Available online at http://scik.org
Commun. Math. Biol. Neurosci. 2023, 2023:38
https://doi.org/10.28919/cmbn/7720
ISSN: 2052-2541

MATHEMATICAL FORMALISM FOR AGENT-BASED MODEL OF PROTEINS INTERACTION INSIDE CANCER CELL

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Abstract. Agent-based models can be used to describe a wide range of complex systems, in which the constituent elements (agents) communicate with one another and the system's global dynamics are governed by the local interactions among the agents. Because formal analysis of complex multi-agent systems is challenging, computer simulations are frequently used to investigate them. While computer simulations are extremely valuable, their results are not formally validated by the observed behavior. As a result, a mathematical framework for representing multi-agent systems and formally establishing their properties is required. One such framework is that which translate the Agent based model to polynomial dynamical system. The aim of this work is to represent our existing Agent based model for the interaction of proteins within cancer cell using mathematical formulation and to analyze its dynamic.

Keywords: agent-based model; polynomial dynamical system; polynomial algebra.

2020 AMS Subject Classification: 92C32.

1. INTRODUCTION

Agent-based models (ABMs) are computational simulations that contain a collection of variables/agents and may take on a finite number of states in a given environment and act according to local update rules (local transition function) that may be deterministic or stochastic. From

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Received September 07, 2022

these local rules, global dynamics emerge. This make the ABMs helpful for understanding the connections between individual decisions and system behavior. For this reason, ABM can be used to describe many complex biological processes as multi-agent systems, in which agents communicate with one another in discrete time steps to produce emergent macro-system behavior [1, 2]. The emergent properties of complex system are characteristics of system that emerge through the interaction of its components over time which make them unpredictable [3].

Agent-based models allow researchers to investigate a complex system by using simulation to study the system's dynamics. Thus AMBs are a method of computing complicated system analysis by limiting agents to a finite number of states, requiring them to follow a set of rules and achieving a limited number of outcomes.

While ABMs have become a powerful tool of today's research and analysis methodologies and provide a suitable environment for studying complex systems, but there are some drawbacks in their use. Firstly, simulation results do not formally guarantee the observed behavior. Another major key obstacle is the lack of standardization in agent-based model description which may change in different settings. The work of Grimm et. al [4] is an essential step in this direction, the authors proposes an ODD-based standard protocol for describing ABMs in standard way. Another significant issue is the lack of rigor in model formulation. The majority of the time, a description of an ABM is provided in the form of numerous paragraphs describing the agents and how they interact with each other and what are the rules that govern their actions which is an exhausting way. This issue would be resolved if there was a rigorous mathematical formulation of the system and instead of spending several paragraphs to explain the model formulation that could been given in few equations. Having a model in such a context help in taking advantage of the general theory that exists and produce results that can be widely applicable. Laubenbacher et al. proposes one such mathematical framework that models ABMs, is the class of temporal discrete dynamical systems over finite state sets [5]. Their proposed mathematical framework is to consider the model's agents as a collection of variables that take values in a finite set, each variable is coupled with a local update function, which captures the rules by which each agent's state changes over time. These functions get together to form a finite dynamical system (FDS),

the dynamics of which are represented by the phase space, a directed graph containing the full state and may be analyzed analytically using techniques like generalized logical analysis.

In [6] the authors propose a mathematical representation for ABMs as polynomial dynamical systems (PDS) over finite fields. The transition function is expressed in terms of polynomial functions, allowing the application of computational tools and theoretical results from computer algebra in analyzing the dynamical properties of models. It was shown that many of the ODD protocol's agent-based models may be translated into time-discrete dynamical systems (algebraic models) that can be characterized by polynomial functions. Without needing to simulate the system, this algebraic form can be used to analyze its global dynamics. This approach was discussed also in [7] where the author proposed an unified framework that concerns all types of discrete models. It was demonstrated that any k-bounded Petri net and logical model, which are particular instantiations of algebraic models, may be translated into polynomial dynamical system.

The framework of algebraic models is more convenient for studying ABMs, as many agent-based simulations fit to this mathematical framework, as stated in [8]. Furthermore, it anchors the inquiry in mathematical domains of polynomial algebra and dynamical systems, which offer rich field of concepts and tools.

