

# The Cell Cycle Model: A Comprehensive Review and Extension Based on Machine Learning

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**Abstract:** The cell cycle is a conserved process comprising of an organized series of interdependent and cross regulatory events that lead to controlled cell growth and proliferation. Genomic and volume regulatory processes are of special interest as they decide the fate of cell cycle. Signaling cascades including MAPK, PI3K, Sonic Hedgehog, Wnt and NOTCH signaling pathways are few well known conventional players contributing in controlling the cell cycle progression through different phases by expressing certain proteins. Moreover, the unconventional volume regulatory players exert influence by regulating membrane potential that is determined by ions influx or efflux across the plasma membrane via ion channels, controlling water movement and ultimately contributing to volume increase in growth phases of the cell cycle. Both of these players are interlinked, therefore, in order to establish a better understanding of the interdependence of these players, principles of machine learning were applied on data obtained on cell cycle. The data was processed by using neural networks and it shows that a significant understanding of conventional regulators is available in the literature and it has been under the limelight as well. However, when it comes to unconventional volume regulatory players, a limited understanding is available. Moreover, the precise role of each component and its interdependence with other is not yet fully understood. Due to which, they are not clearly evaluated for their potential role as cell cycle control elements for therapeutic purposes. Therefore, this study aims to summarize the data on cell cycle that is obtained through machine learning and to discuss the advances in cell cycle modelling mechanisms and designs that are based on different mathematical algorithms. Thus, this review will provide a basis to clearly understand and interlink the discoveries on cell cycle so that a comprehensive cell cycle model could be built which, if manipulated can be used for therapeutic purposes by identifying the least explored regulatory control elements.

**Index Terms:** Cell cycle, Intelligent modelling, computational modelling, and role of Ca<sup>2+</sup> signaling, Artificial Neural Network, machine learning

## 1. Introduction

The cell is a fundamental unit of life and plays a crucial role in organ and system development, transportation and storage of biomolecules, gene expression, signal transduction, and empowerment of molecular machineries [1]. The process of a cell dividing into two daughter cells is known as the cell cycle, which is a universal and complex process and is tightly regulated by different regulatory proteins that either allow or limit its progression [2]. A cell progresses to cell division by receiving growth and proliferative signals from the extracellular environment. In response to these cues, a cell quits G<sub>0</sub> phase and enters into the G<sub>1</sub> phase of the cell cycle. The G<sub>1</sub> is one of the two growth phases in the cell cycle where cell increases in size and accumulates within itself sufficient nutrients to provide energy during a cell cycle. This volume growth is an important regulatory step as it decides the progression of cell into subsequent phase. When all the required conditions are met, a cell progresses to S phase that is the synthesis phase of DNA. Following the S phase is the second growth phase called G<sub>2</sub> phase where cell replenishes its energy reserves and grows in size so that it could enter into the mitotic phase, which terminates this cycle at cell division by passing through four substages, starting from prophase and ending at telophase [3]. The first 3 phases G<sub>1</sub>, S and G<sub>2</sub> comprise the longest period in cell cycle known as interphase [4]. There are few mammalian cells, for instance epithelial cells, which continually grow and divide while other cells stay in quiescent phase and perform normal metabolic functions like muscle cells or neurons. Investigators have postulated and later proved that these cells stay longer in G<sub>0</sub> phase and upon receiving stimulus they continue proliferation or differentiation. This longer stay in the quiescent phase has been distinguished as G<sub>0</sub> phase distinct from G<sub>1</sub> phase [5].

Upon receiving mitogenic signals, changes in cellular dynamics are observed due to activation of certain signalling pathways which ultimately cause transcription of proliferative genes by expressing transcription factors like FOS, JUN,

cMYC etc. Some of these signalling cascades are MAPK pathway, PI3K/Akt/mTOR pathway, NOTCH pathway, SHH and Wnt signalling pathway. All of these pathways play a significant role in cell cycle progression by directly influencing the genetic machinery and transcribing the genes and expressing proteins essential for cell progression through different cell cycle phases. The most crucial regulatory proteins responsible for transition and transversion of cell cycle checkpoints are Cyclins and Cyclin Dependent Kinases (CDKs) along with their inhibitors, and tumor suppressor genes p53 and pRb and associated regulators [2]. These regulatory signalling molecules are considered to be the conventional drivers in cell cycle control throughout its four basic stages to complete the cycle of division, namely: G1, S, G2 and M phase [6].

As research on the cell cycle progressed over years, new regulatory control elements were identified. Initially, the cell cycle was understood to be dependent on a number of different phases that a cell goes through during cell division; however, later, other vital aspects were found. One of these was the role of bioelectricity in driving the process of cell division. This bioelectricity was observed due to influx and efflux of different ions through ion channels that are present on the cell membrane as well as on the nuclear membrane [7]. This flow of ions across the plasma membrane establishes a membrane potential which has been linked with the regulation of the cell cycle since long and are also involved in cancer development and progression. However, how they control cell cycle has not yet been fully elucidated [7].

All these pathways and regulatory elements are intricately interlinked as they all are performing the same function i.e. driving the cell to division. But no study has been conducted till date that would have incorporated these details in a single model to provide a better understanding of the cell cycle. Therefore, in order to get a bigger picture, Artificial Intelligence should be introduced in the domain of biological sciences. Hence, this study aims to evaluate the modelling of the cell cycle of a living organism through machine learning. Previously, the new technologies were only used in the areas of industry and education. But the recent years have seen an increase in the need of integrating the modern age equipment in the field of health and biological sciences [8]. Owing to the increased use of computers and internet sources, machine learning is the idea of vast volumes of data being produced every day in various fields [9,10]. Therefore, approach of machine learning is utilized in this study to evaluate and model the cell cycle. Other than computer, the devices like antennas and wireless devices can also be used for the collection of data. As the data collected through these devices would have large benefits, including the domains of personal wellbeing, and biological sciences [11-16]. Therefore, this study utilizes the effectiveness of Neural Networks in order to better understand this whole process of cell division. These Neural Networks work on the similar principle as that of human brain by processing the information in different layers. These layers are input layer, hidden layer and output layer. Number of layers in hidden layer can be increased depending on availability and complexity of the data. As this study evaluates a huge data set on cell cycle and its regulatory control elements, therefore, we have utilized the effectivity of machine learning and artificial intelligence so that all the data could be processed in the best possible manner through neural networks. The findings of this study would enable researchers to critically evaluate the influence of their research outcomes by incorporating them in a comprehensive cell cycle model. This would on one hand help them in validating their current findings and on the other hand will help in identifying new cellular targets.

## 2. Methodology

The methodology adopted for this research is shown in Fig. 1.

