A Metaphor of Complex Automata in Modeling Biological Phenomena

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Abstract. We demonstrate that Complex automata (CxA) - a hybrid of a Particle method (PM) and Cellular automata (CA) –- can serve as a convenient modeling framework in developing advanced models of biological systems. As a proof_of_concept we use two processes of pathogenic growth: cancer proliferation and *Fusarium graminearum* wheat infection. The ability of mimicking both mechanical interactions of tumor with the rest of tissue and penetration properties of *F.graminearum,* confirms that our model can reproduce realistic 3-D dynamics of complex biological phenomena. We discuss the scope of application of CxA in the context of its implementation in CUDA GPU environment.

Keywords: modeling, tumor growth, *F. graminearum* invasion, CUDA GPU.

1 Introduction

New challenges in systems biology involve searching for new modeling paradigms which allow for simulating multi-scale systems within a unified computational framework. In his seminal book [1] Wolfram advocates that Cellular automata paradigm can be treated as a universal computational metaphor of reality. However, the robustness of CA is still mostly qualitative. Although some CA clones such as lattice gas and lattice Boltzmann gas [2] are able to describe many dynamical properties of physical systems, they simulate mechanical interactions in a very simplistic way.

Meanwhile, for the model of interacting particles or particle model (PM) (e.g. [3,4]) mechanical interactions are its intrinsic property. PM is a discrete, off-grid and very general paradigm of modeling, which has its roots in N-body simulations and well known Molecular Dynamics (MD) method (also the Non-equilibrium Molecular Dynamics NEMD). The system of discrete particles is defined by system boundary, initial conditions and by interactions between particles represented by a collision operator. The particle system evolves according to the Newtonian equations of motion.

Despite of its conceptual simplicity, the method is computationally demanding, when used for modeling macroscopic phenomena involving large number of particles. The state_of_the_art supercomputers allow for simulating more than a trillion atoms in a million time-steps by exploiting highly efficient MD parallel codes [5]. This

G.C. Sirakoulis and S. Bandini (Eds.): ACRI 2012, LNCS 7495, pp. 845–855, 2012.

particle ensemble corresponds to spatial 3-D scales of a few micrometers and time scales of ten nanoseconds. Certainly, as shown in (e.g. [6-8]), Molecular Dynamics can be used as an efficient modeling framework also in larger scales employing various definitions of "particle". However, the main weakness of PM is the difficulty to represent important microscopic and macroscopic degrees of freedom only in the form of particle interactions. The problem becomes especially serious in modeling intrinsically complex biological systems. For example, assuming that a particle represents a cell, the microscopic processes such as chemical signaling, chemotaxis, haptotaxis, oxygen and proteins diffusion influencing cell behavior and its functions cannot be mimicked by a simple mechanical force. On the other hand, just mechanical interactions between cells can be a crucial factor influencing many types of growth.

Instead of developing multi-scale model which consists of many submodels representing various scales coupled by complicated and unreliable scale-bridging mechanisms, we propose here a uniform coarse grained model in which information about finer scales is inscribed both in CA rules and particle interactions. We demonstrate that by coupling cellular automata and particle model we can develop a new computational framework which possesses the advantages of the two. By using as examples two modeling targets, proliferation of cancer and invasion of a pathogen attacking cereal crops (*Fusarium graminearum*) we demonstrate how the concept of CxA works when applied to modeling the realistic phenomena. At the end of the paper we discuss the methods of speeding up the computations by using GPU and CUDA technologies.

