1,98E-155	5,62E-05
41	0,169628443	0,004495775	0,184633539	0,278838933	0,009571666	0,007952387	0,063024779	0,462165805	2,60E-154	5,27E-05
42	0,165157337	0,004248739	0,179724031	0,244958447	0,008021879	0,006635325	0,017640102	0,276154499	6,25E-149	4,95E-05
43	0,161120524	0,004013599	0,175295242	0,21772328	0,006732806	0,005548122	0,015749272	0,130151348	8,72E-71	4,66E-05
44	0,157449505	0,003786278	0,17127091	0,195943578	0,005669237	0,004656556	0,019754382	0,063023757	2,71E-25	4,40E-05
45	0,154090181	0,003564687	0,167590851	0,178604681	0,004794198	0,003926779	0,023128918	0,038405024	4,29E-07	4,15E-05
46	0,150999162	0,003349056	0,164206837	0,164862978	0,004074716	0,003329477	0,030334285	0,028200118	0,053794082	3,93E-05
47	0,148141178	0,00314142	0,161079707	0,154023481	0,003483186	0,002840438	0,042543223	0,022179773	0,302991664	3,72E-05
48	0,145487211	0,002944593	0,158177274	0,145516642	0,002996662	0,002439652	0,058367079	0,017649256	0,451088307	3,53E-05
49	0,143013134	0,002760827	0,155472801	0,138882414	0,002595195	0,002109782	0,074864328	0,014064715	0,435841297	3,36E-05
50	0,140698689	0,0025911	0,152943864	0,133758226	0,002261364	0,001835959	0,089234775	0,01132996	0,256988137	3,55E-05
51	0,13852672	0,002435243	0,15057149	0,129862111	0,001981039	0,00160634	0,100798341	0,009332846	0,10548825	0,004696056
52	0,136482587	0,002292494	0,148339499	0,126974211	0,001743333	0,001411877	0,109915506	0,007897154	0,04268755	0,035382356
53	0,134553702	0,002161927	0,146233997	0,124920443	0,00154021	0,001245995	0,116992769	0,006856761	0,022373369	0,050519225
54	0,132729176	0,002042635	0,144242968	0,123559128	0,00136571	0,001103623	0,122365246	0,006089437	0,014888274	0,056126798
55	0,130999529	0,001933555	0,142355962	0,122779592	0,001213984	9,80E-04	0,12630648	0,005512655	0,011278813	0,058933767
56	0,129356464	0,001833545	0,140563839	0,122494974	0,001080862	8,71E-04	0,129040443	0,005071493	0,009139278	0,058899817
57	0,127792682	0,001741602	0,138858563	0,122633266	9,64E-04	7,76E-04	0,130751101	0,004728888	0,007712176	0,04729629
58	0,12630173	0,001656888	0,137233034	0,123133529	8,60E-04	6,92E-04	0,131591087	0,004459219	0,006692226	0,020212466
59	0,124877882	0,001578687	0,135680954	0,123943806	7,73E-04	6,17E-04	0,131685529	0,004244316	0,00592584	0,008619804
60	0,12351603	0,001506373	0,13419671	0,125019478	7,13E-04	5,51E-04	0,131116972	0,004071083	0,005307591	0,004584111
61	0,122211606	0,001439716	0,132775283	0,126316011	7,02E-04	4,96E-04	0,129941225	0,003930255	0,004753014	0,002825913
62	0,120961476	0,001568504	0,131412177	0,126422779	0,003650868	7,57E-04	0,128129604	0,00381515	0,004251388	0,002027522
63	0,121300411	0,022222929	0,13013257	0,125803951	0,008980177	6,61E-04	0,125262585	0,003720395	0,003810477	0,001592486
64	0,154310054	0,1571144	0,130625794	0,126265608	0,013202182	5,10E-04	0,121453005	0,003641161	0,003429143	0,001198889
65	0,257427114	0,261789876	0,153916047	0,128596549	0,016726271	4,86E-04	0,117084027	0,003573176	0,003101169	8,99E-04
66	0,344656062	0,303260964	0,253545276	0,151102981	0,020860932	7,06E-04	0,112417746	0,003512913	0,002819099	6,91E-04
67	0,377758076	0,30745015	0,347030367	0,269023911	0,028619499	0,001601168	0,107608576	0,003457582	0,002575834	5,46E-04
68	0,388430054	0,292761002	0,380142838	0,472812409	0,047602093	0,003931768	0,10274536	0,003404875	0,00236504	4,43E-04
69	0,392047927	0,255238925	0,389632189	0,685421033	0,091786809	0,008862799	0,09787602	0,00335276	0,002181202	3,67E-04
70	0,393337454	0,190892103	0,392553781	0,859353576	0,182558282	0,016981502	0,09302734	0,003299874	0,002019876	3,10E-04
71	0,393788855	0,120834968	0,393528125	0,979523438	0,330907361	0,024833255	0,088226064	0,003245437	0,001877538	2,65E-04
72	0,39374698	0,070079723	0,393772519	1,063291183	0,520296012	0,029174609	0,083511554	0,003188985	0,00175131	2,30E-04
73	0,392516934	0,041856033	0,39318959	1,130463106	0,728629966	0,03091767	0,078923942	0,00313027	0,001638812	2,02E-04
74	0,387509992	0,027402878	0,390156712	1,188572438	0,943938431	0,031491345	0,074490682	0,003069228	0,001538078	1,78E-04
75	0,373795665	0,019650309	0,380921284	1,233993625	1,160878368	0,031486126	0,070225704	0,003005954	0,001447475	1,59E-04

76	0,346996282	0,015088831	0,361119297	1,253428224	1,376071722	0,03101408	0,066130658	0,002940686	0,001365643	1,42E-04
77	0,310676657	0,012155048	0,331449509	1,231726131	1,585227227	0,030028397	0,06219264	0,002873836	0,001291442	1,28E-04
78	0,276853904	0,010128797	0,300216623	1,167746139	1,65432765	0,028514577	0,058758744	0,002806115	0,001223915	1,17E-04
79	0,251551179	0,008650971	0,274270204	1,076207145	0,011290066	0,026550495	0,165683979	0,00274003	0,00116225	1,06E-04
80	0,232854781	0,007527162	0,254165735	0,973385156	0,012958462	0,024246521	0,728529283	0,002721267	0,001105757	9,72E-05
81	0,218484202	0,006644332	0,238440507	0,870374424	0,018870794	0,021707616	1,409905483	0,002965623	0,001053846	8,93E-05
82	0,20701608	0,005932723	0,225815402	0,773921802	0,020990891	0,01903893	1,874401443	0,004765053	0,00100601	8,23E-05
83	0,197584335	0,005347089	0,215415184	0,687918973	0,018965318	0,016351148	1,842382874	0,040151737	9,62E-04	7,62E-05
84	0,189641034	0,004856822	0,206657154	0,614293173	0,016199155	0,013754702	1,470171543	0,218100693	9,21E-04	7,07E-05
85	0,182823615	0,004440553	0,199146267	0,553540959	0,013496311	0,011346572	1,034476502	0,378278649	8,83E-04	6,57E-05
86	0,176882261	0,004082908	0,192607031	0,505133279	0,011034909	0,009197068	0,631629219	0,455945342	8,47E-04	6,13E-05
87	0,171638756	0,003772498	0,186841754	0,467878121	0,008881291	0,007343126	0,316169782	0,446046583	8,14E-04	5,73E-05
88	0,166962157	0,003500703	0,181704793	0,44024005	0,007055194	0,005790274	0,121189506	0,354605377	7,84E-04	5,37E-05
89	0,162753809	0,00326087	0,177086313	0,420590604	0,005545843	0,004520678	0,036384488	0,224962759	7,55E-04	5,04E-05
90	0,158937762	0,003047789	0,172901762	0,407376171	0,004323883	0,003502872	0,018542178	0,118705693	7,28E-04	4,75E-05
91	0,15545445	0,002857332	0,169084862	0,39921107	0,00335121	0,002699916	0,018748647	0,061202004	7,03E-04	4,47E-05
92	0,152256396	0,002686191	0,165582826	0,394915457	0,002587809	0,002074853	0,018749587	0,036367612	6,96E-04	4,22E-05
93	0,149305209	0,002531813	0,162353018	0,393513511	0,001997093	0,00159545	0,019238396	0,025435665	0,004878426	3,99E-05
94	0,146569461	0,002393876	0,159360563	0,394137088	0,001565258	0,001254245	0,022932125	0,019491763	0,149947235	3,78E-05
95	0,144023127	0,002280598	0,156576614	0,395688757	0,001341867	0,001098027	0,029122172	0,015447126	0,334951556	3,59E-05
96	0,141644445	0,00221173	0,153977072	0,396883256	0,00133447	0,001110338	0,036429271	0,012405058	0,40409268	3,41E-05
97	0,139415048	0,002199859	0,151541616	0,39720724	0,001385427	0,001147438	0,043547753	0,010084932	0,304948038	3,24E-05
98	0,13731931	0,002233717	0,149252976	0,397018487	0,001368701	0,001121135	0,049945867	0,008341309	0,145570468	1,26E-04
99	0,135343839	0,002287323	0,14709636	0,396857275	0,001273273	0,001033272	0,055725666	0,007043303	0,05872364	0,01601872
100	0,133477074	0,002336259	0,145059013	0,39708323	0,00113303	9,13E-04	0,060892421	0,006071772	0,027928786	0,04280232
101	0,131708982	0,002365462	0,143129868	0,397846004	9,80E-04	7,87E-04	0,065327389	0,005334193	0,017061775	0,052376086
102	0,130030796	0,002369243	0,141299267	0,39915781	8,34E-04	6,67E-04	0,068923467	0,004764799	0,012251041	0,056147046
103	0,128434821	0,002348131	0,139558735	0,400964907	7,03E-04	5,61E-04	0,071643648	0,004318031	0,009581242	0,056717016
104	0,12691427	0,002305887	0,137900803	0,403186271	5,90E-04	4,70E-04	0,073518216	0,003962188	0,007872617	0,049077711
105	0,125463127	0,002247451	0,136318852	0,405734113	4,95E-04	3,94E-04	0,074621789	0,00367485	0,006684939	0,024591177
106	0,124076037	0,002177715	0,134806998	0,408525663	4,17E-04	3,31E-04	0,075050717	0,003439855	0,005814198	0,010100203
107	0,122748218	0,00210091	0,133359985	0,411488762	3,64E-04	2,80E-04	0,07490378	0,003245328	0,005146935	0,00512799
108	0,12147538	0,002020414	0,131973101	0,414563516	3,28E-04	2,39E-04	0,074263153	0,003082449	0,004601113	0,003058984
109	0,120253663	0,001942247	0,13064211	0,417309854	5,12E-04	3,94E-04	0,073207717	0,002944662	0,004123852	0,002028009
110	0,11908597	0,002636814	0,129363261	0,413260551	0,007216735	0,001500154	0,071791472	0,00282697	0,003705319	0,001503882
111	0,121384582	0,046972574	0,128208527	0,406984915	0,01797945	0,001359108	0,069906984	0,002725395	0,003342311	0,001172874
112	0,164556166	0,183831013	0,129774814	0,4026168	0,026894335	0,001118886	0,067605464	0,002636602	0,003028925	9,06E-04
113	0,269659056	0,26811806	0,160158703	0,400580584	0,035059256	0,001195527	0,065053448	0,002557922	0,002758366	7,06E-04
114	0,346717968	0,294309256	0,263840701	0,421902257	0,045454572	0,001761161	0,06236926	0,002487243	0,002524189	5,62E-04
115	0,374919872	0,28846995	0,348132425	0,536736582	0,063101316	0,003352598	0,059623066	0,002422877	0,002320714	4,56E-04
116	0,384100041	0,262810853	0,376834537	0,718514134	0,099516639	0,00723184	0,056853966	0,002363285	0,002142943	3,78E-04
117	0,387247199	0,210074437	0,385107165	0,888473614	0,17576767	0,014642262	0,05408055	0,002307128	0,001986638	3,18E-04
118	0,388360469	0,140297633	0,38767067	1,009256669	0,309755273	0,023096833	0,051314964	0,002253488	0,001848451	2,72E-04
119	0,388612301	0,082528083	0,388461455	1,090002643	0,490250575	0,028120648	0,048579738	0,002201715	0,001725679	2,36E-04
120	0,387771487	0,048500536	0,388232268	1,15292047	0,692304583	0,029976734	0,045905543	0,002151308	0,001616088	2,07E-04
121	0,38383049	0,031184823	0,385931316	1,208266818	0,901113939	0,030415676	0,043316843	0,002101885	0,001517818	1,82E-04
122	0,372554698	0,022255793	0,378459717	1,254487425	1,110524467	0,030244698	0,040827493	0,002053176	0,001429319	1,62E-04
123	0,349456436	0,01724297	0,361670506	1,2805154	1,317282226	0,02965558	0,038442475	0,002005013	0,001349297	1,46E-04
124	0,315875023	0,01415416	0,334873655	1,271550551	1,518010099	0,028627401	0,036158832	0,001957326	0,001276662	1,31E-04
125	0,281884096	0,012094826	0,30452363	1,222796757	1,688217198	0,027135494	0,034013407	0,001910174	0,001210497	1,19E-04
126	0,255401712	0,010632022	0,278050427	1,145225407	0,31190223	0,025232956	0,070294085	0,001863939	0,001150023	1,08E-04
127	0,235799098	0,009537967	0,257227559	1,054323921	0,011087669	0,023015015	0,510034962	0,001831188	0,001094576	9,91E-05
128	0,220807197	0,008684001	0,240918497	0,961525172	0,016519833	0,020577552	1,186864228	0,001900147	0,001043589	9,09E-05
129	0,20890526	0,007993258	0,227855169	0,873921419	0,019763664	0,018016856	1,739206018	0,002467885	9,97E-04	8,38E-05
130	0,199159842	0,007417732	0,217126616	0,795647068	0,018208185	0,015435264	1,846026569	0,011883237	9,53E-04	7,75E-05
131	0,190981993	0,006926313	0,208118354	0,728811129	0,015547507	0,01293753	1,493306664	0,148806358	9,13E-04	7,18E-05
132	0,183984023	0,006498233	0,200412752	0,674049527	0,012897094	0,010619604	0,982084938	0,363035634	8,75E-04	6,68E-05
133	0,177900227	0,006119333	0,193718921	0,630923143	0,010482541	0,008555538	0,516501951	0,495441161	8,41E-04	6,23E-05
134	0,17254199	0,005779627	0,187828647	0,598270876	0,008383363	0,006788468	0,197127988	0,498542368	8,08E-04	5,82E-05
135	0,167771334	0,005471857	0,182588977	0,574535562	0,006626682	0,005329045	0,050138828	0,370768509	7,78E-04	5,45E-05
136	0,163484705	0,005190565	0,177884898	0,558039715	0,005203953	0,004160828	0,01627804	0,203830934	7,49E-04	5,12E-05
137	0,159602651	0,004931578	0,173628111	0,547186678	0,004082606	0,003249542	0,015284917	0,094058286	7,23E-04	4,81E-05
138	0,156063048	0,004691648	0,169749579	0,540580479	0,003217409	0,002552633	0,016876383	0,047442393	7,04E-04	4,53E-05
139	0,152816504	0,004468141	0,166194445	0,537075869	0,002559798	0,002026782	0,017911446	0,029881466	0,002829664	4,28E-05
140	0,149823179	0,004258815	0,162918492	0,535778825	0,00206423	0,001632771	0,022053605	0,021941852	0,137914148	4,05E-05
141	0,147050523	0,004061896	0,159885622	0,536015308	0,001692251	0,001338411	0,029163948	0,017117753	0,345779925	3,83E-05
142	0,144471634	0,003876346	0,15706603	0,537286316	0,001413546	0,00111862	0,0378528	0,013632605	0,446857666	3,63E-05
143	0,142064054	0,003701366	0,154434854	0,539235592	0,001202933	9,53E-04	0,046236415	0,010996898	0,377598187	3,45E-05
144	0,139808857	0,003535691	0,151971163	0,541628375	0,001039096	8,23E-04	0,053042358	0,009020221	0,196221958	9,40E-05
145	0,137689967	0,003377489	0,14965719	0,544324604	9,06E-04	7,17E-04	0,058238109	0,007556613	0,077845812	0,014352264
146	0,135693617	0,003225267	0,147477735	0,547230946	7,96E-04	6,31E-04	0,062128462	0,006469583	0,03386855	0,042532966
147	0,133807946	0,003080933	0,145419709	0,550185667	7,24E-04	5,75E-04	0,064975224	0,005650021	0,019317978	0,052957765
148	0,13202266	0,002944012	0,143471765	0,553215539	6,40E-04	5,02E-04	0,067000142	0,005020098	0,013451324	0,057339782
149	0,130328783	0,002807548	0,14162401	0,556512659	5,33E-04	4,14E-04	0,06835582	0,004526507	0,010394742	0,059676914
150	0,128718439	0,002669064	0,139867774	0,560095419	4,32E-04	3,35E-04	0,0691042	0,004132803	0,008501206	0,058797172

