Replicating the MAP Kinase Cascade in Membrane Computing

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Abstract Membrane Computing (MC) is defined as one of the main areas in computer sciences; MC has the aim of discovering novel computational models from studying biological cells, specifically the cellular membranes. Mitogen-Activated Protein Kinases (MAPK) cascade was the subject of research in the areas of modeling and simulation. Various software tools such as Performance Evaluation Process Algebra (PEPA) have been used to solve the MAPK cascade for the purpose of improving the effectiveness of signaling. In this study, the MAPK cascade is modeled by using MC. The models of Membrane Computing could be totally fully utilized by applying parallel computing platforms. P-Lingua can be defined as a programming language for MeCoSim and MC, where MC simulators are used to model and simulate MAPK. P-Lingua will be applied to structure, develop and examine the implementation of MAPK cascades in membrane computing. MeCoSim supports charts, outputs, and inputs which have been adapted to MC. The simulation results have been put to comparison with PEPA model. The results indicate that MC improves the MAPK implementation compared to PEPA. This study showed that MC, with its biological characteristics, could improve the implementation regarding biological processes including MAPK.

Keyword: MAPK; MAPK cascade; Membrane Computing; P-Lingua

1. Introduction

MC is a science that seeks through the study of biological cells to the discovery of new models in terms of the mathematical model. This will be of interest for further research activities, especially ones that involve mathematical models that represent cellular membranes. These new models deal with distributed computing models and with models of parallel computing in which the processing of many sets of objects in certain ways are implemented. Communications between the environment and the compartments are of high importance in the process. There are variations related to the membrane systems including the P-Systems, Active membranes and cells that deal with membrane systems [1].

In this approach of membrane computing, we propose a model that does MC through the use of P-Lingua as a programming language for the purpose of presenting a MAPK cascade case study. P-Lingua have the ability of determining the features related to MC via equations, in addition to offering the software tools for the tasks related to debugging, simulation and compilation.
MC [1] can be thought of as an alternative for the purpose of addressing the rules related to MAPK cascade from ODE representation in Huang & Ferrell (1996) as well as others via considering its properties which are important to biological applications. MC is considered as a theoretical model which abstract from the functionality and structure related to living cell for creating simulators and methods of the cellular phenomena [2]. Therefore, it produces the official specifications, which are very close to the molecular biology, as well as returning useful information in terms to explain this information easily to biologists [2]. Furthermore, MC have the ability of representing non-deterministic characteristics in addition to the stochastic nature related to dynamic biological system in discrete manner [3].

In the presented paper, we analyze the process of the biological process for an MAPK cascade by using MC, the results will be put to comparison with PEPA method for the purpose of determining the efficiency of MC as modelling tool for biological process. The summary related to the presented study will be presented in the following way: The upcoming sections will present MAPK cascade visualized a 3-layer cascade that is structured in MC through the use of P-Lingua [4], after that it will be compared to PEPA method. The results of MC method for MAPK will be discussed in Section 4. Section 5 will provide summarization of the conclusion of the study. The major goal of the presented study is implementing MAPK cascade in MC for the first time through the use of 1 compartment in discrete system by utilizing P-Lingua. SSA (Stochastic Simulation Algorithm) or Gillespie Algorithm will be utilized in P-Lingua stochastically (direct way), after that MAPK cascade will be simulated in MC simulator (MeCoSim), that is considered as a multi-purpose software tool used to simulate the biological phenomena with regard to P systems.

2. Materials and Methods

2.1 Introduction

There are 3 major steps in the presented model. The initial step is preparing the rules from Prism model, in which the preliminary model has been obtained from ODE. After that, the rule will be converted to one off the rules of P-Lingua by ten general rules, them the steps will be counted for activating KKK (MAPKKK), K (MAPK), and KK (MAPKK). The effectiveness of the model will be determined by the results. The second step will be simulating P-Lingua rules through the use of MeCoSim for the purpose of determining the results with high efficiency. The output stage is considered as the last step. The output for the model will be generated and provided via MeCoSim, after that we will have the ability of comparing the results with PEPA as well as other models for proving the efficiency of MC method.