2 Complex Automata

As it was shown in thousands of papers, the cellular automata (CA) is advantageous over other modeling approaches in simulating systems where interactions between individuals can be represented by a language instead of mathematical equations. Using more rules, i.e., more complicated language, one can simulate finer scales using coarse-grained CA representations [9]. The same property holds the particle model. The TC-DPD collision operator in macroscale - much more complicated than conservative MD force in atomistic scales (see [3,10]) - encapsulates in a consistent way averaged degrees of freedom from atomistic scales represented by Wiener stochastic terms. Concluding, the particle model reconstructs in a natural way mechanical interactions while cellular automata performs better when information exchange between individuals cannot be described only in terms of positions, velocities and forces. Therefore, by coupling the particle model with cellular automata, one can obtain the possibility to reconstruct both mechanical interactions and finer intercellular processes mimicked by CA rules. The overall CxA concept consists of the following principal simulation steps.

1. The simulated system is made of a set of particles $\Lambda_N=\{O_i: O(\mathbf{r}_i,\mathbf{v}_i,\mathbf{a}_i), i=1,\ldots,N\}$ where: i - particle index, N - the number of particles, $\mathbf{r}_i,\mathbf{v}_i,\mathbf{a}_i$ - particle position, velocity and attributes, respectively. The vector of attributes $\mathbf{a}_i$ is defined by the particle type, size, and its current states.

2. The particle state may depend on time t, concentration of diffusive substances and total pressure exerted on particle i from its closest neighbors.
3. The collision operator $\mathbf{\Omega}_i(\ldots)$, which is equal to the sum of particle-particle vector interactions $\mathbf{F}_{ij}(|\mathbf{r}_i\text{-}\mathbf{r}_j|, \mathbf{v}_i\text{-}\mathbf{v}_j, \mathbf{a}_i, \mathbf{a}_j)$ between the central particle i and all the particles j confined in the sphere of radius r_{cut}, defines the total force acting on particle i. The type of particle-particle interaction, $\mathbf{F}_{ij}$, may depend on the current attributes of particles i and j.
4. The particle dynamics is governed by the Newtonian laws of motion. Particle positions are shifted just after computing collision operators acting on every particle i. The Newtonian equations are integrated numerically in discrete time-steps Δt.

$$\Delta \mathbf{P}_i^n = \sum_j^{N_{rcut}} \mathbf{F}_{ij} \cdot \mathbf{e}_{ij}^n \Delta t, \qquad \Delta \mathbf{r}_i^n = \frac{\mathbf{P}_i^n}{m} \Delta t \,, \tag{1}$$

where $\mathbf{r}_i$ is the position of particle, $\mathbf{P}_i$ is its momentum N_{rcut} is the number of particles in the interaction range.

5. The attributes of particles i are updated according to its history and the state of particles in its neighborhood according to prescribed CA rules.
6. The particles attributes may also depend on current solutions of other large-scale models formulated in terms of PDEs (partial differential equations) such as reaction-diffusion or hydrodynamics equations.

In the following subsections we present two examples employing CxA metaphor.

2.1 Tumor Growth Using CxA

By skipping the complex genetic processes influencing the appearance of the first tumor cells we assume that a small cluster of cancerous cells is placed inside a healthy tissue. Typically, solid tumor proliferation consists of three phases: avascular growth, angiogenesis, vascular growth, and metastasis (e.g., [11]). Avascular tumor (see Fig.1a) develops due to nutrients diffusion (e.g. O_2) throughout the tissue from neighboring blood vessels. Due to short O_2 diffusion path some of cancer cells located far from the closest blood capillary are in the chronic state of oxygen shortage - hypoxia. The hypoxic cells produce and release chemical species - called tumor angiogenic factors (TAFs) [11]. They diffuse throughout the tissue to neighboring blood capillaries and trigger a cascade of events stimulating the growth of vasculature towards the tumor cluster. Vascularized tumor (see Fig.1b) having access to unlimited resources of nutrients dramatically accelerates its growth. Moreover, the tumor secretes cancerogenic material forming metastases through the blood system.

There exist numerous mathematical models of tumor progression in all its phases (e.g. [12]). However, only a few consider mechanical factors of growth though tumor squeeze through the tight body is a purely mechanical phenomenon. The tissue and vasculature remodeling due to tumor push on influences both the speed and character of its growth. Just tumor remodeling is responsible for its heterogeneity influencing

the drug dosage/rate in chemotherapy. As shown in [13], CxA can be used as a robust metaphor which closes up this gap.

