In silico Tissue Engineering and Cancer Treatment Using Cellular Automata and Hybrid Cellular Automata-Finite Element Models

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Abstract: An innovative approach for *in silico* tissue engineering and cancer treatment is presented in this study. It is based on the employment of cellular automata (CA) and cellular automata hybridised with finite-element models (FEM) for simulating cells within tissue engineering scaffolds. Thanks to the presented strategy, it has been possible to model cells colonising scaffolds, the interactions among different populations of cells and between the cells and the scaffolds as extracellular matrices, and the effects of external stimuli, like temperature, for treating disease. Among the advances incorporated to conventional models based on cellular automata it is important to mention: the establishment of a direct connection between CAD models and the simulation workspace, the incorporation of a wall factor for considering the affinity of cells for the extracellular matrix, the coupling of FEM simulations to the cellular automata for rendering them more versatile, and the modelling of interactions among different types of cells. Results, limitations, and potentials of these simulation approaches are presented and discussed, in connection with current trends in software as a medical device (SaMD).

1 INTRODUCTION

Software as a medical device (SaMD) is gaining momentum and transforming healthcare. For decades active medical devices have been smartly driven by embedded software, but nowadays medical apps and different kinds of standalone software are emerging for a wide set of prevention, diagnosis and monitoring purposes and must be considered medical devices in themselves (Ludvigsen, 2022). These SaMDs not only support medical practice but may render it much more efficient and sustainable, from the different economic, environmental, and social perspectives. In large part they can also contribute to the 3R principles (Replacement, Reduction, Refinement) for ethical biomedical research (Aske, 2017), as the use of simulations can be an excellent alternative to other *in vivo* studies with animals or *in vitro* studies with cells and tissues, along the development lifecycle of innovative medical devices and drugs or in parallel to medical practice.

To cite some examples, minimising the number of animals required for validating innovative therapies or reducing the use of cells and tissues employed for studying disease, by means of *in silico* strategies -based on software and simulations-, can have highly positive ethical, economical, and procedural impacts in remarkable fields such as tissue engineering, biofabrication and cancer therapies. Indeed, *in silico* tissue engineering (Geris, 2018, Keshavarzian, 2019) and *in silico* cancer research (Edelman, 2010, Jean-Quartier, 2018) constitute important trends aimed at speeding up the (R & D & I) Research – Development – Innovation cycle, while reducing associated costs and minimising negative social impacts without compromising safety. Regarding the simulations of cells, several computational approaches, both continuum and discrete, enable the modelling of their collective behaviours, their interactions with extracellular matrices, the progress of disease and the eventual success or failure of a healing or regenerative strategy (Spencer, 2013, Geris, 2013, 2016).

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In vitro, the invention of tissue engineering scaffolds, 3D or 4D porous structures that mimic the extracellular environment providing cells in culture with biomimetic cell niches, has been fundamental for setting the foundations of tissue engineering and biofabrication and for providing more physiological environments for studying disease and therapies (Khademhosseini, 2016).

In many ways, scaffolds can be employed to study the healing and regeneration of tissue and to test the development of innovative therapies for cancer, but the cell sources, growth factors, reagents and cell culture processes involved are often challenging, expensive and require highly trained professionals. If such processes could be simulated, fields like tissue engineering and cancer research could advance even more efficiently and sustainably. Therefore, it is necessary to further progress in the simulation of cells within scaffolds, in the modelling of cell-cell and cell-material interactions, and in the coupling of these simulations with the effects from environmental cues and stimuli. Linking computer-aided designs of scaffolds and biomaterials with the workspaces employed for agent-based models, for considering both the individual and collective behaviours of cells, and with the input from FEM simulations, for considering the effects of different physical/chemical fields on cells' behaviour and fate, is hence required.

Some recent inspiring studies can be cited, which evolve from the foundational works with cellular automata (CA) (Von Neumann, 1966). In short, CA were developed as collections of elements or cells defined upon grids that evolve through time steps or iterations following certain rules. Along the time steps, the state (i.e. colour or value, typically "0" or "1") of the cells within the grid changes according to the rules and to the previous states of the neighbour cells. Since the beginning, these models were conceived as possible simulators for biological systems with remarkable examples, such as Conway's game of life (Gardner, 1970), in which the cells upon a 2D grid have two possible states, dead or alive, and in which cells survive, reproduce, migrate, or die, depending on the 8 neighbouring cells or the previous state. Further studies led to verifying that extremely complex systems could be modelled with CA (Wolfram, 1984).

