



“Review and Analysis of Agent-based Models in Biology”

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1. Introduction

Agent-Based Modeling

Agent-Based Modeling [ABM] constitutes a relatively new computational modeling paradigm, originally derived from the Computer Science and refers to the modeling of various phenomena as dynamical systems of interacting software agents. ABM is also known with the terms ABS [Agent-Based Simulation] and IBM [Individual-Based Modeling].

The term “agent” is used to indicate a “conscious” software entity with potential learning capabilities, which is characterised by some degree of autonomy and asynchrony with regards to its interactions with other agents and its environment. Namely, an agent must be identifiable and this means that it has to be distinguishable from its environment by some kind of spatial, temporal, or functional attribute. Furthermore, autonomy also applies to an agent’s actions and behaviour, enabling it this way to engage in tasks in an environment without direct external control. Regarding asynchrony, in ABM agents’ actions follow discrete-event cues or a sequential schedule of interactions and are not simultaneously performed at constant time-steps. This allows for the cohabitation of agents with different environmental experiences.

A quite interesting observation on agent-based simulation, is that by using simple agents, who interact locally with simple rules of behaviour and actions limited to merely responding befittingly to environmental cues without necessarily striving for an overall goal, we have as result a synergy which leads to a higher-level whole with much more intricate behaviour than those of each component agent. Agents, though, as discrete, diverse and heterogeneous entities, besides having their own goals and behaviour, they share the ability to adapt and modify their behaviour to their environment, placing this way their autonomy characteristic in a more sophisticated level.

Agent-based simulation technology comes to serve various sciences, mostly applied but in general sciences with an outcome of data, experimental or not, the amount and complexity of which hampers the drawing of conclusions and making assumptions, from a computational aspect. Computational methods in science can be proved quite advantageous when the problem in question is not easily analysable, or when the necessity of a different-method approach is needed for a not as reliable approximate theoretical result, occurs, or when an experiment is expensive or not feasible to perform [eg. an *in vivo* protein mutation experiment], or finally when the amount of data produced in the lab exceeds the human resources and capabilities for analysis in a reasonable frame of time and cost. The often huge amounts of experimental data produced in progressing sciences, such as Biology, in combination with the complexity implied, prove such computational methods as agent-based modelling, a handy tool in the hands of the scientist-analyst.

ABM in Biology

The increasing demand for large-scale analysis tools in assistance to the biologist, created the need for searching for a solution in the field of the Computer Science and the new ICT tools designed and implemented to distribute, at least to some extent, the computational burden implied. This lead, almost ineluctably, to the emerging of two disciplines, Bioinformatics and Computational Biology, that aim in the usage of technology to serve the drawing of conclusions and answering complex biological questions by more easily and effectively organising, analysing and distributing

bioinformation. In this case, multi-agent systems can be used for either simulating and modelling biological problems or assisting in the automation of the information-collecting and illation processes.

The usage of agent technology and methods in bioinformatics suggests the implementation of agents that are, within a biological domain, domain-aware and aim to collect and manage information that will assist them in solving the biological problem at hand. Processes that imply resources-consuming activities characterised by repetition, modelling and simulating of complex non-static systems and knowledge management, are best served by agents. Information management, for example, can be quite an important factor in bioinformatics, especially in case someone considers the problematic issue of semantically discovering, retrieving and managing huge amounts of data and services from this deluge of information existing in numerous databases in geographically distinct locations and under independent administrations. In computational biology, though, the usage of agents is related to designing agent-based languages, tools and models with aim to model the biological processes themselves.

Agents and Grid computing [see Luck et al., 2005] are already being used in bioinformatics and computational biology, forming an efficacious combination, to support biologists in searching for meaningful information in highly heterogeneous, semi- or non-structured most of times, and distributed resources and performing effectual analyses. Examples of agent-based modelling in Biology can be encountered in many sub-disciplines. In this review the focus is on biomedicine, diseases and gene mutations developed models.

