A Multi-Agent System Environment for Modelling Cell and Tissue Biology

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Abstract

Tissue simulation at the cellular level is very important to medical research, especially in understanding tumor cell evolution. Although many approaches have been proposed for tissue simulation, they are overly simplistic or too specialized. In this paper, we formulate the first comprehensive design of a multi-agent system for modelling tissue systems at the cellular level. We present our design concerns and our analyses of system features in detail. We believe our system provides a software model and foundation for the study of tissue biology.

Keywords: mobile multi-agent system, distributed decision-making, cell and tissue biology, systems biology

1 Introduction

Tissue biology is crucial to medical research because it could lead to discoveries of novel medical treatments such as new cancer therapies and drug interventions. Tissues are complex biological systems, consisting of many autonomous components (cells). Its behavior is a combination of the cells' behaviors. The complexity of tissue systems give rise to various research approaches such as PDEs (partial differential equations)[6] [2] [1], CAs (cellular automatas) [5] [8] [3] , and agent-based methods [7]

However, since they are so inherently complex, many of these approaches are overly simplistic and/or overly specialized. In PDEs, the whole tissue is described using a set of partial differential equations which ignore the local processes performed by low-level components. CAs take into account local processes but has limitations with modelling continuous spatial domains and behaviors associated with component movements. Mansury [7] introduced an agent-based method, which overcomes the limitations of CAs. In his method, each tumor cell is regarded as an intelligent entity and changes its place according to nutrient conditions. However, this model only considers the interactions and movements of tumor cells, thus could lead to an erroneous representation of the overall tissue behavior. As such, the ability to implement a realistic tissue simulation is of paramount importance to the field. In this paper, we describe the design of a multi-agent system, which provides a generalized simulation environment for cell and tissue behavior. Our approach simulates the tissue behavior at the cellular level in a continuous spatial domain while modelling decision-making processes and interactions among different types of cells [9].

How to deal with the overall complexity is probably the most difficult part in the simulation. The complexity arises not only from the huge numbers of components and the heterogeneity in different types of local processes (decision-making processes, interactions, etc.), but also arises because the processes are highly cross-linked. So, approaches that simply abstract several 'important' aspects in the biological system fail to provide realistic models. In a complex system, there exists hierarchical self-organizational phenomena which dictate the evolution of the system. The processes of self-organization are directed by the internal system goals (regular system functionalities, homeostasis, etc.) and the external environments (nutrient environment, temperature, etc.). The most significant feature in our approach is the implementation of the self-organization mechanism which helps decompose the system to reduce its complexity. We will discuss the self-organization mechanism in detail in Section 3.

Multi-agent systems [10] [4] have been widely used in simulating complex system such as ecosystems, traffic systems, and human crowds. To the best of our knowledge, this is the first time such a generalized mobile multi-agent system for tissue simulation at the cellular level has been proposed.

The remainder of the paper is organized as follows:

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Section 2 presents the overall structure of the mobile multi-agent system. In Section 3, we describe the main features and implementation mechanism. Finally, Section 4 summarizes the paper and points out the difficulties in developing such a system.

2 System Structure

In our system, a tissue is viewed as an interconnected nonlinear discrete-time dynamic system with multiple decision makers (cells). A cell is a component that is aware of its local environment and global constraints, but does not know or control the inner details of other components. Based on each cell's perceptions, cells make their own decisions to perform specialized functions, aggregate into groups, and respond to their environment. It is very natural to map a cell to a cell-agent and a tissue to a multi-agent system.

The tissue behavior is a combination of interactions among components in the tissue, including cell-cell and cell-ECM (extracellular matrix, the network of proteins surrounding cells, functioning as inert scaffolding for tissue) interactions. In our system, these interactions are formulated via graph representations, which are stored in a global data structure called the environment context (EC). The use of EC allows us to implement a dual perception vs. reality simulation model. Here, the perception is the viewpoint of the system's components (cells) kept in each cell agent. The reality, on the other hand, keeps all status information of the system and is stored in EC.