We assume that a fragment of tissue, is made of a set of N particles Λ_N. Each particle represents a single cell with a fragment of ECM (extracellular matrix). The vector of attributes $\mathbf{a}_i$ is defined by the particle type {*tumor cell (TC), normal cell (NC), endothelial cell (EC)*}, cell life-cycle state {*newly formed, mature, in hypoxia, after hypoxia, apoptosis, necrosis*}, cell size, cell age, *hypoxia* time, concentrations of k=TAF, O_2 (and others) and total pressure exerted on particle i from its closest neighbors. The particle system is confined in the cubical computational box with a constant external pressure. For the sake of simplicity the vessel is constructed of tube-like "particles" – EC-tubes – made of two particles connected by a rigid spring. We define three types of interactions: particle-particle, particle-tube, and tube-tube. The forces between particles mimic both mechanical repulsion from squashed cells and attraction due to cell adhesiveness and depletion interactions cause by both ECM matrix and the cell. We postulate the heuristics – two-body interaction potential $V(d_{ij})$ - in the following form:

$$V(d_{ij}) = \begin{cases} a_1 d_{ij}^{\,2}, \text{for } d_{ij} < 0 \\ a_2 d_{ij}^{\,2}, \text{for } 0 < d_{ij} < d_{cut} \\ a_2 d_{cut}^{\,2}, \text{ for } d_{ij} \geq d_{cut} \end{cases} \quad \text{where } a_1 > a_2 \tag{2}$$

where $d_{ij} = |\mathbf{r}_{ij}| - (r_i + r_j)$ and r_{ij}=$|\mathbf{r}_{ij}|$ is the distance between particles while r_i and r_j are their radiuses.

We assume that the interactions between spherical particles and EC-tube particles have similar character. However, as shown in [13], additional rules have to be introduced to enable appropriate growth of the vascular network. The particle dynamics is governed by the Newtonian dynamics while DPD (dissipative particle dynamics) collision operator [3,4] is used for simulating particle-particle interactions.

In dissipative particle dynamics [3,4] the two-body interactions between two fluid particles i and j are assumed to be central and short-ranged. The collision operator, $\Omega(r_{ij}, \mathbf{p}_{ij})$, can be defined as a sum of a conservative force $\mathbf{F}_C$, dissipative component $\mathbf{F}_D$ and the Brownian force $\mathbf{F}_B$. The Brownian factor represents the coarse grained equivalence of thermal fluctuations. The equations below show the basic formula describing the two-body forces.

$$\begin{gathered} \mathbf{F}_C = -\pi \cdot \nabla V(r_{ij}) \cdot \mathbf{e}_{ij}, \quad \mathbf{F}_D = \gamma \cdot m \cdot \omega^2(r_{ij}) \cdot (\mathbf{e}_{ij} \circ \mathbf{v}_{ij}) \cdot \mathbf{e}_{ij}, \quad \mathbf{F}_B = \frac{\sigma \cdot \theta_{ij}}{\sqrt{\Delta t}} \cdot \omega(r_{ij}) \cdot \mathbf{e}_{ij} \\ \omega(r_{ij}) = \frac{3}{n \cdot \pi \, r_{cut}^{\,2}} \left(1 - \frac{r_{ij}}{r_{cut}}\right) \quad \theta_{ij} \in (-1,1) \text{- } random\ number; n - particle\ \ density \\ \Omega(r_{ij}, \mathbf{p}_{ij}) = \mathbf{F}_C + \mathbf{F}_D + \mathbf{F}_B \quad \text{for } r_{ij} < r_{cut} \quad \Omega(r_{ij}, \mathbf{p}_{ij}) = 0 \quad \text{for } r_{ij} > r_{cut} \end{gathered} \tag{3}$$

The value of r_{cut} is the cut-off radius which represents the range of interaction between two interacting DPs.

