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Modeling and Simulation of Cell Biological Systems on Heterogeneous Parallel Computing Platforms: A Review

Aditya Pai H.*, Sreenivasa N. and S. Balaji*****

ABSTRACT

Modeling and simulation are used extensively in science and engineering. This technology has been the powerful tool for the engineers who work on the applications in cell biological systems as well. The primary objective of this paper is to review the research in the area of modeling and simulation of cell biological systems on heterogeneous parallel computing platforms. In particular, this paper reviews the state of the art in the use of modeling and simulation of cell biological systems for (i) creating a model for the communication of molecules and finding its behavior after the antibody facilitated drug delivery, (ii) real time optical data compression with high throughput for biological cell classification, (iii) optical micromanipulation of multiple cell groups, (iv) modeling and simulation of virtual cells, (v) agent based simulation for CASE frameworks, and (vi) membrane computing for a liver cell.

Keywords: Modeling and Simulation, Heterogeneous Parallel Computing, Systems Biology, Cell Biological System.

1. INTRODUCTION

A model basically represents a system under study, object, or may be an idea which might represent other than the entity itself. Simulation actually represents the operation of the model which represents the system as a whole. Hence, a model can be treated as an alternative way to realize the system which might be impractical or too expensive to perform in real to study the system. Modeling and simulation mainly focuses on collecting information about the system under study and building a computational model of that system, which will help in studying the system. Analysis can be done easily once we have built the model and its dependencies across different models without actually building the whole system. A real system can be studied by simulation by taking all the parameters into consideration [1], [2]. In similar lines, computational biology also aims at building algorithms or data structures which help in visualizing and communicating tools to aid modeling and simulation.

2. CELL BIOLOGICAL SYSTEMS

Systems cell biology is the study of the important properties of a cell and its constituent parts by broad and measurable investigation approaches that are inferred by analytical and statistical approaches. Understanding cell biology is fundamentally a multi-scale problem, with many phases and orders of cellular organization. The properties of cells are strength, hysteresis, modularity and heterogeneity. The aim of systems cell biology is, therefore, to realize more than a description of the separate integral properties. It is to accomplish how evidence is transported and inferred by the cell. Systems cell biology is merely gaining of large amount

* Research Scholar- Jain University, Dept. of Computer Science & Engg., K.S. Institute of Technology, Bengaluru–560109, India, *Email: adityapaih2007y@gmail.com*

** Research Scholar – Jain University, Dept. of Computer Science & Engg., Nitte Meenakshi Institute of Technology, P.O. Box6429, Yelahanka, Bengaluru–560064, India, *Email: meetcna@yahoo.co.in*

*** Centre for Incubation, Innovation, Research and Consultancy, Jyothy Institute of Technology, Thataguni, Off. Kanakapura Road, Bengaluru–560082, India, *Email: drsbalaji@gmail.com*

of data or the relationship and imagining of that statistics into systems. Systems cell biology is usually defined as an arrangement for showing qualitative and broad technical investigation. This organization permits a challenging analysis of the complexity of biological systems at all stages of cellular organization. Systems cell biology method often contains numerous common elements such as empirical data acquisition and imagining, data combination and the preparation of computable models, and the analysis of these models along with the hypothesis they produce with further research [1].

3. SIMULATION ON HETEROGENEOUS PLATFORMS

The principal nature of parallel computation is heterogeneity. Parallel computation combines the different processing units that perform processing of multiple instructions at a time using multiple cores of processors and the accelerators like General Purpose Graphics Processing Units (GPGPUs). This particularly exhibits different characteristics like the researches on coarse-grained versus fine-grained providing the variety on the application domains. The progress that has been made in parallel programming for heterogeneous platforms can be appreciated as it uses many core GPU accelerators to improve the performance. While major issues have been resolved, the model still leaves the programmer with the task of writing the accelerator code for various other aspects like segregating, mapping etc. on different processing units.

