DOI: https://doi.org/10.46354/i3m.2019.mas.009

SIMULATION AND ANALYSIS OF A MULTI-SCALE TUMOR MODEL USING AGENT CLUSTERED NETWORK

Ghazal Tashakor [a], Remo Suppi [a]

[a] Universitat Autònoma de Barcelona, Department Computer Architecture & Operating Systems, School of Engineering, Campus Bellaterra,
Cerdanyola del Vallès, Barcelona, 08193, Spain

[a] Ghazal.Tashakor@caos.uab.cat [a] Remo.Suppi@uab.cat

ABSTRACT

The increasing application of network models to translate and analysis of biological systems discusses the necessity of novel methodological and informatics insights for dealing with biological complexity.

Today, using tools from graph theory to simulate the dynamical system and to understand the behavior of a biological network system such as tumor growth is unavoidable.

Perhaps the most significant level of network analysis comes from mining the network measures and configuration data which allow us to explore deeper in multi-scale and multi-level biological models.

This paper presents a graph agent-based tumor model which allows us to mine network measures and visualizing the evolving behavior of tumor in molecular and cellular levels. Besides, in this paper, we have applied three applicable techniques to discover and classify subgraphs in a growing network of agents for the use of a cluster computing system.

Keywords: biological networks, biological informatics, graph, tumor, multi-scale modeling, agent-based modeling (ABM)

1. INTRODUCTION

The study of complex networks involves physics, mathematics, chemistry, biology, social sciences, and information sciences. These networks are commonly represented by directed or undirected graphs which include sets of nodes representing objects such as people or groups of people, cellular and molecular entities, computers or any other thing.

These objects joined together in pairs by edges in the concept of linking and presenting the type of relationship.

The network could be the Internet, the World Wide Web, social networks, information networks, neural networks, metabolic networks, and protein-protein interaction networks (Estrada2006).

However, the representation of complex systems as a network is not enough for the study of a certain problem, because it gives very limited information about the structure of the system in the real world. This limitation guides the study by expanding the network scale and levels to the developing platform for agent-based modeling on networks.

Agent-based modeling of complex network someway drives the emergence of the agent mining field. Agents can support and enhance the knowledge discovery process in many ways.

For instance, agents can contribute to data selection, extraction, pre-processing, and integration, and they are an excellent choice for peer-to-peer parallel, distributed, or multi-source mining. In cases where precise contact network data is unavailable, an alternative is to mine (Cao2009). In this paper, we have proposed and implemented a network simulation system using agent-based modeling and probabilistic finite state machine based on a tumor growth scenario to extract in-depth knowledge.

2. BIOLOGICAL NETWORK COMPLEXITY

Tumor evolution is a complex multi-scale process. The evolution depends on both the molecular growth factors and also on cellular growth factors effective from the cell microenvironment. The molecular growth factors include genetic mutation, gene expression, cell adaptability, robustness but, the cellular growth factors covers from the multiple metabolites and nutrient gradients. On the other hand, tumor cells can mechanically interact with other tumor cells as well as with various other stromal cells, such as fibroblasts, macrophages, and immune cells.

In the beginning, analyzing tumor evolution and metastasis were only taken into consideration at the gene or protein scale, but recently the impact of this evolution at the cellular scale and level also has been considered since the progression of most tumors depends strongly upon the interaction of the cells and the cellular architecture of the host tissue.

Evolution of cell is often modeled using a simulation of the specific cellular process such as cell growth, division, death, or movement. These simulations are determined sequentially by comparing cell status, cell age, nutrients level, the number of cell neighbors, or the

configuration of cell membrane receptors (Rejniak2011).
Another approach involves cell interactions with external factors that are taken a concentration of metabolites or ECM degradation modeled using the neural networks, signaling pathways or protein networks (Rejniak2011).