Both normal and tumor cells change their states from *new* to *apoptotic* (or *necrotic*). The living cell changes its state to *hypoxic* (being the source of TAFs) when oxygen concentration drops below a given threshold. The cell dies and becomes *necrotic* if it remains in *hypoxia* state too long. The life-cycle for EC-tube is different. It can grow both in length and in diameter. Reduced blood flow, the lack of VEGF (*vascular endothelial growth factor*), dilation, perfusion and solid stress exerted by the tumor can cause their rapid collapse. Because the EC-tube simulates a cluster of EC cells, its division onto two adjoined tubes does not represent the process of *mitosis* but is a computational metaphor of vessel growth. The tube can form a sprout of newly created capillary growing from existing vessels. The new sprout is formed when the TAFs concentration exceeds a given threshold. Its growth direction is parallel to the local TAF concentration gradient.

The distribution of hematocrit is the source of oxygen, while the distribution of tumor cells in *hypoxia* is the source of TAFs. We assume that the cells of any type consume oxygen with the rate depending on both cell type and its current state, while TAFs are absorbed by EC-tubes only. TAFs are washed out from the system due to blood flow. The blood circulation is slower than diffusion but still faster than *mitosis* cycle. These facts allow for employing fast approximation procedures for both calculation of blood flow in capillaries and solving reaction-diffusion equation (see [13]).

Summing up, the basic procedures of our CxA particle model consist of: the model initialization phase, i.e., definition of initial and boundary conditions, and its evolution driven by the following phenomena: the Newtonian dynamics of interacting cells, diffusion of oxygen and TAF, cellular life cycle modeled by CxA rules, vessels sprouting and growth, vessels remodeling due to blood flow, vessel maturation and degradation.

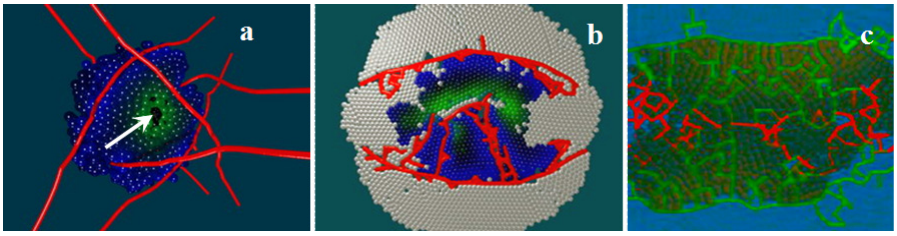

Fig. 1. The snapshots from 3-D CxA simulations displaying two phases of tumor growth: a) avascular and b), c) vascular ones. In a) one can see hypoxic and necrotic parts of cancer globule. The network remodeling process is shown in c) where immature vessels (shown in red) collapse. The tissue cells are invisible in figures a) and c).

In the context of tumor modeling, the main advantage of CxA over other models, consists in more realistic and strightforward simulation of the influence of mechanical remodelling process on tumor growth dynamics. For example, in [13] we show that inward motion of tumor cells in avascular tumor, which results in production of necrotic centre (see white arrow in Fig.1a), is a purely mechanical process. It stabilizes its size in this incipient stage of growth. Similarly, in the following

angiogenic phases mutual interactions between tumor body, vascularization, healthy tissue, and bones may be an important factor of temporar tumor stabilization, or converseley, its rapid growth.

The newly created blood vessel become functional, when they form closed loops (anastomoses) and are covered with adequate quantity of mural cells. Mural cells are vascular support cells that range in phenotype from pericytes to vascular smooth muscle cells [14]. As displayed in Figs.1a,c, the structures of vasculature become very complex and dynamic due to continual vessel maturation and degradation caused also by mechanical interactions. Therefore, the newly created vascular system inside the tumor is very fragile, vulnerable to rapid changes in blood pressure and the speed of volumetric growth. This very dynamic situation influencing majority of the tumor system makes it globally unstable. Very different situation is observed for *F.graminearum* infection in wheat, where mechanical factor is very local.

