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An Overview on Computational Approaches to Modeling Mammalian Cell Cycle

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Abstract: **Biological systems such as cell cycle are "complex systems "consisting of an enormous number of elements interacting in ways that produce nonlinear and complex systems behavior. Computational modeling a promising approach to study such systems. However, representing structural and functional complexity of these systems is a major challenge to these models that can range from simpler discrete models such as Boolean networks to more complex mathematical model. Modeling methods and techniques have become popular for modeling biological systems because they can provide a deep understanding and insight of the complex biological system issues. These techniques can also be used in prediction, diagnosis and treatment of diseases such as cancer.**
This paper overlays current and existing computational modeling approaches used in modeling mammalian cell cycle (discrete, continuous, stochastic and hybrid). In addition, it introduces a set of opened research questions related to cell cycle system. Furthermore, this paper exposes the pros and cons of the existing modeling approaches and presents a more flexible and intuitive fuzzy logic based system framework to modeling cell cycle system.

Keywords - Mammalian Cell Cycle, Computational Modelling Approaches, Logical Or Discrete Models, Ordinary Differential Equations (ODEs), Stochastic, Hybridization, Fuzzy Systems.

I. INTRODUCTION

To develop a theoretical framework that is useful for modeling biological systems expert modelers must have understanding of the mammalian cell cycle system components. Furthermore, they should have a clear conception of their interactions and outstanding issues which are related to the cell cycle. The first section has shown these points. The second section of this paper provides an overview of current and existing computational models with their advantages and disadvantages. The subsequent section presents a set of open questions and introduces our proposed a framework using fuzzy logic method. The final section concludes this paper.

Cell is the smallest basic unit of all living organisms. Cells have been organized and classified into two types depending on the existence of a nucleus inside them. Cells with a nucleus are called eukaryotic cells, and those without a nucleus are called prokaryotic cells.

Mammals consist of a huge number of cells. In this system, the cell is considered as the smallest basic unit of all living organisms. In addition, this unit can control its structure with independent behaviors and it can reproduce itself. Cells together create the composite of life, "building blocks of life" (Hay 1991). A cell can reproduce itself by an ordered sequence of events called the cell cycle. This cell cycle is considered a complex system. It uses a large number of elements and interactions during cell cycle to produce two cells from the mother cell. This process is called cell proliferation.

Cell cycle is the way to produce two daughter cells by leading a cell through duplication (replication) and division (Behl and Ziegler 2014) . Eukaryotic cells need around 24 hours to divide (Wille, Pittelkow et al. 1984, Knoblauch,

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Hibberd et al. 1999) through an ordered and well organized sequence of events. At the end of cell cycle, cells produce a copy of themselves. But, abnormal events can force the cell to die (Florens, Washburn et al. 2002). Each cell cycle has a set of phases (Figure1.a), the two main phases are S phase and M phase which are separated by two gap Phases G1 and G2. So the sequence of the cell cycle is (G1, S, G2, M, and G1).

These phases are ordered in sequence in a dependent manner. These phases are: The G1 phase: this phase starts directly after previous cell division (totic pre-synthesis phase). During this phase, the cell starts to grow and contents of the cell (cytoplasm) along with its functional machineries are developed. The time for this phase is approximately 1/3 of that time hours (24 hours). The S – synthesis- phase: this phase is responsible for DNA replication and creation of histone proteins that are needed for packaging the genomic DNA. The average time for this phase is seven hours. The G2 phase or post-synthesis phase: In this phase a cell prepares itself to be split into two daughter cells. It grows and increases it size. The time for this phase is around four hours. The Mitosis or division phase (M-Phase): In this phase the DNA is segregated and cell divided. The time needed for this phase is between 30 to 60 minutes, and can be divided into five phases (prophase, prometaphase, metaphase, anaphase and telophase; for more Details refer to (Alberts, Johnson et al. 2002, Behl and Ziegler 2014) .

Cell cycle has controllers that move the cell from phase to phase during the proliferation process. The core controllers of all eukaryotes cells consists of complexes of Cdk and cyclin molecules (Cdk/cyclin pairs) as shown in Table 1. These pairs are in charge of a set of tasks such as controlling G1 phase (Cyclin D/ Cdk4, 6) and initiating DNA replication at the transition from G1 to S-phase (CyclinE/Cdk2) or leading the S phase (CyclinA/Cdk2) or controlling cell division in mitosis phase (Cyclin B/ Cdk1). Furthermore, these pairs are responsible for the separation of the chromosomes at the end of mitosis and cell division (Figure1.a).