2.1. Modeling in biological network informatics

Models can be constructed based on existing knowledge of molecular interactions, from the relationship between data profiles, or based on mapping of data onto knowledge-based networks. They have been developed to assist with a variety of decisions (Railsback2019).
Knowledge-based modeling is tackling complex data for studying complex metabolism. The aim is providing support for laboratory test ordering or designing a decision support system for a scientist. The knowledge-based modeling contains the rules and associations of compiled data which mostly is mining from the rules.
Unlike knowledge-based models, non-knowledge-based modeling uses a form of artificial intelligence to allow the computer to learn from past experiences or to recognize patterns in the clinical data. Two types of non-knowledge-based systems are neural networks or genetic algorithms. There is no need for writing rules or configuring expert parametric inputs, but since the system cannot explain the reason it uses the data the way it does, most clinical does not like to use them because of no reliability. This method always relies on existing data, and therefore encounters data security and big data deficiencies will be the consequences.
It is possible to build a Knowledge-based model which will cover multiple scales from the genotype and various biochemical reactions to the details on cell morphology, and the probable behavior pattern of millions of individual cells is interacting with the other cells to form the whole tumor tissue.
Such a model may obtain structural complexity which is comparable with the biological network, but It will be less effective and computational (Railsback2019).
Therefore, it is more desirable to find a way to integrate and bridge independent sub-models rather than build a single mega-model that encompasses all the complexity of tumor development.
This integration may be in terms of separate models that consider distinct parts of the tumor evolving process or the same process but on different scales.
Extracting data from the final discrete model and doing analysis for taking the decision needs studying network informatics modules and algorithms.
Network Informatics is an interdisciplinary science based on informatics, network science, and other related scientific disciplines (Zhang2016).
Network Informatics aims to understand and investigate the structure, properties, and organization of information in the network.
The scope of network informatics covers theories, algorithms, and software of network informatics; mechanisms and rules of flow and organization of information in the network; theory and methodology of dynamics, optimization and control of information networks; network analysis of information networks; factors that affect organization and communication of information, etc. (McGillivray2018).
The integrative network-based analysis aims at identifying coordinated changes in molecular processes. In this sense, network-based analysis of high-throughput data provide the means for generating biologically meaningful hypotheses and for extracting behavior patterns from experiments to unveil the underlying regulatory mechanisms (Railsback2019).

3. AGENT-BASED COMPLEX SYSTEM BIOLOGY

Agent-based models based on complex system biology are dynamic networks of many interacting agents. Since there has not been yet established a general framework for designing, testing, and analyzing bottom-up models of cellular automata or agent-based models, recent advances in modeling have come together in a broad strategy called pattern-oriented modeling.

This strategy provides a unifying framework for discovering the organization of agent-based complex systems and may lead to merging algorithmic theories of the relation between adaptive functioning and behavior in complex systems (Grimm2005).

3.1. Pattern-Oriented Agent-Based Modeling

Pattern-oriented modeling can reduce uncertainty in model parameters in two ways. First, it helps make models structurally realistic, which usually makes them less sensitive to parameter uncertainty (Grimm2005).
Second, the realism of structure and mechanism of pattern-oriented models helps parameters interact in ways similar to interactions of real mechanisms (Grimm2005).
In this case, a technique which is known as “inverse modeling” aids to scale the parameters. The technique is finding values which reproduce multiple patterns simultaneously. In a complex biologic model such as the tumor growth analysis scenario, this inverse modeling can help the scientist to find essential values and profiles.

3.2. Graph-Structure Agent-Based Modeling

Graph algorithms have been used to characterize inter-connectivity and more detailed relationships between nodes. So this method can facilitate the modeling of biological network and its fundamental biological concepts such as cellular pathways and genes expression profiles (Aittokallio2006).
Once a biological network has been represented as a graph, the conventional graph-driven analysis work-flow involves (Aittokallio2006).

- Evaluating the specificity of the model predictions using graph evolving behavior patterns

- The shortest path length of indirectly connected nodes
- Computing the local graph properties such as the number and complexity of clustering subgraphs
- Centrality measures and statistics

Mapping agents to the nodes in the graph-structure model coordinate the assignments of values to their variables in such a way that maximizes their aggregation. Agents work as states, locations or even sometimes as controls of all the variables that map to the nodes.

3.3. Metabolic Network

A reaction in a metabolic network can be described as a weighted directed edge in a directed graph where nodes are the chemicals and edges are the reactions. There is a lack of a well-developed theory for the structural analysis of directed graphs, so two alternative representations of a metabolic reaction are usually utilized (Klamt2009).