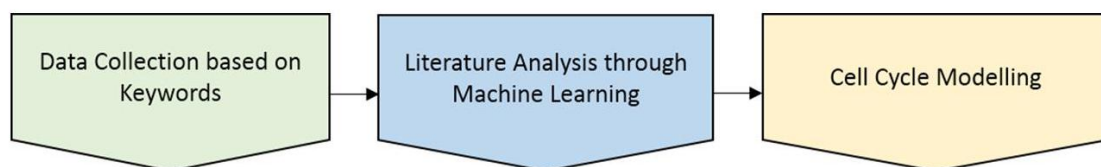


Fig. 1 Methodology based on Machine learning adopted for cell cycle review and modelling

### 2.1 Data Retrieval Through Machine Learning

Data required for conducting this research was collected through an extensive literature retrieval from different search engines including Web of science, ScienceDirect, and Scopus, etc., through a combination of index terms. Research from high index papers published in top-tier journals was selected and was further processed by using machine learning and artificial intelligence. A number of keywords were used to obtain relevant literature on cell cycle. The keywords used for this research includes “Cell cycle, Intelligent modelling, computational modelling, role of  $Ca^{+2}$  signalling, Artificial Neural Network, cyclin and cyclin dependent kinases, cell cycle machine learning”.

2.2 Modelling and Analysis via Neural Networks

For the collection and review of the complex data on cell cycle, Multilayer Artificial Neural Networks were used in four phases. These layers, as shown in Fig. 2, include, Data Extraction, Pre-processing and preparation, Modelling and Evaluation. The neurons links were made in between these phases. The aim of these complex networks is to find the weight of the data on research domains from cell cycle. Using this ANN model all the data is collected and evaluated in this research.

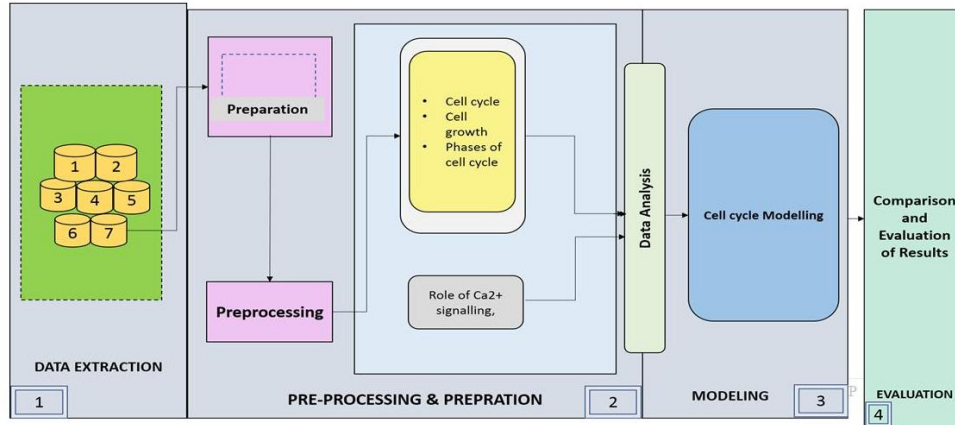


Fig. 2 ANN Model for the data collection

AI based layers are also used for the data classification and evaluation. The layers, as shown in Fig. 3, includes, convolution, pooling, and classifier. The aim of these complex networks is to find the weight of the data. This model helps to collect detailed data on the cell cycle.

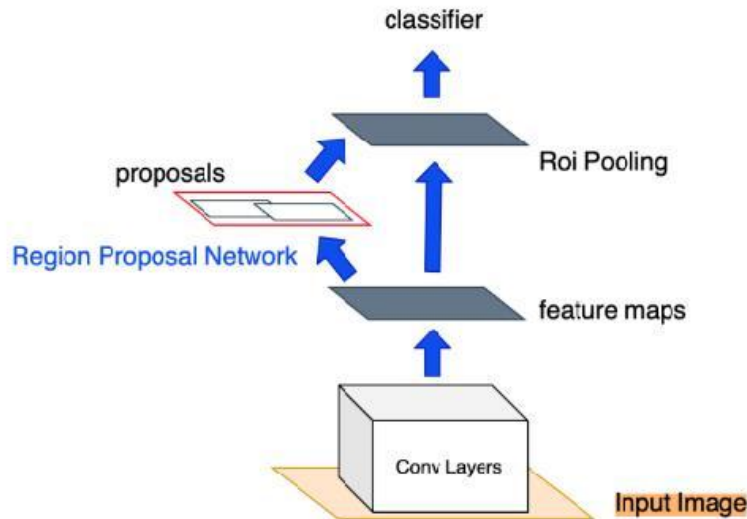


Fig. 3 AI based Model for the data Evaluation

After the data pooling through AI, the data was classified in different cell cycle layers based on ANN. These layers define each stages of cell cycle separately. The framework is shown Fig. 4. Layers adopted in this framework includes input, convolution, activation and full connection with the output layers,

