BRIEFINGS IN BIOINFORMATICS. VOL 10. NO 4. 424–434
Advance Access publication March 6, 2009
doi:10.1093/bib/bbp005

Computational systems biology of the cell cycle

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Submitted: 2nd December 2008; Received (in revised form): 21st January 2009

Abstract

One of the early success stories of computational systems biology was the work done on cell-cycle regulation. The earliest mathematical descriptions of cell-cycle control evolved into very complex, detailed computational models that describe the regulation of cell division in many different cell types. On the way these models predicted several dynamical properties and unknown components of the system that were later experimentally verified/identified. Still, research on this field is far from over. We need to understand how the core cell-cycle machinery is controlled by internal and external signals, also in yeast cells and in the more complex regulatory networks of higher eukaryotes. Furthermore, there are many computational challenges what we face as new types of data appear thanks to continuing advances in experimental techniques. We have to deal with cell-to-cell variations, revealed by single cell measurements, as well as the tremendous amount of data flowing from high throughput machines. We need new computational concepts and tools to handle these data and develop more detailed, more precise models of cell-cycle regulation in various organisms. Here we review past and present of computational modeling of cell-cycle regulation, and discuss possible future directions of the field.

Keywords: *cell cycle; computational modeling; historical review; perspectives; systems biology*

INTRODUCTION

Computational systems biology is rather a new science [82] although its roots can be found in theoretical and mathematical biology. This can be nicely observed in the field of cell-cycle modeling: from the 1960s we can find mathematical models that try to explain some key aspects of cell-cycle regulation from phenomenological observations [3, 5, 6]. The field really started to explode in the early 1990s [42, 65, 71, 73] when some data on the underlying molecular regulatory network came to light [83]. In recent years, with the birth of systems biology, new experimental techniques have led to an extension of these models, and there now appears to be a bright future for models of cell-cycle regulation.

Several excellent reviews are available on computational modeling techniques [84, 85], on cell-cycle regulation [86–88] and even on cell-cycle modeling [89–93], thus we will not go over the same ground here. Rather we review the key advances that cell-cycle modeling gave us and discuss directions the research might go in the future.

CELL-CYCLE REGULATION IN BRIEF

Cell cycle refers to a sequence of events that leads to correct duplication of cells [86]. During this process a cell must replicate its DNA (in S-phase) and properly distribute the two copies into two daughter nuclei during mitosis (M-phase) before the cell divides. During this time the cell need to double all its other components (proteins, ribosomes, etc.) to keep the size of daughter cells similar to that of the mother. Cells introduce two gap phases (G1 and G2) between S and M-phases to ensure that overall cell mass doubling is coordinated with the DNA replication-division cycle (Figure 1). A complex regulatory network controls the proper order of cell-cycle events. The core controllers of this network in all eukaryotes are complexes of Cdk and cyclin

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molecules. Various Cdk/cyclin pairs regulate the critical transitions of the cell cycle. They initiate DNA replication at the transition from G1 to S-phase, and they play key roles in inducing mitosis as well. In addition, Cdk/cyclin inhibits the last steps of the cycle, the separation of the chromosomes at the end of mitosis and cell division (Figure 1). Key cell-cycle transitions are regulated by checkpoints, which ensure that cells start DNA synthesis only if nutrients and growth factors are present, that mitosis can happen only after DNA replication is properly finished, and that chromosomes can separate only if mitotic spindles are intact (Figure 1). In case there is a problem, the checkpoint signals to the core Cdk/cyclin module and inhibits the further steps of the cycle [94].

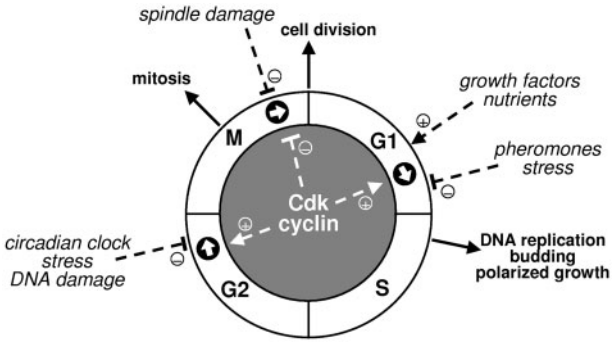

Figure 1: Regulation of the cell cycle. The core cell-cycle machinery is controlled by the activity of Cdk/cyclin complexes, which activate the G1-S and G2-M transitions but inhibit the M-G1 transition (labeled by thick white arrows). These transitions are also controlled by external and internal signals (black, dashed lines). Downstream cell-cycle processes are induced by the core machinery (black, solid arrows).