One is a bipartite graph, and the other is a substrate graph. The bipartite graph is used when modeling relations divided into two different classes of objects such a parent and child. Substrate graph is more useful to study chemical reactions while two nodes are connected if the corresponding chemical compounds take part in the same reaction. Global characterization of the metabolic network can be carried out by obtaining the mean of the average sub-graph centrality. Small subgraphs capture specific patterns of interconnection characterizing the biological networks at the local level (Pavlopoulos2011). Analyzing local characterization of biological networks improves our understanding of evolving diseases such as metastatic cancer.

4. TUMOR AGENT-BASED MODEL

At the agent-directed modeling and simulation of tumor growth, tumor cells are affected, inflamed and turn quiescent. Based on these critical factors we have simulated the tumor growth behavior and measurements such as the tumor volume, density and also we calculate the number of dead, inflamed and tumor-derived cells. The strategy begins with the initial identification of a minor population of cells with the characteristics of "tumor-initiating cancer cells." They will be assumed inflamed or dead under the influence of angiogenic switch factors. In Figure 1 we have illustrated the different states and their variation in three different colors.

4.1. Graph Agent-Based Modeling using Python

In our first paper (Tashakor2018) we have developed a preliminary tumor agent-based model in a bipartite graph architecture considering that in life science data analysis such as tumor almost everything is about connections and dependencies. We used Mesa (Tashakor2018) framework to develop our python agent-based model. Each agent nested in a single-node and changes in three states under the influence of the neighbor nodes. The process goes on until the tumor agent's volume appears as metastasis. Two agent's connection which has shown by the graph edge changes color after the inflammation.

Following on the development of the model and for studying and analyzing the behavior of the tumor model under different conditions, we needed to explore the relevant data of the model using an extensive range of parametric executions. Our first static preliminary model was a limited scale model. To advance the initial idea, we proposed a computational workflow for simulating a multiscale tumor model. The graph-based methodology nested in agent-based modeling aids us to exploit evolving analysis more accurate and on a larger scale and by generating different patterns.

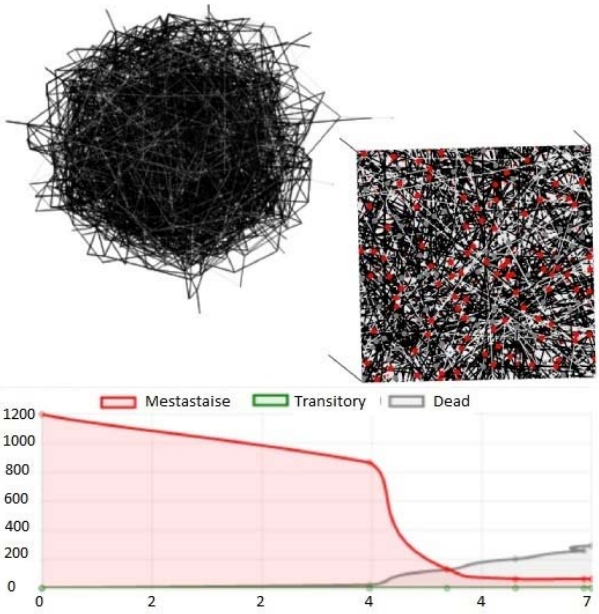

Figure 1: Graph agent-based visualization of tumor growth to 1200 cells

We have deployed two complementary graph-driven methods for analyzing and estimating probable growing network patterns. The selected methods are presented in the context of network analysis in Python using Mesa (Masad2015) and NetworkX (Aric2008) packages. The amount of data which is extracted from the methods address some problems in cell biology.

4.2. Visualization

As you can see in Figure 1, the strength of using Python with packages such as Mesa and NetworkX, first is an interactive data visualization which allows the user such as an oncologist to see the model running in the browser and second is setting up the data, parameters, figures, and plotting interactively while exploring the model data space. Python data visualization provides strong support for integration with several technologies and higher programming productivity across the development life cycle in

comparison to just using agent-based modeling software.

