Directional Cellular Dynamics for Tissue Morphogenesis and Tumour Characterization by Aggressive Cancer Cells Identification

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Abstract: Due to the availability of large amount of medical data and the improvements of computers' capacities, an increase of tools for medical applications has been noted. In the case of cancer, this results in some application and treatment successes in radiotherapy. However, on the one hand, high therapeutic results are yet to be seen, and on the other hand, unpleasant side effects are still widely observed. In the first case, it may arise from the avoidance of any damage to healthy structures implying ineffective treatment, and in the second case it may be, due to lethal doses deposited in the tumour, leading to an unacceptable damage to one or more healthy structures. Thus, it would be useful to simulate the effects of any treatment prior to its application. Thereby, we are focusing on the proposition of computational methods serving to give insights for decisions aid tools in radiotherapy. In this paper, we provide algorithms for tissue growth prediction where cells are elements of a 2D cellular automaton oriented multi-agent system. Then, we propose a novel method to predict and characterize the evolution of a pathological tissue under cells irradiation. We show that the more cells destroyed during the radiotherapy are linked to aggressive cancer cells, the more the treatment lead to an impaired result in terms of growth. By contrast, we highlight that there exists cells less linked to these aggressive cancer cells that are more suitable to target for an effective and efficient radiotherapy. Based on the dominant cells (linked or not linked to aggressive cancer cells), we introduce a novel method to classify tumours.

1 INTRODUCTION

Cancer is one of the most serious worldwide health issues with respect to its incidence and mortality. The main treatment besides surgery and chemotherapy is radiotherapy. Tumour growth and response to radiotherapy have become subject to many studies by computer scientists. This results in techniques which are able, for instance, to give a prediction of the tumour growth, from which it can be possible to decide if it is required or not to invoke immediately a therapy.

Indeed, given the pace of technological advances, software solutions for medical supports are more and more developed despite the considerable challenges. In cancer field, several planning strategies have been developed. For example, early radiotherapy treatment used *forward treatment planning* which consists of specifying values for all parameters, then the dose calculation software computes the dose distribution. If this latter is judged not acceptable by the oncologist, the initial values of the parameters are then adapted by *trial-and-error* until the dose distribution is satisfactory. This is used in (Henzen et al., 2014) for modulated electron radiotherapy. An electron beam model is used to calculate dose distributions of electron beams shaped by a photon multi leaf collimator. Conversely, *inverse planning* is to specify the desired outcome (such as dose distribution) and to compute beam intensities that produce this outcome without any *trial-and-error* process (Ehrgott and Winz, 2008). In any case, planning strategies are expected to be enough efficient and reliable to help achieving highly accurate therapies.

In section 2, we present our morphogenesis model that underlies the growth of tumours and allows to predict their evolution for a desired number of cells to reach. It is in terms of instructions for cells (division by choosing a specific geometric direction, quiescence, differentiation) that have governed the evolution of the tissue from a previous state (which can be

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its first cell) until its current state (made by a few pair of cells). Thus, assuming that the tissue is only subject to these instructions in a well-guided morphogenesis process, we deduce its evolution for latter times (section 3). Thereby, according to the predicted evolution, one can conclude if a therapy is required and which one is more convenient. In the case where this is radiotherapy, we propose to simulate the effects of cells irradiation on the tumour's growth so as to determine if the destroyed cells are linked or not to the aggressive cancer cells (section 4). In this paper, we consider that beams' modality, geometry and intensity are given, while we are focusing on the target of the beams, i.e cells. We are interested in knowing the cells which are relevant to irradiate and those which are not. Besides, since we have an *individual-based* model whose morphological dynamic relies mainly on spatial constraints of cells, we have been much more concerned to know which cells have to be appropriately chosen for irradiation rather than how the radiation parameters have to be set. Hence, we focus on the impacts of the destruction of certain cells on tumour's growth. In other words, the death of which cells of the tumour will make it grow:

- slower ?
- faster ?
- or normally ?

Each cell of the tumour can be classified according to the effect it involves among these three. The largest cell type determines the category of the tumour. The categorization we propose in section 5 allows us to know in advance the expected results of potential radiotherapy of tumours. We present in section 6 some future works that aim to acknowledge some limiting factors of studying cancer *in vivo* and even more so through *in silico* experiments.

2 VIABILITY CONCEPTS FOR MORPHOGENESIS

Rely on the viability theory to tackle issues in morphogenesis requires first to properly define some concepts of this theory in the case of multicellular system. In previous work, we described mathematically the state, controls and both local and global morphological dynamics of tissues. Some points of that formalization are highlighted in this section.

$\mathcal{K} \subset \mathcal{P}(X)$ denotes the *morphological environment* ($X = \mathbb{R}^2$ denotes the set of containment cells, contained in the complement of *vitellus*[1]).

Cells $x \in X \cup \emptyset$ are either characterized by their position (living cells) or by their death made of tissues L which are subsets of cells ($L \in \mathcal{P}(X)$).