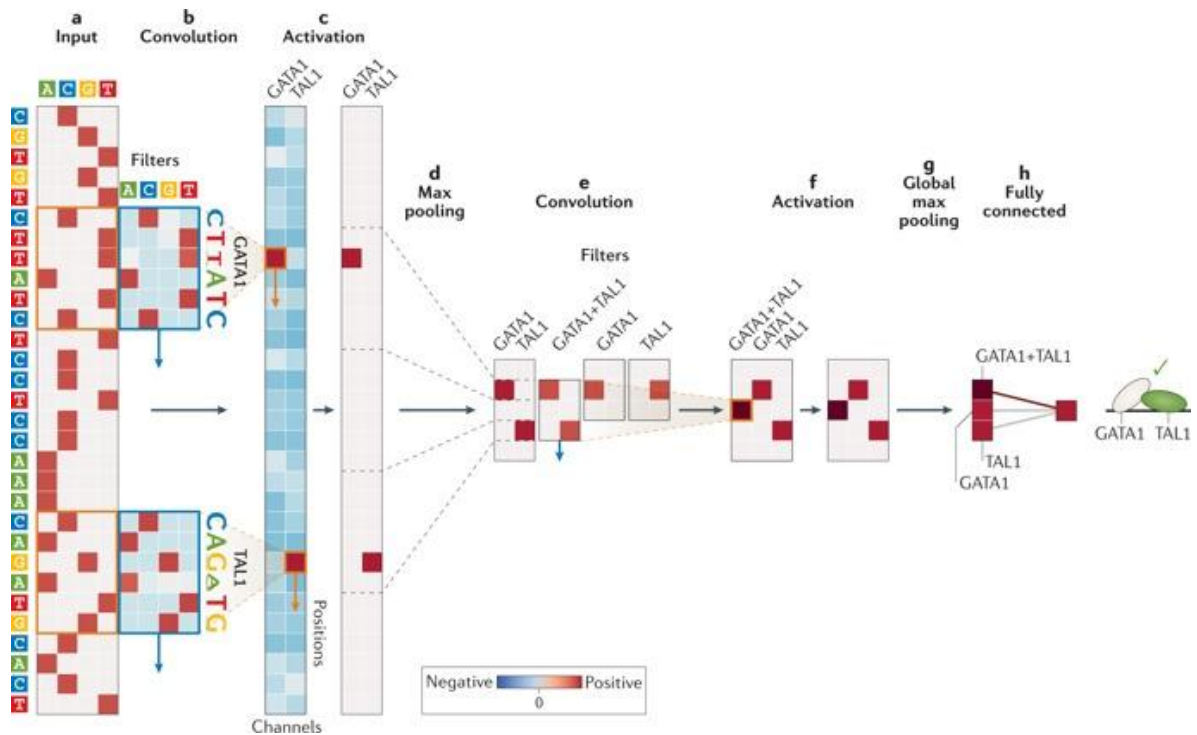


Fig. 4 Data classification based on ANN

### 3. Results

#### 3.1 Neural Networks

VOSviewer software generated a network from output data of ANN Model based on “Visualization of Similarity” as given in Fig. 5. The nodes of this network represent the domains explored for cell cycle while their size represents the weight of the data, or in other words the amount of work done under these domains. The interconnectedness of these research areas is represented by lines between the nodes. The most repetitive keywords found in the articles include cancer, ca2 signaling, inhibitor, differentiation, cell cycle, apoptosis, kinase, neuron, etc. This clearly shows that research on cell cycle is mostly related to genomic machinery and it lacks the concept of comprehensiveness and inclusion of volume regulatory control elements. Therefore, this study presents a review on the available literature on unconventional elements of cell cycle control by focusing on volume regulatory components which is the main exploratory domain of this research.

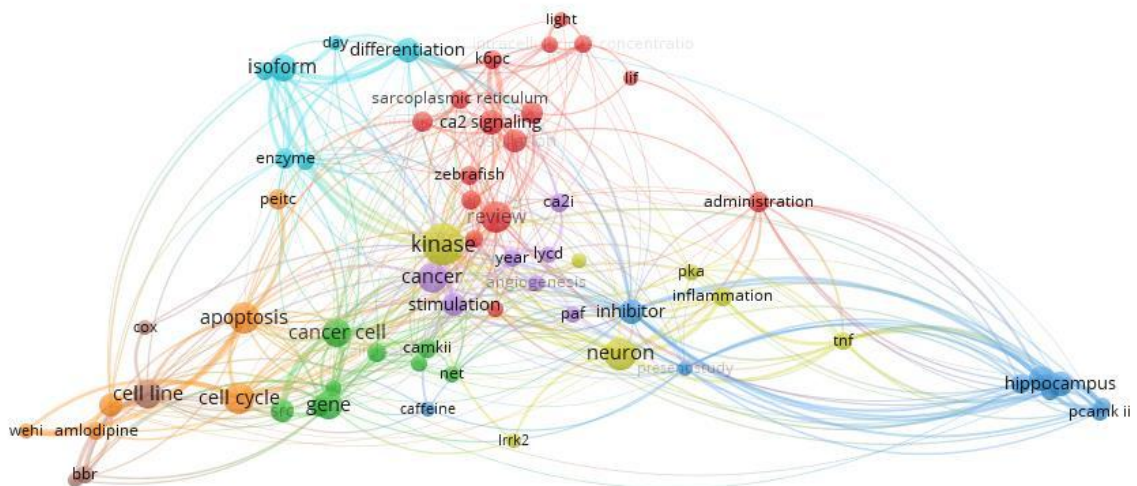


Fig. 5 Most repetitive keywords used in research articles related to cell cycle

### 3.2 Data Derived through Machine Learning On cell cycle

Based on the results of ANN Model, data on cell cycle was retrieved through machine learning from online sources and is discussed below

#### 3.2.1 G1/S phase transition

According to data pool [9, 17, 18] collected through machine learning, cells stay in  $G_0$  phase and perform several metabolic functions unless they receive a signal from extracellular matrix for progression. This overall progress from  $G_0$  to  $G_1$  is tightly controlled by a series of growth factors, including Platelets-Derived Growth Factors (PDGF), Fibroblast Growth Factors (FGF), Insulin like Growth Factors (IGF) and insulin which determine the regulation of the cell cycle phases from one to another. The data also revealed that if the cell does not encounter these growth factors, it then remains in quiescent state [9]. Upon receiving growth factor signals, the cell enters  $G_1$  phase and performs a number of distinct activities. It activates pathways which establish  $Ca^{+2}$  signalling in waves that plays a role in controlling the cell cycle machinery, increment in cell volume to hold DNA and other copied cellular components, and the synthesis of proteins required for entry into S phase as shown in Fig. 6. According to Pledger, this transitional state occurs late in  $G_1$  after satisfying the requirements of the volume control checkpoint and the absence halts the transition into S phase or its deregulation can lead to abnormal cellular transformations and cancer conditions [17]. Moreover, p53 is found responsible in the database for controlling this transition in the case of DNA damage [18] as the controller of cell cycle arrest and DNA repair.

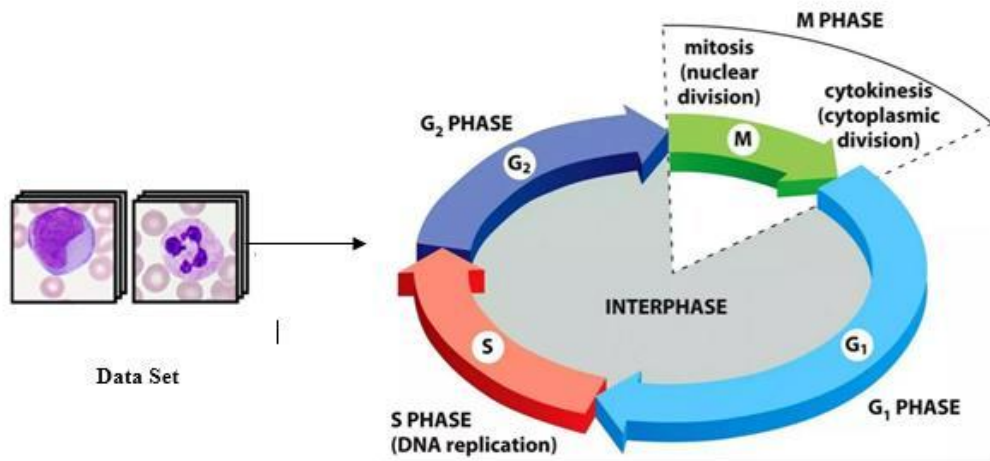


Fig. 6 Phases of Cell Cycle (Interphase and Mitotic phase) (Ravindra B. , 2006)

#### 3.2.2 Establishment of $Ca^{2+}$ signaling

$Ca^{2+}$  is found as a ubiquitous molecule in the data pool. According to Rossow, 1979, it controls cell volume, bioelectricity and cytoskeleton and serving in the process of coordinated cell growth in  $G_1$  and  $G_2$ . It was found in literature that the  $Ca^{2+}$  establishment is achieved through initial cell shrinkage and its influx relies on activation of various tyrosine kinase receptors. ANN also revealed that receptor-ligand binding activates the PI3K and the extracellular signal-regulated kinase1/2 (ERK 1/2), which in turn activates the potassium channels that have kept the membrane potential in a depolarized state to eventually change it to a hyperpolarised state through the activation of calcium channels in mid  $G_1$  and towards the transition of  $G_1/S$  phase [19]. The study of Bartek 2001, states that during mid  $G_1$ , Phospholipase C is activated, which mediates the release of  $Ca^{2+}$  from the endoplasmic reticulum into the cytoplasm that maintains and regulates the activity of the  $Ca^{2+}$  mediated  $K^+$  channels leading to cell volume shrinkage. The hyperpolarized state is thus maintained, mediated by further entry of  $Ca^{2+}$  into the cytoplasm leading to the activation of the transcription factors such as JUN, FOS and c-MYC, which transcribe CDKs and cyclins, such as the p15, p16, p17, p18 and p19 thus inhibiting the activity of the CDK inhibitors (p21 and p27) [20]. Bartek 2001, also states that once the  $Ca^{+2}$  is established, volume increase along with early immediate gene expression takes place.