HISTORY OF CELL-CYCLE MODELING

As mentioned above the story goes back about 50 years, when Prescott found that cells need to reach a critical size to divide [95]. This and other phenomenological observations drove the first wave of mathematical models that tried to understand how cell division is connected to cell growth (Table 1). Once the molecular interactions that control the cell cycle were discovered many groups started to work on mathematical models to figure out the key concepts of these interactions (Table 1). The group of Béla Novák and John J. Tyson stands out from the rest as they produced ~40 papers on cell-cycle regulation, some of which have become benchmarks of computational systems biology. In 1993 they investigated the regulation of mitotic entry in eggs of the frog *Xenopus laevis* and found that a model with two positive feedback loops could provide a reliable switch for entry into mitosis [43]. Their model predicted that the Cdk control system can be bistable: under certain conditions, Cdk may be either active or inactive depending on the recent history of the cell. This bistability and hysteresis was verified experimentally 10 years later [96, 97]. The same group put together the most detailed model (so far) of cell-cycle regulation by describing the Cdk control network in budding yeast *Saccharomyces cerevisiae*. In the first version of the model they proposed that a different hysteretic switch controlled the entry into S phase [21]. This prediction and

Table 1: Computational models of cell-cycle regulation

Modeling methodology		References to models					
		Investigated organisms					
		Prokaryotes	Single cell eukaryotes		Multi-cellular eukaryotes		Generic
		Caulobacter	Budding yeast	Fission yeast	Frog, Sea urchin, Fly	Mammalian	General eukaryote
Phenomenological models							[1–8]
Molecular interaction network models	Logical (Boolean)		[9–13]	[14]		[15]	
	Deterministic (ODE)	[16–18]	[19–29]	[30–37]	[38–46]	[47–62]	[63–75]
	Stochastic (Langevine or SSA)		[76, 77]	[78, 79]		[80]	[81]

Models can be sorted by the organisms they investigate (columns) and by the modeling method they use (rows). See text for description.

others were tested experimentally by Fred Cross's group of in a seminal paper that might be the first case when molecular genetics lab focused solely on verifying a mathematical model of cell-cycle regulation [98]. Later the groups joined forces to create a model that can simulate the behavior of more than 120 mutants [22]. This model also predicted the existence and regulation of a phosphatase that later was identified [99]. Recently other groups have presented their own models of the budding yeast cell cycle, focusing on various aspects of the regulatory system [10, 19, 26, 27].

The other favorite test organism of cell-cycle research is the fission yeast *Schizosaccharomyces pombe*, for which there exist models describing its DNA replication [31, 33], cell division [30] and the behavior of some interesting mutants [36, 79]. Embryonic cell cycles have been modeled not only in frogs but also in the fly, *Drosophila melanogaster* [45], and in the sea urchin [46]. The most challenging task is to model cell-cycle regulation in mammalian cells, where multiple control mechanisms exist that hold cells back from proliferation. The physiological differences among different types of mammalian cells make this task especially difficult. Cancer cell lines are often (possibly always) perturbed in their cell-cycle regulation [100], thus most existing models describe 'generic' proliferating mammalian cells at various levels of detail (Table 1). A few of these models use some data on mouse fibroblasts; still, no model of the cell-cycle network of a specific mammalian cell type has yet been constructed.

Several models exist that do not focus on any specific cell type but rather investigate some important aspects of the regulatory modules of the general Cdk control network (Table 1). These approaches are biologically suitable, since it has been shown that the key cell-cycle controllers and their interactions are universal among eukaryotes [83]. Recent modeling studies on cell-cycle regulation of the prokaryote *Caulobacter crescentus* show that, even though the key controller genes are completely unrelated to their eukaryotic counterparts, the network wiring resembles the eukaryotic system [16, 17]. This conservation of network structure underlines certain key features of cell-cycle regulation. Positive and negative feedback loops have to be wired together for proper cell-cycle regulation. The positive feedbacks are important for robust transitions between cell-cycle phases and they assure that checkpoints can stop progression through the cell cycle, while the negative feedbacks are necessary to reset the system to the beginning and drive the periodic repetition of the process [101]. The significance of positive feedback in robustness of cell-cycle transitions has recently been shown in different organisms [102–104].

Most of the above mentioned models based on molecular networks use systems of ordinary differential equations (ODEs) to describe the dynamics of the system (Table 1). This allows the use of some mathematical analysis tools that can track the steady states and dynamical transitions of cell-cycle control system [20, 38, 58, 64]. As the complexity of the known cell-cycle regulatory network increased in the last few years, logical dynamic modeling [105] and especially Boolean algebra became another fashionable modeling formalism (Table 1). This might be partially influenced by the success of Li *et al*. [9], who showed in a logical model of the budding yeast cell cycle that trajectories from 86% of all possible initial states lead the system into one state representing G1-phase of the cell cycle. Most of these trajectories funneled into a path which steps through the different phases of the cell cycle, showing that the cell cycle is robustly designed.