The plot in Figure 1 shows the change scale of inflammatory (red line) because of angioprevention interfere. The grey line in the plot shows the increasing number of dead cells. In Figure 1, besides showing the ratio of the dead cells to the inflamed cells, we have also been able to demonstrate different tumor growth behavior upon the useful laboratory condition from the angiogenic switch. Furthermore, the efficient multi-level visual exploration of multi-scale tumor model for simulating cell life cycle is one of the most influential achievements of the Python method modeling in Mesa framework using NetworkX.

4.3. A Computational Workflow for Tumor Evolving Analysis

Figure 2 shows four steps (a, b, c, and d) for the scenario of simulating tumor growth model and evolving analysis. The first step is simulating an initial tumor by setting up initial input features including normal cells and cancer cells. The second step is nesting the first graph in an agent-based model which feeds from a probabilistic finite state model of angiogenic switch that acquires the acute inflammation.

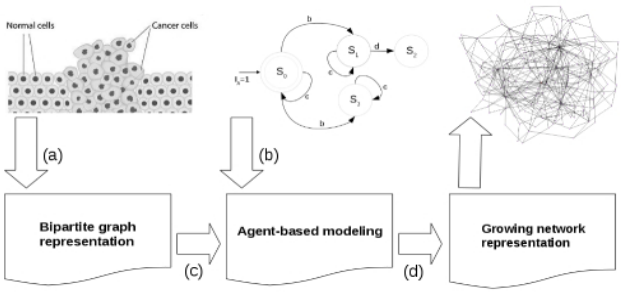

Figure 2: Graph agent-based visualization of tumor growth to 1200 cells

Forwarding the graph agent-based model to the growing module is the final step of the workflow to represent a growing network. The following is the description of each step in the content of reasons and applied techniques of the simulation workflow.

a) Bipartite graph representation: The dynamic bipartite graph is used to simulate disease spread in the behavior stated way except on a very large scale. We have simulated an initial tumor by setting up the graph in two different class of data (Normal Cells, Cancer Cells) to create a bipartite graph model as the static scale of the tumor.

b) Finite state machine: The fundamental biological aspect of the probabilistic finite state model of our tumor growth comes from the acute inflammation based upon the critical factors involved such as an angiogenic switch. Tumor angiogenesis is essential for tumor growth and maintenance. The threshold of angioprevention factor compares with the assessment values of transition probability which is selected by oncologist interactively. The result of the comparison works as a trigger to change the state of the cells from their current state to the proliferation state or the inflammation state. Afterward, under the influence of evolving angiogenic switch values, the inflammation state may turn to the progression state and metastasis happens. Since the stem cell quiescence is a way to control the inflammation in the tumor microenvironment, we have simulated probable immune state at the state model by targeting inflammation using angioprevention and stop cancer cells from moving to the proliferating state. The results in the plot show the reduction of the number of inflamed cells in comparison to the dead cells which is illustrated in Figure 1 for 1200 cells.

c) Agent-based modeling: We have created our new Tumor model in the style and structure of Mesa to facilitate our distributed execution. It is a library for Agent-Based Modeling in Python. The environment of an agent-based model in Mesa is handled by the model class to define the space where the agents evolve. The space range is from a simple square grid to a complex spatial area. The environment represents a scheduler which manages the agents at every time step. For studying the behavior of the system under different conditions, we need to collect the relevant data of the system while it is running which the Data Collector class is defined for this task. Running the model with different string point in Mesa determines in a Batch Runner class. Data collection and batch running are implemented in the appropriately-named analysis modules (Tashakor2018).
Each agent nested in a cell and changes in as many as states it needs under the influence of the neighbor nodes in our tumor growth model. The process goes on until the tumor agent's volume appears as metastasis.

d) Growing network representation: The main available network analysis algorithms are concerned with the network community identification (Hu2018). It means we need to evolve the growing cellular biological network to the molecular level and to develop the model to the other scale like zooming in to get more profound insights.
For moving from the cellular level of the tumor to molecular level, we need to transform our growing bipartite graph to a scale-free molecular format which is a better simulation for cellular interaction and molecular interconnections.

We used a growing network graph with probability (p) of tumor growth using NetworkX for adding a node one at a time with a link to the initial nodes in the premier bipartite graph.

Then by implementing a redirected modeling which is started with 200 initial random parameters and increases to 1200 sets, we reproduced multiple patterns simultaneously.