#### 3.2.3 Increment in Cell Volume and Its Control

The phenomenon of volume control has been speculated in the data sets of CNN, to be an important part of the cell cycle. According to Massagué 2004, nucleus to cytoplasm ratio is found as an important measure in monitoring the increase in cell volume. A continuous increase is evident in the cell volume starting from the  $G_1$  phase all the way to the M phase. According to collected data, the role of the cytoskeleton in the regulation of the cell cycle has not been proven yet and there is a perplexed opinion regarding the regulatory mechanisms since the inhibition of the cytoskeleton

through drugs has shown no effect on the cell volume changes. The size of the nucleus has been said to be directly regulated by the nuclear membrane in the data sets. The important catch data provided is that once the cell actively begins the transcription phase, there is a need to control the volume of the cell and its components. According to Massagué 2004, this is achieved by the involvement of the chloride ions which actively regulate the cell volume. The expression of the EAG2 (K<sup>+</sup>) channels have been found in data to be implicated in the control of the M phase by means of regulating the expression of cyclin B1 through the p38 MAP Kinase, as shown in Fig. 7 [21].

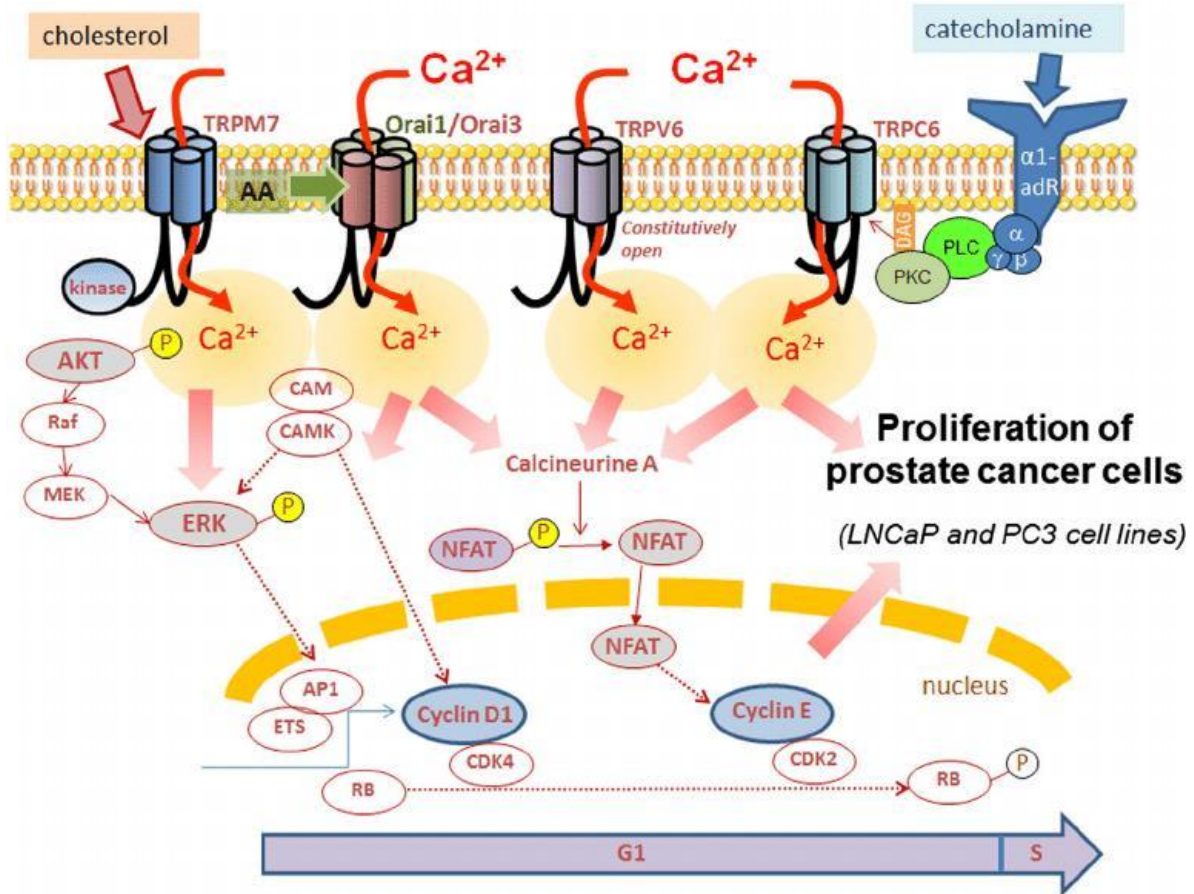


Fig. 7 Alterations and Proliferations in Cell cycle (Source: Massagué J. 2004).

The question is, which ions or proteins are responsible for maintaining ionic transport balance for the control of cell cycle? It is proposed earlier in the articles, that Ca<sup>++</sup> oscillations have a crucial role in the control as a “life and death signal” [22]. Later, it was suggested in the studies, that the oscillations also follow and elicit the NKCC and NHE channels for homeostatic perturbations for planned activities of cell intracellular signalling machinery. These oscillations have been said to produce the membrane potential (V<sub>m</sub>) changes as a by-product (as they are maintained through the activity of a range of ion channels), which in itself is necessary for proliferation. Besides this, a variety of K<sup>+</sup> channels have been implicated in the regulation of proliferation and cell cycle progression. Mechanisms of the activation of many of these channels are currently unknown [23].

As stated earlier in the data, before volume increase, cell proliferation may require transient cell shrinkage initially, which is accomplished by the activation of Cl<sup>-</sup> and K<sup>+</sup> channels. As the electrochemical equilibrium activity of Cl<sup>-</sup> ions is above the threshold inside the cell, the activation of Cl<sup>-</sup> channels is responsible for Cl<sup>-</sup> exit and thus resulting in depolarization. If Cl<sup>-</sup> exit is paralleled by active K<sup>+</sup> channels, then there is net exit of KCl salt, responsible for cell shrinkage. Conversely, the cell growth requires an increase in the K<sup>+</sup> concentration inside the cell. The inward rectifier uptake channels of K<sup>+</sup> activate simultaneously with mechanosensitive channels that are activated by the compression in the plasma membrane that has undergone shrinkage, and help in bringing in higher concentrations of K<sup>+</sup> and water, which increase the turgor pressure, which is needed for cell growth [24].