species	(CyclinD-pCdk4/6)$_{cyt}$	(DP-E2F-pRb)$_{nuc}$	(ubiquitin-Pp27)$_{cyt}$	CyclinB$_{cyt}$	CyclinB gene	mRNA(CyclinB)$_{nuc}$	mRNA(CyclinB)$_{cyt}$	(pDP-pE2F)$_{nuc}$	Cdk1$_{cyt}$	ERK$_{nuc}$
t										
0	0	0	0	0	1	0	0	0	4	0
1	1,33E-33	0	0	0	1	0	0	0	4	2,32E-276
2	3,28E-11	7,75E-145	0	0	1	0	0	0	4	8,00E-96
3	0,001134829	4,32E-51	0	0	1	0	0	0	4	3,05E-33
4	0,118067627	4,01E-23	0	0	1	0	0	0	4	1,85E-14
5	0,468873072	7,25E-14	0	0	1	0	0	0	4	3,61E-08
6	0,888926471	7,68E-10	0	0	1	0	0	0	4	2,10E-05
7	1,314560342	1,86E-07	0	0	1	0	0	0	4	9,20E-04
8	1,71905801	1,07E-05	0	0	1	0	0	0	4	0,014762747
9	2,063977622	3,21E-04	0	0	1	0	0	0	4	0,161111505
10	2,243786308	0,006964643	0	0	1	0	0	0	4	1,80104183
11	2,112187478	0,104353255	0	0	1	0	0	0	4	1,835758923
12	1,79395497	0,901775916	0	0	1	0	0	0	4	1,843328011
13	1,411911124	1,937241321	1,84E-92	0	1	0	0	0	4	1,848508118
14	1,023714083	1,829475887	3,48E-17	0	1	0	0	0	4	1,852663293
15	0,713610032	0,369277904	0,016121208	0	1	0	0	0	4	1,856010205
16	0,535855697	0,017544977	0,3790182	4,59E-225	1	3,43E-221	3,95E-223	0	4	1,858535389
17	0,446908813	0,006849737	0,593949061	1,06E-120	1	3,08E-117	5,67E-119	5,38E-304	4	1,859690825
18	0,401369757	0,004017002	0,69642401	9,54E-68	1	1,93E-64	4,26E-66	1,87E-168	4	1,85980464
19	0,375717355	0,002927064	0,714648748	3,68E-38	1	2,16E-35	8,80E-37	8,57E-94	4	1,859806682
20	0,358740842	0,002419062	0,604079433	5,38E-23	1	8,47E-21	6,57E-22	6,37E-56	4	1,859806701
21	0,344976658	0,002167222	0,383763145	3,58E-15	1	1,62E-13	2,29E-14	7,34E-37	4	1,859806701
22	0,332201753	0,002050495	0,18060387	6,24E-11	1	1,07E-09	2,35E-10	1,12E-26	4	1,859806701
23	0,319914868	0,00200443	0,074187318	3,10E-08	1	2,71E-07	7,97E-08	2,58E-20	4	1,859806701
24	0,308096029	0,001988392	0,035073093	2,46E-06	1	1,22E-05	4,54E-06	5,05E-16	4	1,859806701
25	0,296780762	0,001982152	0,020845269	5,84E-05	1	1,74E-04	7,90E-05	4,74E-13	3,999999994	1,859806701
26	0,285990399	0,0019787	0,014453888	6,15E-04	1	0,001198234	6,32E-04	6,75E-11	3,999999164	1,859806701
27	0,275729467	0,001976064	0,010920085	0,003742553	1	0,005204488	0,003062511	2,98E-09	3,999960548	1,859806701
28	0,265990589	0,001973714	0,008695361	0,015263748	1	0,016814481	0,010714637	5,94E-08	3,999170743	1,859806701
29	0,25675868	0,00197151	0,007182589	0,043769211	1	0,044560409	0,030097771	5,99E-07	3,991096444	1,859806701
30	0,248013894	0,001969412	0,006099848	0,089888767	1	0,103049644	0,072719069	3,06E-06	3,948729942	1,859806701
31	0,239733643	0,001967409	0,005294851	0,144115295	1	0,215574343	0,157791753	1,04E-05	3,823028483	1,859806672
32	0,231893969	0,001965498	0,004678059	0,198812766	1	0,369600954	0,303122003	0,002029072	3,568613425	1,859804865
33	0,22447048	0,001963676	0,004193641	0,239358132	1	0,424842531	0,451186403	0,226362398	3,178430255	1,859785721
34	0,217438982	0,001961943	0,003805173	0,257792987	1	0,278206645	0,499205853	1,483440945	2,701757896	1,859747737
35	0,210775897	0,001960296	0,003487994	0,238264936	1	0,070972682	0,313020377	1,917949095	2,226333181	1,859703809
36	0,204458522	0,001958735	0,003224872	0,174066802	1	0,015729095	0,103760697	1,957396615	1,883482279	1,859657393
37	0,198465191	0,00195726	0,003003426	0,107379982	1	0,005083192	0,023944948	1,968017242	1,719106719	1,859609127
38	0,192775347	0,001955873	0,002814509	0,06773364	1	0,002792051	0,006332913	1,971959911	1,654518791	1,859557538
39	0,187369562	0,001954577	0,002651236	0,047541681	1	0,002156785	0,002884041	1,973561292	1,626059575	1,859490863
40	0,182229511	0,001953381	0,002508325	0,036891205	1	0,001944367	0,002125793	1,974153991	1,610595136	1,859136516
41	0,177337917	0,001952298	0,002381541	0,03085324	1	0,001875403	0,00192804	1,974188726	1,600560575	1,76935377
42	0,17267848	0,001951343	0,002267354	0,027220603	1	0,001856959	0,001873561	1,951866049	1,593152259	1,26E-11
43	0,168235844	0,001950534	0,002162765	0,024942726	1	0,001851991	0,00185908	1,61337699	1,587158648	4,16E-12
44	0,163995648	0,001949874	0,00206531	0,023470372	1	0,001849146	0,001854303	0,762082498	1,582411961	5,72E-12
45	0,159944668	0,001949351	0,001973137	0,022486467	1	0,001846083	0,001851102	0,245183953	1,651807984	2,13E-11
46	0,156070948	0,001948931	0,001885098	0,021751654	1	0,001842397	0,001847687	0,115085235	1,999540968	1,58E-10
47	0,152363795	0,001948577	0,001800703	0,021160291	1	0,001837438	0,00184336	0,073404382	2,514276196	2,29E-09
48	0,148813597	0,001948259	0,001719998	0,02069594	1	0,001830374	0,00183733	0,054090013	3,06769547	5,29E-08
49	0,145411554	0,001947963	0,001643215	0,020339873	1	0,001820593	0,001828868	0,043022793	3,527360097	9,74E-06
50	0,142153511	0,001947688	0,001570512	0,020068931	1	0,001807998	0,001817626	0,035838128	3,752394675	2,09E-05
51	0,147225018	0,001947433	0,001501871	0,019859333	1	0,001792978	0,001803765	0,030785673	3,83255203	2,87E-05
52	0,324513551	0,001947195	0,001437181	0,019689744	1	0,001776093	0,001787761	0,027031633	3,867346348	4,02E-05
53	0,692124563	0,00194697	0,001376305	0,019544806	1	0,001757864	0,001770149	0,024128445	3,886204644	1,07E-04
54	1,105192883	0,001946915	0,001319104	0,019414523	1	0,001738735	0,00175141	0,021813965	3,89801536	9,85E-04
55	1,514120566	0,001952273	0,001265379	0,019292694	1	0,001719067	0,001731949	0,019924095	3,906162608	0,010299125
56	1,884468523	0,002080783	0,001214886	0,019175633	1	0,001699155	0,001712094	0,01834931	3,912186216	0,089847545
57	2,14201636	0,004461122	0,001167393	0,019061283	1	0,001679233	0,001692112	0,016990518	3,916878557	1,266739114
58	2,129489178	0,038812848	0,001122688	0,018948609	1	0,001659486	0,001672211	0,015471904	3,920678899	1,827737774
59	1,886741828	0,349988627	0,001080582	0,018837203	1	0,001640058	0,001652558	0,012224802	3,923788615	1,838463377
60	1,5571349	1,655840273	0,0010409	0,01872703	1	0,001621062	0,001633282	0,007871303	3,925964361	1,844612264
61	1,202680392	1,933250961	0,00100354	0,01861827	1	0,001602585	0,001614483	0,005041047	3,926906022	1,84940115
62	0,873219292	1,377605719	0,001020819	0,018511202	1	0,001584699	0,001596242	0,003392856	3,926953737	1,85323836
63	0,645426319	0,061583673	0,024183992	0,018406145	1	0,001567483	0,001578631	0,002372316	3,926380315	1,856253683
64	0,520346505	0,012095684	0,253845893	0,018303472	1	0,001551045	0,001561748	0,001710906	3,925361112	1,858102947
65	0,454789828	0,005844572	0,450891184	0,018203624	1	0,001535474	0,001545692	0,001267888	3,924013677	1,858535928
66	0,418317752	0,003884564	0,551946603	0,018107058	1	0,001520803	0,001530523	9,64E-04	3,922419503	1,858550969
67	0,395124345	0,003060276	0,522856796	0,018014171	1	0,001507034	0,001516258	7,50E-04	3,920636654	1,858523536
68	0,377374451	0,002662628	0,369287968	0,017925262	1	0,001494156	0,00150289	5,98E-04	3,918707446	1,858475271
69	0,361645163	0,002471548	0,195251734	0,017840576	1	0,001482319	0,00149047	4,87E-04	3,916663303	1,858403725
70	0,346898193	0,002388614	0,08880792	0,017761	1	0,00147445	0,0014802	4,05E-04	3,914527851	1,85830343
71	0,332911936	0,002356217	0,04371349	0,017698494	1	0,001509535	0,001489581	3,47E-04	3,912317733	1,858167875
72	0,319638775	0,002343118	0,025774179	0,017778034	1	0,001882901	0,001671337	3,29E-04	3,910028542	1,857989834
73	0,307057192	0,002336562	0,01749458	0,018769407	1	0,003823188	0,002766781	5,49E-04	3,907524804	1,85776142
74	0,295145312	0,002332328	0,012949423	0,023515968	1	0,010517595	0,006976499	0,002617908	3,904017076	1,857473888
75	0,283877579	0,002329097	0,010132004	0,038283503	1	0,027820274	0,018826877	0,015063977	3,895913503	1,857116151