These multiple patterns keep us from the difficulty of building models that are too complex and uncertain. Also, it helps to reproduce an array of probable patterns without tuning of parameter values taken from the scientist. In Figure 6, we have presented three probable tumor behavior patterns for four redirected growing tumor model.

Practically, passing through the graph-driven analysis work-flow and changing four parameters as features subsets which were particularly uncertain, shows relatively independent effects on different outputs from the patterns. The model could be calibrated manually and also independently for generating big data-set of tumor behavior patterns.

In more deep layers of a growing network module, using network analysis algorithms which are explained in section 5 helps us to extract important microenvironment information from the model.

5. METHODS AND RESULTS OF NETWORK ANALYSIS

Use of a cluster computing system for analyzing and extracting information allows us to scale the very large complex models and also to run many replicates of the large parametric simulation.

To implement a discrete model from a dynamic coherent agent-based model and distribute the subsets among the clusters, we need to discover the complex network community structure of the agent-based model and classifying the total number of agents based on detected scales. The growing agent network model is one of the most complex models for distribution because since the agents behave in a stochastic, nonlinear manner over time, so there is a need to discover a class of the agents based on a kind of similarity such as their scale or states at their community.

In order to achieve the goals described above, practically we selected three main algorithms and techniques in network analysis for discovering, classifying and sub graphing our agent network to distribute the agents. All the techniques implemented in python using NetworkX and other packages.

5.1. Power-Law Distribution for ABM

Discovering a complex network community structure is an important challenge. Many advanced algorithms have been proposed to detect community structures in complex networks, but most have limitations. The limitations include supporting the large-scale network discovery, overlapping communities, large multiple parametric dependencies, specific structures. Therefore still cannot generate stable partitions (Liu2016).

Some methods proposed to detect the community utilizing one kind of network representation like topological measures. For example, spectral clustering (SC) for discovering the community in the graph network can effectively cluster networks, but finding the critical factor to affect the graph clustering in biological networks is very difficult by using this method because the algorithm for this task needs to overcome the problem of data representation of heterogeneous information in multi-scale biological models.

Considering the heterogeneous cell-agent population as a scale-free or very large scale network model in paper (Sugimori2015), they have proposed using Power-Law for growth of a heterogeneous population of the cells.

Power-laws are contrary to traditional Gaussian averages in that they demonstrate correlated phenomena. Examples of power laws are over eighty types of natural and social power-law phenomena in different fields. In biology, tumor growth is one of the examples (Sugimori2015).

Their idea is that a power-law encodes the high frequency of single cell identical profile. With the same hypothesis, we have cut off our graph agent-based tumor model using an algorithm for growing graphs with power-law degree distribution and approximate average clustering to achieve this identical cell profile. The algorithm joined to the growth model with an extra step that each random edge is followed by a chance of making an edge to one of its neighbors too (and thus a triangle).

5.2. Egocentric Network Analysis

Many computational methods have been developed to extract genome profiles or pathway information from biological or clinical networks for identifying subnetworks and hub nodes which have an essential role among other nodes and at the neighborhoods.

For example analysis of protein-protein interaction (PPI) networks helped to understand better the complex biology of specific disease complex system including cancer. Gene expression data have been collected from PPI networks on cancer tumors for developing algorithms. These algorithms functionally express gene profiles into some common modules which could be shared in a subset of the different type of cancers and tumors.

Genes are mapped to the corresponding proteins for representing a network graph of PPI to achieve the best-translated modules.

For modeling a multi-scale tumor network graph, we need to estimate many analysis techniques and modules which could translate the most relevant expression of PPI networks.

Egocentric network analysis techniques and modules frequently use in the social network, but there are some proposed new methods in bioinformatics such as EgoNet in (Yang2014) which present their method based on egocentric network-analysis techniques, to search and prioritize disease subnetworks and gene markers from a large-scale biological network. They have developed an algorithm to identify significant sub networks that are functionally associated with diseases, as well as predict clinical outcomes.

From a new perspective, we also used an ego-network module using NetworkX for subnetworking our graph agent-based tumor growth model.

Figure 3 shows the visual egocentric network format of our tumor growth model which is identifying seven subgraphs in the tumor model. Each subgraph has its different ego node which has its agent's role also. Each ego node works as a hub node among the other nodes in the subgraph.