Data from studies confirmed that the Kv10.1 cause a reduction in the current on the cell membrane. The reduced current is known to be associated with the mitosis-promoting factor (MPF- p24) and Na<sup>+</sup>. The K<sup>+</sup> concentrations also regulate the entry of Ca<sup>2+</sup> inside the cell by ensuring that the membrane potential is negative enough to allow the entry of Ca<sup>2+</sup> [25]. According to the study of Lang 2007, the Kv1.3 channel in conjunction with the KCa3.1 (a Ca<sup>2+</sup> dependent K<sup>+</sup> channel) works towards the cell growth and proliferation. Ca<sup>2+</sup>/CaM is required at two points during the re-entry from quiescence, early after mitogenic stimulation and later near the G1/S boundary. Cell volume not only participates

in the regulation of cell function by hormones, but also regulates hormone release. The release of several hormones is triggered by cell swelling, conversely inhibited by cell shrinkage. The link between cell volume and hormone release is ill-defined in the data sets but partially involves cell volume sensitive alterations of cytosolic  $Ca^{2+}$  activity [25].

3.2.4 G2/M phase transition

Studies revealed that, once DNA duplication is completed, the cell proceeds towards the G2 phase where it prepares itself for division into two daughter cells in M phase. A series of events, as shown in Fig. 8, beginning with prophase and then prometaphase, metaphase, anaphase and lastly cytokinesis takes place-which divides the cell into two genetically identical copies during the M phase. A clear role, found in literature, of the dynamic distribution of  $Ca^{2+}$  and Ca/CaM is seen in S/G2, G2/M and during M phase. Towards the end of M phase, it was found in studies that, Ca/CaM concentrates itself below the membrane and helps cleave the cell into two. Just prior to M phase, DNA damage checkpoint have the responsibility to give a “Go” signal for advancement to checks whether the DNA is intact or has any mutations to repair. A study by Sanchez et al., stated that it would be catastrophic if cell proceeds to divide with the damage. Studies also revealed that, during G2, mammalian Cyclin B/CDK2 complexes are held in an inactive state by phosphorylation of CDK1 at the two negative regulatory sites, threonine 14 (Thr14) and tyrosine 15 (Tyr15) [26].

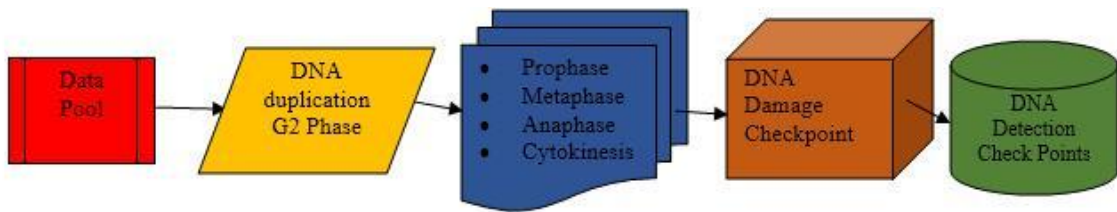


Fig. 8. Data collected through machine learning on G2/M Transition

The data suggested that a study by Kahi et al., 2003, the  $Ca^{2+}$ /CaM is implicated in the G2/M transition, M phase progression, and exit from mitosis. During the M phase the MPF increases the selectivity and rectifies the current, promoting the loss of  $K^+$  from the cell. Moreover, calcineurin was found as  $Ca^{2+}$  waves regulators in G2/M transition. Another prevalent enzyme, in addition to cdc25, CAMKII is found as important for G1 progression and G2/M transition. As demonstrated in glioma cells, a drastic volume decrease (or distribution per se) occurs during the M phase to reach a preferred volume state in the division. This relates to the chromatin and cytoskeleton condensation and depolymerization in M phase [27].

3.2.5 Role of  $Ca^{2+}$  in cell cycle

There are a number of different classes of calcium receptors, found in literature through machine learning, which play a crucial role in the maintenance of cellular homeostatic conditions and regulation of cell cycle by mediating the entry and exit of the calcium ions and also stimulating the intracellular release of calcium. Even it was found that the endoplasmic reticulum has calcium receptors, which help in storing calcium and releasing it as and when needed inside the cell during the cell cycle. The detailed classes of calcium receptors were reported by the data which includes the Voltage Gated Calcium Channel (VGCC) which is itself comprised of three different families of receptors, including the Cav1, Cav2 and Cav3. The other classes of calcium receptors include the Receptor-Operated Calcium Channels (ROCCs), the Ryanodine Receptor (RyR) present at the endoplasmic reticulum and the Inositol-1,4,5-trisphosphate receptor (IP3R), as shown in Fig. 9 [28].

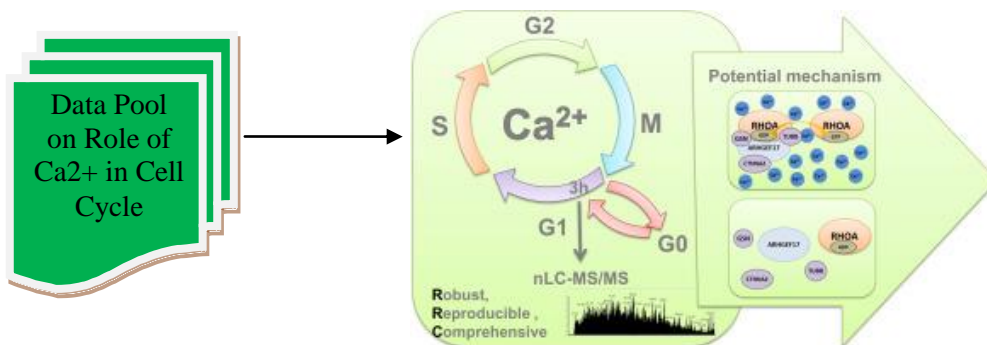


Fig. 9 Role of  $Ca^{2+}$  in Cell Cycle (Source: Villalobos et al., 2001)

Data collected through machine learning showed that, the  $\text{Ca}^{2+}$  channels control and regulate the cell cycle. In excitable cells such as the muscles, neurons and the endocrine cells, voltage gated calcium channels are used for the entry of  $\text{Ca}^{2+}$ . The increase in  $\text{Ca}^{2+}$  concentration inside the cell leads to the phosphorylation of the Mitogen-Activated Protein Kinase (MAPK), ultimately leading to the progression of the cell cycle. The downstream processes following the entry of  $\text{Ca}^{2+}$  ions are diverse and include expression of a number of different genes, depending on the cell type. The concentration of  $\text{Ca}^{2+}$  in the resting stage of the cells is very low (around  $10^{-7}$  M), while in the calcium stores such as the endoplasmic reticulum and the extracellular matrix,  $\text{Ca}^{2+}$  concentrations are much higher (around 10,000 times higher, approximately  $10^{-3}$  M). The maintenance of this gradient is ensured by the efflux of calcium from the intracellular organelles [29].