The purpose of this work is to analysis our agent based model presented in our previous work [9]. This ABM shows how 6 different proteins interact inside cancer cell and how their interactions affect tumor cell motility and metastasis. These proteins are: P53, MIR-145, MDM2, OCT4, MIR-200 and ZEB. For detailed description of the model and its biological background as well as the agent based simulations see [9].

The remainder of this paper is structured as follows: The biological background of cancer-related genes and how their expression is regulated is presented in "ABM for proteins interaction inside cancer cell" section. In "ABMs represented as a PDS" section, we translate our ABM to polynomial dynamical system and we analyze it.

2. ABM FOR PROTEINS INTERACTION INSIDE CANCER CELL

the P53 tumor suppressor protein plays a critical function in cell integrity protection during physiological or low-stress conditions. It functions as a transcription factor by binding to

genes' regulatory regions and directing their expression, enhancing the production of many genes involved in apoptosis, cell cycle arrest, and DNA repair [18]. When a cell is stressed, P53 experiences post-translational alterations that make it more active and gives it the power to decide whether the cell lives or dies. As a result, under normal conditions, the level of P53 in a normal cell is tightly regulated by the MDM2 gene, its main inhibitor. The existence of P53 in high number activate MDM2 to down regulate it.

The growing amount of MDM2 expression in certain human tumors could possibly be due to the control mechanisms of MDM2 transcript translation. Certain microRNAs (MIRNAs) such as MIR-145 and MIR-200 are involved in this regulatory mechanism. MIR-145 and MIR-200 belong to a category of non-coding RNAs known as significant regulators of gene expression. MIR-145 inhibits MDM2 translation [21] which increases P53 expression and activity, whereas P53 activates MIR-200 and MIR-145 [19, 20].

The involvement of cancer stem cells (CSCs) in tumor spread and resistance is crucial. The ability to destroy tumors is used to evaluate several novel anti-cancer medicines. If the cancer stem cells are not eradicated by the therapy medicine, cancer cells will quickly reappear and develop such resistant to the prior medicine. The epithelial-mesenchymal transition (EMT), considered as critical phase in tumor growth and metastasis, is one of the processes that causes cancer stem cells to develop (CSCs). The Octamer-binding transcription factor 4 (OCT4) and Zinc-finger E-box binding protein (ZEB) are two stem cell genes implicated in this process. P53 controls EMT by inhibiting ZEB and OCT4 expression via MIR-200 and MIR-145 [22]. MIR-200 and ZEB are coupled in a reciprocal feedback loop that suppresses each other's expression [23]. The same can be said about MIR-145 and OCT4 and MIR-145 and ZEB. MIR-200 is activated directly by OCT4 which bind to promoter regions [24]. P53, ZEB, and OCT4 are example of genes that have self-activations as well.

All these genes and types of regulation that govern their interactions are described by a gene regulatory network of the Model of gene regulatory network for cancer and development presented in [10], which includes six nodes (genes) and sixteen edges as it is shown in Figure 1.

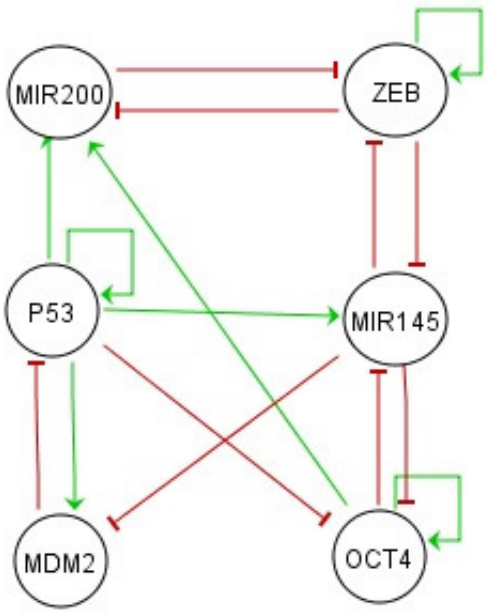

FIGURE 1. The gene regulatory network is represented in this diagram. Activation regulations are represented by green lines, whereas repression regulations are represented by red lines.

The 6 types of cell proteins in our ABM simulations move around a NetLogo grid that mimics space inside a tumor cell at a speed of one patch each time step. Our results and observations suggest that the MIR200 family appears to play a significant role in the metastatic process by suppressing the expression of key angiogenesis components. One of our simulations using the NetLogo software platform is shown in Figure 2. This simulation begins with the same number of proteins interacting with one another for 6000 minutes. For more details on simulations and results, see [9].