4. CURRENT STATUS

Modeling and simulation for heterogeneous platforms using multiple GPUs lead to high level computation. In this paper, we discuss mainly on the experiments carried out in domains under antibody-mediated drug delivery systems, real time optical data compression with high throughput for biological cell classification, optically micromanipulation of multiple cell groups, modeling and simulation of virtual cells, agent based simulation for CASE frameworks and membrane computing for a liver cell. The sub section describes the necessity of heterogeneous parallel processing in each domain. The simulation methods being used for the mentioned domains. The review on the domains we discuss explains all the aspects of the simulation being done in heterogeneous parallel processing.

4.1. The Communication of Molecules and Finding Its Behavior after The Antibody Facilitated Drug Delivery

The Antibody-Mediated Drug Delivery Systems (ADDS) is emerging as the promising method for treating cancer patients. The technology makes use of the antibodies which are large in number and is provided to stick to the receptors of the sick cells known as antigens. The Molecular Communication (MC) being the core part of the atom provides support in constructing ADDS. The ADDS uses point-to-point response for infusion of medicine into cells. Breakdown of medicine from the cells is numerically calculated on the basis of the cell geometry that counters these acting agents. The kind of accuracy received from MC depends upon the limited module restorations [3].The MC paradigm [4] is used to carry the data through the particles.

The ADDS contemplates the exclusive properties of the antibodies and the possibility of addressing the drawbacks in the Physiologically-based Pharmacokinetics (PB/PK) models that are being used for molecular communication in ADDS. This method actually has many shortcomings that make it unsuitable for the recently emerging nano medicine [5], [6]. The problem with the pharmacokinetic model which are physiologically monitored is that these ailments are actually meant to direct the ADDS like the tumours which are restricted to that location and also meant to develop very fast. Also, these frameworks do not assist in providing the dimensional accuracy in order to measure the competence in the ADDS [7], [8].

The tools used for modeling and simulation are essential to evaluate different designs for the molecular communication networks [72]. The simulation techniques have been designed and developed to show how there is an interaction between cells in the biological systems. The researchers in molecular communication

primarily focus on the interaction between the biological cells. They also focus on how, by reengineering, they can produce new communication methods for the biological systems. The simulation method in the computer network - NanoNS [68] has been designed to represent molecular communication through diffusion processes. There is another simulation method - N3Sim [69] which is also used for the same purpose as that of NanoNS simulator. A few other simulators for simulation in the nano-scale networks are under development using common set of libraries [70]. Although there are no tools being used for evaluation of molecular communication networks. The main challenge here is to bring many tools into a single package and aid in evaluating various designs for molecular communication networks. The molecular communication is said to be used in the nanomachines. In the nanomachines how the communication takes place between the nano particles are to be seen. Now in that nano particles communication we use the simulation platform that BiNS2 [76]. The BiNS2 is a software platform which uses heterogeneous parallel processing. From communication point of view in the nano networks the drug injection that introduces the antibodies which acts as transmitters, when the same are being transported by the blood flow and diffused through the tissues, it acts as the receivers.

4.2. The Classification of Biological Cell That Features Real-time Compress of The Optical Data

The classification of the biological cells which features real-time compression of the optical data uses the telecommunication devices to produce, collect and then examine the collected data at high computational speeds using GPUs. The method used for capturing the real-time signals is time-stretch dispersed method of the Fourier transform. It lets the capturing of optical spectra in a stretch with millions of frames per second speed leading to the rogue wave detection [10] and collaboration to track the conversion of the signal from analog to digital [11]. A camera is used in the telescope known as STEAM [12-18], [64] that detects the breast cancer cells in the blood with high sensitivity [18-23]. Another technique called FIRE [24] has very high capturing speed with higher magnitude as the present gold standard in higher-speed fluorescence imaging [25]. Even in the most advanced computers, the biggest problem faced is producing real-time data of the order of one Tera bits per second [26-30]. The compression method for faster real-time operation uses a completely different method to get similar functional compressive sensing [31].

The real-time optical data compression requires high performance computing in order to attain the output at real time. To achieve high performance computing at the data rate of 970 Mbps a Panchromatic (PAN) band [73] and Multi-Spectrum (MS) band are used in the Remote Sensing Instrument (RSI) [73]. There are 3 Xilinx Vertex and 5 Field Programmable Gate Arrays (FPGAs) with the external memory which are used to perform optical data compression at real time. To attain high computational performance - parallel and concurrent handling strategies are used in the process.