76	0,273225578	0,002326427	0,008241922	0,069059872	1	0,064673809	0,045671053	0,058520777	3,869712589	1,856666688
77	0,263159285	0,002324141	0,006901175	0,113505596	1	0,137051785	0,099939952	0,14442919	3,79281826	1,856058238
78	0,253648041	0,00232215	0,005908597	0,165036561	1	0,263827043	0,202189196	0,252979712	3,620033042	1,855065398
79	0,244661217	0,002320395	0,00514825	0,210772586	1	0,332794651	0,326997136	0,419804729	3,319589245	1,853116724
80	0,236168672	0,002318836	0,00454933	0,233137808	1	0,254680161	0,37924529	1,284724021	2,921427645	1,85021296
81	0,228141085	0,002317441	0,004066553	0,218166655	1	0,076870539	0,252229907	1,87354618	2,510141141	1,847061885
82	0,22055019	0,002316185	0,003669812	0,16008369	1	0,017978367	0,08748135	1,931467928	2,210827572	1,843836425
83	0,213368933	0,002315048	0,003338407	0,10059122	1	0,005752524	0,021850706	1,945558083	2,065564297	1,840571736
84	0,206571582	0,002314014	0,003057673	0,064783757	1	0,002986505	0,00630325	1,950699649	2,006376522	1,83725944
85	0,200133786	0,002313069	0,002816999	0,04602601	1	0,002168257	0,00293626	1,9529855	1,979500429	1,833830352
86	0,194032594	0,002312203	0,002608535	0,035852904	1	0,001849973	0,002080051	1,954077807	1,964740038	1,829969315
87	0,188246447	0,002311406	0,002426326	0,029918158	1	0,001709308	0,001797223	1,954565899	1,955209554	1,823418989
88	0,182755152	0,002310671	0,002265782	0,026232679	1	0,001649449	0,00168631	1,954651332	1,9482778	1,765443356
89	0,177539833	0,002309989	0,002123305	0,023848059	1	0,001627672	0,001642919	1,949636376	1,942779163	0,020661235
90	0,172582878	0,002309361	0,001996044	0,022267235	1	0,00162085	0,001627691	1,83364923	1,938127646	1,65E-07
91	0,167867875	0,002308848	0,001881719	0,021202054	1	0,001617985	0,001622345	1,29878512	1,934015199	7,33E-08
92	0,163379547	0,002308505	0,001778489	0,020473858	1	0,001615702	0,001619541	0,593854721	1,934874068	8,48E-08
93	0,159103753	0,002308236	0,001684873	0,019960416	1	0,001613504	0,001617235	0,230706668	2,053442947	2,02E-07
94	0,15502823	0,00230774	0,001599976	0,019562277	1	0,001611201	0,001614978	0,121353493	2,417789442	9,84E-07
95	0,151145419	0,00230626	0,001524818	0,01923808	1	0,001608433	0,001612435	0,082338676	2,905511433	9,81E-06
96	0,147452067	0,002303686	0,001463308	0,018978745	1	0,001604889	0,001609266	0,063797184	3,386570798	9,12E-05
97	0,14393992	0,00230098	0,001418468	0,018776691	1	0,001600417	0,001605241	0,053084985	3,702032766	0,003884709
98	0,140706487	0,002298773	0,001388384	0,018622221	1	0,001595027	0,001600292	0,046094093	3,825154823	0,005160309
99	0,182223876	0,002297129	0,001367785	0,01850314	1	0,001588803	0,001594468	0,041158331	3,872906617	0,006013841
100	0,45318372	0,002295959	0,001351406	0,018408377	1	0,001581839	0,001587856	0,037479463	3,896208687	0,006967132
101	0,84161664	0,002295588	0,001335556	0,018329683	1	0,001574233	0,001580549	0,034627397	3,909630929	0,009383214
102	1,246634797	0,002301432	0,001318174	0,018261282	1	0,001566098	0,001572655	0,032349445	3,918218067	0,020502443
103	1,628626795	0,002382881	0,00129835	0,018199255	1	0,001557561	0,001564294	0,030486323	3,924114376	0,081239633
104	1,931147164	0,003400787	0,001275874	0,018141038	1	0,00154875	0,001555594	0,028924329	3,928375948	0,509507997
105	2,026198203	0,014930636	0,001250944	0,018085027	1	0,001539786	0,001546679	0,027499702	3,931578851	1,815542347
106	1,883230823	0,11062902	0,001223958	0,018030288	1	0,001530777	0,001537666	0,025581372	3,934050242	1,833424131
107	1,63701277	0,629131218	0,001195389	0,017976338	1	0,001521813	0,001528652	0,022360568	3,935910562	1,840991094
108	1,355098596	1,771482927	0,001165708	0,017922992	1	0,001512971	0,001519723	0,019259526	3,936956761	1,846482068
109	1,067661708	1,887691693	0,001135957	0,01787025	1	0,001504311	0,001510945	0,017289087	3,937149708	1,850932879
110	0,812806878	1,068487483	0,001340761	0,017818213	1	0,001495881	0,001502374	0,01607139	3,936726249	1,854449212
111	0,640304053	0,037424811	0,061138765	0,01776703	1	0,001487724	0,001494054	0,015287216	3,935854148	1,856999079
112	0,541562748	0,010282185	0,301383276	0,017716884	1	0,001479888	0,001486033	0,014768444	3,934646652	1,858059267
113	0,486220462	0,005479849	0,470630758	0,017667988	1	0,00147242	0,001478358	0,014420199	3,933182857	1,858134327
114	0,452964139	0,003860783	0,530312963	0,017620568	1	0,001465354	0,001471068	0,014185331	3,931519574	1,858126227
115	0,42978485	0,003167523	0,446922068	0,017574851	1	0,001458746	0,001464207	0,014027626	3,92969857	1,858112058
116	0,410402123	0,002848072	0,269718553	0,017531141	1	0,001452891	0,001457927	0,013923258	3,927751148	1,858090016
117	0,392456363	0,002709694	0,125309245	0,017490579	1	0,001450575	0,001453518	0,0138562	3,925701032	1,858057365
118	0,375461539	0,002656252	0,05635332	0,017463455	1	0,001481659	0,001464771	0,013816539	3,923565226	1,85801087
119	0,359362769	0,00263542	0,030093174	0,017546208	1	0,001774172	0,001608614	0,013807531	3,921343591	1,857946771
120	0,344152247	0,002625054	0,0192997	0,018346782	1	0,003332955	0,002481628	0,013913831	3,918934631	1,857860749
121	0,32981278	0,002617917	0,013916268	0,022229277	1	0,008898369	0,005946439	0,014861606	3,915723757	1,857747813
122	0,316315463	0,002611889	0,010773127	0,034829602	1	0,0238125	0,016038973	0,020881327	3,908890691	1,857601619
123	0,303623456	0,002606359	0,00874781	0,062765002	1	0,056644534	0,039687589	0,043716328	3,887404581	1,857410794
124	0,291695334	0,002601149	0,007358041	0,105466632	1	0,1215538	0,088270029	0,089994174	3,821984328	1,857141953
125	0,280487483	0,002596206	0,006360946	0,156156258	1	0,240057894	0,180782183	0,148799536	3,668264771	1,85667949
126	0,26995577	0,002591511	0,005620571	0,205688632	1	0,351723672	0,31718085	0,224782114	3,388412786	1,855676281
127	0,260056667	0,002587055	0,0050552	0,236943921	1	0,339097178	0,417929926	0,762463735	2,99271704	1,853840715
128	0,250748004	0,002582831	0,004613067	0,239888671	1	0,143736254	0,363678049	1,8003972	2,545546469	1,85169791
129	0,241989447	0,00257883	0,004259986	0,196177638	1	0,032766186	0,162096862	1,927819524	2,161108193	1,849473504
130	0,233742785	0,002575043	0,003972594	0,128507554	1	0,008681222	0,043294487	1,949743345	1,940416563	1,847210085
131	0,225972077	0,00257146	0,003734453	0,079824404	1	0,003725267	0,010722302	1,956846986	1,848272633	1,844907585
132	0,2186437	0,002568072	0,003533731	0,05387819	1	0,002472528	0,003913478	1,959691582	1,809834863	1,842511939
133	0,21172633	0,002564869	0,003361805	0,040338529	1	0,002062691	0,002417645	1,960888646	1,790575619	1,839667061
134	0,205190879	0,002561842	0,003212247	0,032812016	1	0,001911599	0,002019543	1,961320284	1,778929365	1,831071439
135	0,199010394	0,002558981	0,003080187	0,02834687	1	0,001860643	0,001896744	1,960678277	1,770793518	1,36989791
136	0,193159946	0,00255628	0,002961869	0,025573654	1	0,00184668	0,001859462	1,912974306	1,764481523	8,20E-14
137	0,187616502	0,002553732	0,002854395	0,023798026	1	0,001842564	0,001848817	1,480343705	1,759200661	2,20E-14
138	0,182358794	0,002551332	0,002755533	0,022634454	1	0,00183999	0,001844882	0,673746924	1,756319665	2,34E-14
139	0,177367187	0,002549076	0,002663533	0,0218473	1	0,001837453	0,001842153	0,23066808	1,849717972	6,54E-14
140	0,172623555	0,002546961	0,00257698	0,021257738	1	0,001834691	0,001839479	0,112431903	2,210410282	4,26E-13
141	0,168111201	0,002544977	0,002494763	0,020788377	1	0,001831239	0,001836364	0,072742781	2,716670371	6,56E-12
142	0,163814802	0,00254311	0,002416171	0,020421809	1	0,001826626	0,001832315	0,054021398	3,239882234	1,09E-10
143	0,159720242	0,002541364	0,002340715	0,020142494	1	0,001820587	0,001826962	0,043192498	3,627271472	1,50E-08
144	0,155886641	0,002539757	0,002267846	0,019933155	1	0,001813163	0,001820199	0,036112408	3,791515004	2,49E-08
145	0,189634891	0,002538309	0,002196823	0,019775027	1	0,001804607	0,00181218	0,031102457	3,851885861	3,84E-08
146	0,451884525	0,002536953	0,002126988	0,019651499	1	0,001795207	0,001803174	0,027358243	3,879866675	2,35E-07
147	0,844352553	0,002535591	0,002058911	0,019550611	1	0,001785212	0,001793446	0,024446293	3,895568224	2,16E-05
148	1,260026316	0,002534735	0,001992744	0,019464348	1	0,001774822	0,00178322	0,022112077	3,905515526	7,75E-04
149	1,662219933	0,002541527	0,001925883	0,01938748	1	0,001764196	0,001772677	0,020195984	3,912347946	0,011905783
150	2,013900684	0,002755948	0,001856974	0,019316659	1	0,00175346	0,00176196	0,018590575	3,917320254	0,124906538