In connection with biodevices, these models have also proven useful for studying the biodegradation of tissue engineering scaffolds (Erkizia, 2010), for studying scaffolds' colonization processes (Garijo, 2012, Vivas, 2015), and, by our team, for simulating and optimising biomimetic cell culture systems (Ballesteros Hernando, 2019).

In this study, we intend to advance to the next step by linking three-dimensional CAD models of tissue engineering scaffolds with the grids of CA and by hybridising CA and FEM simulations for obtaining multi-scale and multi-physical/chemical simulators with more versatile functionalities, as described in the following sections. Applications in tissue engineering and cancer research are foreseen and discussed.

2 MATERIALS AND METHODS

2.1 Software Resources

Siemens NX 12.0 and Autodesk Inventor 2020 are employed as main CAD software resources. The FEM capabilities of NX 12.0 are used for the thermal simulations performed. Regarding programming, Matlab r2020a is used as main resource for creating the codes for cellular automata. Ultimaker Cura, a 3D printing slicer is utilised for slicing the CAD models and obtaining images used as input for generating the workspaces for the CA models, as described below.

2.2 Fundamentals of Models Used

2.2.1 From CAD Models to Cellular Automata

Once the usual lattice-like or porous structures of tissue engineering scaffolds are designed, it is possible to generate the workspaces or grids for CA models by slicing their geometries, performing digital tomographs, and processing the images obtained. The process is based on previous studies by our team with some minor modifications that allow us to work with voxels, instead of pixels (Ballesteros Hernando, 2019), and is schematically illustrated in figure 1.

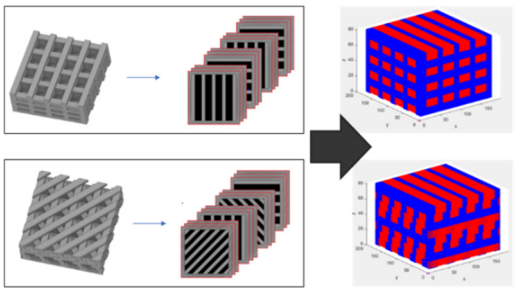


Figure 1: From CAD models of tissue engineering scaffolds to the working grids for cellular automata. Left: CAD models are sliced to generate grayscale images with allowed and forbidden regions. Right: model space in Matlab with allowable (red) and restricted (blue) voxels -or volumetric pixels-.

2.2.2 Modelling the Colonization of Tissue Engineering Scaffolds

Once the working space is obtained, cell proliferation can be modelled following different proliferation rules and illustrated along the temporal iterations by means of colour changes to the voxels, as shown in figure 2. Depending on the resolution of the images obtained through the slicing process and on the distance between slices, voxel size can be adjusted to represent single cells (i.e., voxels of c.a. 10 x 10 x 10 μm^3) or cell populations or clusters. The size of the scaffold employed as extracellular matrix and its porosity, which defines the allowed space for cell proliferation, together with the resolution or number of voxels employed per volume unit, define the computational cost of these simulations.

By means of example, figure 2a presents three iterations of a cell or cell cluster proliferating following a rule, by which all voxels normally connected to a voxel filled with a seed cell or cluster become populated by cells or clusters in the following step. However, figure 2b presents four iterations of a cell or cell cluster proliferating following an irregular pattern, giving options for asymmetric growth patterns and even for steps without any proliferation, based on the incorporation of random functions. Apart from the proliferation, the possibility of cell death is taken into account by adding a probability of death in each iteration. This is represented in figure 2c, in which green voxels represent living cells, while dead cells are represented in red and, in general, occupy that space until the end of the simulation.

In order to consider the affinity of cells for the scaffold's trusses and the effects of adhesion, we have also decided to study the incorporation of a "wall factor", which modifies the proliferation rules or probabilities, by employing different probability proliferation values for cells surrounded by cells and for cells in contact with trusses. To our knowledge, this is reported for the first time and leads to results that better mimic what happens with cells cultured within real scaffolds, as additionally analysed in section 3.1.

2.2.3 Modelling Interactions Among Cells

Current tissue engineering strategies face the great challenge of reconstructing large defects involving different types of cells and tissues. In cancer research, the progression of tumours affecting the various kinds of cells and tissues within organs is also pivotal. In consequence, simulating interactions among different cell populations is essential.