Table.1 Cyclins complex that control the cell cycle

Name of cyclin-Cdk complex	Name of component Cyclin	Name of component Cdk partner
G1-cdk	Cyclin D	Cdk4,Cdk6
G1/S-Cdk	Cyclin E	Cdk2
S-Cdk	Cyclin A	Cdk2
M-cdk	Cyclin B	Cdk1

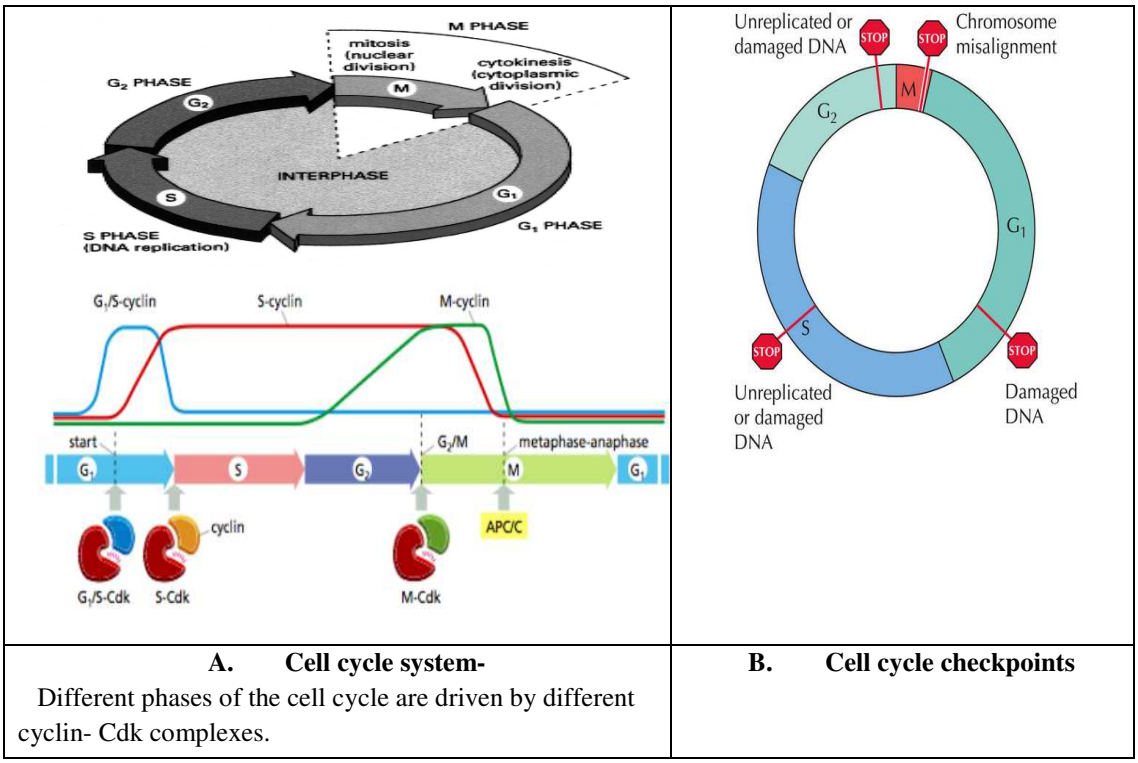
The transitions inside the cell cycle are controlled by checkpoints (G1/S checkpoint, G2/M checkpoint and cell division checkpoint) as shown in (Figure1.b). These checkpoints ensure the integrity in DNA synthesis; this can be done by ensure that cells start DNA synthesis only if nutrients and growth factors are present. Check points can control the mitosis phase by making sure that DNA replication is properly finished. As a rule if there is any problem checkpoint will trigger a DNA damage to arrest the cell cycle for doing DNA repair or guiding the cell to programmed death (apoptosis).

II. COMPUTATIONAL MODELS

Complex biological systems such as cell cycle have several issues that need addressing; these include system structure, interactions, function and dynamic behavior. Recently, several computational models and approaches have been developed for cell cycle. They have provided useful information that help researchers (biologists) study and predict outcomes.