species	pTGF-β_{nuc}	pCyclinB$_{nuc}$	pCdk1$_{nuc}$	hypRb$_{nuc}$	pCyclinA$_{nuc}$	pCyclinB$_{cyt}$	pCyclinA$_{cyt}$	pRas$_{cyt}$	pRaf$_{cyt}$	pMEK$_{cyt}$
t										
0	0	0	4	0	0	0	0	0	0	0
1	0	0	4	0	0	0	0	1,514358771	1,841374234	1,871684504
2	0	0	4	0	0	0	0	1,589483114	1,851541368	1,872599396
3	0	0	4	0	0	0	0	1,58986483	1,85158968	1,872603644
4	0	0	4	0	0	0	0	1,582393581	1,850993113	1,872568135
5	0	0	4	0	0	0	0	1,492801292	1,842824714	1,872045139
6	0	0	4	0	0	0	0	1,099281511	1,792070538	1,868666869
7	0	0	4	0	0	0	0	0,511448995	1,576932305	1,851996808
8	0	0	4	0	0	0	0	0,144282665	0,985187425	1,770864608
9	0	0	4	6,10E-275	0	0	0	0,024797838	0,416846548	1,489981323
10	0	0	4	7,84E-185	0	0	0	0,003502078	0,105213188	0,858409609
11	0	0	4	6,16E-105	0	0	0	4,77E-04	0,01698688	0,332736147
12	3,22E-154	0	4	1,34E-40	0	0	0	6,46E-05	0,002367136	0,075348634
13	9,27E-19	0	4	5,34E-06	0	0	0	8,74E-06	3,22E-04	0,011584342
14	0,00297188	0	4	0,157531309	0	0	0	1,18E-06	4,36E-05	0,001599393
15	1,866877263	0	4	1,623134348	2,64E-299	0	0	1,61E-07	5,90E-06	2,17E-04
16	1,980580957	0	4	1,975520306	2,33E-124	0	0	2,23E-08	7,98E-07	2,94E-05
17	1,991558306	2,68E-258	4	1,986244909	4,38E-71	0	1,36E-282	3,44E-09	1,08E-07	3,98E-06
18	1,994531356	2,68E-152	4	1,989077773	1,45E-43	0	4,46E-173	8,42E-10	1,46E-08	5,38E-07
19	1,995358201	3,93E-92	4	1,990167711	5,44E-28	0	1,51E-110	4,54E-10	1,98E-09	7,28E-08
20	1,995581241	1,34E-60	4	1,990675713	1,30E-19	2,43E-240	1,01E-76	3,71E-10	2,68E-10	9,86E-09
21	1,995625034	4,43E-44	4	1,990927553	5,64E-15	8,65E-175	5,09E-58	3,34E-10	3,62E-11	1,33E-09
22	1,995629404	9,64E-35	3,999999999	1,991044281	2,67E-12	2,38E-137	4,20E-47	3,06E-10	4,90E-12	1,81E-10
23	1,995629575	9,74E-29	3,999999985	1,991090346	1,24E-10	3,53E-113	3,00E-40	2,83E-10	6,63E-13	2,44E-11
24	1,995629578	1,95E-24	3,999999896	1,991106384	1,58E-09	6,87E-96	1,14E-35	2,63E-10	8,98E-14	3,31E-12
25	1,995629578	3,16E-21	3,999999631	1,991112624	9,20E-09	6,24E-83	1,83E-32	2,45E-10	1,22E-14	4,48E-13
26	1,995629578	8,98E-19	3,999999094	1,991116075	3,34E-08	5,19E-73	4,20E-30	2,29E-10	1,64E-15	6,06E-14
27	1,995629578	7,57E-17	3,999998205	1,991118712	8,99E-08	3,29E-65	2,79E-28	2,15E-10	2,23E-16	8,20E-15
28	1,995629578	2,68E-15	3,999996862	1,991121062	1,99E-07	6,42E-59	8,23E-27	2,03E-10	3,01E-17	1,11E-15
29	1,995629578	4,85E-14	3,999994815	1,991123266	3,89E-07	8,40E-54	1,40E-25	1,91E-10	4,08E-18	1,50E-16
30	1,995629578	4,73E-13	3,999991022	1,991125364	7,08E-07	9,85E-50	1,68E-24	1,81E-10	5,52E-19	2,03E-17
31	1,995629577	2,49E-12	3,999969926	1,991127366	1,32E-06	1,05E-46	1,87E-23	1,72E-10	7,47E-20	2,75E-18
32	1,995629556	7,63E-12	3,962131737	1,991129272	8,65E-05	1,36E-44	3,05E-17	1,64E-10	1,01E-20	3,72E-19
33	1,995629335	1,57E-11	3,302100379	1,991131039	0,00540913	3,68E-43	1,30E-09	1,56E-10	1,37E-21	5,04E-20
34	1,995628895	2,48E-11	2,471101055	1,991132665	0,026264415	3,33E-42	1,53E-06	1,49E-10	1,85E-22	6,82E-21
35	1,995628387	3,41E-11	1,960868016	1,991134187	0,074574402	1,60E-41	1,19E-04	1,43E-10	2,50E-23	9,23E-22
36	1,995627849	4,34E-11	1,893981858	1,991135616	0,22510062	5,31E-41	0,009118379	1,37E-10	3,39E-24	1,25E-22
37	1,995627291	5,28E-11	2,200750634	1,991136953	0,463549715	1,40E-40	0,211077409	1,32E-10	4,59E-25	1,69E-23
38	1,995626693	6,23E-11	2,755627501	1,991138194	0,578043406	3,18E-40	0,378588729	1,27E-10	6,21E-26	2,29E-24
39	1,995625921	7,21E-11	3,30574494	1,9911393	0,576054529	6,47E-40	0,387685363	1,22E-10	8,40E-27	3,09E-25
40	1,995621819	8,36E-11	3,705261636	1,991139487	0,49041254	1,23E-39	0,361264186	1,18E-10	1,14E-27	4,19E-26
41	1,994577865	1,00E-10	3,898795724	1,990883968	0,387298279	2,36E-39	0,310972138	1,14E-10	1,54E-28	5,67E-27
42	1,845346513	7,11E-10	3,95036112	1,954097135	0,311283105	1,21E-37	0,262429285	1,10E-10	2,08E-29	7,67E-28
43	0,295689872	5,68E-05	3,957416794	1,449586381	0,269959551	4,16E-18	0,229470455	1,07E-10	2,82E-30	1,04E-28
44	0,032234501	0,030042979	3,957685727	0,250889964	0,247839684	8,22E-07	0,209300729	1,04E-10	3,81E-31	1,41E-29
45	0,016292725	0,30794393	3,957828495	0,005032792	0,234054854	0,022937042	0,19636817	1,01E-10	5,16E-32	1,90E-30
46	0,01338698	0,509436346	3,953513096	7,38E-04	0,220325402	0,309637698	0,186214781	1,44E-08	1,51E-32	2,57E-31
47	0,012899051	0,551605378	3,943680239	4,91E-04	0,205573423	0,375242648	0,176562951	0,004545481	2,27E-10	3,48E-32
48	0,012860828	0,514975746	3,92981307	4,75E-04	0,190834917	0,368037312	0,167084422	0,46466438	0,052646169	2,34E-06
49	0,012860343	0,392083252	3,914930798	4,75E-04	0,17795952	0,318757457	0,15818414	1,542711459	1,845712915	1,872099033
50	0,012860343	0,280767257	3,901898489	4,75E-04	0,168331586	0,250884241	0,150392129	1,582004225	1,850846903	1,872552197
51	0,012860343	0,228229375	3,891450587	4,75E-04	0,161557323	0,209171541	0,143909495	1,579357708	1,8506227	1,87253834
52	0,012860343	0,201345998	3,883270991	4,76E-04	0,156741981	0,18483621	0,138614785	1,556948192	1,84867547	1,872415207
53	0,012860343	0,185094377	3,876988335	4,76E-04	0,153262209	0,16904702	0,13430078	1,406235784	1,833888872	1,871460159
54	0,012860343	0,174138382	3,872294461	4,76E-04	0,150714758	0,157896195	0,130776891	0,89717072	1,749165746	1,865635005
55	0,012860343	0,166223027	3,868936867	4,76E-04	0,148828265	0,149547346	0,127887964	0,359950651	1,420381424	1,837062483
56	0,012860343	0,160221721	3,866709004	4,77E-04	0,147413155	0,143033312	0,125510948	0,084518439	0,777628817	1,714075335
57	0,012860343	0,15549769	3,865440648	4,77E-04	0,146333373	0,137793157	0,123548026	0,013193431	0,283081576	1,300828971
58	0,012860343	0,151615361	3,864989632	4,90E-04	0,145489725	0,133473038	0,121920585	0,001827181	0,059869142	0,661700712
59	0,012860343	0,14784183	3,865239367	0,001128908	0,144811923	0,129802557	0,120564851	2,49E-04	0,008970644	0,217669658
60	0,012860343	0,142040652	3,866115686	0,00330754	0,144267334	0,126385177	0,119430163	3,41E-05	0,001232979	0,041870328
61	0,012860724	0,136101139	3,867567015	0,015602325	0,143842663	0,122927771	0,118479409	5,09E-06	1,67E-04	0,006086932
62	0,129030521	0,131040091	3,869800793	0,591599582	0,143497063	0,119576037	0,117682201	1,30E-06	2,26E-05	8,32E-04
63	1,946194751	0,12665389	3,873256945	1,910547643	0,143182487	0,116415926	0,117009749	1,00E-06	3,06E-06	1,13E-04
64	1,984665475	0,122799674	3,877485658	1,96030378	0,142849936	0,11347329	0,116433099	1,23E-06	4,15E-07	1,53E-05
65	1,991818984	0,119374136	3,882122288	1,966559645	0,142468485	0,110747063	0,115924284	1,53E-06	5,61E-08	2,07E-06
66	1,993628547	0,116300394	3,886966295	1,968519614	0,142023292	0,108224429	0,11545833	1,77E-06	7,59E-09	2,80E-07
67	1,994105093	0,113519837	3,891901909	1,969343811	0,141508862	0,105888143	0,115014258	1,91E-06	1,03E-09	3,79E-08
68	1,994210938	0,110986859	3,896864246	1,969741319	0,140924637	0,103720222	0,114575421	1,96E-06	1,39E-10	5,12E-09
69	1,994224291	0,108665346	3,901819789	1,969932195	0,140272359	0,10170397	0,11412976	1,94E-06	1,88E-11	6,93E-10
70	1,994224009	0,10652626	3,906746622	1,970014844	0,139554568	0,099824294	0,11366879	1,88E-06	2,55E-12	9,38E-11
71	1,994222465	0,104545938	3,911612312	1,970046855	0,138774113	0,098067563	0,113186454	1,81E-06	3,45E-13	1,27E-11
72	1,994220403	0,102704868	3,916371467	1,970059448	0,137934563	0,096421595	0,112678605	1,73E-06	4,67E-14	1,72E-12
73	1,994217756	0,100986789	3,920986858	1,970065355	0,137040645	0,094875608	0,11214277	1,65E-06	6,32E-15	2,33E-13
74	1,994214424	0,099378022	3,925437103	1,970068772	0,136098132	0,093420088	0,111577938	1,57E-06	8,55E-16	3,15E-14
75	1,994210277	0,09786696	3,929712483	1,970070985	0,135114232	0,092046648	0,110984378	1,50E-06	1,16E-16	4,26E-15

76	1,994205065	0,096443682	3,933812897	1,970072377	0,134100812	0,090747889	0,110363698	1,44E-06	1,57E-17	5,77E-16
77	1,994198006	0,095099642	3,937746062	1,970072931	0,13308292	0,089517269	0,109719678	1,38E-06	2,12E-18	7,81E-17
78	1,994186487	0,093827437	3,939297793	1,970072098	0,132105724	0,088348995	0,109059965	1,33E-06	2,87E-19	1,06E-17
79	1,994163884	0,09262061	3,608100099	1,970068308	0,132772713	0,087237918	0,10844597	1,28E-06	3,89E-20	1,43E-18
80	1,994130194	0,091473504	2,730657828	1,970061603	0,145764338	0,086179454	0,108840263	1,24E-06	5,27E-21	1,94E-19
81	1,994093604	0,090381136	2,051423013	1,970054023	0,177148915	0,085169506	0,113405716	1,20E-06	7,29E-22	2,62E-20
82	1,994056108	0,089339094	1,840410874	1,970046082	0,26310708	0,084204404	0,138468179	1,16E-06	1,12E-22	3,55E-21
83	1,994018104	0,088343461	2,030637587	1,970037897	0,42563829	0,083280853	0,266062957	1,13E-06	2,68E-23	4,80E-22
84	1,993979485	0,087390737	2,454083818	1,970029459	0,515475269	0,082395898	0,355921831	1,10E-06	1,41E-23	6,49E-23
85	1,993939435	0,08647779	2,908487744	1,970020579	0,525511497	0,081546868	0,367379116	1,07E-06	1,13E-23	8,79E-24
86	1,993894283	0,085601804	3,322335908	1,97001037	0,498081477	0,080731323	0,358755697	1,05E-06	1,01E-23	1,19E-24
87	1,993817793	0,084760237	3,646419831	1,969992405	0,446780292	0,079947037	0,336972234	1,02E-06	9,14E-24	1,61E-25
88	1,993141884	0,083950794	3,848619842	1,969827344	0,383658457	0,079191987	0,304059693	1,00E-06	8,36E-24	2,18E-26
89	1,959606163	0,083171389	3,939440863	1,961596958	0,322066361	0,078464334	0,267031953	9,81E-07	7,69E-24	2,95E-27
90	1,290500881	0,082420835	3,962214011	1,793614122	0,27237552	0,077762412	0,233271261	9,62E-07	7,10E-24	3,99E-28
91	0,105762404	0,083356316	3,965987378	1,077637758	0,241651551	0,077093925	0,208635528	9,44E-07	6,58E-24	5,40E-29
92	0,0343365	0,153650009	3,969160282	0,290190868	0,224023026	0,078079125	0,192184415	9,28E-07	6,12E-24	7,31E-30
93	0,023076385	0,391027814	3,971179574	0,058627372	0,210441356	0,173045734	0,180549891	9,54E-07	5,99E-24	9,89E-31
94	0,020750727	0,504585193	3,969448571	0,030665804	0,196877509	0,345178939	0,170778082	9,55E-05	3,65E-17	1,34E-31
95	0,02044619	0,517248427	3,964739118	0,027796509	0,183706447	0,364410535	0,161829271	0,051672075	5,58E-06	2,04E-22
96	0,020434574	0,447058685	3,958411028	0,027690855	0,171839551	0,341468845	0,153615145	1,055435574	1,698176324	1,840940139
97	0,020434848	0,322562697	3,951800984	0,027693399	0,16216539	0,278371825	0,146296564	1,577063732	1,850223385	1,872497858
98	0,020434989	0,247123457	3,945624623	0,027695722	0,1548172	0,225167215	0,139992292	1,580692018	1,850737076	1,872545555
99	0,020435036	0,210353456	3,939996409	0,027697474	0,149255338	0,19413264	0,134655192	1,573415567	1,850100935	1,872504729
100	0,02043505	0,189342273	3,93503826	0,027698789	0,144990321	0,174760767	0,130151321	1,518006133	1,84510278	1,872185197
101	0,020435056	0,175603567	3,930896867	0,027699803	0,141684897	0,161452619	0,126341418	1,231351975	1,812453189	1,870043859
102	0,020435058	0,165837449	3,92765341	0,02770061	0,139099146	0,151655182	0,123105416	0,643291318	1,65830486	1,858740587
103	0,020435059	0,158513775	3,925307191	0,027701282	0,137054805	0,144087524	0,12034457	0,208125293	1,149673223	1,801713208
104	0,020435059	0,152813393	3,923798107	0,027702038	0,135416237	0,138037836	0,117978252	0,039470043	0,537092983	1,595904706
105	0,020435059	0,14823996	3,923033175	0,027707217	0,134079263	0,133075608	0,115940275	0,005715612	0,155824349	1,01828035
106	0,020435059	0,144381635	3,922907159	0,02791441	0,132964113	0,128916034	0,11417586	7,82E-04	0,027271292	0,440001027
107	0,020435059	0,140388643	3,923319552	0,030169314	0,132012486	0,125317819	0,112639471	1,06E-04	0,003867627	0,114240296
108	0,02043506	0,135056108	3,924189666	0,033809053	0,131190616	0,121958979	0,111293871	1,48E-05	5,27E-04	0,018715529
109	0,020464615	0,130140042	3,925440851	0,075761087	0,130470654	0,118712845	0,110109217	2,47E-06	7,14E-05	0,002615756
110	0,382061462	0,125866933	3,9270732	0,911141125	0,129820576	0,115645654	0,109060066	9,04E-07	9,66E-06	3,56E-04
111	1,960349015	0,122103139	3,929233517	1,94418243	0,12921039	0,112782893	0,108123912	8,43E-07	1,31E-06	4,82E-05
112	1,98627159	0,118751323	3,93174144	1,97141541	0,128610926	0,110124834	0,107280303	1,01E-06	1,77E-07	6,52E-06
113	1,99167907	0,115738678	3,934433366	1,976218067	0,128002076	0,107660576	0,106510546	1,18E-06	2,39E-08	8,82E-07
114	1,993016043	0,113009466	3,937216972	1,97783711	0,127372316	0,105374695	0,105798007	1,30E-06	3,24E-09	1,19E-07
115	1,993320408	0,110520159	3,940039639	1,978530329	0,126715425	0,103250585	0,105128299	1,36E-06	4,39E-10	1,62E-08
116	1,993366731	0,108236183	3,942874029	1,978849717	0,126028173	0,10127239	0,104489572	1,37E-06	5,94E-11	2,19E-09
117	1,993369813	0,106129658	3,945708541	1,978988003	0,125308831	0,099425878	0,103872541	1,35E-06	8,03E-12	2,96E-10
118	1,993369387	0,104177812	3,948529148	1,979041313	0,124556356	0,097698238	0,10326974	1,31E-06	1,09E-12	4,00E-11
119	1,993368648	0,102361827	3,951305869	1,979061963	0,123770481	0,096077954	0,102675062	1,27E-06	1,47E-13	5,42E-12
120	1,993367652	0,100665991	3,954006976	1,979072084	0,122952282	0,094554767	0,102083632	1,22E-06	1,99E-14	7,34E-13
121	1,993366345	0,099077062	3,956612298	1,9790789	0,122104247	0,093119593	0,101491742	1,17E-06	2,70E-15	9,93E-14
122	1,993364652	0,09758379	3,95911185	1,979084513	0,121230169	0,091764395	0,100896767	1,13E-06	3,65E-16	1,34E-14
123	1,993362443	0,096176539	3,96150239	1,9790895	0,120336295	0,090482063	0,100297134	1,09E-06	4,94E-17	1,82E-15
124	1,993359331	0,094847005	3,963784407	1,979093946	0,11943548	0,089266297	0,099692535	1,05E-06	6,69E-18	2,46E-16
125	1,993353977	0,093587981	3,965779959	1,979097575	0,118551567	0,088111505	0,099084574	1,02E-06	9,06E-19	3,34E-17
126	1,993342361	0,092393177	3,851124362	1,979099417	0,118220956	0,087012711	0,098486402	9,88E-07	1,23E-19	4,51E-18
127	1,993321105	0,091257076	3,006735663	1,979098654	0,127121633	0,085965472	0,098305784	9,60E-07	1,66E-20	6,11E-19
128	1,993296287	0,090174814	2,250155168	1,979096785	0,152629318	0,084965817	0,100468288	9,35E-07	2,25E-21	8,27E-20
129	1,993270518	0,089142082	1,92583326	1,979094459	0,21535561	0,08401018	0,112670505	9,11E-07	3,10E-22	1,12E-20
130	1,993244292	0,088155046	2,012411495	1,979091807	0,367558732	0,083095357	0,197547209	8,90E-07	4,64E-23	1,51E-21
131	1,993217607	0,087210285	2,430485144	1,979088837	0,513909475	0,082218463	0,345178224	8,71E-07	1,04E-23	2,05E-22
132	1,993189836	0,08630473	2,963287723	1,979085407	0,560169297	0,081376905	0,378672025	8,52E-07	5,15E-24	2,77E-23
133	1,993156849	0,085435621	3,440120575	1,979080511	0,526663399	0,080568312	0,371826049	8,36E-07	4,15E-24	3,75E-24
134	1,993057127	0,084600467	3,767879484	1,979059053	0,445565511	0,079790507	0,339824044	8,20E-07	3,76E-24	5,08E-25
135	1,987559323	0,083797015	3,921765472	1,977711907	0,359097533	0,0790415	0,293114639	8,05E-07	3,48E-24	6,88E-26
136	1,687160108	0,08302324	3,961299512	1,903450233	0,291852199	0,078319487	0,249235388	7,92E-07	3,24E-24	9,31E-27
137	0,169798807	0,082576946	3,966869894	1,279760955	0,252788739	0,077624087	0,218414907	7,79E-07	3,03E-24	1,26E-27
138	0,032758018	0,127751577	3,968902393	0,258217673	0,231255738	0,077609413	0,198721553	7,67E-07	2,85E-24	1,70E-28
139	0,01927205	0,375641484	3,970695655	0,018809863	0,216721081	0,149559628	0,185560741	7,72E-07	2,73E-24	2,31E-29
140	0,016641859	0,513223618	3,968740556	0,005885371	0,202777986	0,345620894	0,17509067	4,36E-05	1,50E-18	3,12E-30
141	0,016250564	0,537860839	3,963313953	0,004785015	0,189111934	0,371640807	0,165683582	0,038081078	1,56E-06	1,19E-24
142	0,016228901	0,482332189	3,955920375	0,004730753	0,176480586	0,356242814	0,157037103	0,959400012	1,470113313	1,7169561
143	0,016228794	0,352559547	3,948535212	0,004732174	0,165926128	0,297001519	0,149272474	1,574302556	1,849890597	1,872469807
144	0,016228808	0,261315129	3,942504261	0,004733781	0,157887369	0,236262326	0,142556116	1,580666612	1,850730757	1,872544891
145	0,016228818	0,218392649	3,937919092	0,004735229	0,151837381	0,200796433	0,136878153	1,574970875	1,850236154	1,872513328
146	0,016228825	0,195108104	3,934520686	0,004736586	0,147183527	0,179392565	0,132099258	1,527017107	1,845951872	1,872240334
147	0,016228832	0,180413344	3,932071965	0,004737947	0,14352538	0,165072111	0,128061033	1,26205853	1,816666873	1,870327053
148	0,016228835	0,170211498	3,930364806	0,004738944	0,140596318	0,154729405	0,124625863	0,67602144	1,67378519	1,859961511
149	0,016228835	0,162682702	3,929292762	0,00473962	0,138212379	0,146854282	0,12168257	0,225560798	1,188259696	1,807736638
150	0,016228835	0,156886215	3,928822883	0,004740162	0,136240401	0,140628363	0,119142833	0,04390349	0,567337604	1,616049468