4.3. The Study of The Micromanipulation of The Multiple Cells Group Done Optically

Micromanipulation connects disease cells and foundational microorganism responses in the middle of cells and drugs by understanding different hetero cell cooperation and by researching multicellular arrangement. This microbiology aspect is concerned with how different microorganisms interact, react and try to be in coexistence with each other. The biological framework comprises primarily cooperating groups of these microorganisms that optically control the most aiding devices [32]. It can also control few of the groups of microorganisms, which is a pivotal step for concentrating how these microorganisms impart themselves and try to coordinate in order perform an extensive variety of multicellular practices. Furthermore, these disintegration of cellular groups into a finer group will provide the adaptability in controlling the roles that each group does and thus increment its cooperation towards the environment.

The capacity to control small scale measured particles and natural cells assumes a key part in material science and organic exploration. Optical Tweezers have increasingly been used as a result of their non-

obtrusive and non-ruinous nature in micromanipulation. This optical catching marvel was invented by Ashkin [33] by watching that a couple of counter engendering laser shafts can build micrometer estimated dielectric elements. It was then displayed that a solitary centred laser pillar can trap the small scale particles and molecules in steady manner [34]. The single-shaft optical trap is competent to trap nanometer to micrometer estimated particles by creating strengths in the scope of pico-Newton to nano-Newton. The Optical Tweezers have been habitually utilized as a part of different fields of bio-photonics research [35]. Single optical catching tool has been used for the single cell studies [36]. In numerous applications, it is essential to have various traps, for example, aberrant cell control [37], different molecule sorting, cell combination, cell to cell collaborations [38], arrangement of microstructures [39], and control and amassing complex microstructures. Different optical traps can be provided either by diffractively partitioning the bar into numerous traps utilized as a part of Holographic Optical Trap (HOT) [40], or by time-sharing a solitary laser bar utilized as a part of filtering mirrors, piezo-stages and acousto-optic redirectors (AODs) [42].

The interest for the quick and exact cell control has prompted the advancement of programmed micromanipulation systems [41], [10]. In [43], [65-66] movement making arrangements for cell transportation have been attempted. The execution of straight and nonlinear controllers are examined in [44]. The capacity of cells to communicate and arrange with one another is fundamental for some natural procedures [63]. In spite of the fact that programmed control issues of multi-robot frameworks have been broadly studied [48, 49, 63], the robotized optical control issues of numerous smaller scale particles or cells are less surely known and few results have been gotten as such. Chapin et al. [50] developed a methodology for consequently controlling and sorting numerous optical traps utilizing holographic optical tweezers. Chen and Sun proposed [51] a control scheme to deal with move miniaturized scale particles into an exhibit. Chen et al. [52] introduced smaller scale particles utilizing optical tweezers. Considering a