The subset of eight genetic actions d of cells is: $\mathcal{A} := \{(1,0,0),(-1,0,0),(0,1,0),(0,-1,0),(0,0,1),(0,0,-1),(0,0,0),\emptyset\}$

$\mathcal{A}$ is made of the six geometric directions, the origin and the empty set. Here, we restrict morphogenesis in the plan:

$$\mathcal{A} := \{(0,1),(0,-1),(1,0),(-1,0),(0,0),\emptyset\}$$

For convenience, we replace $(0,1)$, $(0,-1)$, $(1,0)$, $(-1,0)$, $(0,0)$ *and* $\emptyset$ respectively by 1, 2, 3, 4, 5 *and* 6.

$$\mathcal{A} := \{1,2,3,4,5,6\}$$

These genetic actions allow to describe cells' behaviours:

1. *Transitions* $x \mapsto x+d$, where $d \in \{1,2,3,4\}$ (action)
2. *Quiescence* $x \mapsto x+5 = x$ (no action)
3. *Apoptosis* $x \mapsto x+6 = 6$ (programmed cell death)

A *genetic process* g is a possible combination of *genetic actions* $g := \{d^1,...,d^i\} \in \mathcal{A}^i$. Operating a *genetic process* under a given criterion, either for migration or for division, means that the process scans successively $x+d^1,...,x+d^i$ until the first time when the criterion is satisfied. For every tissue (phenotype), there is a set of specific *genetic processes* (genotype) that allows to achieve it starting from a single cell. We had generated the all phenotypes that can be obtained after any number of division (1, 2, 3 or 4) of a single cell (Sarr et al., 2014). Indeed, starting with a single cell, at each step, we compute from the previous tissues all the possible configurations of tissue we can reach by cell division. This issue is a particular case of polyominoes computing while we have added some biological constraints. The configurations are saved in the edges of a graph. Besides, we save in vertices all the events that have been involved : division, quiescence, differentiation. Thereby, from any edge in the graph, we can reconstruct the way back to the single cell. This characterization results in the determination of the lineage of any phenotype and using that lineage we construct the underlying genotype with respect to our model (see example in figure 1). A *genetic process* is identified by its colour. All cells whose last division is achieved with that *genetic process* carry its colour and thus define a pattern. For prediction, these *genetic process*es will be the controls that allow cells to behave in their environment according to some rules that will be described in the following section.

[1] In biology, the vitellus is the energy reserve used by the embryo during its development.

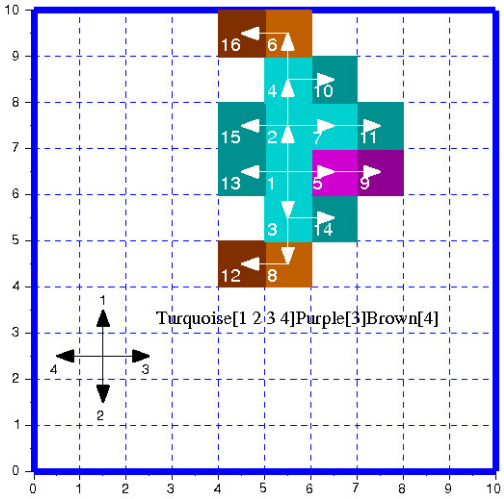

Figure 1: One of the 1029 possible phenotypes and its genotype obtained after 4 division of a single cell. The tissue shows three colours representing three *genetic processes* : `turquoise`, `purple` and `brown`. Each is an ordered sequence of the four *genetic actions* (1:north, 2:south, 3:east and 4:west). These *genetic processes* are the minimum required ones to design this tissue. The colour level distinguishes cell status during the division cycle. Light coloured cells are the ones already divided and the dark ones are those newly created in the cycle, they are both quiescent. The third category does not appear in this figure, they are the proliferating cells which are awaiting to division (medium coloured). Besides, the three colours show that two differentiations occur while generating this tissue. Indeed, if a cell has to change a *genetic process* to be able to divide, its colour and that of its daughter are set to the colour of the new *genetic process*. A tissue appearing with one colour would mean that it is made of just one *genetic process* and no differentiation occurs, i.e all cells were able to divide using the same ordered sequence of *genetic actions*. The arrows distinguish cell lineage as the creation of the tissue goes on.

3 TISSUE'S SHAPE PREDICTION

The prediction determines the state of a tissue in any latter times, given a number of cells or a number of division cycles. The *genetic processes* are applied to make the tissue grow for latter times through the cellular mechanisms of *mitosis*, *quiescence* and *differentiation*. The action of one cell x involves a local morphological dynamic which locally transforms the tissue L at a local process time. The global morphological dynamic transforms the morphological environment K at the end of every cell division cycle after the processing of all cells. The only constraints this growth can face are spatial ones, arising from the morphological environment and cells themselves.

Our 2D model consists of a grid of automaton elements which represent our biological cells. The state of each element is defined by a state vector including three components that correspond to the features of interest in this case study: (i) occupation, i.e. an element is either occupied by a cell or is an empty space, (ii) cell status, i.e. the cell is either in a proliferative state (allowed to divide), quiescent (to prevent cells newly created or already processed in the current division cycle to divide) or locked due to a lack of space for division in the four possible directions (by setting to "on" the evolution lock factor of the cell : ELF) and (iii) cell colour that identifies the *genetic process* it is associated with (dark level meaning that ELF is "on" and light level meaning that ELF is "off").