Researchers depend on available information to develop models to address one or more of these issues. For example, they use gene regulatory networks and protein – protein networks to analyze cell cycle events and activities in relation to gene expression (Kohn 1998). Researchers have to understand the structure and behaviors of these networks depending on the limited available data (Csikász-Nagy 2009).

Modeling approaches can be classified into several classes (Csikász-Nagy 2009) , **The first class** is logical or discrete models which describe a system in qualitative form. **The second class** is continuous models used to express continuous changes in protein concentrations in biological systems. **The third class** represents biological systems along with noise; these are called stochastic models. **The fourth class** is called hybrid models; in this model a combination of different techniques are used. In this kind of model two or more techniques work together to complement each other in representing the biological problem. In some cases more than three techniques can be used.



A. Cell cycle system-
Different phases of the cell cycle are driven by different cyclin- Cdk complexes.

B. Cell cycle checkpoints

Figure1: a. Cell cycle system (Kumar 2007), b. Bell cycle checkpoints (O'connor 1996)

2.1. Logical or discrete Models

This modelling methodology which depends on the discrete or logic based concepts is considered a simple and basic deterministic model an example of which is Boolean Network. The first Boolean model was developed by Kauff man and Thomas (Glass and Kauffman 1973, Thomas 1973). Boolean models consist of a set of entities that represent the biological system components such as genes, proteins and small molecules. The relation between entities (Nodes) is represented by the edges and the activity state of each node is represented as inactive or active in the form of [0, 1]. In a biological system nodes represent proteins and genes and interactions are represented by edges. Figure 2.a represents the structure of Boolean network where A, B and C represent network nodes and the directed arrows denotes activation and inhibition. Figure 2.b shows the rules that manage the activities in the Boolean network system. In cell cycle system, components can be represented by Boolean entities with binary values referred to as OFF and ON.

Boolean models of the cell cycle system have been proposed previously, most of which were developed to represent and mimic the yeast cell cycle. However, very few models have been developed to model the mammalian cell cycle.

The well-known Boolean model to represent the yeast cell model was developed by Li, Long et al. (2004). They examined the temporal robustness of the cell cycle with respect to checkpoint conditions in budding yeast for construction of a Boolean network. However, their approach is only suited to small and well-characterized systems. Braunewell and Bornholdt (2007) also proposed a Boolean network to study dynamical attractors of yeast cell cycle. Their proposed Boolean model consists of 11 genes that coordinate yeast cell cycle dynamics. Braunewell and Bornholdt (2007), developed the framework for their proposed model using the concept of discrete threshold dynamics which allowed them to introduce fluctuations in the process time. They introduced noise into the model to account for the effects of biochemical stochasticity.

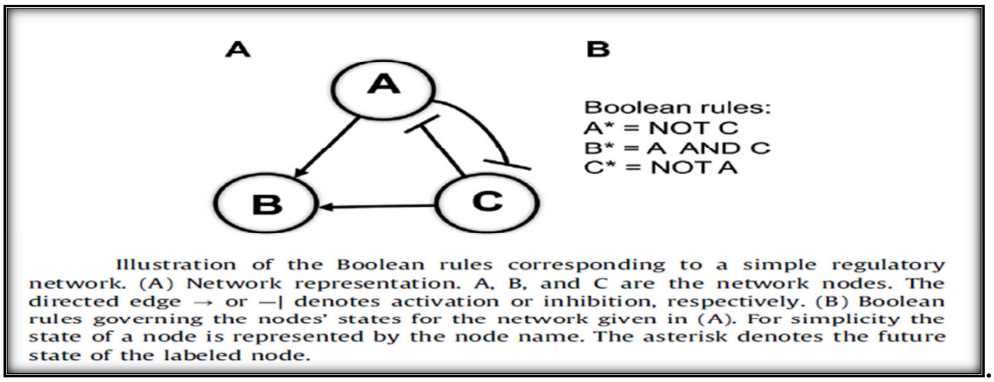


Figure 2: Boolean network: A. Boolean network structure, B. Boolean rules and network activities.

However, Braunewell and Bornholdt (2007) used a very simple model and neglected a detailed description of the system with different time scales involved in different processes. Their result may not be translated directly to the cell cycle system.