The presented CA models can be also applied to simulate the interactions among different types of cells. From a visual point of view the voxels (e.g., green and blue in figure 2d). From a modelling perspective, different kinds of cells are employed as proliferation seeds, by initially selecting one or more voxels in distinct regions of the allowable space of the grid. The invasiveness of one cell type can be modelled by establishing a simple colour change rule whenever one invasive cell reaches the boundaries of a normal cell, respectively illustrated in blue and green in figure 2d. In this way, tumoral processes can be simulated as further discussed in section 3.2.

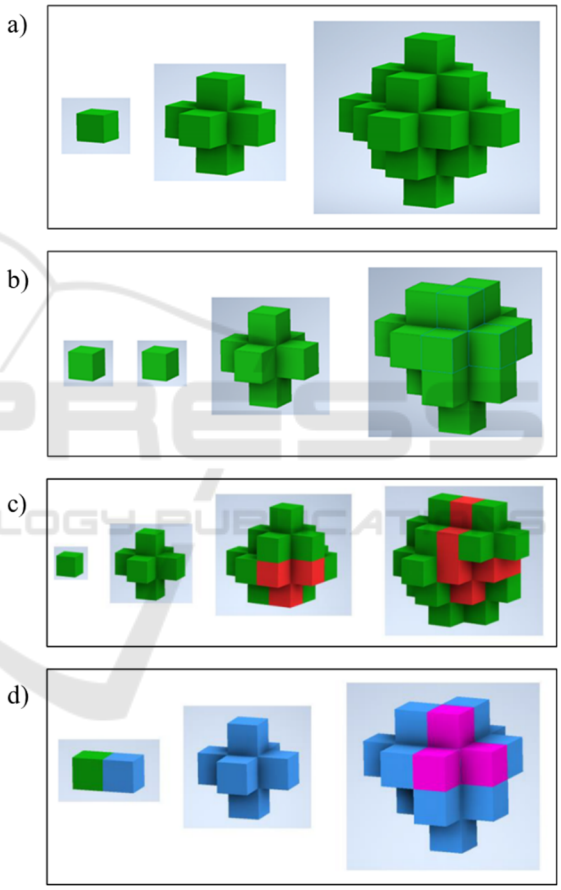


Figure 2: Examples of cell proliferation and cell-cell interactions along different iterations using CA models. a) Three iterations of a symmetric growth pattern. b) Four iterations of an asymmetric growth pattern with a proliferation probability lower than 1, due to which dead cells (red) appear after some time steps. c) Four iterations showing proliferation after including the probability of death. d) Cell-cell iterations showing an invasive cell (blue) attacking, invading, or cannibalising (Fais, 2018) a healthy cell (green), subsequently proliferating, or dying (pink).

2.2.4 Coupling Finite Element Models and Cellular Automata

More complex behaviours of cells within scaffolds should take account of existing physical/chemical fields, microenvironmental cues and external stimuli that may affect processes like gene expression, cell differentiation and final cell fate. FEM prove excellent for numerically solving partial differential equations upon complex geometries and domains, hence being fundamental in modern engineering for mechanical, electromagnetic, fluidic, and thermal problems. All these physical domains can be used for modulating cellular behaviour. Thus, the connection of FEM simulations to agent-based models can prove extremely useful, as we aim to demonstrate.