Although some of these logical models were already using stochastic updating, recently some much more detailed formalisms have started to consider the effects of molecular noise in the cell-cycle regulatory network (Table 1). The two simulation methods that have been used for such models are Langevin-type stochastic ODEs and the exact stochastic simulation algorithm (SSA) [106]. These stochastic models can investigate how individual cells might differ from the average behavior of the population (the output of deterministic ODE models). Stochastic fluctuations could be relevant for certain mutant cell populations that show partial viability [76]. Furthermore, recent advances in experimental observations on single cells allow us to measure the distribution of behaviors in a population of cells, for example, the measurements of the noisiness of the G1/S transition in budding yeast cells provided by Cross's group [107, 108].

EXPERIMENTAL ADVANCES THAT WILL HELP FUTURE MODELING

Single cell measurements and other new technologies enable us to develop much more detailed, quantitative models of cell-cycle regulation.

Mass spectrometry can provide data on protein level fluctuations during the cell cycle [109], identify members of important protein complexes [110], and tell the phosphorylation states of Cdk-regulated proteins [111–113]. Future targeted analysis of key cell-cycle components could provide invaluable data for modelers. Such time-course measurements are already available for mRNA fluctuations during the cell cycle of various organisms [114], but for a detailed qualitative model of cell-cycle regulators we need the time course data of various forms of the proteins as well. We also need to know how cell-cycle regulator molecules interact with each other and how they regulate transcription and translation. Genome-scale protein interaction databases [115, 116], phosphorylation network predictions [117], as well as specific cell-cycle regulatory interaction databases [118, 119] help us address these questions. In the case of budding yeast cells, microarray data on mRNA levels [120, 121] was used to computationally infer the transcriptional regulatory loops of cell-cycle regulation [122–125]. Recently, these methods started to incorporate ChIP-chip [126], mutant and other data types to provide a better prediction of the transcriptional network of cell-cycle regulation in budding yeast [127, 128]. Furthermore, some literature mining tools are available [129, 130] to search for specific experimental results on molecular interactions. All these resources support the development of more detailed, quantitative computational models.

Models have to be tested and fitted to physiological observations as well, not only in the case of wild type cells but in various mutants. Investigations on single or double gene-deletion strains [131–133] and phenotype analysis of protein overexpressing cells [134, 135] provide another kind of constraint for models. The phenotypes of these mutant strains have to be fitted by cell-cycle models. Earlier models were parameterized by fitting similar types of data on cell sizes, cell-cycle phase distributions and viabilities of mutants after painstaking literature mining [21, 22]. The above mentioned large-scale measurements will provide modelers with the data needed to formulate larger, more detailed, more precise models in the future.

COMPUTATIONAL CHALLENGES

Comprehensive databases force modelers to face new challenges. They have to handle somehow this huge amount of data, develop platforms to build large models, and find the suitable methods to analyze them. Conventional, hand-written systems of ODEs have been studied by numerical simulations, sensitivity analysis and bifurcation theory, in order to understand the model's behavior. As our knowledge base is growing, we have reached a point where we need new tools to build large models [136], to code them in a platform-free language [137] and to store them for community use [138, 139]. For example, cell-cycle models now have their own database with links to experimental data [140].

Several modeling platforms have been used in cell-cycle research [141–144]. These usually guide the user from model building to some type of analysis. JigCell has been developed precisely for cell-cycle model simulations and data fitting [144]. It can run multiple parameter sets to simulate various mutants and it includes a comparator that can test how well the simulations fit physiological details of mutants. Although it is difficult to define a suitable objective function for data that is not time dependent, JigCell provides tools for such estimations [145]. Indeed parameter optimization is one of the major challenges for modeling. High-throughput measurements rarely give reliable kinetic rates; most often they should be estimated from concentration profiles by a parameter optimization algorithm [146–150].

Search for missing rate values is just one part of the job that computational tools can do for us. All models we create are some abstractions of the real biological system, thus we know that we are missing some part of the whole network. Experimental data can also be used to infer yet unknown molecular interactions, propose existence of regulating proteins, etc. Some useful tools can handle such network data [151] and also some methods are developed that can help the search for missing interactions and to infer network topology [152–155]. Since high throughput data is available for cell cycle of various organisms now, we can start to think about how to fuse these data to measurements on single gene perturbations to achieve a detailed understanding of the system. The computational identification of cell-cycle-related transcription factors [127, 128] is a promising initial result on these lines.

Another layer of complexity in cell-cycle models is the matter of spatial distribution of regulatory molecules. Many crucial events happen in the

nucleus and many molecules are moved in/out of the nucleus during the cycle. Still only a few cell-cycle models consider compartmentalization of the cell [22, 59]. Even in compartmental models, diffusion and protein gradients are not considered, even though they might have important roles in regulation [156]. Simulation packages are available to deal with spatial distributions of proteins [157], but experimental data on protein localization during the cell cycle is too spotty to give meaningful constraints for such models.