Another model was introduced to study fission yeast (Schizosaccharomyces pombe); Davidich and Bornholdt (2008) introduced a Boolean network model for cell cycle of fission yeast (Schizosaccharomyces pombe), that was based on known biochemical interaction topology. Using this model, they dropped the essential 47 kinetic constants and parameters of the ODE approach and still obtained the same results for the biological sequence of activation. However, their work was limited to a single cell size checkpoint. Furthermore, they also neglected the DNA damage checkpoints.

Studying the wild type and mutant phenotypes have been done by using Boolean network such as Irons (2009) who developed a new Boolean model for budding yeast cell cycle which consist of a wide range of wild type and mutant phenotypes. Irons (2009) model was robust against perturbations for reaction times and network component states. They overcame the FEAR pathway limitations of the Boolean model developed by Li, Long et al. (2004). They included the Men pathway components in their proposed model. Furthermore their model was more suitable for sub network analysis that can be used to identify key sub dynamics for viable cell cycle control. (Irons (2009) model produced different times took to pass through each phase compared to real biological times.

Yeast model was limited in providing a better understanding of complex biological systems due to its simplicity (Gérard and Goldbeter 2012). To understand the behavior of complex biological systems, the integration of molecular data into a formal dynamical model is required (Fauré, Naldi et al. 2006) . This is the situation of mammalian cell cycle. Fauré, Naldi et al. (2006) proposed a Boolean model for the mammalian cell cycle based on Novak and Tyson (2004) ODE system to describe cell cycle behavior. Novak and Tyson (2004) model was based on 27 equations and experimentally derived parameters. Fauré, Naldi et al. (2006) model is still considered a benchmark for all later developed Boolean models. The major contribution of Fauré, Naldi et al. (2006) model was simplicity due to the reduction of the number of equations and the focus on some important elements including cyclins (D, A, E and B), Rb and E2F. However, limitation of their model is that it did not incorporate cell cycle checkpoints. Moreover, this model did not account for the effect of some key cell cycle regulatory proteins such as Cdc25, Wee1 and p16.

The Boolean models have become more popular because they can be easily used for large scale and can explain the dynamic behaviour of complex networks by using for instance attractors. Boolean networks attractors are utilized in explaining several biological cases. For instance, attractors are used to explain cell cycle events such as cell cycle phases, and several studies depend on attractors to elucidate cell cycle phases like (Fauré et al. 2006;Li, Long et al. 2004). In other studies, attractors are used to study the wild-type gene-expression patterns; Albertand Othmer used the companion of attractors in a Boolean model of Drosophila melanogaster with the wild-type gene-expression patterns of the segment polarity genes (Albert and Othmer 2003). Adult tissue cells states such as growth, differentiation and apoptosis (programmed cell death) can be explained by attractors. Huang considers the three states and shows that cycles of multiple states represent growth of the cell, but single-state attractors represent differentiation or apoptosis (Huang 1999). On other hand, the disruptions of cell states balance are a characteristic of neoplasia (i.e. tumors).

Boolean models have also been used in investigations of diseases such as cancer. This kind of modelling can tool up new insights into the origins of cancer For instance Sahin, Fröhlich et al. (2009) in their model use Boolean network to model single and multiple protein loss of function. In their model they used single and double knockdowns of network elements then they measured their effects on G1/S transition inside the cell cycle process. Moreover, they studied the sensitive and the resistant of cells responded to some of perturbation. Sahin et al. 2009 discovered that c-MYC as a novel potential target protein in breast cancer cells (Orlando, Lin et al. 2008, Sahin, Fröhlich et al. 2009).

Boolean networks are easy to be designed and programmed they provide information on the interactions and system properties in a simple and qualitative way. Furthermore, this kind of network does not depend on model parameters. However, these models have limitations. For instance, they cannot appropriately represent slow interactions and events or different timescales of events. Another limitation with discrete model is that the results are represented in qualitative form and this is not enough for researchers to gain a deep understanding of system behavior. Furthermore, Boolean models cannot describe the intermediate activity level of elements or which element is more active than others, because they are not part of Boolean model functionality.

Also, this kind of model can only represent the local state change of the proteins (Nodes) in discrete time steps. The time is assumed in the temporal development of the system in synchronous or asynchronous form. In synchronous form, all nodes update their states at each time step where in asynchronous form randomly selected nodes update their state at each time step. In either case, actual timing events are not considered in the model to produce realistic results for temporal evolution of elements.