In the following subsections, we present the details in building such a multi-agent system.

2.1 System Modules

There are 3 main modules in the system: Simulation Builder, Simulation Controller, and User Interface. Figure 1 shows the system architecture:

The function of Simulation Builder is to create the starting point of the simulation. The starting point consists of two parts, a snapshot of system status and entity model. The snapshot includes cell agent objects and an environmental context, generated randomly using a group of given parameters. The entity model is the internal model in cell agents, including three submodels: physical model, defined by finite state machines (FSMs), behavior model, defined by Bayesian Networks (BNs), and interaction model, defined by message-based protocols. A user interface is provided to set up parameters in FSMs, BNs, and protocol scenarios. This makes the cell/tissue model easily configurable and very flexible.

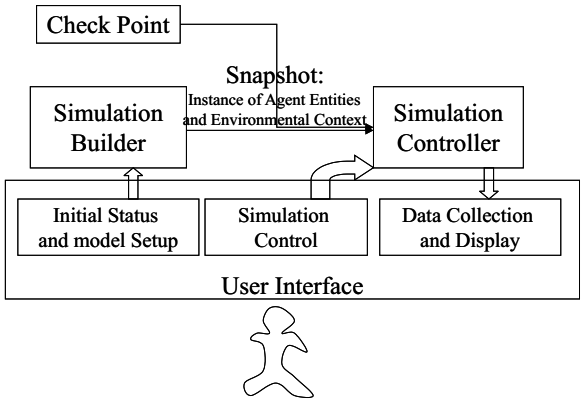

Figure 1: *System Modules*

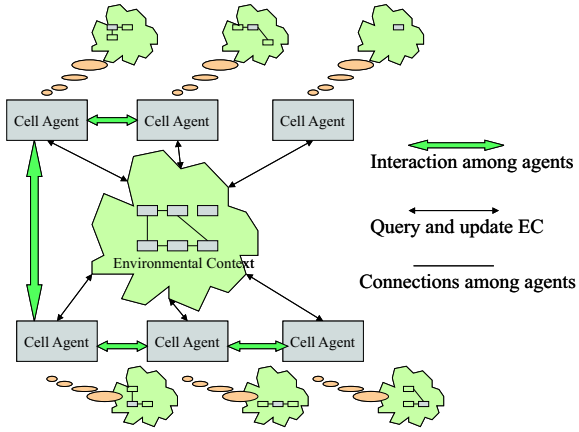

Figure 2: *Runtime Relationship*

The constructed starting points or saved checkpoints are loaded by Simulation Controller, which perform a discrete event-driven simulation.

2.2 Runtime Relationship in Simulation

Simulation controller is in charge of maintaining the runtime environment. Figure 2 shows the runtime relationship among core buildings blocks in our simulation.

From this figure, we can see that each cell gathers its perceptions from the environmental context. As mentioned earlier, perception is the cell agent's view of the environment and its own status. Thus, it is straightforward to model the dualilty of reality vs. perception model under this framework. First, the environmental context is used to keep all information in the system, including topology among cells and ECM, the status of cells, etc. The cell agents query EC to obtain its surrounding environment and make

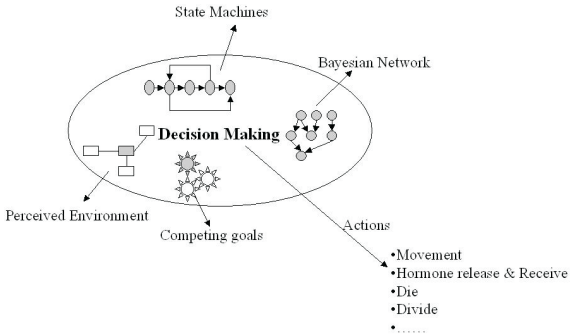

Figure 3: *Cell Model*

decisions based on it.