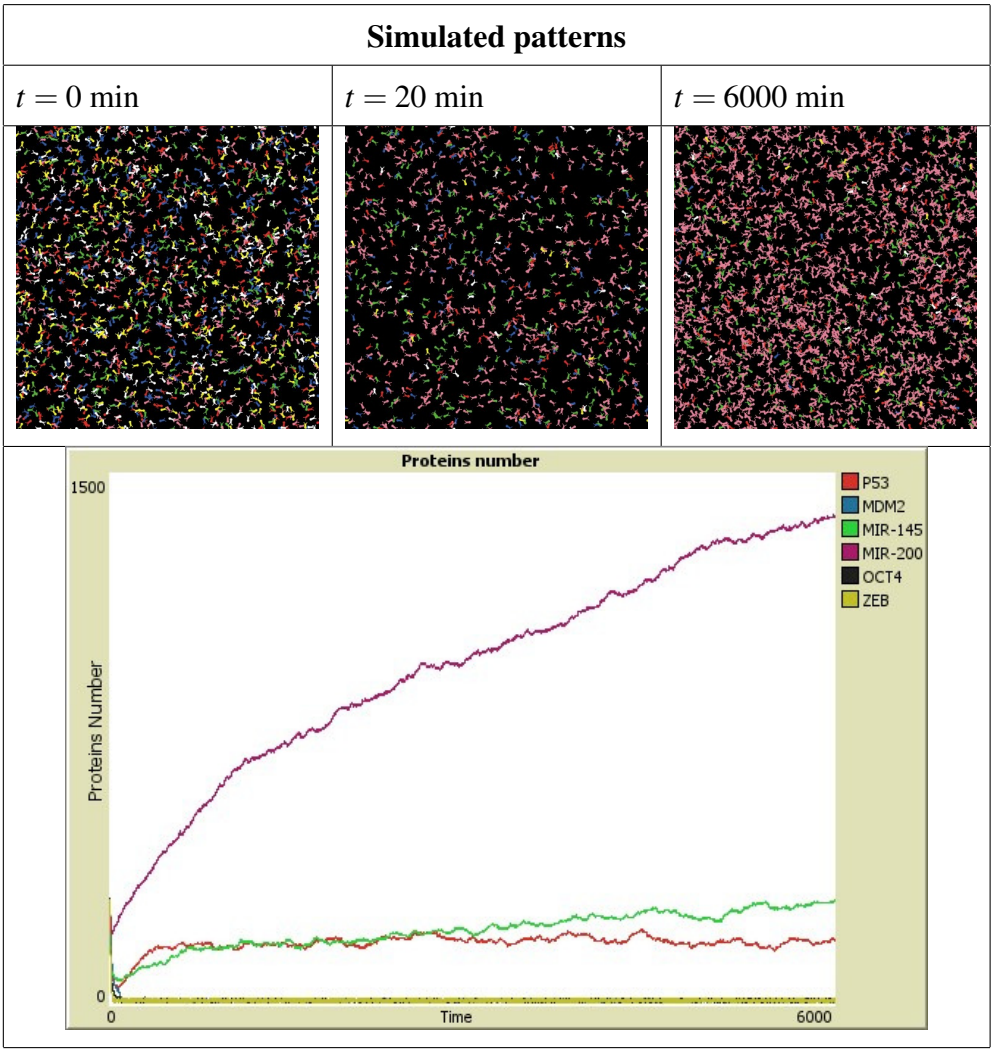

FIGURE 2. The interaction of proteins inside a tumor cell. $N_0(P53) = N_0(MDM2) = N_0(OCT4) = N_0(MIR145) = N_0(MIR200) = N_0(ZEB) = 1000$.

3. ABMs Represented as a PDS

The ABM consists of rules that govern how the system evolves from one state to another, so this process may be considered as a finite dynamical system (FDS)

$$f : F^n \longrightarrow F^n$$

Let $a_1, a_2, \ldots, a_n$ be a set of variables representing model entities (agents) and take values in a finite set F, where the elements of F reflect their states. There is a local update function f_i for each variable a_i, which specifies the method by which the variable a_i is updated at each time step. These functions are grouped into a dynamical system

$$\phi = (f_1, \ldots, f_n) : F^n \longrightarrow F^n$$

We don't have many mathematical tools to analyze f since f is considered as only a set of functions. A number system's algebraic structure is then imposed on F [5, 6, 7] in order to have a more powerful set of tools. As a result, the description of an ABM as a set of functions became a mapping between vector spaces over the finite field F. Once the set F carries such structure, then it become possible to use a fundamental property of finite fields [7] :
for any local function g, there exists a polynomial k such that $g(a_1, \ldots, a_n) = k(a_1, \ldots, a_n)$ where $(a_1, \ldots, a_n) \in F^n$ and F is a finite filed with p elements.