2.2 Continuous Models

This class mainly represents mathematical approaches of ordinary differential equations (ODEs). It is a deterministic model like Boolean models (Glass and Kauffman 1973, Thomas 1973. ODE models can successfully explain the continuous behaviour of biological system.

For cell cycle several ODE models have been developed to provide detail information such as concentrations of proteins and other cell cycle components. In the last century researchers discovered that the molecular interactions control the cell cycle. Since that era many groups have commenced to work on mathematical models to analyse these interactions. (Table 1). The group of Be´la Nova´k and John J. Tyson is one of the leaders in this filed, this group published more than 40 papers on cell-cycle regulation. Until this moment there models are considered a benchmarks of computational systems biology.

In 1993 they study the mitosis phase in eggs of the frog Xenopus laevis and discovered that their model can provide reliable switch for entry into mitosis [43]. Novak and Tyson (1993) revealing ""Hysteresis" which exists in the MPF–Cyclin relationship. Later on, they provide a detailed model for cell-cycle regulation by describing the Cdk control network in budding yeast Saccharomyces cerevisiae. Novak and Tyson (2004) developed a new mathematical model with inclusion of restriction points that control mammalian and yeast cell cycle. Their model was mainly based on the growth factor effects on cell cycle. Moreover, they examined the changes and mutations in some key elements of mammalian cell cycle including Cyclin E and Retinoblastoma protein (Rb). Their model had many shortcomings regarding cell growth and division.

More recent models such as Chen, Calzone et al. (2004) who proposed another continuous model for modelling yeast cell cycle based on biochemical rate equations. However, their model has documented few inconsistencies between the model and experiments. Also, their model requires to estimate the effective values of biochemical rate constants which were difficult to measure. Also, (Ferrell, Tsai et al. 2011) proposed a mathematical model to explain the oscillatory biochemical circuits in the context of Xenopus embryonic cell cycle and system stability. The major contribution of their model was the specification of kinetic parameter sets that produced oscillations. Furthermore, they documented the reasons for the oscillation in their model.

Generally, the above models and the others models in Table.2 can accurately represent continuous biochemical reactions. However, the problem with ODE models is that when the model has a large number of components such as genes and proteins, it becomes very difficult to analyse them (Irons 2009). Moreover, the source of parameters used in continuous models is generally experiential estimation or inference. Researchers or the modelers always face the problem of parameters availability and their reliability. If they are used for large complex systems such as cell cycle system, a large number of unknown parameters need to be estimated. Also, these models cannot provide a clear view of the order and sequence of biological events.

Table 2. Some of ODE mathematical models of the mammalian cell cycle

Year	Organism/Cell Type	Type of Model	Reference
1969	No specific organism	ODE	(Sel'kov 1969)
1974	No specific organism	ODE	(Gilbert 1974)
1999	Mammalian somatic cells	ODE	(Aguda and Tang 1999)
2006	Mammalian somatic cells	Delay differential equations	(Srividhya and Gopinathan 2006)
2008	Mammalian somatic cells	ODE	(Yao, Lee et al. 2008)
2009	Mammalian somatic cells	ODE	(Alfieri, Barberis et al. 2009)
2010	Mammalian somatic cells	ODE	(Ling, Kulasiri et al. 2010)
2010	Mammalian somatic cells	ODE	(Iwamoto, Hamada et al. 2011)
2011	Mammalian somatic cells	ODE	(Zhang, Cheng et al. 2013)
2014	Mammalian somatic cells	ODE	(Weis, Avva et al. 2014)

2.3 Stochastic Models

Stochastic models represent a complex system such as cell cycle system along with its inherent noise. It randomly chooses items or nodes. In these kind of models, stochasticity behaviour is offered by utilize mathematical methods. The most popular mathematical methods that used Gillespie Stochastic Simulation Algorithm (GSSA) (Kar, Baumann et al. 2009) and Stochastic Langevin Equations (SLA)(Steuer 2004).