species	$pERK_{cyt}$	$pERK_{nuc}$	$pCyclinD_{nuc}$	$pCyclinD_{cyt}$	$Pp27_{cyt}$	$Pp27_{nuc}$	$pCyclinE_{cyt}$	$pCyclinE_{nuc}$	$pCdk2_{nuc}$	$pCdk2_{cyt}$
t										
0	0	0	0	0	0	0	0	0	0	0
1	1,442822997	0,496423496	0	0	0	0	0	0	0	0
2	0,569545537	1,388862883	0	0	0	0	0	0	0	0
3	0,295121853	1,669887553	0	0	0	0	0	0	0	0
4	0,231039506	1,737716167	0	0	0	0	0	0	0	0
5	0,200584304	1,770698407	0	0	0	0	0	0	0	0
6	0,181707655	1,791416434	0	0	0	0	0	0	0	0
7	0,168409523	1,805249743	0	0	0	0	0	0	0	0
8	0,158260719	1,802633011	0	0	0	0	0	0	0	0
9	0,149982847	1,665216515	3,67E-267	0	0	4,41E-267	0	7,35E-268	0	0
10	0,142869329	0,032578733	6,48E-182	0	0	7,41E-182	0	1,24E-182	0	0
11	0,136809498	0,003933886	2,52E-104	0	0	2,91E-104	0	4,85E-105	0	0
12	0,131648778	0,001525702	8,25E-41	8,13E-162	1,50E-161	9,62E-41	1,16E-164	1,60E-41	0	0
13	0,127184927	8,09E-04	2,66E-06	7,72E-24	1,92E-23	3,34E-06	1,48E-26	5,56E-07	0	0
14	0,123268841	5,70E-04	0,056233491	1,08E-05	8,85E-05	0,097740641	5,38E-08	0,014131691	0	0
15	0,119793007	6,99E-04	0,347640065	0,047134801	0,267653156	0,616783985	0,001775391	0,125282892	6,90E-146	1,21E-292
16	0,116677685	0,001289417	0,502742726	0,321089449	0,407773843	0,647984249	0,172426655	0,245106713	2,30E-59	1,11E-118
17	0,113862258	0,002949408	0,557289288	0,375700782	0,395032707	0,601444923	0,33566311	0,228182364	3,90E-33	6,26E-66
18	0,111299674	0,005398177	0,561223824	0,381640518	0,387767267	0,575518056	0,340571442	0,225841979	1,07E-19	8,00E-39
19	0,108952756	0,007743053	0,499601355	0,363329754	0,367008759	0,508690828	0,335379118	0,242873464	2,69E-12	9,37E-24
20	0,106791663	0,009904127	0,396771825	0,317097104	0,324253208	0,411995124	0,330360114	0,271608391	1,66E-08	6,84E-16
21	0,104792119	0,011903671	0,307118291	0,262765779	0,272954369	0,325041867	0,321670828	0,306258013	1,50E-06	1,04E-11
22	0,102934135	0,013761656	0,253378424	0,223190012	0,232285221	0,266555476	0,301191186	0,325766013	1,66E-05	2,15E-09
23	0,101201073	0,015494717	0,223854491	0,198025152	0,203820252	0,228540086	0,269800589	0,30957779	6,97E-05	5,85E-08
24	0,099578955	0,017116835	0,206629897	0,181613494	0,183522533	0,202548743	0,237039681	0,272274569	1,72E-04	5,26E-07
25	0,098055932	0,018639859	0,195595993	0,170296534	0,168511131	0,184191909	0,21039486	0,238949995	3,14E-04	2,43E-06
26	0,096621882	0,020073908	0,187879077	0,16206799	0,157058614	0,170901049	0,190876997	0,215709963	4,79E-04	7,48E-06
27	0,0952681	0,02142769	0,182070035	0,155806266	0,148081819	0,161020186	0,176772659	0,200148209	6,63E-04	1,79E-05
28	0,093987045	0,022708745	0,177428448	0,150851942	0,140877951	0,15348154	0,166368605	0,189432733	8,78E-04	3,69E-05
29	0,09277215	0,02392364	0,173538949	0,146797596	0,134979459	0,147593713	0,158465385	0,181689893	0,001178437	7,01E-05
30	0,091617663	0,025078127	0,170155601	0,143380788	0,130067107	0,142899595	0,15227969	0,175801865	0,001839859	1,38E-04
31	0,090518519	0,026177271	0,167126239	0,140426715	0,125916893	0,139087929	0,147300184	0,171107046	0,007054861	5,41E-04
32	0,08947024	0,02722555	0,164353029	0,137815778	0,122367311	0,135940015	0,143186667	0,167205383	0,391005574	0,228289024
33	0,088468847	0,028226943	0,161770624	0,13546426	0,119298861	0,13329758	0,139707457	0,163847364	0,160088059	0,326755551
34	0,087510792	0,029184998	0,159333501	0,133312336	0,116620967	0,131043039	0,136701098	0,160872023	0,074649404	0,081308413
35	0,086592897	0,030102893	0,157007678	0,131316283	0,11426344	0,129086808	0,134052582	0,158171333	0,06992233	0,070918166
36	0,085712308	0,030983482	0,154765085	0,129443167	0,112170737	0,127358747	0,131678112	0,155668975	0,066948048	0,06781731
37	0,084866452	0,031829338	0,152579529	0,127667108	0,110297995	0,125802072	0,129515039	0,153307162	0,062825468	0,064006972
38	0,084053	0,03264279	0,15042273	0,125966561	0,108608224	0,124368542	0,127515028	0,151037404	0,058268251	0,059598785
39	0,083269843	0,033425947	0,148259895	0,124321921	0,107070117	0,123014159	0,125638934	0,148813049	0,05368948	0,055097255
40	0,08251506	0,034180729	0,146044995	0,122713135	0,105656138	0,121695082	0,123852572	0,146582701	0,049262903	0,050711507
41	0,081786901	0,034908888	0,143718015	0,121118051	0,104341121	0,12036435	0,122123768	0,144285526	0,045097906	0,046558371
42	0,081083766	0,035612022	0,141211318	0,119511899	0,103101237	0,11897215	0,120420681	0,141853426	0,041261578	0,042710042
43	0,080404187	0,036291598	0,138476485	0,117869844	0,101913793	0,117474808	0,118712846	0,139229442	0,037782155	0,039201212
44	0,079746819	0,036948958	0,135529534	0,116174164	0,100758492	0,115854238	0,116976366	0,136404364	0,034656489	0,036035584
45	0,079110422	0,037585336	0,132473492	0,114423458	0,09962017	0,114134076	0,115201731	0,133444229	0,031862147	0,033196002
46	0,078493852	0,038201861	0,129460613	0,112635813	0,098491121	0,112372764	0,113397845	0,130472669	0,029369825	0,030655698
47	0,077896055	0,038799573	0,126630803	0,11084272	0,097371112	0,110639268	0,111588396	0,127622774	0,027150522	0,028386316
48	0,077316052	0,039379424	0,12404837	0,109077596	0,096264835	0,108982659	0,109802389	0,124979285	0,025177451	0,026361186
49	1,232183388	0,713181204	0,121687611	0,107364391	0,09517805	0,107414864	0,108063461	0,122549189	0,023424163	0,024555163
50	0,457190969	1,50274486	0,119500135	0,10571477	0,094115044	0,105927427	0,106385316	0,120301056	0,021862267	0,022942671
51	0,275113776	1,69066561	0,117455188	0,104132648	0,093078392	0,104510692	0,104773895	0,118205202	0,02046347	0,021497764
52	0,22276375	1,746465568	0,115541804	0,102618486	0,09206954	0,103160085	0,10323084	0,116245353	0,019202571	0,020196173
53	0,195786527	1,775757581	0,11378126	0,101172805	0,091089619	0,101883341	0,101756793	0,114431999	0,018058805	0,019016828
54	0,178459201	1,793978836	0,112129253	0,099795383	0,090139566	0,100670217	0,100351608	0,11273943	0,017016794	0,017942877
55	0,165997753	1,798486803	0,110537331	0,098480698	0,089218803	0,099499896	0,099010999	0,111122717	0,016061659	0,016960337
56	0,156325251	1,729589022	0,109013484	0,097223215	0,088326145	0,098370127	0,097729759	0,109576233	0,015179151	0,016055847
57	0,148300841	0,561223769	0,107563832	0,096019186	0,087460593	0,09728262	0,096503769	0,108102519	0,014359007	0,015218102
58	0,141404774	0,007209908	0,106186955	0,094865666	0,086621318	0,096237537	0,095329729	0,106701045	0,013593811	0,014438472
59	0,13556665	0,002326347	0,104878641	0,093759972	0,085807541	0,095233681	0,094204749	0,105368706	0,012873783	0,013709544
60	0,130580072	0,001164061	0,103634247	0,092699545	0,085018478	0,094269261	0,093126145	0,104101407	0,012189686	0,013021846
61	0,126251929	7,03E-04	0,107075669	0,09171928	0,084261236	0,094697756	0,092122159	0,105514506	0,011517419	0,012372247
62	0,122444086	6,73E-04	0,271596318	0,10800335	0,087634141	0,197679108	0,100717091	0,196490761	0,00941962	0,011429052
63	0,119056325	0,001043402	0,459140846	0,290209983	0,258392451	0,466240489	0,238769951	0,26587021	0,00726799	0,009956917
64	0,116013868	0,002231278	0,53260214	0,364138992	0,373125689	0,556236114	0,327000948	0,245005215	0,005906949	0,008588701
65	0,113259586	0,004541754	0,554814153	0,377819766	0,38338537	0,568439252	0,336151037	0,233874119	0,004980886	0,00747475
66	0,110748945	0,007017861	0,513506021	0,36742994	0,370819916	0,521806569	0,33158038	0,245482698	0,004312044	0,006586484
67	0,108446622	0,009315532	0,422175452	0,329271702	0,3351314	0,435106364	0,32622047	0,269601672	0,003809556	0,005874111
68	0,106324175	0,01143692	0,333873324	0,278302248	0,287098258	0,349365714	0,318537538	0,299494699	0,003425401	0,005296094
69	0,1043584	0,013402342	0,276564621	0,237751322	0,245723889	0,287908991	0,301701297	0,319810994	0,003136267	0,004822326
70	0,10253014	0,015230426	0,242778355	0,210668836	0,215441856	0,246373871	0,274719704	0,312347377	0,00293124	0,004432158
71	0,100823416	0,016937019	0,221607873	0,192396025	0,193308883	0,21709486	0,244328519	0,281742726	0,002797853	0,004111217
72	0,099224774	0,018535527	0,206992107	0,179345854	0,176705376	0,195954213	0,217634903	0,248974299	0,002716836	0,003848123