The following formula is used to find the polynomial form of k

$$k(a_1, \ldots, a_n) = \sum_{c \in F^n} g(c) \prod_{j=1}^{n} \left(1 - (a_j - c_j)^{p-1}\right) \tag{1}$$

The right side of the formula is computed modulo p.

Since $f = (f_1, \ldots, f_n)$ is represented using its coordinate functions, with f_i being polynomial function, then we may call $f : F^n \longrightarrow F^n$ a polynomial dynamical system (PDS) over F of dimension n.

The phase space of ϕ is commonly used to represent the dynamics of f, which is a directed graph on the vertex set F^n. There is a directed edge from v to w where v and $w \in F^n$ if and only if $\phi(v) = w$. On the other hand, the dependency graph is another graph that is frequently related with PDS. It is also called the wiring diagram, and it is a directed graph with the variables as vertices; if a_i appears in f_j, then there is an edge from i to j.

Thereby, our ABM could be described as a polynomial dynamical system $f : F^6 \longrightarrow F^6$ where $F = F_2 = \{0, 1\}$ is Boolean field made up of two elements that represent the state of a gene as either ON (1) or OFF (0). Because F is over F_2, all calculation are done "modulo 2".

Here a_1, a_2, a_3, a_4, a_5 and a_6 represent respectively the model agents P53, MDM2, MIR-145, MIR-200, OCT4 and ZEB.

The variable a_1 has values based entirely on those of the variables a_2 and a_4 and it self a_1 . In this case the truth table contains the following information.

a_1	a_2	a_4
0	0	0
0	0	1
0	1	0
0	1	1
1	0	0
1	0	1
1	1	0
1	1	1

Using the formula (1) and the values in table 1, we want to find a polynomial over F_2 that returns the value of a_1 for the given values of a_2, a_4, and a_1. The following polynomial represents this truth table:

$$f_1(a_1,a_2,a_4) = (1-a_1)(1-a_2)(1-a_4)+(1-a_1)a_2a_4+a_1(1-a_2)(1-a_4)+a_1(1-a_2)a_4+a_1a_2a_4 \tag{2}$$

which may be simplified to

$$f_1(a_1,a_2,a_4) = 1+a_2+a_4+a_1a_4+a_1a_2a_4 \tag{3}$$

Similar constructs can be used for each of the variables. Thus the polynomial dynamical system is given by:

$$f = (f_1, f_2, f_3, f_4, f_5, f_6)$$

where

$$\begin{cases} f_1(a_1,a_2,a_4) & = 1+a_2+a_4+a_1a_4+a_1a_2a_4 \\ f_2(a_1,a_5) & = 1 \\ f_3(a_1,a_5,a_6) & = 1+a_5+a_6+a_1a_6+a_1a_5a_6 \\ f_4(a_1,a_5,a_6) & = 1+a_5+a_6+a_1a_6+a_1a_5a_6 \\ f_5(a_1,a_3,a_5) & = 1+a_3+a_5+a_1a_5+a_1a_3a_5 \\ f_6(a_3,a_4,a_6) & = 1+a_4+a_6+a_3a_6+a_3a_4a_6 \end{cases}$$

The dependency graph in Figure 1 shows the interdependence of the variables. The directed graph in Figure 2 represents the dynamics of the function $f = (f_1, f_2, f_3, f_4, f_5, f_6)$ where the

state space $\mathscr{P}(f)$ of f has four components of size 18, 35, 6 and 5, containing four limit cycles: 3 of length 1 and 1 of length 2. This graph was generated using the software package DVD [17].