2.2 Fusarium Graminearum Infection

CxA model can be also applied for simulation of cereal infection by parasite fungi called *Fusarium graminearum* (*F.graminearum* - Fg). Fg is one of the main causal agents of Fusarium head blight (FHB) infection. It attacks cereal crops what results in significant crop losses. Another effect of this plague is the contamination of grain with mycotoxins, which is extremely harmful for animals and humans.

According to [15], we can distinguish four types of *Fusarium* cells namely: tip cells, active cells, inactive cells and spores. Tip and active cells are involved in nutrient uptake, branching and translocation. Additionally, the tip cells are responsible for growth and its direction. Active cells secrete also the acid substances and toxins used for breaking mechanical barriers (such as cellular wall) and disarming plant immunological system. The necrotic cells and spores are inactive cells i.e. the cells that are no longer directly involved in translocation, branching or uptake. Meanwhile the spores are reproductive structures that are adapted for dispersal and surviving for extended periods of time in unfavorable conditions.

F.graminearum is well adapted for growth in vascularized tissue due to their network structure and filamentous growth nature. This growth process is the forward and lateral movement stimulated by the extension of hyphal tips and branching respectively. As a result of tip movement, the hyphae are able to penetrate plant tissue and break hard obstacles such as cell or chitin walls. Breaking cell wall the hyphae secrete enzymes devastating its interior by leaching nutrients. The nutrients are absorbed then by the hyphae cells. Nutrient translocation is the crucial process for *Fusarium* expansion and function in heterogeneous environments. It allows the redistribution of internal metabolites throughout the mycelium by using at least two translocation mechanisms: diffusion and active movement of nutrients. We assume that:

1. Every *Fusarium* and plant cell is modeled by a particle which interacts with other particles (cells) in their closest neighborhood.
2. Every cell has a number of attributes that evolve in time.

3. The concentration of nutrients is uniform in a single cell and constant in the specific time step.
4. Nutrients circulation in the fungi body, which allows *Fusarium* to proliferate, is the effect of diffusion and translocation mechanism [15].
5. Each *Fusarium* and plant cell is in one out of three discrete states which models cell-life cycle.

The laboratory experiments from Fig.2a,b were conducted *in vitro* in artificial conditions. This means that no nutrients were produced in the course of experiments and the initial amount of food was only consumed by *F.graminearum*. The experiments were performed on flat surfaces on so called Petri dishes. Two types of environment were tested: PDA which is nutrient-rich and SNA which is nutrient-poor. Both substances are water solutions. This allows for two important assumptions: the fungus does not encounter much strain from the environment and diffusion does not need to be modeled directly. We may safely assume that the diffusion in water is fast enough to keep uniform nutrients concentration in the whole volume. As the result all fungi cells have identical external nutrients level and there is also no need to model diffusion inside the fungus. In this early modeling stage only model of the hyphae growth and physical behavior has been developed. Due to the absence of plant cells in experiments interactions with environment were not modeled.