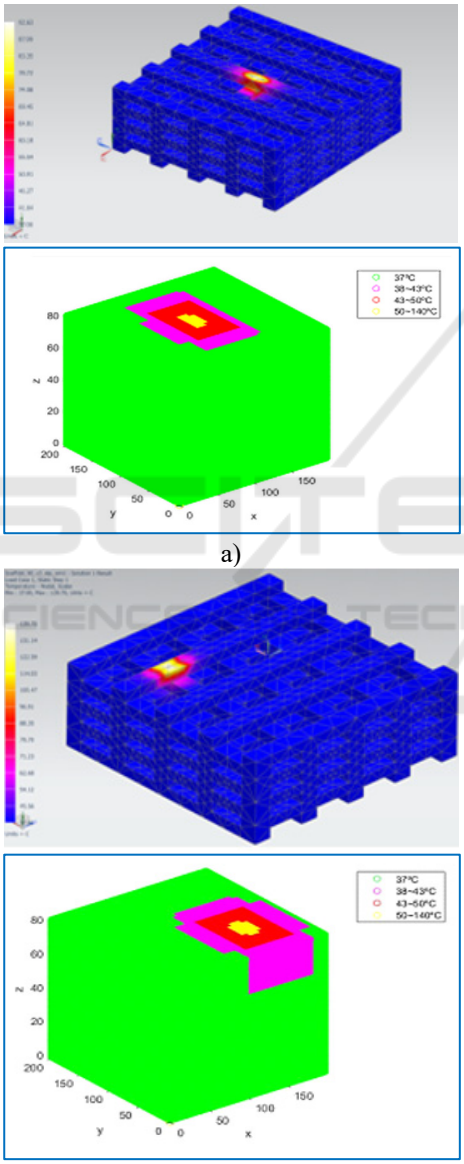


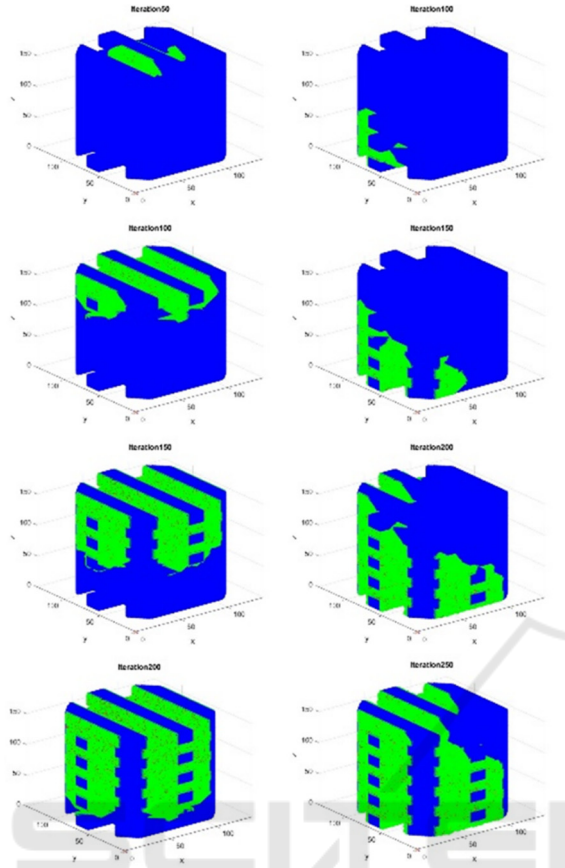
Figure 3: Temperature fields obtained by heating the central upper (a) and upper corner (b) regions of tissue engineering scaffolds and their mapping upon CA grids as ranges associated to death probabilities.

Accordingly, results from FEM simulations stored in matrices have been mapped upon the three-dimensional grids of CA models. So as to modulate cellular responses, the values mapped can be employed to modify the proliferation and survival or death probabilities, depending on the actual fields calculated with FEM simulations. To illustrate this possibility, thermal simulations have been performed, in connection with the possible cancer treatment employing high temperatures (hyperthermia), and the survival probabilities modified. Figure 3 presents the temperature fields obtained by heating two tissue engineering scaffolds and their mapping upon CA grids, as ranges associated to death probabilities. In these examples we consider temperatures around 37ºC as adequate, temperatures in the 38-43ºC as risky, temperatures in the 43-50ºC as critical and temperatures above 50ºC as necessarily deadly.