76	0,09370556	0,024053152	0,173167486	0,14951487	0,139362665	0,1528014	0,160604714	0,182070931	0,00294836	0,003230847
77	0,092504861	0,025252657	0,167435632	0,144655335	0,133848753	0,146922312	0,153210989	0,174016707	0,004388362	0,003276287
78	0,091363364	0,026392222	0,162310178	0,140343705	0,129146904	0,14195787	0,147086734	0,167350557	0,106299966	0,032649586
79	0,090276145	0,027476416	0,157687845	0,136472665	0,125074195	0,137676156	0,141892742	0,161669772	0,552740464	0,458975451
80	0,089238846	0,028509139	0,15349062	0,132965542	0,121498536	0,133919551	0,137400759	0,15672098	0,081549175	0,104967908
81	0,088247593	0,029493699	0,149656742	0,129765044	0,118322711	0,130577612	0,133453214	0,152337363	0,071522342	0,073322284
82	0,087298924	0,030432883	0,146135511	0,12682669	0,115473786	0,127570422	0,12993825	0,148403516	0,068200492	0,069055053
83	0,086389742	0,031329011	0,142885405	0,124114961	0,112896034	0,124838642	0,126774294	0,144836574	0,064085307	0,065284564
84	0,085517257	0,032183993	0,139872334	0,121601031	0,110546197	0,122337231	0,123900461	0,141575208	0,059127366	0,060570666
85	0,084678955	0,032999382	0,13706801	0,119261105	0,108390142	0,120031307	0,121270244	0,138572728	0,053962221	0,055546917
86	0,083872562	0,033776416	0,134448703	0,117075226	0,1064005	0,117893342	0,118847319	0,135792689	0,048835971	0,050523448
87	0,08309601	0,034516065	0,131994329	0,115026546	0,104555081	0,115901255	0,116602874	0,133206027	0,0438933	0,045658158
88	0,082347421	0,035219073	0,129687764	0,113100741	0,102835706	0,114037074	0,114513707	0,130789149	0,03923581	0,04105619
89	0,081625081	0,035885993	0,127514301	0,111285563	0,101227344	0,112285979	0,1125609	0,128522603	0,03492844	0,036785296
90	0,080927419	0,036517225	0,125461232	0,109570478	0,099717454	0,110635606	0,110728842	0,126390144	0,031004628	0,032881542
91	0,080252998	0,037113048	0,123517533	0,107946346	0,098295468	0,109075542	0,109004483	0,124378064	0,0274738	0,029356372
92	0,079600498	0,037673664	0,121678682	0,106405286	0,096952416	0,107598236	0,107376872	0,122477871	0,024328816	0,026203934
93	0,0789687	0,038199693	0,120081357	0,104945286	0,095681534	0,106235964	0,105840514	0,120775558	0,021553416	0,023407529
94	0,078356484	0,038696431	0,1198513	0,103617349	0,094487825	0,105323033	0,104431926	0,120061319	0,019157048	0,020953599
95	0,07776281	0,0391818	0,123390953	0,102662154	0,093420332	0,105766292	0,103337844	0,122279361	0,017321048	0,018895059
96	1,753976825	0,124880623	0,129428889	0,102434393	0,092571072	0,107678518	0,102855187	0,127146458	0,016375551	0,017420101
97	0,858656194	1,090957835	0,133716319	0,10291925	0,091978014	0,109720601	0,10304181	0,131529049	0,016191785	0,016644387
98	0,346493676	1,61112147	0,135120513	0,103707635	0,09158374	0,110948276	0,103628048	0,133780058	0,016182928	0,016354769
99	0,248658163	1,712715085	0,134556689	0,104412982	0,091295597	0,111278882	0,104271563	0,134074501	0,01593388	0,016168579
100	0,210154486	1,753203704	0,13295151	0,104840686	0,091037268	0,11094772	0,1047389	0,133076131	0,01536748	0,01582611
101	0,187996752	1,775044195	0,130864852	0,104942047	0,090761653	0,11019881	0,104928237	0,13135322	0,014572904	0,015265581
102	0,172988127	1,780524566	0,12856628	0,104739703	0,090445005	0,109197175	0,104825607	0,129258464	0,013663025	0,0145382
103	0,161830179	1,732154614	0,126199167	0,104281384	0,090077982	0,108047185	0,104460124	0,126997311	0,01272059	0,01372012
104	0,152924848	1,313586038	0,123853119	0,103620951	0,089659803	0,106819424	0,103877866	0,124695896	0,011797098	0,012873399
105	0,145366471	0,015397195	0,121577981	0,102809193	0,089194479	0,105560212	0,103127672	0,12242811	0,010922858	0,012039873
106	0,138915499	0,003994314	0,11939803	0,101889575	0,088688294	0,104298742	0,102253996	0,120233961	0,010113369	0,011244906
107	0,133450385	0,001893104	0,117323327	0,100897268	0,088148274	0,103053075	0,101294207	0,118133201	0,009369075	0,010500766
108	0,128751121	0,001101389	0,115356477	0,099859779	0,08758134	0,101834291	0,100278278	0,116134053	0,008697102	0,00981225
109	0,124648522	7,53E-04	0,130120924	0,099069201	0,087051301	0,106355819	0,099441587	0,12359816	0,008094029	0,009183273
110	0,121021776	8,63E-04	0,327293585	0,139948518	0,100648659	0,264116383	0,122545982	0,228722285	0,007008021	0,008538306
111	0,117782183	0,001551886	0,477834392	0,319798747	0,309014884	0,495632062	0,275163553	0,264294773	0,005750156	0,007712796
112	0,11486289	0,003408613	0,536275432	0,367292841	0,376126398	0,558011464	0,329570505	0,243575191	0,004876419	0,006903196
113	0,112212379	0,005979295	0,540077293	0,374061271	0,378894046	0,551271543	0,332729676	0,240136127	0,004244277	0,006195777
114	0,109790199	0,008401015	0,475706642	0,35336091	0,357576546	0,485961132	0,326831	0,257518721	0,003769559	0,005597531
115	0,107564057	0,010627157	0,371929756	0,303401065	0,312037566	0,389419321	0,319918859	0,287119929	0,003405998	0,005095422
116	0,105507808	0,012683405	0,291973955	0,251779961	0,262298849	0,309335011	0,307784424	0,315331847	0,003129254	0,004674051
117	0,103600015	0,014591199	0,247671752	0,217134989	0,225184047	0,257500205	0,283995447	0,318753805	0,002928663	0,004320666
118	0,101822903	0,01636831	0,223697922	0,195470355	0,199308057	0,223532771	0,253383156	0,292242238	0,002796168	0,004025756
119	0,100161588	0,018029626	0,209615045	0,181346576	0,180709951	0,200190495	0,224942514	0,258171882	0,002716625	0,003781532
120	0,098603492	0,019587722	0,200443036	0,171594079	0,166879724	0,183756047	0,202884756	0,231471036	0,002674469	0,003580706
121	0,097137902	0,021053312	0,193867304	0,164483455	0,156309945	0,17198588	0,186785292	0,21320647	0,002665461	0,003417173
122	0,095755623	0,02243559	0,188758548	0,159038489	0,148046163	0,163409641	0,175037009	0,200828634	0,002708474	0,003288081
123	0,094448714	0,023742499	0,184530496	0,154682253	0,141460261	0,157048687	0,166275569	0,192128767	0,002891701	0,003199646
124	0,093210271	0,024980943	0,180861402	0,151059893	0,136126007	0,152244132	0,159553487	0,185688811	0,003769107	0,003204643
125	0,092034257	0,026156956	0,17756655	0,1479462	0,131745544	0,148544915	0,154239958	0,180657777	0,024357415	0,005648907
126	0,090915372	0,027275842	0,174535944	0,145194763	0,12810466	0,145636474	0,149914915	0,176528668	0,698515074	0,366724699
127	0,08984893	0,028342283	0,171701986	0,142708565	0,125045084	0,143295734	0,146295306	0,172995532	0,093526724	0,156285284
128	0,088830781	0,029360432	0,16902188	0,140422272	0,122447009	0,141362441	0,143187763	0,169870083	0,069816317	0,073057452
129	0,087857224	0,030333989	0,166467611	0,13829121	0,120217853	0,139720466	0,140458442	0,167033873	0,066017993	0,066936079
130	0,086924953	0,031266261	0,164020145	0,136284337	0,11828488	0,138285257	0,138013585	0,16441068	0,062207665	0,063359934
131	0,086030999	0,032160214	0,16166596	0,134379751	0,116590245	0,136995175	0,135786819	0,161950278	0,057389305	0,058830875
132	0,085172691	0,033018522	0,159394884	0,132561711	0,115087558	0,135805313	0,133730668	0,159618675	0,052291925	0,053895472
133	0,084347615	0,033843598	0,157198712	0,130818393	0,113739262	0,134683001	0,131810538	0,157392092	0,047215134	0,04893141
134	0,083553583	0,03463763	0,155070255	0,129140615	0,112514831	0,13360444	0,130000846	0,155253159	0,042326892	0,044123257
135	0,082788609	0,035402604	0,153002622	0,127520999	0,111389423	0,132552151	0,128282376	0,153188396	0,037752302	0,039596561
136	0,082050882	0,036140331	0,150988583	0,125953427	0,110342832	0,131512968	0,126640454	0,151186454	0,033578866	0,035438292
137	0,081338749	0,036852464	0,149019877	0,124432501	0,109358575	0,130476381	0,12506352	0,149236736	0,029855709	0,03169858
138	0,080650696	0,037540517	0,147086353	0,12295296	0,108423015	0,129433076	0,123541902	0,147328158	0,026597053	0,02839444
139	0,079985334	0,038205879	0,14517575	0,121509232	0,107524634	0,128373866	0,122066939	0,145448368	0,023789038	0,025516436
140	0,079341386	0,038849827	0,143282579	0,120095808	0,106653631	0,127292606	0,120630847	0,143588879	0,02139784	0,023036437
141	0,078717674	0,039473539	0,141427468	0,118710166	0,105802514	0,126196313	0,119228643	0,141760008	0,01937896	0,020915426
142	1,668585096	0,061850971	0,13962202	0,11735382	0,104966699	0,125094954	0,117859132	0,139973915	0,017686449	0,019111218
143	0,915373897	1,037140486	0,137819885	0,116024899	0,10414237	0,123973106	0,11651985	0,138203831	0,01627312	0,017582273
144	0,358689768	1,603689268	0,135955617	0,114713232	0,103323606	0,122796309	0,115202366	0,136397362	0,015085803	0,016285765
145	0,25219093	1,714964225	0,133986725	0,113403907	0,102502163	0,121532514	0,113893585	0,134508726	0,01406852	0,015176812
146	0,211954032	1,758212793	0,13219721	0,112096105	0,101673082	0,120286079	0,112589466	0,132693159	0,013175902	0,014212359
147	0,189141711	1,783143648	0,130688705	0,110842298	0,10085278	0,119191222	0,111325573	0,131131644	0,012432659	0,01337297
148	0,173805626	1,799343718	0,12817472	0,109572935	0,10002553	0,11765584	0,110061139	0,128958265	0,011791068	0,012657403
149	0,162459936	1,800791695	0,125321971	0,108205391	0,09915143	0,115785311	0,108726663	0,126350794	0,011070335	0,01198901
150	0,153442292	1,697630721	0,122602572	0,106764801	0,09822457	0,113846989	0,107322561	0,123699601	0,010265781	0,011296719