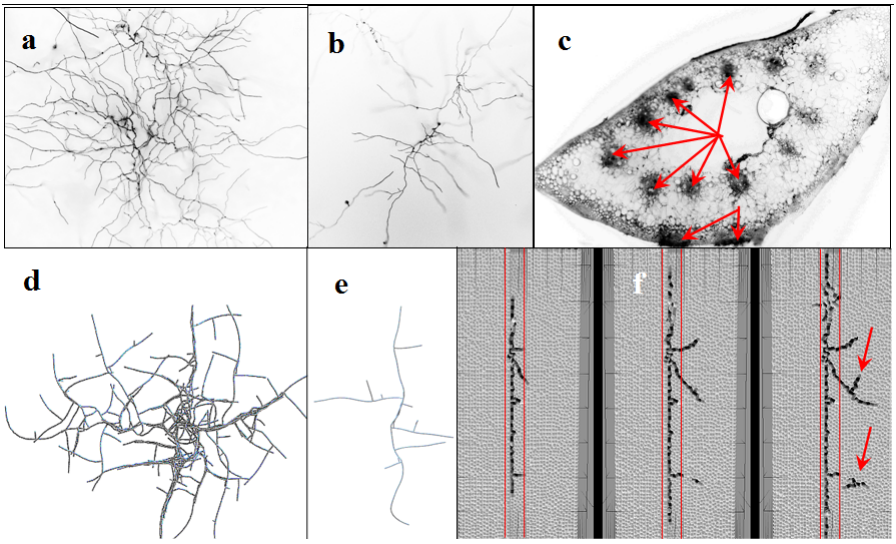

Fig. 2. The development of *F.graminearum* in *in vitro* - nutrient rich (a) and nutrient poor (b) - and *in vivo* (c) environments. Figure c displays the cross-section of stem of wheat head. Experimental results (a,b,c) (courtesy of Dr Shea Miller and Dr Margaret Balcerzak from Agriculture and Agri-*Food* Canada, ECORC, *Ottawa*) are compared to corresponding snapshots from CxA simulations (d,e,f). As shown in (c) and (f), *F.graminearum* (black stains pointed by arrows) proliferate mainly in vascular bundles and rachis, i.e., nutrient poor environment.

As shown in Fig.2d,e, the comparison of simulation results with experimental data is cautiously optimistic. The qualitative character of growth is very similar. However, the structural characters of networks produced by *F.graminearum* and and CxA model are clearly different. This artifact can be improved, by using higher resolution (smaller Fg cells) and playing the parameters responsible for the sprouting. Another confrontation of simulation with experiment, displayed in Fig.2c,f, also shows a good qualitative agreement of the two. *F.graminearum* spreads mainly through vascular bundles (vertical growth), penetrating also the closest neighborhood (lateral growth) [16]. When pathogen finds the nutrient rich part of the plant, it shifts the type of growth from vertical to lateral one completely devastating attacked plant organ.

3 GPU Acceleration of CxA Model

In general, CxA modeling approach in which a particle represents a single cell is computationally demanding [17,18]. Assuming that plant cell perimeter is about 20μm and taking into account the intercellular space and blood vessels, one can estimate that it is about 10^8 cells of order in tissue volume of 1 cm^3. Assuming computational power of modern laptop processors, the Complex Automata can be used for simulating in a reasonable time the fragments of tissue not larger than a few cubic millimeters. This is enough to model initial stages of tumor growth or Fg infection in particular fragments of organs. However, in case of simulating Fg where the dynamics is very local the situation is more favorable. The spatio-temporal scale of modeling can be considerably increased taking into account that:

1. The region of interest can be narrowed to the infected fragments of plant decreasing the number of simulated cells by orders of magnitude.
2. Plan cells are motionless thus they do not need updating its neighbors list.
3. The only moving particles (cells) are *Fusarium* tip cells and fungi cells in their closest vicinity.

We have estimated that using clusters of multi-core CPUs empowered by GPGPU boosters our model can be used for simulating fragments of plant much above a few centimeters of size.

For modeling global dynamics of large tumors, a hybrid continuum-discrete model should be used. We have estimated the speedup obtained by using GPGPU for tumor modeling using CxA approach. The most advantageous are calculations of tube-tube interactions. However, there are rather rare and it appears that the most consuming part of calculations is connected with tube-particle interactions.