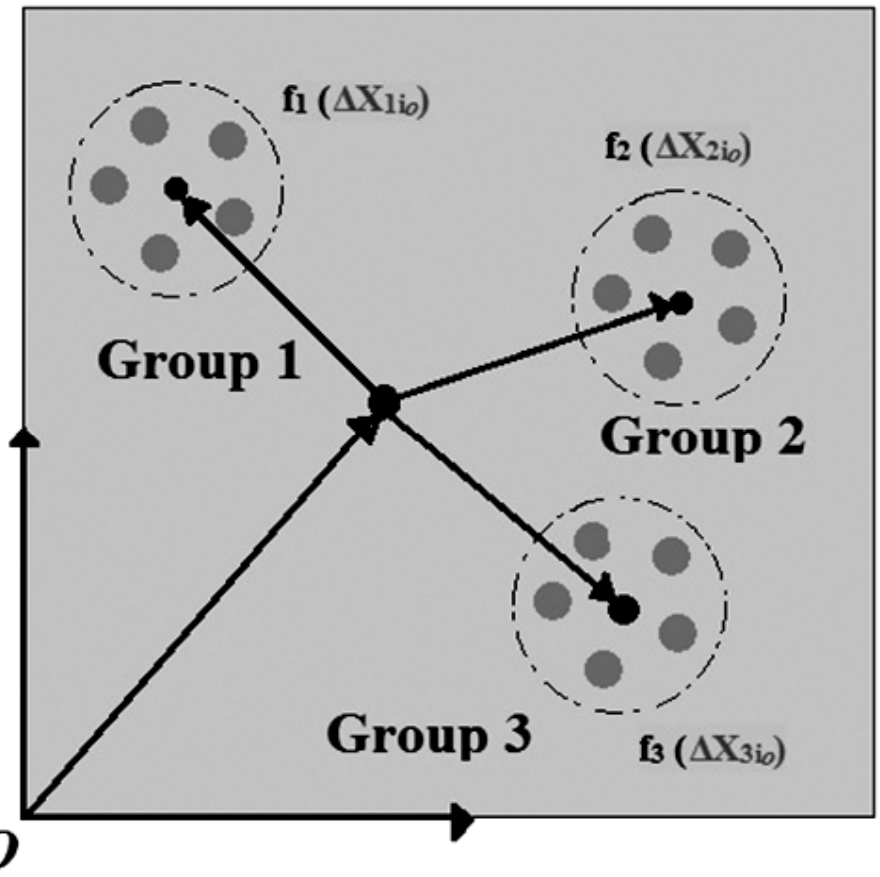

Figure 1: A Multi-Group Cell system

(Source: Reza Haghighi et.al. [32])

group of cells in general amid control restricts the control errands and makes accomplishing the adjustment to the earth extremely troublesome. Decay of a gathering of cells into less gatherings gives ability and adaptability in assignments and surprisingly increments natural customizability. Indeed, the capacity to control a few gatherings of different cells is a fundamental step towards seeing how gatherings of cells convey and work together all in all. Besides, autonomous control of every gathering of cells gives capacity in concentrating on gathering connections between distinctive sorts of living life forms.

The numerous gathering micromanipulation issue utilizes optical tweezers. This is a control system which exhibits an element multi bunch arrangement control to control a few gatherings of smaller scale particles into the sought time-fluctuating developments while keeping away from impact with one another. A thorough strength examination is given and a few tests are directed to represent the pertinence of the proposed system in smaller scale. Figure 1 delineates a multi-bunch cell framework comprising of 3 groups of cells.

The availability of high computational power by way of heterogeneous parallel processors has added advantage to the optical tweezers to do modeling and simulation. In order to achieve the modeling and simulation various techniques such as FDTD – Fine Difference Time Domain [74] are used to demonstrate the movement of the cells that are trapped within the viscous medium.

4.4. The Software Environment for The Modelling and Simulation of A Virtual Cell

The troubles connected with the plan of quantitative scientific models and PC re-enactments of organic procedures have hindered the growth in the new field of computational science [53]. This is backing off the development of framework science in the journey to understand a definitive potential guaranteed by the quickly procured new, vast scale, “omic” information sets [9]. In the PC instruments there has been lot of improvements done and also it makes use of the information in order to assemble the models and implement the rebuilding of the model. The site of the Systems Biology Markup Language (SBML) at present records more than 100 programming bundles backing to some degree the SBML standard. But since scientists infrequently have adequate preparation in the science and material science required to manufacture quantitative models, demonstration has frequently remained the domain of theoreticians who have the proper preparation yet little involvement in the laboratory. This separation from the research centre has restricted the effect of scientific demonstration in cell science.

The Virtual Cell (VCell) undertaking is building up a measured computational system that allows development of models, utilization of numerical solvers to perform recreations and investigation of re-enactment results. To address the issues mentioned above, VCell encompasses the early starting point to the computational demonstration stage that is effortlessly available to cell researcher [10]. This is accomplished by abstracting and robotizing the scientific and physical operations included in building models and producing recreations from them. VCell is accessible by means of the web, permitting clients to team up, offer, and distribute their work, and get to outer assets. Also, the client–server usage permits clients to run vast and complex re-enactments without obliging them to have admittance to their own superior PC equipment and modern numerical instruments and programming libraries. The present components empower clients to make and run recreations of biochemical systems, layer transport and electrophysiology. These can be defined as compartmental customary differential mathematical statement models and numerically understood with a decision of ODE or stochastic solvers.