Since we implemented the egocentric algorithm in our agent-based growing model, each ego node shows a different color based on its agent state. Six red agents are the metastasis, and one purple agent is inflamed but not yet become metastasis. Finding these seven hub nodes was made possible by growing the cells in the power-law distribution algorithm.

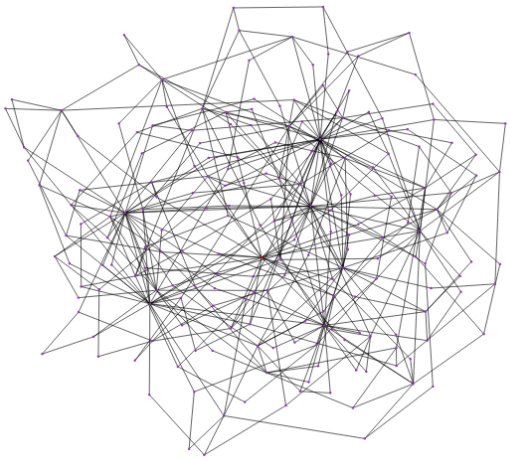

Figure 3: Egocentric visual graph of an agent-based tumor model

5.3. Discovery of Sub-Graph Centrality

One of the most critical tasks in the analysis of protein-protein interaction (PPI) is to predict a group or cluster of transiently interacting proteins that together can accomplish a biological function. These groups can be mapped to specific subgraphs in the network (Shen2012).

Characterizing nodes in a network is according to the number of closed walks starting and ending at the node. Each closed walk is associated with a connected subgraph, and the measure counts the times that a node takes part indifferently connected subgraphs of the network. The node behaves like a hub. They have called this measure the "sub-graph centrality" (SC) for nodes in a network.

Since molecular sub-typing could be done based on gene expression patterns and it helps for tumor-derived cell classification (Goodspeed2016), we used the sub-graph centrality measure as a benchmark for assessing essential genome profile of the tumor-derived cells. Each genome profile in molecular level is related to the transiently interacting proteins and identify as hub genes.

Assessing the essential genome profile of the tumor-derived cells could be an optimal partitioning function for classification of tumor cells at the large multi-scale model clustering and analysis.

Accordingly, an exclusive characteristic distribution for tumor-derived cells is illustrated by the result of the sub-graph centrality measuring in Figure 4.

These measures are labeled as genome profile of tumor- derived cells.

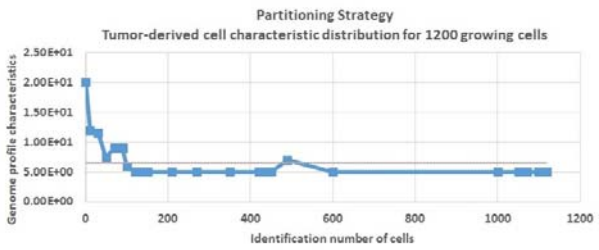

Figure 4: Tumor-derived cell characteristic distribution for 1200 growing cells

In Figure 4, from another point of view, we can see the genomic evolution of the tumor-derived cells which causes biological function such as changing the state of the neighbor cells in the subgraphs. In each run, we mine a dictionary of nodes with sub-graph centrality measures as the values. Sub-graph centrality value of a tumor-derived cell is the sum of weighted closed walks of all lengths starting and ending at the cell.

At the molecular level, tumor-derived cell acts as a hub gene and key pathways among the others so their genome profile could be the critical factor to affect the graph clustering and data classification of heterogeneous information in multi-scale models.

In this experiment, we could identify 30 tumor-derived cells among 1200 cells, but not all of them are a metastasis. With the help of Egocentric networking, we can identify how many of them are a metastasis. Also based on the obtained value of sub-graph centrality, we can estimate the scope of influence of them on the others. We have identified six metastasis cells in the egocentric graph of our model.

Finally, figure 5 shows six prepared clusters from Q1 to Q6 based on the obtained subgraphs in section 5.2. They are considered as the tumor-derived cell clusters, and six metastasis hub genes of 1200 growing cancer cells are considered as hub nodes which create the clusters.