It was also confirmed in articles [27-30] that,  $\text{Ca}^{2+}$  interacts with the Cyclin-Dependent Kinases (CDKs) to regulate the cell cycle. The CDK family is considered to be important in the transition of the cell through the different phases of the cell cycle and also in the maintenance of the different phases. As the data suggested, CDK4 and CDK6 are found as important in the G1 phase, CDK2 is important in the G1 as well as the S phase, and also speculated to be a part of the M phase, while CDK1 is predominantly reported to be important in the M phase.  $\text{Ca}^{2+}$  in complex with Calmodulin (CaM) interacts with the CDKs and controls their activity throughout the cell cycle.  $\text{Ca}^{2+}$  and CaM together regulate the expression of the CDK1, CDK2 and the Cyclin B in human cells (particularly reported in the T lymphocytes). Moreover, it was found that the activation of the stored  $\text{Ca}^{2+}$  (SOCE: Store Operated Calcium Entry) activates CaM protein, which in turn leads to the blockage in the activity of Cyclin A and E [30].

According to the study of Se et al., 2004,  $\text{Ca}^{2+}$  oscillations also play a role in the gene expression. This has been documented in the case of the early and late gene expressions in the G1 phase. In the early phase of G1,  $\text{Ca}^{2+}$  affects the expression of the Serum response element (SRE), the Cyclic AMP Response Element (CRE), MYC, JUN and FOS genes, which are all important for the proliferation of cells. The activity of  $\text{Ca}^{2+}$ /CaM leads to the activation of CDK4/Cyclin D1 complex, which is involved in the regulation of the retinoblastoma protein (RB1), which is one of the main inhibitors of the DNA synthesis process. The RB1 is found as responsible for interaction with T2F transcription factor for the inhibition of cell cycle. However, the regulatory activities and the phosphorylation of the RB1 protein leads to the transition of the cell cycle from the G1 to S phase. According to Se et al., 2004, this transition is mediated by the regulatory activity of Cyclin D1 and the  $\text{Ca}^{2+}$ /CaM pathway. Here, the RB1 is inhibited and the p21 and p27 (better known as CDKN1A and CDKN1B) are also negatively regulated [31].

Next, the role of  $\text{Ca}^{2+}$  has been reported in the transition from G2 to M phase. It has been seen that  $\text{Ca}^{2+}$ /CaM regulate CAMKII in the G2 phase [59] and lead to the CAMKII mediated phosphorylation of the Microtubule Associated Protein 2 (MAP2), which leads to the inhibition of the microtubule polymerization [32].

#### 4. Advancements in Cell Cycle Modelling

Mathematical modelling and simulation of the cell cycle started a couple of decades ago. This includes, high throughput screening, modelling and simulations, topological interactions for the prediction of the system function and many others. None so far included the machine learning processes, including the training and test sets. No doubt, the engineered models share a systems level approach for biological systems and elucidate an advantageous picture of cell cycle framework and predictions, but a comprehensive illustrative picture is still missing.

We also applied machine learning on computational modelling performed in last 2 decades. The data revealed that Li et al. (2004) were pioneers among others for modelling the complete yeast cell cycle from regulatory proteins [33]. They investigated the global dynamicity and cell cycle proliferation drivers' trajectory and concluded that the network is robustly stable for conducting its functions and declared G1 as a global attractor from simulation dynamics, and that it is stable against all perturbations. Later, Davidich et al. (2008) presented a Boolean network model of the cell cycle sequences which was solely based on the biochemical topology of the interactions reproducing the biological cell cycle time sequence of protein activations. This minimalistic approach boosted the idea of predicting dynamical features of proteins along with protein interaction networks of cell cycle. Furthermore, data suggested that in subsequent years, Mangla et al. (2010) worked on synchronous models of the Budding and Fission yeast cell cycle and concluded that the timing and robustness can be used as the basis for a testable hypothesis that could account for several needs-based refinements in the model [33].

In addition to that Fauré et al. [34] were among the pioneers to model the mammalian cell cycle. They used the most prominent drivers of the cell cycle machinery, i.e., Cyc D, E, A and B along with other regulators and effectors, e.g., P27, Rb and E2F. Their synchronous and asynchronous Boolean modelling demonstrated the asymptotic behavior of the regulatory proteins based on the experimental data and provided the biological justification for using multilevel variables in future research.

Lately, Abroudi et al. (2017) published a paper on 'A comprehensive complex systems approach to the study and analysis of mammalian cell cycle control system in the presence of DNA damage stress'. They even considered G1-S and G2-M checkpoints unlike Fauré et al. [34]. They first refined the published research on ODE mathematical models and then included sub-systems, i.e., growth factors (GF), DNA damage, and G1/S and G2/M checkpoints. As advised by Magla et al. [35], they applied a multi-level systems approach. The model was also used to assess the efficacy of



DNA damage checkpoints in correctly arresting damaged cells and avoiding incorrect arrest of healthy cells and results revealed 98.6% accuracy in correctly releasing healthy cells through checkpoints. Using ANN all of these models can be computed completely and precisely in different layers, as shown in Fig. 10.

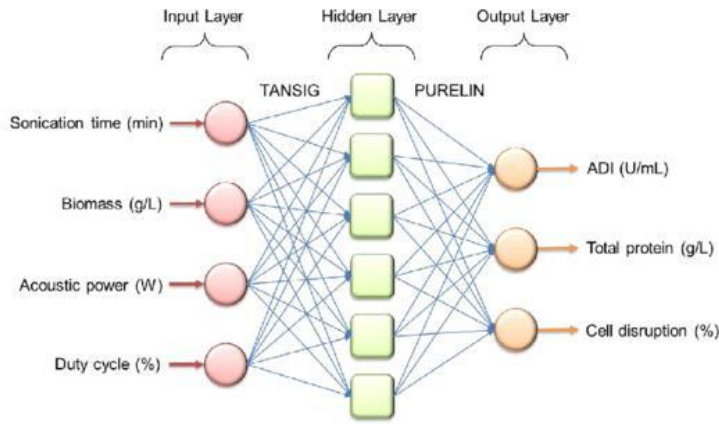


Fig. 10 Cell cycle modelling through ANN

Recently, Castro et al. (2019) developed an agent-based model of cell cycle adhering to the view that kinetic parameters are a crucial aspect when studying reactions involving proteins in real cell cycle [36]. They compared the results to a Boolean network model and found similar results in terms of following the correct sequence of phases. This model could be a starting point for being used in the development of cancer drugs by adding cell cycle mutations that match a specific type of tumor cell cycle and an agent representing the medication or treatment. Recently, Laomettachtit et al. [37] applied different mathematical modelling approaches including Boolean, discrete (stochastic), ODEs and hybrids, as shown in Fig. 11, and concluded the same as previous in terms of cell robustness and stability, although their models lacked the technical sophistications for mutated cell cycles.