For this report, a total of 17 articles, chosen on the basis of ABMs developed with relation to the field of Biomedicine and Human Biology, were examined. Of these 17, a final selection of six papers to be reviewed and analysed was made, covering various biomedical issues, approached by different perspectives with regards to Computer Science and serving different, practical or theoretical purposes. The criteria, based on which the assessment of the chosen models was made, are described and explained on the following section.

2. Assessment Criteria

In the following table, a presentation of the criteria used for the assessment of the models discussed in this report, is made. A description for each criteria is provided, for better understanding of the purpose they serve and the reason of their usage.

Criteria	Description
<ul style="list-style-type: none"> ▪ How much detail they give for the model? 	<p>This is to examine, how much detail is provided for the model itself and whether this information is adequate for the scientist-reader as to reproduce the model from the beginning.</p>
<ul style="list-style-type: none"> ▪ Is the problem practical or theoretical? 	<p>This is to answer the question whether the model was developed to be used in real [lab] environment or as an attempt to understand and use this new technology.</p>
<ul style="list-style-type: none"> ▪ What scale? <ul style="list-style-type: none"> ✓ Level 1: Molecule ✓ Level 2: Cell ✓ Level 3: Tissue ✓ Level 4: Organ ✓ Level 5: Body ✓ Level 6: Human ecosystem 	<p>This is, to practically identify with which biological level of organization, the agents implementation corresponds, namely which organizational role the agents play.</p>
<ul style="list-style-type: none"> ▪ Maturity: Is it built/implemented or just planned/designed? 	<p>This is to examine the maturity of the model designed, namely if it is implemented or not, if it is an abstract ABM or a real software tool that can be used to produce results.</p>
<ul style="list-style-type: none"> ▪ If built, is it free to public access? 	<p>In case it is not only designed but also implemented, is it free for anyone interested in using it to do so?</p>
<ul style="list-style-type: none"> ▪ More focus on Computer Science, Biology or Mathematics? 	<p>This criteria, is set to answer the question of the intentions of the makers. This is to say whether they designed the model in question with a intention to contribute to Biology, Computer Science or Mathematical Modeling.</p>
<ul style="list-style-type: none"> ▪ Is the model static or dynamic? 	<p>This is to examine whether, from a programmer's point of view, the agents of the model in question are evolving, whether they gain experience from their interaction with their environment and have a non-deterministic, stochastic behaviour.</p>
<ul style="list-style-type: none"> ▪ Did they use any standard packages for its implementation? 	<p>In case the model was actually implemented and not only designed, did the developers use any off-the-shelf packages e.g. SWARM, NetLogo, Repast?</p>
<ul style="list-style-type: none"> ▪ What language was used? What software? 	<p>What kind of programming software was used for the model's development?</p>
<ul style="list-style-type: none"> ▪ Is it used in real environment? Is it under use? 	<p>This is to examine, whether the model designed and probably implemented, was/is actually used under real environment, for the scientific purposes it was designed for.</p>
<ul style="list-style-type: none"> ▪ Why agent-based model? <ul style="list-style-type: none"> ✓ To understand the real world? ✓ To intervene to the real world? 	<p>Was this model designed with the intention to understand the real world, or to intervene to it [e.g. deciding when should some action be taken to avoid a potential spread of a disease in the real population]?</p>

3. Assessment of Models

Model 1

“An agent based model for real-time signaling induced in osteocytic networks by mechanical stimuli.”

Brandon J. Ausk, Ted S. Gross, Sundar Srinivasan

The agent-based model that was investigated in the paper was designed and implemented with the focus on understanding real-time signaling induced in mechanically stimulated osteocytic networks. The authors’ inspiration behind creating this model was to focus on Biology, and more specifically on how bone responds to physical stimuli, answering questions about the mechanotransductive properties of bone. Incorporated with a data mining approach for identification of first-order interactions between cellular functions, this model enabled simulation of “unique real-time osteocyte network responses to distinct mechanical stimuli” and besides any idealization, the conclusion that rest-inserted stimuli enhance real-time signaling by taking advantage of properties inherent to the communication among cells within the osteocyte network, was drawn.