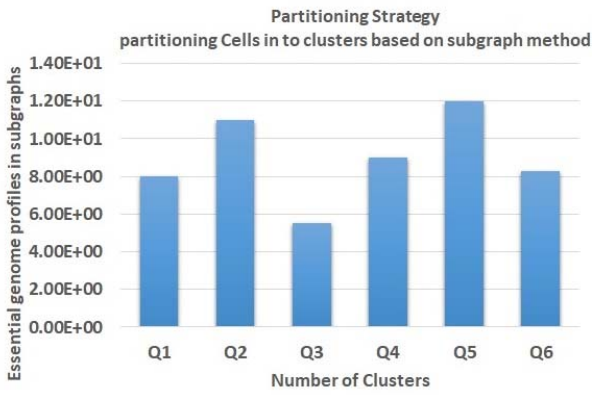

Figure 5: Partitioning Cells into clusters based on sub-graph centrality

Each cluster includes all the neighbors of a determined distance less than the intended radius of the hub node and the connected neighbors who are in the same class of the genomic profile collect in the same cluster.

Tumor cells in cluster number five (Q5) have the most effective behavior and essential genome profile which probably can accomplish an aggressive function among the others or become the genetic reason of the metastasis.

Figure 6 is illustrated the three redirected behavior pattern representations of tumor-derived cells in four different tumor model during parametric executions.

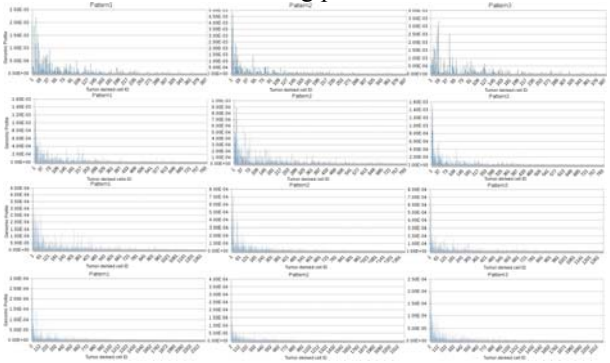

Figure 6: Three probable behavior patterns for four redirected growing tumor model based on tumor-derived cell distribution

This figure shows that each tumor could grow into different pattern based on the probability of tumor-derived cells distribution. Each pattern shows the analyzing of the tumor-derived cells variation by identifying genomic profiles of those cells.

6. CONCLUSION

In this paper, we developed a multiscale graph agent-based model. The model uses for extracting and analyzing cell information from the growing network of a tumor.

The dynamic behavior of tumor-growth seems interesting to oncologists and scientist since they can study the probable predictive power of pathways in the cellular network of the tumor.

Also, it shows that creating a discrete model from a growing multi-scale agent-directed simulation that each agent is in the transition to several possible states and is in communicate with own neighborhood is an important challenge in dynamic modeling and simulation.

This paper presents a graph workflow simulation system for modeling, growing behavior, and sub-graphing analysis which practically allows the scientist to distribute their large scale parametric models distribute on clusters.

ACKNOWLEDGMENTS

This publication is supported under contract TIN2017-84875-P, funded by the Agencia Estatal de Investigación (AEI), Spain and the Fondo Europeo de Desarrollo Regional (FEDER) UE and partially funded by a research collaboration agreement with the Fundacion Escuelas Universitarias Gimbernat (EUG).

REFERENCES

Estrada E, Rodríguez-Velázquez JA. Subgraph centrality and clustering in complex hyper-networks. Physica A: Statistical Mechanics and its Applications. 2006 May 15;364:581-94.

Rejniak KA, Anderson AR. Hybrid models of tumor growth. Wiley Interdisciplinary Reviews: Systems Biology and Medicine. 2011 Jan;3(1):115-25.

Railsback SF, Grimm V. Agent-based and individual-based modeling: a practical introduction. Princeton university press; 2019 Mar 26.

McGillivray P, Clarke D, Meyerson W, Zhang J, Lee D, Gu M, Kumar S, Zhou H, Gerstein M. Network analysis as a grand unifier in biomedical data science. Annual Review of Biomedical Data Science. 2018 Jul 20;1:153-80.