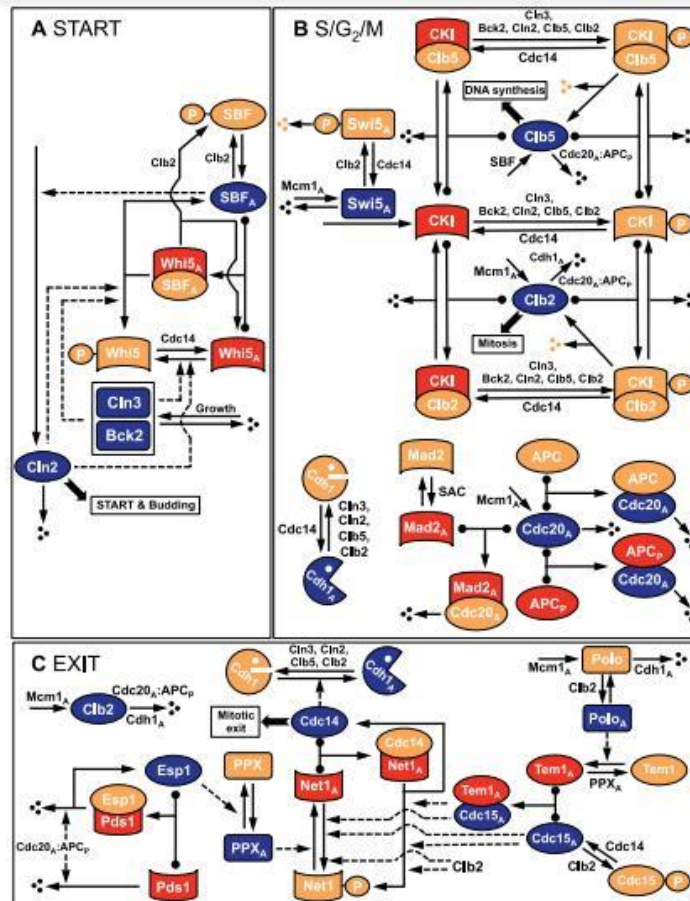


Fig. 11 A cell cycle model by Laomettachtit et al.

Scientists are working hard in order to model a cell cycle in a best possible way. As for now the models are quite complicated. Microbiologist, botanists, and zoologists are working to model the cell cycle. Similarly, scientists in the field of artificial intelligence are also trying to compare all models of cell cycles through machine learning [38-40]. The use of innovative technology such as machine learning and Artificial Intelligence will help efficiently to model the cell cycle using data of recent research [41,42].

## 5. Conclusion

The proliferative process of cell is important, and it has aided in research studies related to different areas of biological sciences. Data derived through machine learning indicates that our current comprehensive understanding of cell cycle is lagging and therefore, it requires the utilization of Artificial Intelligence in this domain so that mathematical algorithms and machine learning techniques could be applied to sort the huge volumes of data. This study was conducted with the same aim to demonstrate the role of different unconventional players that are actively controlling cell cycle. It has been observed in our study that though a significant attention has been given to conventional genomic regulators of cell cycle and their participation in different disease conditions have also been evaluated, but a clear picture of mechanism of action of these unconventional players is still missing. Thus, we have identified some key volume regulatory control elements in our study and presented the work that has been done on them to better understand the process of cell cycle.

In order to efficiently evaluate our current progress in the field of cell biology, computational biologists are working hard to identify different regulatory components of cell, its processes, machineries and cell cycle and combining them to develop a computational model so it could aid in better understanding of the process along with predicting the effects of perturbations that may be associated with any pathological condition. Different computational tools were being used in these studies and computational models were built for different cellular processes of both prokaryotic and eukaryotic cells. But our study through machine learning by using neural networks has found that though, a lot of work has been done on cell and cell cycle, but we still lack an all-inclusive picture of cell cycle model. Therefore, the unconventional players identified in our study would enable researchers to improve the current models of cell cycle by incorporating more regulatory elements in them.

As previous computational models of cell cycle have not considered the importance of inclusion of volume regulatory control elements in cell cycle, therefore, our work will provide a basis to improve the current knowledge available on cell cycle through artificial intelligence. It would help in developing a comprehensive cell cycle model by incorporating as many details as possible in the simplest possible way so that it could assist biologists in identifying and evaluating the effects of perturbations in pathways. It will help in evaluating the role of various drugs on regulating membrane potential, ionic homeostasis in the microenvironment and volume regulation in wet lab so that new targets could be identified and their efficacy could be determined. Our study demonstrates that researchers need to emphasize on volume regulatory machinery as well by identifying their mechanism of action and their utilization in therapeutics. It would ultimately shift a focus from genome regulatory components to volume regulatory elements and if it will work well, it would enable us to overcome the effect of Multi Drug Resistance (MDR). The jump from wet lab experimentation to computational modelling has proven vital. There is now a need to take a leap towards machine learning and artificial intelligence methodologies to better understand the working of the cell. Together, these phenomena may pave the path for bringing innovation in the field of regenerative medicine and to develop new therapeutic solutions to prevent or restore disease states such as uncontrolled cell proliferation in cancer.

## References

- [1] Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., & Walter, P. (2002). *Molecular Biology of the Cell* 4th edn (New York: Garland Science). Ann Bot, 91, 401.
- [2] Gali-Muhtasib, H., & Bakkar, N. (2002). Modulating cell cycle: current applications and prospects for future drug development. *Current cancer drug targets*, 2(4), 309-336.
- [3] Norbury, C., & Nurse, P. (1992). Animal cell cycles and their control. *Annual review of biochemistry*, 61(1), 441-468.
- [4] Lodish, H., Darnell, J. E., Berk, A., Kaiser, C. A., Krieger, M., Scott, M. P. & Matsudaira, P. (2008). *Molecular cell biology*. Macmillan.
- [5] Patt, H. M., & Quastler, H. (1963). Radiation effects on cell renewal and related systems. *Physiological reviews*, 43(3), 357-396.
- [6] Howard, A., c. *Heredity suppl*, 1953. 6: p. 261-273.
- [7] Blagosklonny, M. V., & Pardee, A. B. (2002). The restriction point of the cell cycle. *Cell cycle*, 1(2), 102-109.
- [8] Munawar HS, Awan AA, Khalid U, Munawar S, Maqsood A. Revolutionizing Telemedicine by Instilling H. 265. *International Journal of Image, Graphics & Signal Processing*. 2017 May 1;9(5).
- [9] Munawar, H. S., Qayyum, S., Ullah, F., & Sepasgozar, SBig Data and Its Applications in Smart Real Estate and the Disaster Management Life Cycle: A Systematic Analysis. *Big Data and Cognitive Computing*; 2020, 4(2).
- [10] Munawar, H. S., Zhang, J., Li, H., Mo, D., & Chang, L. Mining multispectral aerial images for automatic detection of strategic bridge locations for disaster relief missions. In *Pacific-Asia Conference on Knowledge Discovery and Data Mining* (pp. 189-200). Springer, Cham. . (2019, April).