species	(CyclinB-ppCdk1)$_{cyt}$	(CyclinB-pCdk1)$_{nuc}$	inact-mitogen-receptor	(CyclinA-ppCdk1)$_{nuc}$	p$_x$CyclinA$_{nuc}$	(CyclinB-ppCdk1)$_{nuc}$	receptor	mitogen	inact-receptor
t									
0	0	0	0	0	0	0	0	0	0
1		0	0	0	0	0	0	1,99E-35	1,99E-35
2		0	0	0	0	0	0	1,58E-12	1,58E-12
3		0	0	0	0	0	0	1,67E-04	1,67E-04
4		0	0	0	0	0	0	0,053536506	0,053536506
5		0	0	0	0	0	0	0,456266222	0,456266222
6		0	0	0	0	0	0	1,372404812	1,372404812
7		0	0	0	0	0	0	2,249554598	2,249554598
8		0	0	0	0	0	0	2,419558324	2,419558324
9		0	0	0	0	0	0	2,45775838	2,45775838
10		0	0	0	0	0	0	2,472728078	2,472728078
11		0	0	0	0	0	0	2,479939761	2,479939761
12		0	0	0	0	0	0	2,483767637	2,483767637
13		0	0	0	0	0	0	2,485960909	2,485960909
14		0	0	0	0	0	0	2,487264379	2,487264379
15		0	0	4,15E-293	6,90E-146	0	0	2,488047381	2,488047381
16	0	0	0	3,76E-119	2,30E-59	0	0	2,488551936	2,488551936
17	2,04E-242	6,58E-247	0	2,11E-66	3,90E-33	2,04E-245	0	2,488921763	2,488921763
18	5,12E-136	8,99E-141	0	2,65E-39	1,07E-19	3,80E-139	0	2,489223726	2,489223726
19	1,42E-76	7,54E-81	0	3,00E-24	2,69E-12	1,82E-79	0	2,489486991	2,489486991
20	6,07E-46	1,28E-49	0	2,06E-16	1,66E-08	1,52E-48	0	2,489724626	2,489724626
21	4,72E-30	2,59E-33	0	2,77E-12	1,50E-06	1,87E-32	0	2,489942625	2,489942625
22	2,40E-21	3,40E-24	0	4,61E-10	1,66E-05	1,47E-23	0	2,490143896	2,490143896
23	8,61E-16	2,37E-18	0	8,69E-09	6,97E-05	7,07E-18	0	2,490330255	2,490330255
24	7,42E-12	3,49E-14	0	4,90E-08	1,73E-04	7,64E-14	0	2,490503184	2,490503184
25	5,63E-09	4,29E-11	0	1,41E-07	3,16E-04	7,03E-11	0	2,490663993	2,490663993
26	8,15E-07	9,42E-09	0	2,85E-07	4,85E-04	1,19E-08	4,40E-291	2,490813858	2,490813858
27	3,82E-05	6,32E-07	0	4,77E-07	6,79E-04	6,30E-07	1,31E-259	2,490953825	2,490953825
28	7,96E-04	1,82E-05	0	7,33E-07	9,12E-04	1,46E-05	3,73E-234	2,491084828	2,491084828
29	0,00846909	2,66E-04	0	1,14E-06	0,001243035	1,68E-04	1,25E-213	2,491207697	2,491207697
30	0,04825914	0,002060246	0	2,16E-06	0,0019686	9,51E-04	2,03E-197	2,49132317	2,49132317
31	0,165683789	0,008610347	0	1,39E-05	0,007567329	0,002677382	4,03E-185	2,491431904	2,491431904
32	0,404594064	0,021974667	0	0,028191979	0,746585437	0,004817845	1,96E-176	2,491534485	2,491534485
33	0,765143604	0,033196232	0	0,398846396	1,330511711	0,023229909	1,86E-170	2,491631435	2,491631435
34	1,120206578	0,035526348	0	0,575365153	0,642267451	0,142509177	2,05E-166	2,491723223	2,491723223
35	1,180131423	0,036239907	0	0,438566417	0,23147379	0,557295489	1,53E-163	2,491810267	2,491810267
36	0,729531683	0,036610752	0	0,198180647	0,141845605	1,350375286	2,40E-161	2,491892941	2,491892941
37	0,221505139	0,037008246	0	0,098598623	0,121070518	2,022379895	1,41E-159	2,491971586	2,491971586
38	0,071481932	0,038016252	0	0,067787954	0,109342718	2,235983025	4,29E-158	2,492046504	2,492046504
39	0,050328723	0,043109762	0	0,054516729	0,09940964	2,28050194	8,14E-157	2,492117971	2,492117971
40	0,049695629	0,085061236	0	0,045522897	0,090382095	2,254647999	1,13E-155	2,492186235	2,492186235
41	0,051993659	0,380788414	0	0,038179496	0,082172986	1,966657352	1,48E-154	2,492251522	2,492251522
42	0,053599858	1,162338445	0	0,031998778	0,074783454	1,190909437	3,38E-150	2,492314036	2,492314036
43	0,054010373	1,947446169	0	0,026833934	0,06819186	0,411327998	4,26E-72	2,492373962	2,492373962
44	0,053564549	2,278848213	0	0,022559891	0,06234549	0,055556185	2,62E-26	2,49243147	2,49243147
45	0,052624183	2,033417013	0	0,019042587	0,057172656	0,005765711	9,04E-08	2,492486679	2,492486589
46	0,051437529	1,482456912	0	0,016152619	0,052597612	0,00244469	0,027733332	2,452036464	2,424303132
47	0,050049417	0,874041468	0	0,013776537	0,048550387	0,002505711	0,389731512	1,606086132	1,21635462
48	0,048422673	0,339617939	0	0,011819851	0,044969347	0,002970101	0,1768809	0,183653604	0,006772704
49	0,046564071	0,052934289	0	0,010204873	0,041798356	0,003587605	0,022854825	0,029645373	0,006790548
50	0,044538194	0,005013758	0	0,008866736	0,038982516	0,004239535	0,021502025	0,032841089	0,011339064
51	0,042436121	0,001952278	0	0,007751072	0,036469365	0,004832617	0,019307187	0,048255057	0,028947869
52	0,040338485	0,001784758	0	0,006813503	0,034212306	0,005323436	0,020766258	0,17038084	0,149614581
53	0,038304158	0,001761387	0	0,006018896	0,032172377	0,005697473	0,016248368	0,70268371	0,686435342
54	0,036372595	0,001737926	0	0,005340294	0,030319482	0,005954235	0,011405516	1,718275328	1,706869812
55	0,034568055	0,001708005	0	0,004756653	0,028626723	0,006101204	0,008608882	2,315839589	2,307230707
56	0,032903385	0,001672699	0	0,004250554	0,027069143	0,006150528	0,006900707	2,402192948	2,39529224
57	0,031383143	0,001636962	0	0,003808251	0,02562741	0,006116705	0,005778004	2,42514055	2,419362546
58	0,030006067	0,001655342	0	0,003419281	0,024286907	0,006014913	0,004985742	2,434318947	2,429333205
59	0,028766995	0,002256662	0	0,003075104	0,02303188	0,005859833	0,004396491	2,437138632	2,432742141
60	0,027658421	0,00568965	0	0,002767343	0,021846809	0,005664458	0,003927752	2,436606046	2,432678294
61	0,026671811	0,010246593	0	0,00249176	0,020704161	0,005439078	0,003512223	2,433905019	2,430392796
62	0,025798339	0,01467494	0	0,002069603	0,018044659	0,005191623	0,003136528	2,429352646	2,426216118
63	0,025032348	0,018984829	0	0,00148047	0,015147642	0,004917493	0,002806352	2,423687307	2,420880955
64	0,024370324	0,023185671	0	0,001061336	0,013070751	0,004611765	0,002521206	2,418395135	2,415873929
65	0,0238053	0,027272507	0	7,94E-04	0,011519266	0,004287472	0,002276476	2,414448725	2,41217225
66	0,023327774	0,031237701	0	6,16E-04	0,010317466	0,003963003	0,002066479	2,412058406	2,409991927
67	0,022927676	0,035078542	0	4,90E-04	0,00936806	0,003652523	0,001885771	2,411000362	2,409114591
68	0,022595429	0,038798072	0	3,90E-04	0,008623651	0,00336406	0,00172952	2,4108974	2,409167881
69	0,022322416	0,042403442	0	3,04E-04	0,008070862	0,00310064	0,001593521	2,411385993	2,409792473
70	0,022101194	0,045903908	0	2,26E-04	0,007708744	0,002862127	0,001474379	2,412197077	2,410722698
71	0,021926675	0,04930917	0	1,62E-04	0,007516866	0,00264701	0,001369416	2,413160764	2,411791348
72	0,021810612	0,052628589	0	1,17E-04	0,007447867	0,002454203	0,001276455	2,414177435	2,41290098
73	0,02188554	0,055873842	0	8,92E-05	0,007459367	0,00228749	0,001193707	2,415190939	2,413997232
74	0,022889683	0,059077753	0	7,22E-05	0,007534056	0,002175426	0,001119692	2,416170917	2,415051225
75	0,028149713	0,06238274	0	6,18E-05	0,007692324	0,0022491	0,001053187	2,417102104	2,416048917

76	0,050123381	0,066380109	0	5,64E-05	0,008066215	0,002967839	9,93E-04	2,417977996	2,416984821
77	0,118822538	0,072850386	0	6,13E-05	0,009766206	0,005141083	9,39E-04	2,418797109	2,417858303
78	0,276745854	0,084595308	0	0,001943463	0,141079355	0,008670736	8,89E-04	2,419560768	2,418671405
79	0,553600993	0,099625493	0	0,226215922	1,638760024	0,017610298	8,44E-04	2,420271796	2,419427552
80	0,877898501	0,10408114	0	0,540812889	0,918053456	0,087371739	8,03E-04	2,420933734	2,420130798
81	1,005990606	0,105080934	0	0,538671504	0,352125328	0,369894244	7,65E-04	2,42155038	2,420785379
82	0,642675059	0,10550286	0	0,285187683	0,16252481	1,032406821	7,30E-04	2,422125528	2,421395464
83	0,138865342	0,105841693	0	0,126979538	0,126683504	1,681426095	6,98E-04	2,422662816	2,421965015
84	0,027080502	0,106419691	0	0,075744639	0,111975028	1,852087508	6,68E-04	2,423165672	2,422497746
85	0,017819768	0,10799561	0	0,057035753	0,100502752	1,886898603	6,40E-04	2,423637285	2,422997087
86	0,018056633	0,11398588	0	0,046034873	0,090048701	1,895666939	6,14E-04	2,424080507	2,423466096
87	0,020387772	0,144103455	0	0,037410387	0,080385596	1,872970014	5,90E-04	2,424497882	2,423907501
88	0,023124495	0,299656897	0	0,030190653	0,071539885	1,721820306	5,68E-04	2,424891697	2,424323752
89	0,02551564	0,806828725	0	0,024174649	0,063536788	1,217953116	5,47E-04	2,425264028	2,424717075
90	0,027259882	1,530735053	0	0,019243811	0,056368199	0,49713988	5,27E-04	2,425616778	2,425089502
91	0,028380011	1,951455204	0	0,015263975	0,04999861	0,077933823	5,09E-04	2,425951642	2,425442814
92	0,029058805	1,953747346	0	0,012090131	0,044376752	0,006264505	5,00E-04	2,426254142	2,4257544
93	0,029465197	1,622627121	0	0,00958203	0,039445306	0,001442017	0,002392062	2,423407065	2,421015003
94	0,029698291	1,096445896	0	0,007619304	0,035180595	0,001230971	0,118730414	2,14391372	2,025183306
95	0,029783417	0,553226858	0	0,006138711	0,031767088	0,001326791	0,517841072	0,989301385	0,471460313
96	0,02972362	0,148020457	0	0,0051597	0,02961018	0,001473816	0,032419978	0,039960223	0,007540245
97	0,029534088	0,014989082	0	0,004651264	0,028645307	0,001635103	0,022181318	0,031885205	0,009703887
98	0,029240966	0,002008447	0	0,00442951	0,028205126	0,001790866	0,02021524	0,04052675	0,02031151
99	0,028872289	0,001245623	0	0,004277924	0,027681635	0,001936042	0,018047671	0,080160579	0,062112908
100	0,028451924	0,001202786	0	0,004069319	0,026829321	0,002069286	0,017527659	0,339681259	0,3221536
101	0,027999745	0,001198432	0	0,003775745	0,02566194	0,002186549	0,012759929	1,089930648	1,077170719
102	0,027532702	0,001195324	0	0,003423123	0,024290157	0,002282592	0,00936693	2,08353722	2,07417029
103	0,027065018	0,001191059	0	0,003049161	0,022825368	0,002353432	0,007264367	2,367939359	2,360674992
104	0,026608088	0,001186182	0	0,002683678	0,021351409	0,002397485	0,00591571	2,414791542	2,408875832
105	0,0261705	0,001193432	0	0,002345036	0,019924653	0,002415541	0,004990669	2,43016395	2,425173281
106	0,025758257	0,001325408	0	0,002042124	0,018578656	0,002410169	0,004319612	2,435943242	2,43162363
107	0,025375161	0,002287084	0	0,001776668	0,017324474	0,002384946	0,003810126	2,437498383	2,433688258
108	0,025023313	0,005369928	0	0,001547181	0,016174674	0,002343594	0,00339829	2,436794243	2,433395953
109	0,024703569	0,008817724	0	0,001351433	0,015129522	0,002289606	0,003040749	2,434495595	2,431454846
110	0,024415826	0,012225093	0	0,001135327	0,013631033	0,002226247	0,002727662	2,430863443	2,428135781
111	0,024160171	0,015591959	0	8,59E-04	0,011952412	0,002153649	0,002456484	2,426662269	2,424205785
112	0,023937131	0,018918252	0	6,53E-04	0,010683403	0,002071721	0,002222826	2,42296693	2,420744104
113	0,023745912	0,022200966	0	5,13E-04	0,009695994	0,001984688	0,002021523	2,42036082	2,418339297
114	0,023584553	0,025438023	0	4,14E-04	0,008910675	0,001897097	0,00184765	2,418911665	2,417064016
115	0,023450587	0,02862953	0	3,37E-04	0,008285879	0,001811879	0,00169687	2,418407628	2,416710758
116	0,023341488	0,031777203	0	2,72E-04	0,007806832	0,001730505	0,00156539	2,418544288	2,416978898
117	0,023255012	0,034883619	0	2,11E-04	0,007477536	0,001653486	0,001449984	2,419049285	2,4175993
118	0,023190402	0,037951665	0	1,56E-04	0,007296269	0,001580884	0,001348103	2,419737805	2,418389702
119	0,023159583	0,040984364	0	1,14E-04	0,007233065	0,00151311	0,001257704	2,420500845	2,41924314
120	0,023267453	0,043987226	0	8,75E-05	0,007250111	0,001453468	0,001177105	2,421277681	2,420100577
121	0,024096868	0,046984024	0	7,09E-05	0,007328302	0,001419841	0,001104908	2,422035839	2,420930931
122	0,028281462	0,050090432	0	6,07E-05	0,007480812	0,001491337	0,001039954	2,422759007	2,421719053
123	0,046077496	0,053800137	0	5,51E-05	0,007801932	0,001955602	9,81E-04	2,423440045	2,422458772
124	0,104628651	0,059674585	0	5,68E-05	0,008897993	0,00339424	9,28E-04	2,424076952	2,423148899
125	0,24559509	0,070364994	0	2,07E-04	0,032041572	0,005865768	8,80E-04	2,424670533	2,423790924
126	0,505777533	0,086264053	0	0,078581553	1,473349183	0,010013922	8,35E-04	2,425223055	2,424387691
127	0,854855485	0,094093261	0	0,483229375	1,08611193	0,049152455	7,95E-04	2,42573746	2,424942638
128	1,110314698	0,09558153	0	0,562980603	0,445736174	0,239700715	7,58E-04	2,426216924	2,425459361
129	0,953952474	0,096127621	0	0,334960722	0,174619723	0,780258055	7,23E-04	2,426664603	2,425941378
130	0,412757697	0,096491541	0	0,141561936	0,125111664	1,542063443	6,91E-04	2,427083501	2,426392007
131	0,097377842	0,097036676	0	0,076208193	0,108809917	1,949306883	6,62E-04	2,427476414	2,426814316
132	0,042656032	0,098732867	0	0,05462734	0,097247771	2,041018637	6,35E-04	2,427845935	2,427211139
133	0,036542205	0,107702193	0	0,043377474	0,086923621	2,057655806	6,09E-04	2,428194385	2,427584998
134	0,038242629	0,174198209	0	0,034992528	0,077434609	2,001325409	5,86E-04	2,428523774	2,427938073
135	0,040852308	0,543116053	0	0,0280957	0,068800508	1,638141048	5,64E-04	2,428835851	2,428272272
136	0,04267544	1,328974186	0	0,022422448	0,061070817	0,856967631	5,43E-04	2,429132192	2,428589318
137	0,043516399	1,98180859	0	0,017845188	0,054259453	0,208459425	5,23E-04	2,429414263	2,428890803
138	0,043670754	2,129979226	0	0,014221224	0,048340658	0,018416299	5,08E-04	2,429678249	2,429170011
139	0,043434304	1,826557707	0	0,0113929	0,043256639	0,002515217	0,001440367	2,428443919	2,427003553
140	0,042991461	1,280655286	0	0,009205839	0,038927501	0,001713525	0,102613348	2,203233127	2,100619779
141	0,042389114	0,699127782	0	0,007522099	0,035263085	0,001811479	0,533760795	1,083792442	0,550031647
142	0,041625842	0,225225986	0	0,006226825	0,032175176	0,002019123	0,042008677	0,049607955	0,007599278
143	0,04072229	0,026871125	0	0,005228373	0,029578973	0,002253723	0,025092571	0,033790578	0,008698007
144	0,039723112	0,003052668	0	0,004453382	0,027386735	0,00246477	0,023251093	0,039915917	0,016664824
145	0,038679135	0,001640717	0	0,003842799	0,025509598	0,002628494	0,021160908	0,071640808	0,050479901
146	0,037631537	0,001552932	0	0,003350853	0,023871907	0,002743342	0,020910032	0,30489402	0,283983988
147	0,036608927	0,001530222	0	0,002952811	0,022479946	0,002814665	0,014556976	1,036138183	1,021581207
148	0,035629735	0,001507298	0	0,002635052	0,021278896	0,002849689	0,010341943	2,057834726	2,047492783
149	0,03470493	0,001481983	0	0,002351417	0,020050294	0,002855603	0,007908249	2,364927992	2,357019743
150	0,033840825	0,001455738	0	0,002072917	0,018749911	0,002837281	0,00640263	2,413645012	2,407242382