One unmistakable element of VCell is that it allows the joining of reasonable exploratory geometries inside the full 3D spatial models. In this way, the impacts of dissemination and stream can be unequivocally joined into models, and recreations give answers to the related incomplete differential comparisons. A natural graphical interface incorporates alternatives for database access, geometry definition (counting specifically from magnifying lens pictures), detail of compartment topology, species definition and task, compound response information, film transport components (counting voltage reliance), starting conditions,

limit conditions, re-enactment solver decisions and computational lattice. Apart from this graphical model building interface, VCell also gives a numerical interface that permits theoreticians to inspect and expound models through absolutely scientific plans. It takes into account the immediate passage of scientific comparisons that depict a model, through a definitive dialect (Virtual Cell Mathematics Description Language, VCMDL). The arithmetic is then naturally deciphered into C++ programming code that can then be sent to the numeric solvers. In this way, modellers are mitigated of the drudgery of composing impromptu code for each new displaying assignment. Besides, a VCMDL portrayal of a model can be delivered specifically and consequently from a model that has been made inside of the graphical organic interface. This double interface has the extra advantage of empowering correspondence and coordinated effort between the exploratory and demonstration groups. As a consequence of this methodology, VCell has been quickly received as an instrument of decision for dynamic models, specifically, by test scientists and specialists intrigued by spatially determined re-enactment.

4.5. Utilization of The Case Framework for Modeling and Analysis of The Agent-based Simulations

Agent-based simulations are regularly utilized to analyse Complex Adaptive Systems (CAS) [54], [55]. The CAS [54] [55] are being described by using non-straight elements which is used to administer the rise of complex communications. It is also difficult to uncover the utilizing customary of scientific displaying these strategies, take for an example, the frameworks of differential comparisons. The Agent Based Simulations (ABSs) have gotten a developing enthusiasm to look at an assortment of CAS (e.g., biochemical frameworks, fighting, securities exchanges). To examine CAS using ABSs is very complicated as it requires multiple iterations. In every iteration modeling, simulation analysis are conducted in progressive manner leading to well defined phenomenon.

Data farming [56] is a computational strategy commonly used to direct such iterative studies. In information cultivating tests, a wide range (several thousands) of re-enactment models are consequently assessed. This investigation of recreation models is brought out through the robotized variety of particular model parameters (as indicated by pre-determined extents). The examination of the recreation results gives a review of conceivable results in a given re-enactment model. This empowers one to distinguish the key conditions prompting the rising marvels of hobby. In [57], the creators consider a mechanized and goal based way to deal with data farming where the displaying, execution and investigation of reproductions is consequently directed and headed to show a solitary target wonder (interestingly with the “scene of conceivable outcomes” diagram given by the information cultivating strategy). This target based information cultivating methodology might drastically diminish the processing spending plan prerequisites when one is occupied with a solitary specific framework conduct. The investigation of models is brought out through the utilization of nature-propelled seek calculations. James Decraene et. al. [54] have proposed a transformative structure, authored CASE for “complex versatile framework evolver”, to analyse operators based recreations for a more extensive scope of utilization areas. The idea is to present this adaptable computational strategy which might have advantages in related fields including ABSs (e.g., financial aspects, frameworks science, and counterfeit life).

There are several modeling and infrastructure challenges in the high performance computing environment in order to achieve agent-based simulations. The latter depends on the implementation using hardware and software and execute the simulation in high performance computing environment; the former is mainly related to the interdependence and the interactions of the agents being used. Also, how to develop the models by achieving the corresponding benefits in these environment of parallel processing [75] is another challenge.