3 RESULTS

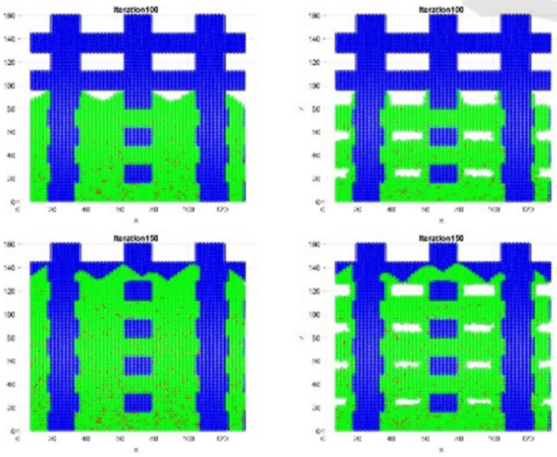
3.1 Cells Colonising Scaffolds

Figures 4 and 5 provide examples of cells colonizing scaffolds measuring 10 mm in height and 10 in diameter, which correspond to 100 x 100 x 100 voxels with the slicing and resolution employed. The voxels corresponding to scaffolds' trusses are represented in blue, while those voxels corresponding to living/dead cells are respectively drawn in green/red. Figure 4 shows different colonization patterns emulating colonization of scaffolds starting from distinct regions. Proliferation and death probabilities of 0.9 and 0.05% are used. Four selected iterations (100, 150, 200, 250) of a simulation performed along 400 steps. Iterations represent time steps, which should be adjusted by means of in vitro experiments monitoring cell growth within real tissue engineering scaffolds, as we reported previously for lab-on-a-chip devices (Ballesteros Hernando, 2019). The challenges linked to these experimental validations are discussed in section 4. Figure 5 presents the influence of using a wall factor for adjusting the simulations to the fact that cells tend to colonize scaffolds by growing preferentially along the trusses and finally filling the voids.



a) b)

Figure 4: Cells (green) colonizing scaffolds (blue). a) Four iterations showing colonization from above. b) Four iterations starting from a lower side.

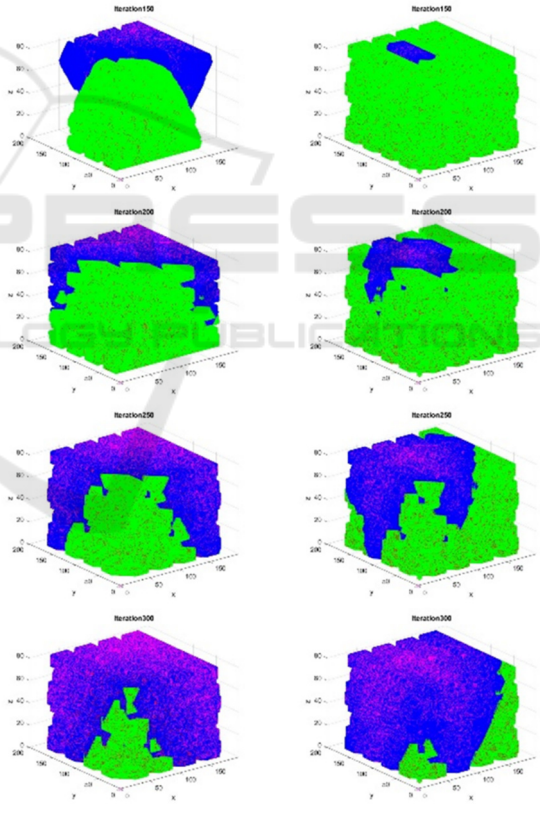


a) b)

Figure 5: Influence of wall factor on colonization patterns. a) Without wall factor. b) With increased proliferation probability for cells touching scaffold's trusses as compared to cells far from the trusses (0.9 vs 0.5% as proliferation probabilities for this model).

3.2 Cellular Interactions

To illustrate the possibility of modelling these interactions, Figure 6 provides two examples of cells interacting within a tissue engineering scaffold. For visualization purposes the trusses of the scaffold are not drawn, although they are considered as forbidden regions for the cells, and the different cell types are shown in green/red and in blue/pink, respectively for living/dead healthy and invasive cells. Both examples show features from patterns typically obtained when diseases progress within *in vitro*, which have been previously reported as extension along the scaffold, cell clumps on the borders, and large cell clusters (Zhang, 2013). In these examples no wall factor is used and, for each iteration, proliferation probabilities of 0.5 and 0.9 and death probabilities of 0.05% and 0.5% respectively for healthy and cancerous or invasive cell types are employed.