Criteria	Model 1
▪ How much detail they give for the model?	Sufficiently detailed, mostly mathematical
▪ Is the problem practical or theoretical?	Practical
▪ What scale? ✓ Level 1: Molecule ✓ Level 2: Cell ✓ Level 3: Tissue ✓ Level 4: Organ ✓ Level 5: Body ✓ Level 6: Human ecosystem	Cell
▪ Maturity: Is it built/implemented or just planned/designed?	Implemented
▪ If built, is it free to public access?	No
▪ More focus on Computer Science, Biology or Mathematics?	Biology
▪ Is the model static or dynamic?	Static
▪ Did they use any standard packages for its implementation?	Yes
▪ What language was used? What software?	Netlogo 2.1
▪ Is it used in real environment? Is it under use?	Yes
▪ Why agent-based model? ✓ To understand the real world? ✓ To intervene to the real world?	To understand

Model 2

“The epitheliome: agent-based modeling of the social behaviour of cells.”

D.C. Walker, J. Southgate, G. Hill, M. Holcombe, D.R. Hose,
S.M. Wood, S. MacNeil, R.H. Smallwood

This paper refers to the design and implementation of an ABM for predicting the social behavior of cells in the epithelial tissue, which is part of the broader Epitheliome Project. With a dual motivation behind its development, namely to demonstrate how this computational paradigm can be applied to Biology and to actually understand important clinical problems using ABM technology, the prototype model was developed in Matlab and was later transferred into a C-based X-machines framework called Flame. The results of this static rule-based model, where cells are considered as autonomous agents executing a set of rules depending to their immediate environment, their position in the cell cycle or the differentiation state, in comparison with the in vitro systems examined, suggest that even a model based on simple rules like this can successfully reproduce the behaviour of a real biological system.

Criteria	Model 2
▪ How much detail they give for the model?	Sufficiently detailed
▪ Is the problem practical or theoretical?	Practical
▪ What scale? ✓ Level 1: Molecule ✓ Level 2: Cell ✓ Level 3: Tissue ✓ Level 4: Organ ✓ Level 5: Body ✓ Level 6: Human ecosystem	Cell
▪ Maturity: Is it built/implemented or just planned/designed?	Implemented
▪ If built, is it free to public access?	Yes [http://www.flame.ac.uk/drupal/] [http://www.epitheliome.com/]
▪ More focus on Computer Science, Biology or Mathematics?	Computer Science - Biology
▪ Is the model static or dynamic?	Static
▪ Did they use any standard packages for its implementation?	No
▪ What language was used? What software?	Prototype: Mathworks Matlab v3.5 & v6 Current : Flame [C-based X-machines]
▪ Is it used in real environment? Is it under use?	Yes
▪ Why agent-based model? ✓ To understand the real world? ✓ To intervene to the real world?	To understand

Model 3

“Emerging patterns in tumor systems: simulating the dynamics of multicellular clusters with an agent-based spatial agglomeration model.”

Yuri Mansury, Mark Kimura, Jose Lobo, Thomas S. Deisboeck

Aim of this paper is to present a novel ABM of spatio-temporal search and agglomeration, designed to investigate the dynamics of cell motility and aggregation, assuming that tumors behave as “complex dynamic self-organising biosystems”. Rather than simulating cells to obey fixed instructions imposed upon them externally, a new, entirely different, approach is attempted, by introducing non-deterministic stochastic elements in the behaviour of tumor cells and allowing for sequential observation of the spatio-temporal progression of brain tumors in a space- and time-discrete model. With an aim to understand the dynamical relationship between the “main tumor and its satellites” as well as the tumor system itself, the dynamic ABM in question, proving the authors’ hypothesis, showed that the spatio-temporal dynamics of the evolving tumor system is distinctly influenced by the cluster patterns.