A serious problem of spatial models with many interacting components could be the extensive computational time needed for simulations. Stochastic simulations face similar problems, in large models with many interacting components the calculations could slow down dramatically. In both cases, we need reliable methods for speeding up the simulations. In the case of stochastic simulations, there is a promising idea, based on the total quasi-steady-state assumption of enzyme kinetics [158], for handling the coupled enzymatic reactions that are implied by the positive and negative feedback loops of the cell-cycle network [159, 160]. This and other methods [106] that decouple different time-scales can help us to handle stochastic noise in larger models in the future.

Other advances in the field of model analysis will extend the reach of bifurcation analysis, for tracking qualitative changes in the dynamics of a system on ODEs [64], and sensitivity analysis, for identifying parameter combinations that crucially determine specific aspects of a simulation [161]. Recently biological modeling has been enriched by some new concepts that help to decompose cell-cycle models into sub-networks [162], find the exact timing of cell-cycle transitions [25] and check the irreversibility of these transitions [163]. The last example uses a model-checking approach developed by computer scientists, and it is based on the automated verification of properties of the modeled systems that are encoded using some temporal logic formulae to verify if a system can reach a given state. This approach has opened some new and interesting research lines in biological modeling [164–167].

Some other interesting concepts have invaded biological modeling from computer science. Rule-based modeling [168, 169] and especially various process algebras [170–173] were proposed to circumvent the problem of combinatorial complexity caused by modeling the nested network of multisite modification processes and multi-component complex formations, which are both relevant issues for cell-cycle models [174, 175]. The Beta Workbench modeling environment was developed to handle this type of problem with a biologically friendly computational language based on process algebra [141, 176]. This tool has been thoroughly tested and extended to handle large-scale models of cell-cycle regulation.

OPEN QUESTIONS

Evidently, the core regulatory machinery of the cell cycle is quite well understood, thanks to experimental and theoretical research over the last few decades. The main challenge for the future is to put this core cell-cycle machinery into larger contexts of cell physiology, and to figure out, for example, how a cell copes with problems at checkpoints, how it responds to environmental changes, why some cells leave the cell cycle and commit suicide, etc. As Figure 1 shows the core cell-cycle module is regulated by several incoming signals and it drives several downstream events. The duty of this central controller is to process the information it receives and decide how to handle DNA replication and nuclear division. Current models use some parameters as incoming signals and can tell how this input determines the timing of cell-cycle events. Some models already investigate how the circadian clock interacts with the cell-cycle machinery [80, 177, 178] and how the cell-cycle is regulated in response to checkpoint signals [23, 48, 51, 179]. These models are very detailed either on the cell-cycle machinery or on the signaling network, but comprehensive models that incorporate both control systems in detail do not exist yet.

Several models are available for pathways that signal to the cell-cycle machinery the presence of nutrients, pheromones, stress inducing agents, etc. [180–186]. These could be merged with appropriate cell-cycle models to reveal if our current knowledge of the signaling pathway—cell-cycle network interactions is indeed complete. Similarly, many other biological pathways have been proposed to interact with the cell cycle, such as polarized growth [187], the NF-κB pathway [188], p53 regulation [189]. While computational models also exist for these processes [190–193], they have yet to be connected to cell-cycle models and to each other.

Another perspective is to step up from the single cell level and simulate how cell-to-cell interactions alter cell proliferation at the tissue level. This requires multi-scale parallel handling of the cell-cycle controls within individual cells while simulating their interactions through signaling at the same time. For this problem we need, first of all, reliable cell-cycle models for animal cells, desirably specific models of specific cell types, and in addition we need experimental measurements on the signaling between cells. Such detailed models are far in the future, but we already can learn from some models that take steps in this direction [194–197].

These steps lead us to the major future goal: to understand how perturbations of the human cell-cycle machinery lead to tumor formation. Indeed mathematical modeling of cancer development is another active research field [198–201]. Various ideas exist on how to handle tissue growth computationally [202–204]. Predictive cell-cycle models embedded into complex tissue models can help us in the future to understand the dynamics of cancer formation.

Key Points

- Cell-cycle modeling is one of the early success stories of computational systems biology.
- Systems biology is bringing new types of experimental data to the field.
- We need new computational tools to handle these challenges.
- Cell-cycle modeling will expand, to encompass the pathways that connect to the core machinery, and to investigate the regulation of cell division in tissues and organs.

Acknowledgements

I am thankful to my great tutors, Béla Novák and John J. Tyson for introducing me to this field and for their constant support. I am grateful to colleagues at CoSBi, especially Ivan Mura, Corrado Priami and Sean Sedwards for their useful comments on this manuscript.

FUNDING

Italian Ministry of University and Research, FIRB (RBPR0523C3).

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