Table 10: Concentration values of the ODE model components for 150 simulated timesteps (including the last 18 pages)

7.11 MATLAB Codes

7.11.1 minmax.m

```
% minmax is a function that reads maximal and minimal values out of the columns of a matrix;
% it is used for the human cell cycle ODE model (SBML), whose simulation gives out a  .txt file with
% the concentration values of the model compounds for each simulated time step
% developed by Judith Wodke

clear all;

a = input('Type in the file name of the matrix: ');      % enables the user to specify the
                                                          % matrix file

M = load(a);                                              % defines matrix M as the input file

a = size(M);                                              % computes the size of M
j = a(1);                                                 % j = #lines
k = a(2);                                                 % k = #coloums

p = 0;                                                    % defines a check variable

b = 1:j;                                                  % defines an array of size j
s = 1:k-1;                                                % defines an array of size k-1
t = 1:k-1;                                                % defines an array of size k-1

% transcribes each column k of the matrix into a linear vector, whose minimal and maximal % values
% are saved in the linear vectors s and t, respectively:
for (x = 2:k)
   for (y = 1:j)
      b(y) = M(y,x);
   end

   s(x-1) = min(b);
   t(x-1) = max(b);
end

% if there are maximal concentracions > 10 the check variable p will be set to 1:
for (f = 1:k-1)
   if (t(f)>10)
      t(f) = 0;
      s(f) = 0;
      p = 1
   end
end

c = 1:k-1;                                                % defines a linear vector, that includes the
                                                          % numbers, which display the model components
                                                          % on the x-axis , and that is plotted against
                                                          % the extracted min & max values

% defines a linear vector of zeros to plot the “zero line”:
z = [0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0];

% if there are only maximal concentration <= 10, then only one figure is plotted:
if (p == 0)
   hold on;

   plot(c, s, 'mx')                                       % plots minima
```

```
   xlabel('compounds in numbers')                % labels x-axis
   ylabel('concentration in arbitrary units')    % labels y-axis; titles ↓
   title('minimal & maximal concentrations of ODE model compounds after 150 arbitrary time steps')
   axis([0 95 -1 5.5])                           % defines the plotted area

   plot(c, t, 'kx')                              % plots maxima
   plot(c, z, 'k');                              % plots "zero line"

   hold off;

% if there are maximal concentrations > 10 there will be plotted two subfigures, one that gives an
% overview over the minimal and maximal concentrations of all ODE model compounds, and one, that
% focuses on a lower concentration area:
elseif (p == 1)
   subplot(2, 1, 1);
   hold on;

   plot(c, s, 'mx')
   xlabel('compounds in numbers')
   ylabel('concentration in arbitrary units')
   title('minimal & maximal concentrations of ODE model compounds after 600 arbitrary time steps')
   axis([0 95 -10 75])

   plot(c, t, 'kx')
   plot(c, z, 'k');

   hold off;

   % if there are maximal concentrations > 10, they and their corresponding minimal values are set to
   % zero, to allow a better observation of smaller maximal concentrations:
   for (f = 1:k-1)

      if (t(f)>10)
         t(f) = 0;
         s(f) = 0;
      end
   end

   subplot(2, 1, 2);
   hold on;

   plot(c, s, 'mx')
   xlabel('compounds in numbers')
   ylabel('concentration in arbitrary units')
   axis([0 95 -1 5.5])

   plot(c, t, 'kx')
   plot(c, z, 'k');

   hold off;
end
```

7.11.2 compareMins.m

```
% compareMins is a program, that compares the minimal and maximal values of compound
% concentrations for consecutive cell cycle rounds
% written by Judith Wodke

clear all;

a = input('Type in the file name of the matrix: ');        % enables the user to specify the
```

```
                                        % matrix file

M = load(a);                            % defines matrix M as the input file

a = size(M);                            % computes the size of M
j = a(1);                               % j = #lines
k = a(2);                               % k = #coloums

A = []; B = []; C = [];                 % defines one matrix for each of the consecutiv
                                        % cell cycle rounds
aminv = [1:k-1]; bminv = [1:k-1]; cminv = [1:k-1];  % defines a linear vector for each CC round,
                                        % that later includes the minimal concentration
                                        % values of all model compounds
amint = [1:k-1]; bmint = [1:k-1]; cmint = [1:k-1];  % defines a linear vector for each CC round, that
                                        % include the time steps, corresponding to the
                                        % minimal values
amaxv = [1:k-1]; bmaxv = [1:k-1]; cmaxv = [1:k-1];  % defines a linear vector for each CC round,
                                        % that later includes the maximal concentration
                                        % values of all model compounds
maxt = [1:k-1]; bmaxt = [1:k-1]; cmaxt = [1:k-1];   % defines a linear vector for each CC round, that
                                        % include the time steps, corresponding to the
                                        % minimal values
% saves the concentration values of the first CC round in matrix A:
for (x = 1:49)
   for (y = 1:k)
      A(x,y) = M(x,y);
   end
end

% saves the concentration values of the second CC round in matrix B:
for (x = 1:48)
   for (y = 1:k)
      B(x,y) = M(x+49,y);
   end
end

% saves the concentration values of the third CC round in matrix C:
for (x = 1:46)
   for (y = 1:k)
      C(x,y) = M(x+97,y);
   end
end

big = size(A);                          % computes the size of matix A
bigr = big(1);                          % bigr = #lines of A

doub = [1:bigr;1:bigr];                 % defines a (2xbigr)-matrix
vec = [1:bigr];                         % defines a vector of size bigr

% compute for each column of A, i.e.for each ODE model compound, a matrix, that in the first row
% shows the concentration values of the respective compound, and in the second row shows the
% corresponding timestep; afterwards the minima and maxima are computed and, like their
% corresponding time steps, saved in the respective vectors:
for (y = 2:k)
   for (x = 1:bigr)
      vec(x) = A(x,y);
      doub(1,x) = A(x,y);
      doub(2,x) = A(x,1);
   end
```

```
   for (x = 1:bigr)
      if (min(vec) == doub(1,x))
         aminv(y-1) = doub(1,x);
         amint(y-1) = doub(2,x);
      end
      if (max(vec) == doub(1,x))
         amaxv(y-1) = doub(1,x);
         amaxt(y-1) = doub(2,x);
      end
   end
end

big = size(B);                          % computes size of matrix B
bigr = big(1);                          % resizes bigr = #lines of B

doub = [1:bigr;1:bigr];                 % resizes doub
vec = [1:bigr];                         % resizes vec

% compute for each column of B, i.e.for each ODE model compound, a matrix, that in the first row
% shows the concentration values of the respective compound, and in the second row shows the
% corresponding time step; afterwards the minima and maxima are computed and, like their
% corresponding time steps, saved in the respective vectors:
for (y = 2:k)
   for (x = 1:bigr)
      vec(x) = B(x,y);
      doub(1,x) = B(x,y);
      doub(2,x) = B(x,1);
   end

   for (x = 1:bigr)
      if (min(vec) == doub(1,x))
         bminv(y-1) = doub(1,x);
         bmint(y-1) = doub(2,x);
      end
      if (max(vec) == doub(1,x))
         bmaxv(y-1) = doub(1,x);
         bmaxt(y-1) = doub(2,x);
      end
   end
end

big = size(C);                          % computes size of matrix C
bigr = big(1);                          % resizes bigr = #lines of C

doub = [1:bigr;1:bigr];                 % resizes doub
vec = [1:bigr];                         % resizes vec

% compute for each column of C, i.e.for each ODE model compound, a matrix, that in the first row
% shows the concentration values of the respective compound, and in the second row shows the
% corresponding time step; afterwards the minima and maxima are computed and, like their
% corresponding time steps, saved in the respective vectors:
for (y = 2:k)
   for (x = 1:bigr)
      vec(x) = C(x,y);
      doub(1,x) = C(x,y);
      doub(2,x) = C(x,1);
   end

   for (x = 1:bigr)
      if (min(vec) == doub(1,x))
```

```
            cminv(y-1) = doub(1,x);
            cmint(y-1) = doub(2,x);
        end
        if (max(vec) == doub(1,x))
            cmaxv(y-1) = doub(1,x);
            cmaxt(y-1) = doub(2,x);
        end
    end
end

% defines a matrix T, that includes minimal and maximal values of all three CC rounds, and their
% corresponding time steps:
T = [aminv; amint; bminv; bmint; cminv; cmint; amaxv; amaxt; bmaxv; bmaxt; cmaxv; cmaxt]

csvwrite ('minmaxCompare3.csv', T, 'float');            % writes T to an output file

% graphical description of the variances in min and max values of protein concentrations for
% consecutive cell cycle rounds:

% defines a linear vector of zeros to plot the “zero line”:
z = [0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0];
numb = [1:k-1];                                         % defines a linear vector, that includes the
                                                        % numbers, which display the model components
                                                        % on the x-axis , and that is plotted against
                                                        % the extracted min & max values

% plots the minima and maxima for each of the three consecutive CC rounds in three among each other
% arranged subfigures, thus enabeling a good comparison of the value changes from one CC
% round to the next:
subplot(3, 1, 1);
hold on;

    plot(numb, aminv, 'mx')                             % plots minima of A
    xlabel('compounds in numbers')
    ylabel('concentration in arbitrary units')
    title('minimal & maximal concentrations of ODE model components in the first cell cycle round')
    axis([0 95 -1 5.5])

    plot(numb, amaxv, 'kx')                             % plots maxima of A
    plot(numb, z, 'k');                                 % plots “zero line”

hold off;

subplot(3, 1, 2);
hold on;

    plot(numb, bminv, 'mx')                             % plots minima of B
    xlabel('compounds in numbers')
    ylabel('concentration in arbitrary units')
    title('minimal & maximal concentrations of ODE model components in the second cell cycle round')
    axis([0 95 -1 5.5])

    plot(numb, bmaxv, 'kx')                             % plots maxima of B
    plot(numb, z, 'k');                                 % plots “zero line”

hold off;

subplot(3, 1, 3);
hold on;
```

```
plot(numb, cminv, 'mx')                          % plots minima of C
xlabel('compounds in numbers')
ylabel('concentration in arbitrary units')
title('minimal & maximal concentrations of ODE model components in the third cell cycle round')
axis([0 95 -1 5.5])

plot(numb, cmaxv, 'kx')                          % plots maxima of C
plot(numb, z, 'k');                              % plots “zero line”

hold off;
```

8. Appendix B

8.1 Stoichiometric Matrix

Because of its size, the stoichiometric matrix is printed out seperately and appended in the cover at the end of this thesis. Stoichiometric coefficients displaying synthesis are highlighted in green, those displaying consumption in pink.

8.2 Activation Matrix

Because of its size, the activation matrix is printed out seperately and appended in the cover at the end of this thesis. Activators are highlighted in green, inhibitors in pink.

8.3 Boolean Matrix

In the Boolean matrix, just as in the Boolean conditions, two mitogen-receptor-complexes are included. The compounds included in the two different ways of inactivation of the mitogen-receptor complex are seperated visibly through two blank columns. In this printed version of the Boolean matrix the behaviour of the regulated network depends on mitogen-receptor2 complex, i.e. as in the ODE model after the parameter adaptation it includes the delay between two cell cycle rounds.
Because of its size, the Boolean matrix is printed out seperately and appended in the cover at the end of this thesis. Active states are highlighted in yellow.

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11. Eidesstattliche Erklärung

Ich versichere, diese Masterarbeit selbstständig und ohne Zuhilfenahme anderer als der oben angegeben Quellen und Hilfsmittel verfasst zu haben.