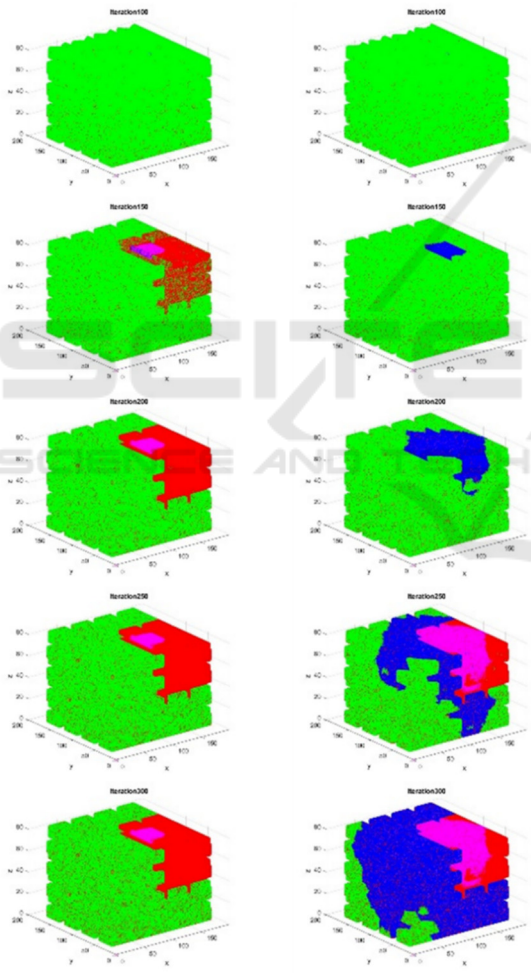
a) b)

Figure 6: Examples of cell-cell interactions within a tissue engineering scaffold. a) Scaffold being colonized by healthy and invasive (cancerous) cells. b) Tumour growing within an already colonized scaffold. Colour code: green = healthy cells, blue = invasive cells, red = dead healthy cells, pink = dead invasive cells. Four selected iterations for each case.

3.3 Hyperthermia Therapy

Hyperthermia, as a therapy, refers to the controlled heating of a region of the human body for a medical purpose, usually cancer treatment. It has shown high potential for cancer therapy, either in conjunction with immunotherapy, chemotherapy, radiotherapy, and surgery (Yagawa, 2017), or as standalone technique, although the heating affects surrounding healthy tissues, which is still concerning. Different approaches are being studied for minimizing its invasiveness and reaching remote regions, based on magnetic and optical systems (Casanova-Carvajal, 2021, Zeinoun, 2021). The use of simulations is expected to support the 3Rs in this field.

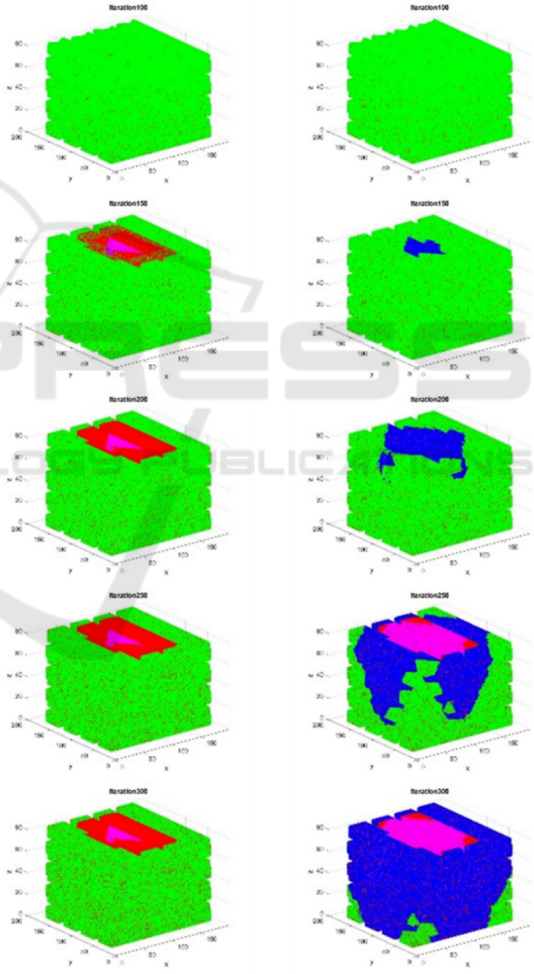
Figures 7 and 8 present two examples of CA simulations coupled to thermal FEM representing cancer treatments by hyperthermia. First the scaffolds are colonized by healthy cells, as shown in the first rows of images corresponding. Just before iteration 150 a tumoral seed is added by modifying some voxels in the upper regions of the scaffolds. Rapid interventions (figs. 7a and 8a) show the killing effect of the thermal hyperthermia applied in iteration 150, while delayed interventions (figs. 7b and 8b) apply the thermal field in iteration 200, when the tumour progress cannot be halted anymore. Figure 8a shows the result of a thermal field more aligned with the tumour, which helps to minimise the heat-affected zone (HAZ) without compromising effectivity.



a) b)

Figure 7: CA simulation coupled to thermal FEM representing cancer treatment by hyperthermia. Misaligned intervention with large HAZ.

a) Rapid intervention stopping the tumour.
b) Delayed and unsuccessful intervention.



a) b)

Figure 8: CA simulation coupled to thermal FEM representing cancer treatment by hyperthermia. Focused intervention with reduced HAZ.

a) Rapid intervention stopping the tumour.
b) Delayed and unsuccessful intervention.