2.2 MAPK

MAPK cascade is involved in the pathways that send the information from the outside to the inside (nucleus), and they are very important signaling pathways because MAPK overstimulation may cause: breast cancer, pancreatic cancer, human melanoma cells, Rheumatoid and Alzheimer’s disease. Each group of the traditional MAPK consist of a group of 3 sequentially acting and evolutionarily conserved kinases: MAPK, MAPK kinase (MAPKK), in addition to MAPKK kinase (MAPKKK). The cascade will be initialized via the phosphorylation regarding MAPKKK that will activate MAPKK via phosphorylating at 2 residues of serine. This then will activate MAPK through phosphorylating at tyrosine and threonine residues. Initializing the pathway could be a result of a group with a wide variety of stimuli, such as cytokines, neuro-transmitters, and growth factors. Figure1 indicates the pathway structure, as indicated in Huang and Ferrell [7].

The pathway of MAPK is considered to be of high importance since it respond to variety of stimuli: neurotransmitters, growth factors, cytokines, cell adherence and cellular stress, also it is of high importance in various key cellular processes: cellular adaptation to physical and chemical stress, cell survival and differentiation and growth control in all its variations. MAPK deregulated in a lot of diseases: cancer; immunological, inflammatory and degenerative syndromes. Furthermore, MAPK represent a significant drug target.
In 1996, Ferrell and Huang have suggested the first model [7], they indicated the ultra-sensitivity which is related to signaling cascade. In the year 1997, 2 models which indicated 2-collision, distributive method for activating the dual phosphorylation related to the actual MAP have been suggested in quick succession [13]. The pathway has been important, due to the fact that it regulates differentiation, proliferation growth, and apoptosis (i.e. cell-death) regarding the main major cell types [8]. The path-way of MAPK could be modelled for capturing in vivo metabolic complexities which are related to abnormal growth of cells, like cancer [9]. It could act as efficient drug target [9]. Thus, it has been scientifically challenging and significant modeling such path-way and getting improved understanding of all the cellular machineries.

2.3 Replicating of MAPK in Membrane Computing with the use of P-Lingua

P-Lingua can be defined as a programming language that is used for MC; it is planned to turn out to be a standard for P system definitions. In Díaz-Pernil [4], P-Lingua has been provided as framework for defining cell-like P system models, involving various algorithms for simulating P system calculations for the supported approaches, in addition to different formats for representing P system with the related parsers for translating from each other. In Díaz-Pernil [4], the supported P systems models in P-Lingua 2.0 and above have the ability of supporting Stochastic P Systems in many methods, like the direct way used in the presented study.

ODE rules will be converted to discrete system through the use of re-writing rules (“Bezem et al. 2003”) for being modelled in Membrane Computing through the use of the same rules for solving MAPK in Membrane Computing. The processes which will interact between compartments and parameters that are assigned for every one of the processes, system’s structure, and the chemical substances, will be extracted from ODE model. Prior to modelling the system via Membrane Computing, it must be converted in discrete form through considering differential equations, also the next re-writing rules for certain system procedures will be formulated as P-Lingua representation. The computational steps include the application of discrete sets regarding such rules required (typically in Membrane Computing) by maximal parallelism. This multi-set should not be implemented in the case when there is a possibility of carrying out a step which includes strictly larger multi-set of rules, that the reason we have utilized discrete way with a single compartment (a single membrane). A computation can be considered as effective in the case where it begins in initial configuration (defined as the membrane’s discrete objects, and infinite supply of objects in environment) and ends in halting configuration, a configuration in which

![Figure 1. MAPK cascade pathway](image-url)
no rule is valid. The result of effective computation is the number of objects in output membrane. Here, the main steps for execution in P-Lingua:

1. Converting rules.
2. Initialization.
3. Propensity calculation.
4. Reaction time generation.
5. Reaction selection.
6. Reaction execution.
7. Termination.

The first step converts the rules to implement MC, and examples for converting rules are: the processes which interact with objects and parameters specified for each one of the processes, the system’s structure, and chemical substances will be are extracted from ODE model.