However, the perception is not necessarily identical to parts of the environmental context because a cell could have a distorted view of reality. For example, a cell might think it has a neighbor while the neighbor is actually non-existent. The mismatch between perception and reality can be imitated through using probability models. These models and the perception information is captured individually in each cell/agent. The decision-making process for a cell is, of course, perception-based, but actions taken by the cell/agent will change the reality, which is stored in the environmental context.

2.3 Building Blocks in Simulation

The basic building blocks in our simulation are: cell agent, tissue agent, and environmental context. A tissue agent is an aggregation of cell agents. We will describe the cell agent and environmental context in the following subsections.

2.3.1 Cell Agent

There exists a large quantity of cell agents in the system. The design of a cell agent model is a core part of the system. Figure 3 shows the mechanisms in a cell agent model.

- Status transition

  The status transitions (like aging process or health status changes) are represented in Finite State Machines (FSMs) embedded in each agent.

- Decision-making process

  The decision-making is affected by several factors, the status of the cell, the environmental context (EC), and goals. In general, there are multiple competing goals for each agent. Although decision-making is an individual behavior of a cell, the goal selection of a cell always belongs to the collective behavior. We will discuss this issue later regarding self-organization.

- Actions

  The actions taken by an agent includes cell movements, death, Mitosis, and chemical exchanges among cells. The chemical exchanges are imitated by message passing among cell agents. In the process of mitosis, a new cell-agent object is created and inserted into EC. When a cell dies, the agent is removed from EC and the object is destroyed. The movements of cell agents also need to update the environment context through the reshaping of the graphs representing topology information.

2.3.2 Environmental Context

Environmental context models the complete state of the cellular and tissue system. It is composed of (1) the set of cells including locations and attributes, (2) ECMs including location and attributes, and (3) submodels – each one representing one interaction backbone for cell-cell or cell-ECM communication.

The design of EC is key to the efficiency of the system. First, there exist lots of different search operations performed on EC because every cell agent needs to query EC to obtain its perception in each simulation cycle. Geometric information can be used to prune the search range in graphs. Second, to run a large-scale simulation, it is necessary to put EC in a parallel computing environment. We should maintain the integrity of EC while make it distributed around multiple machines. The communication for synchronizing the updates of EC could be a bottleneck of the system. So, a well-designed distributed data structure for EC is the key to the scale of simulation.

3 Features in the System

In this section, we analyze several key mechanisms in our multi-agent system to facilitate the specific requirements of decision-making process in a cell-agent.

3.1 Self-Organization

As mentioned above, each cell agent has multiple, competing goals that direct the decision making process. High-level goals can be formed autonomously and posed to individual agents to coordinate the actions among them. For example, when a healthy cell

detects a tumor cell, it would switch its focus to monitoring the existence of the specific type of tumor cell. It might convert its neighboring healthy cells to verify the detection by setting up a high-level goal. This phenomenon is the self-organization in a tissue system. In a word, it is to form a group of cells that share the same goal, called the group goal. This formation is not controlled by high-level components in the system, but initialized by a general cell-agent, which is aware of important issues that should be handled collectively.

To support such a self-organization mechanism, several functions are needed in the cell-agent.

- Goals selection. In cell-agent, goals should be ordered according to their importance. Higher-level goals (group goals) always have higher priorities. A cell could exist in several groups, which give different group goals of various importance.

- Group goal initiation. Each cell agent can initiate a group goal. When a cell detects some important issue that should be handled by the group, it initiates a group goal by sending specific messages to its neighbors. However, the situation should not happen too frequently to avoid over competition. A set of thresholds is needed to adjust the frequency.

- Leader selection. The relationship among agents in a group could be peer-to-peer (P2P). However, P2P relationship requires more communications to coordinate the group goal. A better structure of a group is the master-slave pattern. A leader is selected from members in the group and is in charge of coordinating the actions of other cells. The leader can be selected using different policies such as selecting the initiated or the most stable cell in the group. For example, the stability of a cell can be determined by checking the age and health status of the cell. Also, the cell with highest stability can be found through a tournament approach.