A number of stochastic models of cell cycle have been produced such as Chiorino and Lupi (2002) who proposed a stochastic ordinary differential equations approach to investigate G 1 phase variability depending on the molecular point of view. In addition they modelled the transition from the G 1 phase to the phase of DNA synthesis. Their model can be successively used to predict protein behavior. However, their model cannot describe cell cycle progression so easily and linearly.

Zhang, Qian et al. (2006) proposed a stochastic model for the network regulating cell cycle of budding yeast. They advanced a probabilistic Boolean network model which consists of 11 nodes. The stochastic effect was controlled by Markov chain depending on a temperature factor such as parameter β. They concluded that both the biological stationary state and the biological pathway had a stable state for a wide range of "temperature". But, their model showed a sharp transition such as a behavior at critical temperature βc which made the dynamics dominated by noise. Another model was built by Bean, Siggia et al. (2006) investigate the coherence of the Start phase in the division cycle; Bean, Siggia et al. (2006) developed a stochastic model based on quantitative time-lapse fluorescence microscopy on a multicell cycle timescale. Multiple fluorescent markers were used to examine the coherence of the Start phase in the division cycle. The major contribution of their model involved its applicability to yeast grown under time-lapse conditions and applicability to semi-automated assignment of microcolony pedigrees. Furthermore, their model could be used for stochastic effects in prokaryotic transcriptional regulation. Braunewell and Bornholdt (2007) examined the cell cycle of the budding yeast based on the concept of discrete threshold dynamics to study stability and dynamical attractors of the cell cycle system. However, the major limitation of their model was that it did not represent checkpoint mechanisms.

Zámborszky, Hong et al. (2007) developed a simplified version of a 4-variable mammalian circadian clock Model. They adapted Novak and Tyson's mammalian model (2004) to build their model. They built the model on set of assumes ion to make the system more simple for example they assumed that some elements in the system are the same and some system components are stable more than other which introduces an autocatalytic positive feedback in the system. In the stochastic simulations, Zámborszky et al. (2007) introduced noise into the cell cycle regulatory equations. They rewrote the cell cycle model equations as Langevin type equations with multiplicative noise (Steuer 2004). The result of their simulation reported and recommended that the clock would play an important role in cell size control via Wee1 element in their model. However, Zámborszky, Hong et al. (2007)did not address a comprehensive mammalian circadian rhythm model.

More recent models such as Kapuy, He et al. (2009) who designed a model to simulate mitotic exit of mammalian cells. Their model predicted that in the time interval between 30 and 70 min the percentage of cells which completed their irreversible mitotic exit will be gradually increased. In addition, they observed that mammalian and yeast cells are sharing an important point, the activation of Cdh1/APC in the model and the inactivation of CycB transcription at low Cdk1 activity. This happen due to the additional feedback loops which help in irreversibility of mitotic exit. However, their model has a challenge particularly in mammalian cells the phosphatase that counteracts Cdk1–CycB is yet to be identified and illustration of the implied Systems level mechanisms will be a challenge for future research.

Also, Gérard and Goldbeter (2012) developed a model to investigate the conditions that make mammalian cell cycle entrained by the circadian clock. They observed that entrainment to a circadian period can be happened when the period of the cell cycle prior to coupling is either smaller or larger than 24 h. This stochastic model reported a potent predication especially when the cell cycle entrainment from the circadian variation of a growth factor gating entry into G1. Also, the transition from entrained period from 24 hours period to double time 48 hours might outcome from the level of growth factor or by decrease in coupling strength. However, coupling to the circadian clock can lead to complex periodic oscillations, or chaotic oscillations dynamics of the cell cycle in the form of end replication.

Generally, the advantages of the above models are that they can represent a system more realistically than deterministic models. In addition, this kind of model can be helpful when the protein concentration is low. Further, they can be used when it becomes hard for the ODE models to handle the system (Wolkenhauer, Ullah et al. 2004). However, in these model every time the model is run results are different from the other runs because it is non-deterministic. They can also produce unreliable or predictable results in each interaction.

2.4 Hybrid Models

In hybrid models, modelers combine several methods to benefit from their advantages. The expected outcome from a hybrid model is to cover the shortcoming and issues in one methods by another and thus provide a better understanding of the complex system. For instance, hybrid models can use both the discrete and continuous aspects in the same model, to realistically represent corresponding aspects in the system.