4 LIMITATIONS AND FUTURE RESEARCH PROPOSALS

Main limitation of the study is linked to the still pending experimental validation with real cells. In the previous study from our team, in which CA were employed for modelling cells within lab-on-a-chip devices (Ballesteros Hernando, 2019), we demonstrated the possibility of adjusting cell growth patterns using proliferation rates obtained directly from cultures in Petri dishes. In those systems, simple microscopy upon the lab-on-a-chip platforms is adequate for monitoring growth. However, within tissue engineering scaffolds the visualization is much more challenging and monitoring the colonization and the cell-cell and cell-material interactions in their core requires alternatives to microscopy. Currently we are exploring the applicability of magnetic resonance microscopy, as a non-invasive technology capable of exploring the inside of scaffolds with cells, following the example of pioneering research (Führer, 2017).

Considering future research, together with the experimental validation employing *in vitro* cultures for adjusting the CA models, it is important to consider the following: First, the coupling of FEM simulations with CA models has proven useful for mapping temperature fields and simulating cancer treatment using hyperthermia. Apart from that, several phenomena can be modelled following this hybrid CA-FEM approach, including: the effects of fluid flow and shear stresses on scaffolds' colonization, if computational fluid dynamics simulations are used; the impact of nutrients and drugs' diffusion on cell viability or disease progression; or, even more challenging, potential mechanobiological effects (vibrations, cyclic compressions / tractions, pulsatile stimulation) on cell differentiation during tissue repair processes.

Second, the geometries of scaffolds employed and the control volume and working space for the performed simulations remain fixed during the calculations, that is, a 3D grid with a fixed number of elements with fixed sizes is always employed. The size of the grid and elements depends only on the actual scaffold's size and slicing employed, which can be adjusted to the dimensions of individual cells or cells' clusters. From a computational point of view this is not yet optimal; it would be interesting to explore models, in which the grid's size and the number of elements varies along the simulation, as has proven useful in advanced FEM simulations, in which elements can be switched off and on during a simulation.

In addition, size changes are often involved in gene expression and differentiation processes, so counting with agents or cells within the automata capable of modifying their size would be an interesting incorporation.

Finally, towards societal impact, once validated, these models should undergo a certification process under the appropriate regulation, the Medical Device Regulation 2017/745 in the case of the European Union. Thus, they could become commercially available solutions that healthcare professionals and engineers devoted to medical technologies could employ, in parallel to their research on tissue engineering and cancer therapies, for supporting both the design of medical devices like scaffolds and the development of drugs for cancer treatment. Ideally, for increased reach out, these SaMDs may be shared as open-source solutions accessible to all.

5 CONCLUSIONS

This study has presented an innovative approach for modelling cells colonising scaffolds, the interactions among different populations of cells and between the cells and the scaffolds as extracellular matrices, and the effects of external stimuli, like temperature, for treating disease. To this end, different advances have been incorporated to conventional models based on cellular automata. First, a direct connection between CAD models and the simulation workspace has been provided, by using digital tomographs, employing additive manufacturing slicers upon the CAD files, to create the grid. Furthermore, the option of incorporating a sort of wall factor, capable of considering the affinity of cells for the extracellular matrix, has been discussed. In addition, FEM simulation upon the scaffolds' environment have been coupled to the cellular automata for making them more versatile. Finally, interactions among different types of cells have been simulated.

Despite the pending *in vitro* experiments, simulations presented show the possibility of modelling complex interactions and phenomena directly working with the CAD models of biomaterials and scaffolds. Besides, a connection between designed geometries and the grids used for agent-based simulations has been established, and the utility of hybridising CA with FEM for studying cells, tissues, scaffolds, and cancer therapies has been illustrated and discussed. The fact that wisely implemented cellular automata can perform as universal Turing machines (Wolfram, 1984) points out the relevance and potentials of this approach.

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