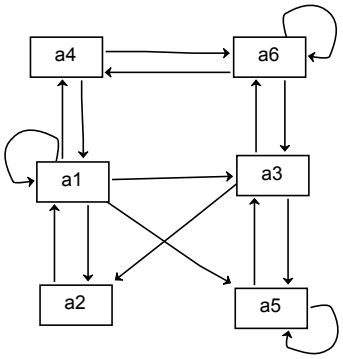

FIGURE 3. The wiring diagram of the function f

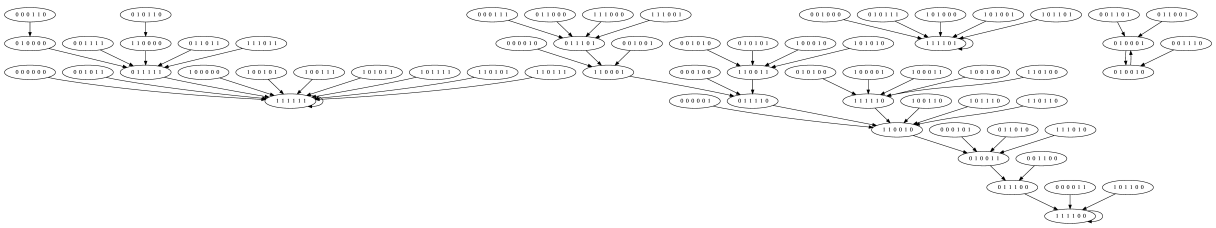

FIGURE 4. The phase space of the function f with $2^6 = 64$ nodes

To determine the steady states of the PDS, we have to solve a system of polynomial equations:

$$f_1 - a_1 = 0,\ f_2 - a_2 = 0,\ f_3 - a_3 = 0,\ f_4 - a_4 = 0,\ f_5 - a_5 = 0,\ f_6 - a_6 = 0$$

which is equivalent to solving the system :

$$\begin{cases} 1 + a_2 + a_4 + a_1a_4 + a_1a_2a_4 - a_1 &= 0 \\ 1 - a_2 &= 0 \\ 1 + a_5 + a_6 + a_1a_6 + a_1a_5a_6 - a_3 &= 0 \\ 1 + a_5 + a_6 + a_1a_6 + a_1a_5a_6 - a_4 &= 0 \\ 1 + a_3 + a_5 + a_1a_5 + a_1a_3a_5 - a_5 &= 0 \\ 1 + a_4 + a_6 + a_3a_6 + a_3a_4a_6 - a_6 &= 0 \end{cases}$$

Now we consider the ideal $I =< f_i(a) - a_i : i = 1, \ldots, n >$. Using the Macaulay2 package, we aim to determine this ideal's Grobner basis. We start by defining the polynomials ring, then the ideal formed by the polynomials we want to be zero, and at the end, we determine the Grobner basis generators for this ideal. The generators build an equivalent system that allows for backward substitution [7].

Thus, we can now find the equivalent system that allows for backward substitution:

$$\begin{cases} 1 + a_1 & = 0 \\ 1 + a_2 & = 0 \\ 1 + a_3 & = 0 \\ 1 + a_4 & = 0 \\ a_5 a_6 + a_5 & = 0 \end{cases}$$

The solutions of this system are:

$$S_1 = (1,1,1,1,0,0), \text{ in a component of size 35.}$$

$$S_2 = (1,1,1,1,0,1), \text{ in a component of size 6.}$$

$$S_3 = (1,1,1,1,1,1), \text{ in a component of size 18.}$$

The first steady state corresponds to the state where there is no stem cell genes OCT4 and ZEB involved in tumor progression and metastasis process. The second one is the state where OCT4 proteins implicated in the EMT induction are absent. The third steady state corresponds to the state where all the proteins are present and try to regulate each other.

4. CONCLUSION

Discrete models, including ABMs, are important method for modeling many complex systems such as tumor formation and growth. The issue of providing mathematical framework to ABMs has been investigated by several authors [5, 6, 7, 8] where the ABM has been translated into polynomial dynamical systems and the agent interactions are described by polynomials in numerous variables over a finite field. This representation makes polynomial algebra's theoretical concepts, algorithms, and software accessible for the study of such systems.

In this paper we have used the mathematical framework proposed in [5, 6, 7, 8] in order to give mathematical formalism and to compute all steady states and limit cycles of our ABM [9] which describe the impact of local proteins interactions between six types of proteins inside cancer cell on tumor cell motility and metastasis. It's worth noting that in ABM analysis we have focused on finding the steady states not because it's the only application of ABM's mathematical structure, but because it may be reformulated without much difficulty into the algebraic issue of solving polynomial equations.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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