Aittokallio T, Schwikowski B. Graph-based methods for analysing networks in cell biology. Briefings in bioinformatics. 2006 Sep 1;7(3):243-55. [Digests 9th Annual Conf. Magnetics Japan, p. 301, 1982

Grimm V, Revilla E, Berger U, Jeltsch F, Mooij WM, Railsback SF, Thulke HH, Weiner J, Wiegand T, DeAngelis DL. Pattern-oriented modeling of agent-based complex systems: lessons from ecology. science. 2005 Nov 11;310(5750):987-91.

Tashakor G, Luque E, Suppi R. High Performance Computing for tumor Propagation Agent-based Model. In: XXIII Congreso Argentino de Ciencias de la Computación (La Plata, 2017)

Tashakor G, SuppiR. : Agent-based model for tumor-analysis using Python+Mesa. In: European Modeling and Simulation Symposium, pp. 248-253, EMSS (2018)

Masad D, Kazil J. MESA : an agent-based modeling framework. In: Proceedings of the 14th Python in Science Conference, pp. 53-60, SCIPY(2015)

Aric A. Hagberg, Daniel A. Schult and Pieter J. Swart.: Exploring network structure, dynamics, and function using NetworkX, In: Proceedings of the 7th Python in Science Conference, pp. 11–15. SciPy (2008)

Yang R, Bai Y, Qin Z, Yu T. EgoNet: identification of human disease ego-network modules. BMC genomics. 2014 Dec;15(1):314.
Hu P, Niu Z, He T, Chan KC. Learning Deep Representations in Large Integrated Network for Graph Clustering. In2018 IEEE First International Conference on Artificial Intelligence and Knowledge Engineering (AIKE) 2018 Sep 26 (pp. 101-105). IEEE.
Shen R, Goonesekere NC, Guda C. Mining functional subgraphs from cancer protein-protein interaction networks. BMC systems biology. 2012 Dec;6(3):S2.
Goodspeed A, Heiser LM, Gray JW, Costello JC. Tumor-derived cell lines as molecular models of cancer pharmacogenomics. Molecular Cancer Research. 2016 Jan 1;14(1):3-13.
Cao L, Gorodetsky V, Mitkas PA. Agent mining: The synergy of agents and data mining. IEEE Intelligent Systems. 2009 May;24(3):64-72.
Sugimori M, Hayakawa Y, Boman BM, Fields JZ, Awaji M, Kozano H, Tamura R, Yamamoto S, Ogata T, Yamada M, Endo S. Discovery of power-law growth in the self-renewal of heterogeneous glioma stem cell populations. PloS one. 2015 Aug 18;10(8):e0135760.
Liu W, Pellegrini M, Wang X. Detecting communities based on network topology. Scientific reports. 2014 Jul 18;4:5739. Zhang W. Network informatics: A new science. Selforganizology. 2016;3(2):43-50.
Klamt S, Haus UU, Theis F. Hypergraphs and cellular networks. PLoS computational biology. 2009 May 29;5(5):e1000385.
Pavlopoulos GA, Secrier M, Moschopoulos CN, Soldatos TG, Kossida S, Aerts J, Schneider R, Bagos PG. Using graph theory to analyze biological networks. BioData mining. 2011 Dec;4(1):10.

AUTHORS BIOGRAPHY

GHAZAL TASHAKOR is Research Fellow and Ph.D. Candidate for trainee research staff position (PIF) at the Computer Architecture & Operating Systems Department (CAOS) of the University Autònoma de Barcelona. Her research interests include high performance simulation, agent-based modeling, and their applications, service systems, integration, resource consumption, and execution time. Her e-mail address is ghazal.tashakor@caos.uab.cat

REMO SUPPI received his diploma in Electronic Engineering from the Universidad Nacional de La Plata (Argentina), and the Ph.D. degree in Computer Science from the Universitat Autonoma de Barcelona (UAB) in 1996. At UAB, he spent more than 20 years researching on topics including computer simulation, distributed systems, high performance and distributed simulation applied to ABM or individual-oriented models. He has published several scientific papers on the topics above and has been the associate professor at UAB since 1997, also a member of the High- Performance Computing for Efficient Applications and Simulation Research Group (HPC4EAS) at UAB. His email address is remo.suppi@uab.cat.