- [11] Munawar HS, Hammad A, Ullah F, Ali TH. After the flood: A novel application of image processing and machine learning for post-flood disaster management. In Proceedings of the 2nd International Conference on Sustainable Development in Civil Engineering (ICSDC 2019), Jamshoro Pakistan 2019 Dec (pp. 5-7).
- [12] Munawar, H. S. Applications of Leaky-wave Antennas: A Review. *International Journal of Wireless and Microwave Technologies (IJWMT)*; 2020, 10(4), 56-62.
- [13] Munawar, H. S. An Overview of Reconfigurable Antennas for Wireless Body Area Networks and Possible Future Prospects. *International Journal of Wireless and Microwave Technologies (IJWMT)*; 2020, 4, 1-8.
- [14] Munawar, H. S., Khalid, U., Jilani, R., & Maqsood, A. (2017). Version Management by Time Based Approach in Modern Era. *International Journal of Education and Management Engineering*, 4, 13-20.
- [15] Munawar, H. S. Reconfigurable Origami Antennas: A Review of the Existing Technology and its Future Prospects. *International Journal of Wireless and Microwave Technologies (IJWMT)*; 2020, 4, 34-38.
- [16] Munawar, H. S., & Maqsood, A. Isotropic Surround Suppression based Linear Target Detection using Hough Transform.
- [17] Pledger, W. J., Stiles, C. D., Antoniadis, H. N., & Scher, C. D. (1977). Induction of DNA synthesis in BALB/c 3T3 cells by serum components: reevaluation of the commitment process. *Proceedings of the National Academy of Sciences*, 74(10), 4481-4485.
- [18] Campisi, J. U. D. I. T. H., & Pardee, A. B. (1984). Post-transcriptional control of the onset of DNA synthesis by an insulin-like growth factor. *Molecular and cellular biology*, 4(9), 1807-1814.
- [19] Rossow, P. W., Riddle, V. G., & Pardee, A. B. (1979). Synthesis of labile, serum-dependent protein in early G1 controls animal cell growth. *Proceedings of the National Academy of Sciences*, 76(9), 4446-4450.
- [20] Bartek, J., & Lukas, J. (2001). Pathways governing G1/S transition and their response to DNA damage. *FEBS letters*, 490(3), 117-122.
- [21] Massagué J. (2004). G1 cell-cycle control and cancer. *Nature*, 432(7015), 298.
- [22] Grissmer, S., Nguyen, A. N., & Cahalan, M. D. (1993). Calcium-activated potassium channels in resting and activated human T lymphocytes. Expression levels, calcium dependence, ion selectivity, and pharmacology. *The Journal of general physiology*, 102(4), 601-630.
- [23] Lang, F., Busch, G. L., Ritter, M., Volkl, H., Waldegger, S., Gulbins, E., & Haussinger, D. (1998). Functional significance of cell volume regulatory mechanisms. *Physiological reviews*, 78(1), 247-306.
- [24] Lin, C. S., Boltz, R. C., Blake, J. T., Nguyen, M., Talento, A., Fischer, P. A., ... & Garcia, M. L. (1993). Voltage-gated potassium channels regulate calcium-dependent pathways involved in human T lymphocyte activation. *Journal of Experimental Medicine*, 177(3), 637-645.
- [25] Lang, F. (2007). Mechanisms and significance of cell volume regulation. *Journal of the American college of nutrition*, 26(sup5), 613S-623S.
- [26] Sanchez, Y., Wong, C., Thoma, R. S., Richman, R., Wu, Z., Piwnicka-Worms, H., & Elledge, S. J. (1997). Conservation of the Chk1 checkpoint pathway in mammals: linkage of DNA damage to Cdk regulation through Cdc25. *Science*, 277(5331), 1497-1501.
- [27] Kahl, C. R., & Means, A. R. (2003). Regulation of cell cycle progression by calcium/calmodulin-dependent pathways. *Endocrine reviews*, 24(6), 719-736.
- [28] Devault, A., Cavadore, J. C., Fesquet, D., Labbé J. C., Lorca, T., Picard, A., ... & Doree, M. (1991, January). Concerted roles of cyclin A, cdc25+ mitotic inducer, and type 2A phosphatase in activating the cyclin B/cdc2 protein kinase at the G2/M phase transition. In *Cold Spring Harbor symposia on quantitative biology* (Vol. 56, pp. 503-513). Cold Spring Harbor Laboratory Press.
- [29] Takuwa, N., Zhou, W., Kumada, M., & Takuwa, Y. (1993). Ca<sup>2+</sup>-dependent stimulation of retinoblastoma gene product phosphorylation and p34cdc2 kinase activation in serum-stimulated human fibroblasts. *Journal of Biological Chemistry*, 268(1), 138-145.
- [30] Diehl, J. A. (2002). Cycling to cancer with cyclin D1. *Cancer biology & therapy*, 1(3), 226-231.
- [31] Se, V., Rajala, N., Spiller, D., & White, M. (2004). Calcium-dependent regulation of the cell cycle via a novel MAPK–NF-κB pathway in Swiss 3T3 cells. *Abbreviations used in this paper. The Journal of Cell Biology*, 166(5), 661-672.
- [32] Ohta, Y., Ohba, T., & Miyamoto, E. (1990). Ca<sup>2+</sup>/calmodulin-dependent protein kinase II: localization in the interphase nucleus and the mitotic apparatus of mammalian cells. *Proceedings of the National Academy of Sciences*, 87(14), 5341-5345.
- [33] Davidich, M. I., & Bornholdt, S. (2008). Boolean network model predicts cell cycle sequence of fission yeast. *PLoS one*, 3(2), e1672.
- [34] Fauré A., Naldi, A., Chaouiya, C., & Thieffry, D. (2006). Dynamical analysis of a generic Boolean model for the control of the mammalian cell cycle. *Bioinformatics*, 22(14), e124-e131.
- [35] Mangla, K., Dill, D. L., & Horowitz, M. A. (2010). Timing robustness in the budding and fission yeast cell cycles. *PLoS One*, 5(2), e8906.
- [36] Castro, C., Flores, D. L., Vargas, E., Cervantes, D., & Delgado, E. (2019). Agent-Based Model of the Budding Yeast Cell Cycle Regulatory Network. In *World Congress on Medical Physics and Biomedical Engineering 2018* (pp. 531-534). Springer, Singapore.
- [37] Laomettachit, T., Chen, K. C., Baumann, W. T., & Tyson, J. J. (2016). A model of yeast cell-cycle regulation based on a standard component modeling strategy for protein regulatory networks. *PLoS one*, 11(5), e0153738.
- [38] Munawar, H. S., Khalid, U., & Maqsood, A. Fire detection through Image Processing; A brief overview.
- [39] Munawar, H. S., Khalid, U., & Maqsood, A. Modern day detection of Mines; Using the Vehicle Based Detection Robot.
- [40] Munawar HS, Awan AA, Maqsood A, Khalid U. REINVENTING RADIOLOGY IN MODERN ERA.
- [41] Munawar, H. S. (2020). Flood Disaster Management: Risks, Technologies, and Future Directions. *Machine Vision Inspection Systems: Image Processing, Concepts, Methodologies and Applications*, 1, 115-146.
- [42] Munawar, H. S. (2020). Image and Video Processing for Defect Detection in Key Infrastructure. *Machine Vision Inspection Systems: Image Processing, Concepts, Methodologies and Applications*, 1, 159-177.

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