Criteria	Model 3
▪ How much detail they give for the model?	Highly detailed
▪ Is the problem practical or theoretical?	Practical
▪ What scale? ✓ Level 1: Molecule ✓ Level 2: Cell ✓ Level 3: Tissue ✓ Level 4: Organ ✓ Level 5: Body ✓ Level 6: Human ecosystem	Cell
▪ Maturity: Is it built/implemented or just planned/designed?	Implemented
▪ If built, is it free to public access?	No
▪ More focus on Computer Science, Biology or Mathematics?	Biology
▪ Is the model static or dynamic?	Dynamic
▪ Did they use any standard packages for its implementation?	Yes
▪ What language was used? What software?	Microsoft Visual C++ v5.0 Repast
▪ Is it used in real environment? Is it under use?	No
▪ Why agent-based model? ✓ To understand the real world? ✓ To intervene to the real world?	To understand

Model 4

“Multidisciplinary investigation into adult stem cell behaviour.”

Mark d’ Inverno, Jane Prophet

Subject of this paper is the multi-disciplinary project CELL, investigating new theories and approaches of stem cell organization in the adult human body. Main goal of this multi-disciplinary group was to design and develop a software tool, using Z Notation, which would be of use to medical researchers for testing and running new hypotheses about the nature of stem cells. Using an agent-based approach they produced a formal model of stem cells, which’s main characteristic, among others, is that of allowing for a non-deterministic stochastic behaviour of the agents in a dynamic environment, where the effects of actions are not guaranteed. As the agent-based approach to modeling stem cells makes the prediction of the behaviour of the overall system using formal techniques impossible, a cellular automata approach was attempted to serve for formal proof. Great emphasis was given to the model being general as this would allow for “alternative theories and models to be formalized, compared, evaluated and subsequently simulated”.

Criteria	Model 4
▪ How much detail they give for the model?	Basically detailed, general approach
▪ Is the problem practical or theoretical?	Practical
▪ What scale? <ul style="list-style-type: none"> ✓ Level 1: Molecule ✓ Level 2: Cell ✓ Level 3: Tissue ✓ Level 4: Organ ✓ Level 5: Body ✓ Level 6: Human ecosystem 	Cell
▪ Maturity: Is it built/implemented or just planned/designed?	Implemented
▪ If built, is it free to public access?	N/A
▪ More focus on Computer Science, Biology or Mathematics?	Computer Science
▪ Is the model static or dynamic?	Dynamic
▪ Did they use any standard packages for its implementation?	No
▪ What language was used? What software?	Z Notation
▪ Is it used in real environment? Is it under use?	Yes
▪ Why agent-based model? <ul style="list-style-type: none"> ✓ To understand the real world? ✓ To intervene to the real world? 	To understand

Model 5

“*In silico* experiments of existing and hypothetical cytokine-directed clinical trials using agent-based modeling.”

Gary An, MD

An abstract ABM of the Innate Immune Response [IRR] comprises the subject of this paper. The ABM presented, is intended mostly as an introduction and demonstration of this new technique of simulating *in silico* experiments. It mainly focuses on the reproduction of the general behaviour of the IRR with regards to “outcome and cause of system “death””. This abstract model was implemented using StarlogoT, and on the basis formed by experimentally identified cellular and molecular mechanisms, to respond to those insults that simulate infectious and non-infectious tissue injuries.