Initially, the first rule related to the chemical system is (1). This rule will be converted to Membrane Computing.

\[
\begin{align*}
    \text{KKK} + \text{E1} \rightarrow \text{KKK:E1} & \rightarrow \text{KKK*} + \text{E1} \\
    \text{d1} & \\
    \text{a1} & \\
    \text{k1} \\
\end{align*}
\]

Analyzing the equation indicates the existence of 3 operations in one equation, in addition to the existence of 3 rules in each equation. Prior to modelling the system with Membrane Computing, it must be converted to discrete form. The next re-writing rules for every process involved in the system will be formulated as follows:

\[
\begin{align*}
    \text{KKK} + \text{E1} & \rightarrow \text{KKK: E1} & \text{(a1)} & \text{(1)} \\
    \text{KKK} + \text{E1} & \leftarrow \text{KKK: E1} & \text{(d1)} & \text{(2)} \\
    \text{KKK: E1} & \rightarrow \text{KKK*} + \text{E1} & \text{(k1)} & \text{(3)}
\end{align*}
\]

This representation could be grasped from Membrane Computing and will be converted in order to be utilized in P-Lingua. In the differential eq. (1), E1 has constant rate of 1, KKK has initial amount, parameter a1 has initial amount of 150, and such procedure contribute to the association of MAPKKK via a1. Yet with the same rate in the differential eq. (2), MAPKKK is going be dissociating via d1. Last rule in the differential eq. (3) for product formation for MAPKKK is achieved via k1. The procedure is determined in re-writing rule in the following way:

\[
\begin{align*}
    \text{KKK,E1}^0 & \rightarrow \text{KKK_E1}^0 & \text{:: a1;} \\
    \text{KKK_E1}^0 & \rightarrow \text{KKK,E1}^0 & \text{:: d1;} \\
    \text{KKK_E1}^0 & \rightarrow \text{KKKs, E1}^0 & \text{:: k1};
\end{align*}
\]

This implies that differential eq. (1) will be converted to (3) rules for being represented in P-Lingua. In such manner, all the rules will be converted for using P-Lingua.

In the second step, which is the initialization step, we read the rules and initialize the data structure. Then the propensity calculation is conducted, where the propensity function for each reaction will be calculated. After that, the occurrence time related to next reaction will be estimated via the reaction time generation. Regarding the step of reaction selection, we will be selecting which one of the reactions is going to happen next and execute such reaction in the next step, referred to as the reaction execution: Updating the species variables and the current simulation for reflecting the execution related to the designated reaction. In the case when the simulation time
hasn’t attained the required end time yet, go to stage2.

The aim behind the use of P Lingua as a programming language is defining that the cellular machines is a concept in creating applications for MC which result in standardizing, and has these benefits [4]:

- The users have the ability of defining the cellular machines in modular through the use of simple programming language.
- The modules’ libraries could be specified which will be shared among users for the purpose of facilitating the development of novel programs.
- Such approach of specifying P systems decoupled from their applications, the same P-Lingua programs could be utilized in various software environments.

2.4. MeCoSim

MeCoSim can be defined as a simulator for membrane computing that is utilized in order to prove the ability to simulate the programming that solved the problems and case studies in membrane computing (MC). MeCoSim is designed to help users deal with a simulator that has customized interfaces with charts, outputs, and inputs adapted to every family from MC, and this will help entering data from various families of the membrane to instantiate. MeCoSim is extended to use many algorithms and models in order to prove the ability of this simulator, and it comes with packages that are called MeCoSim plugins. Anyone may contribute to these plugins because they are easy to use this simulator through the configuration file. MeCoSim have the ability of providing platform for integrating various tools for verification, analysis, modelling, property extraction and simulation of P systems.

3. Results

The same concentrate that used before has been utilized again for implementing MAPK cascade on Prism model [6]. MC is used through the implementation of P-Lingua, and comparing the activation for 3 significant objects in the cascade (MAPKKK, MAPK, and MAPKK). After that, such rules will be simulated on MeCoSim simulator. New results will be obtained (as indicated in Fig. 2) for first MAPKKK (referred to as KKK as well), as displayed.