In our tests we use the same machine: Intel Xeon E5540 at 2.53GHz CPU with Nvidia GeForce GTX 295 (containing 240 CUDA cores). Machine runs Red Hat Enterprise Linux Server release 6.0. CUDA version was 3.2.16. We compare performance of a single core of the CPU processor with GPU board. The simple (naive) GPU version of cell-cell interactions runs 6 times faster than its CPU counterpart. By use of advanced CUDA mechanisms such as shared memory, textures, atomic operations, and tailoring algorithms to GPUs, we managed to increase the speedup of our

CUDA kernel up to 60 times. The entire simulation runs 10-20 times faster than the single threaded CPU version. In Fig.3 we collected our averaged timings. In the extreme case, tubes are so dense that their interactions considerably affect overall performance. When the number of tubes reaches 9996, tube-tube interactions take 29% of the total execution time. Normally, blood vessels are sparse and hardly ever interact with each other so we can expect much better results than these shown in Fig.3.

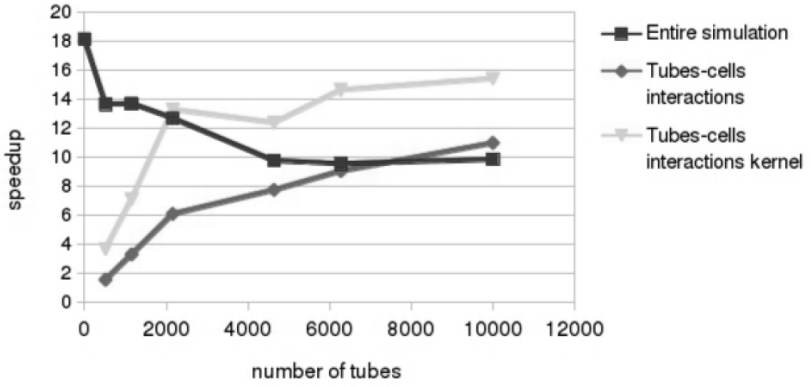

Fig. 3. Speedups for the most intensive calculations compared to the entire simulation

4 Conclusions and Discussion

We have introduced here a novel modeling concept, called Complex Automata, which integrates the two types of modeling techniques, namely, particle method and cellular automata. We have shown that the particle method decides about the mechanical properties of the system. Microscopic phenomena involving fluctuations and dissipative behavior can also be added in a consistent way exploiting widely known modeling techniques such as DPD or TC-DPD [4,10]. Apart from system properties resulting from simple Newtonian mechanics, other microscopic biological processes can be encapsulated in CA rules. These rules depend on the current configuration of the nearest neighbors and other phenomena, e.g., described by the continuum fields obtained from integrating PDEs. We have also presented a proof-of-concept of our approach by employing CxA as a metaphor in modeling of two different biological phenomena. The ability of mimicking both mechanical interactions of tumor with the rest of tissue and penetration properties of *F.graminearum,* shows that our model can reproduce realistic 3-D dynamics of these complex biological systems.

The model presented is only a pure phenomenological metaphor of *F.graminearum* and tumor growth being a proof-of-concept of Complex Automata paradigm application in these domains. Only basic principles of growth were taken into account. However, including more sophisticated processes to the framework of CxA model such as tissue defense mechanisms and toxines devastating effects should be straightforward.

To make our model functional the crucial task is to incorporate to the model a data assimilation module. Up to now the model parameters were matched coarsely using very general data which bases mainly on the results of analysis of microscopic pictures. We believe that using Complex Automata computational framework with data assimilation module will allow for attacking many biological problems in a more systematic and focused way.

Acknowledgements. This research is financed by the Polish Ministry of Higher Education and Science, project NN519 443039 and partially by AGH grant No.11.11.120.777. The Author thanks: Professor AZ Dudek from Division of Hematology, Oncology, and Transplantation at the University of Minnesota, dr. Shea Miller and Margaret Balcerzak from Agriculture and Agri-Food Canada (AAFC), Ottawa for mediacal and biological expertise. Thanks are also due to Mr Przemysław Głowacki and Mr Marcin Worecki for their contribution to this paper. We would like to thank Nvidia Company for donating Authors with Tesla C1060 GPU.

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