Criteria	Model 5
▪ How much detail they give for the model?	Sufficiently detailed
▪ Is the problem practical or theoretical?	Theoretical [abstract ABM]
▪ What scale? ✓ Level 1: Molecule ✓ Level 2: Cell ✓ Level 3: Tissue ✓ Level 4: Organ ✓ Level 5: Body ✓ Level 6: Human ecosystem	Cell
▪ Maturity: Is it built/implemented or just planned/designed?	Implemented [abstract]
▪ If built, is it free to public access?	Yes [http://ccl.sesp.northwestern.edu/cm/models/community/]
▪ More focus on Computer Science, Biology or Mathematics?	Computer Science
▪ Is the model static or dynamic?	Static
▪ Did they use any standard packages for its implementation?	No
▪ What language was used? What software?	StarlogoT
▪ Is it used in real environment? Is it under use?	Yes
▪ Why agent-based model? ✓ To understand the real world? ✓ To intervene to the real world?	To understand

Model 6

“Modeling the effect of exogenous calcium on keratinocyte and HaCat cell proliferation and differentiation using agent-based computational paradigm.”

Dawn Walker, Tao Sun, Sheila MacNeil, Rod Smallwood

The primary aim of the work presented in this paper, was the further development and improvement of an existing cell-based computational model of the growth characteristics of urothelial cells in monolayer culture in low up to physiologic levels of calcium, so as to investigate the impact of extracellular calcium on normal and transformed keratinocyte and HaCat cells proliferation and differentiation. The ABM was developed using Matlab and simulates the behaviour of cells, which are represented by autonomous agents, in differing exogenous calcium ion concentrations. One of the most important conclusions that can be drawn by using this model, is that “a simple failure of HaCat cells to differentiate at some stage is not sufficient to explain the very different response of these cells to changing extracellular calcium”.

Criteria	Model 6
▪ How much detail they give for the model?	Basically detailed
▪ Is the problem practical or theoretical?	Practical
▪ What scale? <ul style="list-style-type: none"> ✓ Level 1: Molecule ✓ Level 2: Cell ✓ Level 3: Tissue ✓ Level 4: Organ ✓ Level 5: Body ✓ Level 6: Human ecosystem 	Cell
▪ Maturity: Is it built/implemented or just planned/designed?	Implemented
▪ If built, is it free to public access?	No
▪ More focus on Computer Science, Biology or Mathematics?	Biology
▪ Is the model static or dynamic?	Static
▪ Did they use any standard packages for its implementation?	No
▪ What language was used? What software?	Mathworks Matlab
▪ Is it used in real environment? Is it under use?	Yes
▪ Why agent-based model? <ul style="list-style-type: none"> ✓ To understand the real world? ✓ To intervene to the real world? 	To understand

4. Conclusions

This report was designed to provide technical information on models designed and developed with the usage of agents. The writer's intention was to provide a detailed analysis and comparison of ABMs developed to address certain biological issues, mostly in the biomedical field and always with the inevitable crucial contribution of Computer Science and Mathematics.

Any attempt of comparison imposed the necessity of a set of carefully selected and meaningful to the reader criteria, which would provide the scientist-reader with a reference for the practicalities in the field of agent-based model's analysis, design and development.

As this report suggests, there is a plethora of purposes, intentions and reasons for which a research team or an organization would like to develop an ABM. Sometimes the intention is to understand and examine a certain phenomenon, others to find and decide upon mechanisms needed to be adopted and put into effect as precautions for the spread of a dangerous disease, by attempting various potential human interventions into the ABM environment before applying them in the real world, having this way a better insight of the potential impacts.

There is also a variety of implementing an ABM, once again depending on its purpose of existence and usage. Many different programming languages and even more standard, off-the-shelf software packages can be used to implement an ABM, without needing to be an expert in software engineering.

Summarising, the writer should confess the benefit of gaining a significant insight in the wider field of agent-based modeling on the one hand, and in biomedical problems addressed through ABM on the other. A whole new field has made its appearance the past years, where Biology and Computer Science collaborate, to make the usage of the huge experimental data amounts an efficacious process and to provide both biologists and computer scientists a new technology, effective in their hands as well as in the hands of their hybrids. Bioinformaticians, have now a surprisingly capable new ally-technology, which can be used to assess evidence, draw conclusions and make decisions issues of vital sometimes importance for the human health, not mentioning its contribution to other sub-fields of Biology or even other disciplines.

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