4.6. Modeling a Biological Process in Liver Cell

Comparing membrane computation is done with biological framework cell. The cell in the biological system acts as the main regulator and is very complex as well as properly organized where the different processes

occur in parallel and are stochastic at every instances. The cell and the compartments inside of it are encompassed by a layer to delimit each of these compartments from its outer surroundings [58]. In the meantime, the compartment itself gives nearby environment that controls particular hereditary and metabolic procedures. The film of the compartment has the two principle capacities: first is to go about as separator to limit the procedures to happen inside of a compartment; second, it goes about as the channel of correspondence by framing correspondence pathways to connect with one compartment to another by means of complex systems. A large portion of the organic procedures have been displayed by utilizing ODEs as a part of which the centralization of substances fluctuates consistently and deterministically without fusing the structure and attributes of the natural framework. In spite of the fact that ODE permits the procedures to be portrayed in the point of interest, various verifiable supposition fundamental ODEs are no more relevant to the atomic level [59]. Membrane computing [60] is being considered as a distinct option for location of these restrictions by taking into account its crucial elements that are of interest for natural applications. The computational aspects of the membrane is used to find out the new computational models in the biological cell domain study especially in the membranes of the cells. It is an additional task of generating a model of cells. The computation of membranes deals with parallel computing in the distributed environment, where the processing is done on the objects in localized manner.

5. CHALLENGES AND POSSIBLE SOLUTIONS

The theoretical challenges reflect that the computational methods on cell biological systems using modeling and simulation techniques in heterogeneous platforms leads to complexity. If we undertake to build biological systems in a modular fashion, modeling concepts are essential to support modularity, i.e., to combine models out of other models [62]. Thus, there is a requirement to advance standard illustrations for building models from sub-models and spreading such methods to multicellular systems. The problems surrounding standardization is mainly sociological and technical - many of these problems can be resolved. The real question is community acceptance. Many of the problems, for example, have been explained by the group who established CellML (Multi Levels) and the associated MLs. However, the results are very difficult and one surprises if a simpler method is not possible. Also, the question of semantically correct re-use of models still looms large. The re-usage of these models involves proper understanding and also what are evidence that is needed to support reusing of models and also how the same should be presented by developing the mechanisms to collect and record the information by properly understanding how to design the model for reuse.

To decrease a model's unpredictability, the level of point of interest at which subsystems are depicted may be picked in an unexpected way, prompting multi-level demonstration. The part of the model is being represented as deterministic and consistent. Stochastic recreations of natural frameworks are known not computationally serious. Approaches towards tending this issue incorporate parcelling the model and utilizing crossover reproduction systems, presenting enhanced booking calculations, applying parallel and appropriate recreation strategies, or approximating future occasions. Notwithstanding recreation, the investigation of models is likewise essential as it offers us some assistance with exploring the motions that are characteristic in a model and to contrast it and our insight. Nonetheless, a standout amongst the most evident holes in the frameworks tool kit are solid and easy to use. Most noticeable among the examination strategies as of now connected is bifurcation investigation. In any case, investigation procedures in view of check systems are progressively pulling in consideration. The investigations of the certain states are being done using rationale based methodologies.

6. CONCLUSIONS

In this paper, we have briefly reviewed different techniques used in in cell biological systems modeling and simulation. In particular, we reviewed various aspects such as using molecular communication method of

modeling for achieving antibody mediated drug delivery. We also looked upon how high-throughput of the biological cell will classify that features in the real-time compression of the optical data. The next aspect of the study is on how the study of the micromanipulation of the multiple cells group is done optically. The next aspect is the virtual cell modeling and simulation in the software environment. We also looked at automated analysis as well as modeling of agent-based simulations and lastly the comparison of the membrane computing by using ordinary differential equation in order to achieve modeling of a biological processes involved in the liver cell. We have seen that all these simulations mandate huge computing resources both in terms of computing power and memory. The advent of heterogeneous parallel processing that exploit the inherent parallelism of multi-core CPUs and many-core GPUs to scale up the processing power is a promising approach to scale up the processing power. Groups of researchers have initiated work in this direction and some interesting results are being reported. The complexity of programming heterogeneous parallel systems is a big bottleneck which need to be addressed by the multi-disciplinary fraternity of computational and medical scientists and engineers.

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