The presented results in Fig. 2 display the amount of projected activation for KKK, which is created after sixty steps, putting N value to start from 100, in which N defines the initial amount related to MAPK/MAPKK and MAPKKK. Through the use of N value (100) (like before), Figure 3 results indicated the amount related to the projected activation for KK created after sixty steps, with same N value indicated for MAPK activation, which gives the results, as indicated in Figure4.

![Figure 2. Activate MAPKKK](image-url)
In the case of comparing the activations regarding MAPKK, MAPK, and MAPKK, the various activations must be grasped in such cascade for MAPK, as displayed in Fig. 5. Their distribution range and concentricity rate will be displayed in Figure 5.

Note: results of the plot figure step have been obtained from the simulation of MeCoSim.

4. Discussion

The main summary related to the pathway of MAPK in PEPA consist of three-tiered cascade created via 3 kinase/phosphatase cycles. The presentation will be assisted through using a language of high-level, and it permits
various different test types to be implemented on the same model (“M. Calder al., 2004”). Reagent-centric method, that allows converting SSAs and ODEs has been utilized for PEPA model (“M. Calder, S. et.al 2004”). PEPA removes the doubt related to the reversibility of any certain reaction due to the fact that each reaction should be defined through the using Prefix of PEPA.

Nonetheless, PEPA model, that utilizes various methods for solving MAPK, still have certain drawbacks. Likely reason why SSA results (Tau-leap simulation) are not identical to the results that have been returned from the original model involve the greater precision of SSA in case when the population size is very small or the existence of error in the model which is utilized for implementing the stochastic simulation.

The modelling abilities related to the membrane systems in terms of certain MAPK cascade were proved. The biological information that is related to certain biological system supports the specification which is related to Membrane Computing model that was verified to have the ability of defining more natural conditions compared to the ones that have been tested in labs via micro-biologists. Membrane Computing method, dissimilar to PEPA approach, retain the features related to discrete systems. Such approach could provide assistance to the biologists to be familiar with formal approaches which were demonstrated in Membrane Computing for the purpose of demonstrating appropriate methods to maintain the behavior and structure related to the biological systems for the purpose of providing more optimum solutions than PEPA model.

5. Conclusions

In the presented study, we prove that the cascade arrangement has unanticipated effects for MAPK signaling, and P-Lingua is used to solve MAPK cascade. MAPK, MAPKKK, and MAPKK concentrations have been defined as a function of time. Although MAPKKK behaved in compliance with the theoretical projections, certain abnormal behavior has been identified in MAPKK and MAPK. Future works could be implemented with the incorporation of Michaeli-Menten kinetics into analysis and modelling regarding the complicated simulations of cascading.

Carrying out the is more possible to offer awareness into the model’s dynamics, or identifying anomalous or interesting behavior. For the purpose of illustrating this, Figure 5 display the results acquired with P-Lingua for MAPK cascade case study.

The features that are taken into account are of expected percentage related to the activated MAPK at time instant \(t\) for PEPA model which belong to ODE, and the presented study was with MC after the simulation on MeCoSim. The likely number regarding the reactions are between MAPK up until time \(t\), and the likely time, until each MAPK is activated, is in the same interval. The biological case study indicated that the biological systems might be modelled through utilizing Membrane Computing such that it maintains the biological behavior and the physical structure.

The presented case study validated the modelling capabilities regarding the membrane systems of certain MAPK cascade. Biological data related to specific biological system supports the description of Membrane Computing that have the capability of defining more natural conditions compared to the ones that have been examined in the labs via micro-biologists. Membrane Computing modeling method preserve the features related to discrete systems which are not present in PEPA method. The method could provide assistance to the biologists to become acquainted with formal approaches that are embodied in Membrane Computing for the purpose of modelling suitable methods which preserve the behavior and structure related to the biological systems which offer more optimum solutions than PEPA model [5].

Thus, this method of modelling the biological system defined via Membrane Computing utilizing P-Lingua could offer rules for computational biologists to benefit from Membrane Computing as formalism for modeling regarding the biological systems.

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