Singhania, Sramkoski et al. (2011) proposed a hybrid model to represent the mammalian cell cycle. Their model was based on the best features of continuous differential equations, discrete Boolean networks and stochastic approaches. The model represented the continuous change in cyclin (CycE, CycA, CycB) synthesis and degradation which were tracked by piecewise linear differential equations, while the regulator of Cyclin synthesis (transcription factors (TFE and TFB) and ubiquitination machinery (SCF, Cdc20 and Cdh1) were represented by discrete variables (0 or 1). The variation in the state of discrete variables was based on a predetermined sequence. Also the timing between transitions was determined in part by cyclin accumulation and degradation. This is a simple model which represents the most important regulations elements in cell cycle system. However, this model missed some of important elements such as CycD. More can be done by incorporating the additional elements like Cyc D with their interactions to ascertain new knowledge. In addition, it is challenged by available experimental data because this model needs to estimate realistic values for the many kinetic constants that determine the reaction rates. Noël, Vakulenko et al. (2013) proposed another hybrid model for mammalian cell cycle. Their model was based on a combination of continuous and discrete to model the cell cycle dynamics. The model depended on hybridization from a smooth biochemical model. However, the appropriate hybridization scheme depends on the learning from training a set of smooth model trajectories.

Another hybrid model developed by Noel, Grigoriev et al. (2012) was based on a tropical geometry heuristics which unravels commonalities of cell cycle models. The model combined quasi-equilibrium states, represented by slow invariant manifolds and excitability. Their system had a simple structure of monomial differential or differential-algebraic equations. However, their model was limited to ODE such as the availability of experimental data. Behaegel, Comet et al. (2015) documented that time was pivotal in many biological systems especially in cell cycle. Their model was based on a five variable model of mammalian cycle. They determined the parameters by applying formal methods to an underlying discrete model using timing observations of cell cycle.

III. Open Questions And Suggested Model

The main challenge for current and future models is to utilize the understanding of cell cycle system to investigate cell physiology. Comprehensive detailed models are needed to support and explain cell signaling network along with cell

cycle Machinery. Models are also needed to mimic interactions at cell to cell level as current models explore cell activities at one cell level. These models can provide more insight to mammalian cells which can be helpful in treatment process for diseases.

In this paper, we introduce and suggest an alternative model which can describe and cover both the discrete (fast) and continuous (slow) aspects of the same model. This model depends on fuzzy logic theory (Fuzzy logic model). Fuzzy logic allows modelling imprecise, uncertain and limited knowledge and data domains to capture essential trends and behaviour.

Fuzzy systems are very helpful for tasks that are vague and missing information. In addition, it provides a simplified continuous approach to represent events. Furthermore, Fuzzy logic enables us to consider the intermediate levels and can state which element is more active than others, because it is an approach to computing based on "degrees of truth" rather than the usual "true or false" (1 or 0) Boolean logic. It allows the variables to be continuous and more finely valued. It can provide a continuous approximation by making variables continuous between the interval [0, 1]. The fuzzy model provides a fully quantitative representation that is more intuitive and simpler than ODEs.

The proposed model can represent each entity in cell cycle elements by *fuzzy inference system (FIS)*. The Multi FIS's Model is expected to simplify and realistically represent the system and bridge the existing shortcoming of discrete and continuous representations, such as the outcome of discrete model is in [0,1] form and the shortcoming of continuous models (ODE) is need to many kinetic parameters which is limited. It is also expected to provide approximate continuous dynamics for the discrete events using limited available data. When applied to the cell cycle system, the model will produce accurate concentrations of proteins in each cell cycle event.

IV. Conclusion

This survey paper highlights pros and cons of current and existing computational modeling approaches. It also introduces a set of open questions. It presents more flexible and intuitive fuzzy logic based systems framework for modeling mammalian cell cycle system.

Modeling approaches can provide specific information. One of the main uses of the modelling is to predict temporal change of state or level of the interacting elements. They are also used for addressing system events or emerging properties arising from collective behavior of elements. These may include a cell passing various cell cycle phases with the support of participatory elements. They can be used for studying system malfunction which can give rise to diseases such as cancer. A deep understanding with rich knowledge can be attained by studying several important aspects of cell cycle such as, checkpoint pathways, growth of tumors, DNA damage and repair, inter-cellular signaling and other processes involved in cell cycle regulation (Hanahan and Weinberg 2000).

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