- Limitation on the group size. The group cannot be enlarged infinitely. The stopping condition can be proportional to the strength of the signal from the initiater.

- Group release. A group should be released if the situation returns to normal. This is easy to implement using the master-slave pattern.

The evolution of complex systems is always characterized by self-organization. So, it is crucial to implement a self-organization mechanism in a realistic tissue simulation system. The methods discussed above provide a realistic approximate of self-organization while keeping the cost of communications for initializing and group maintenance at a feasible level. Through self-organization, decision-making processes in our system are organized in three levels: individual, group, and global decision-making.

3.2 Mobility

We have to consider the mobility of agents because the cells do change their relative position in a tissue. From the viewpoint of physical reality, the movement has certain constraints. First, the movement is continuous in space and time. This is different from movement, say, based on a computer network, which can be done in one step from the source to destination. Second, the speed and success of movement is affected by the environment such as the density of cells on the pathway. In general, the movement of an agent does not change its internal state. It only changes an agent's relationship with other agents. The following procedures show the mechanism supported:

- An agent makes the decision to move, which direction they want to go, and how strong their desires are. They then call EC to perform their movement.

- EC receives the requirements from each agent and determines the actual movement. The actions taken by EC include: check if an agent satisfies the conditions for movement, calculate the distance it can move depending on its strength of desire and obstacles in the pathway, and, change the maps in EC. After the movement, the cell-cell and other maps in EC are changed due the change in relative positions among agents.

From the point of view of the agent, the movement is transparent, since EC hides the complexity of operations brought on by the movement. For example, EC is a data structure distributed over different hosts. The movement of cell agents could lead to the agent moving from one host to another. However, the agent exchanges among hosts are only seen by the EC, which is handled through resource management in the system. The cell agent itself only perceives its physical position change. The advantage of this is so that we can focus on the behavior model of cells when we design the agents, and leave the scaling and efficiency problems in the design of EC.

3.3 Signal Fading, Noise and Error

The interactions among cells are simulated using message passing. The messages are send out in point-point or multi-cast pattern. The destinations of messages are selected from the cell-cell or other networks in EC. Here, some important issues cannot be ignored in the message passing: signal fading, noise and error.

- The strength of the message should fade with increasing distance because the density of the real signal (like a hormone) decreases as the distance increases. So, in the format of the message, a field to define the source coordinates of an agent is used in calculating signal strength.
- The decision-making process should capture the presence of signal noise. We can incorporate noise effects by introducing a recognized rate of messages in the perception model. This means that messages are interpreted wrongly at a percentage associated with signal quality, which is a function of the strength of the signal and the several other factors.

4 Conclusions

Every year, cancer kills millions of people in the world and thousands of researchers devote their lives to study how tumor cells develop in tissues to find corresponding therapies. However, without realistic tissue simulations, it is difficult to obtain insights into the processes in such complex systems as tissues. In this paper, we presented a multi-agent framework for building a tissue simulation system. Compared with previous work in this field, our approach captures the phenomena of multi-cell self-organization in tissues. Self-organization reflects the evolutionary patterns in complex systems and help us decompose such a complex system in a hierarchical fashion.

Though the computing power of a single machine has kept increasing, it is still far from the requirements needed for realistic tissue simulation. In our approach, an environmental context that stores all system status information should be kept integrally and be queried frequently. This brings about the difficulty of distributing the simulation system over multiple machines due to the communications overhead in order to maintain the integrity of EC. We have discussed the design of the overall system but have kept the design of EC open. The next step is to expand the EC to a parallel computing environment for larger-scale simulation.

We believe our work will provide a software model and foundation for tumor study. This is an important first step towards novel diagnostic and therapeutic strategies for tumors as well as other medical treatments.

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