An example is presented below. Figure 2 represents the current state of the tissue and figure 3 the results of the prediction.

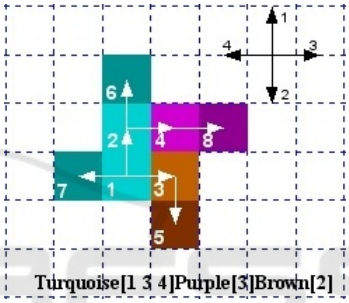

Figure 2: This is one of the 61 phenotypes reached after 3 division cycles of a single cell. We can notice also the three *genetic processes* that are put into play.

After having predicted the evolution of the tumour, it may appear that a radiotherapy is required to give some survival benefits to the patient. In the following section, we propose a decision support to assess the impacts of cells irradiation on a tumour's growth. By the way, this simulation allows us to make a classification of the tumour's cells with respect to the impact of their removal from the tumour. We assume that the cells whose removal causes a high growth of the tumour are strongly linked to the aggressive cancer cells.

4 TUMOUR'S CELLS IRRADIATION

To the point that surgeons cannot remove the tumour, radiotherapy can be an interesting alternative since it can shrink or at least slow down the growth of the tumour over time. This would significantly improve patients' quality of life.

Radiotherapy is one of the many therapies to treat cancer. It consists of using high energy doses

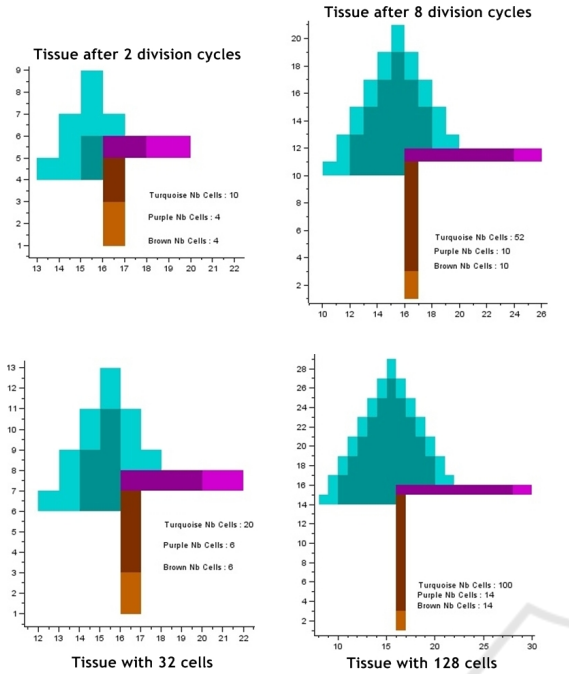

Figure 3: We show two prediction cases: after some given number of division cycles (*top*) and with a certain number of cells (*down*).

of radiation to destroy cancer cells while sparing the surrounding healthy tissues. Radiotherapy is directed towards a particular location of the body unlike chemotherapy, for instance, which is a systemic treatment that spreads throughout the whole body.

Even though the prediction method we present above can provide a future view of the tumour, for probable comparison, classification and even for prescribing suitable therapeutic scenarios, it gives no proposal towards the therapy itself. For the sake of effective and efficient radiotherapy, it would be interesting to know the role of the cells which are intended to be destroyed in the fate of the tumour. In fact, according to the phenotype of a tumour and its morphological dynamic governed by its genotype, there exists among all cancer cells, some which are strongly linked to the aggressive ones. Knowing that destroy those cells will result in a high growth, we would better identify them and avoid them while irradiating the tumour. Some studies reported that sublethal radiation could promote expansion of cancer stem cells which are a subpopulation of the tumour resistant to the conventional cancer therapies including radiotherapy (Suh and Lee, 2015). The aggressive cancer cells can be identified by the most proliferative cells after the tumour radiation. Indeed, the removal of a cell can either flow to the degeneration of the tumour or lead to its regeneration with a higher growth.

In our proposition, to assess if a cell is linked or not to the aggressive cancer cells, we simulate its removal and then let the tumour grows during a given number of division cycles. Finally we compare the growth rate with the one if there is no irradiation. If we notice that the growth is faster than the normal, we consider that the irradiation of that cell will be "dangerous", because linked to the aggressive cancer cells. If it is similar to that, we consider that the irradiation will have neither a benefit, nor a harmful effects, it is just "unproductive". And if it is slower than that, the irradiation will be an "effective" one, because the cell is independent from the aggressive cancer cells.

We have implemented algorithms relying on these principles to identify each cell in any given tumour with respect to the aggressive cancer cells. When the technique is applied to the tissue depicted in figure 2, the results are as follows (assessment of the growths are done after 20 division cycles):

- Removal of `cell number 6` is the most effective, it leads to the slowest growth (4% smaller than the normal).
- Removal of `cell number 3` is the most dangerous, it leads to the fastest growth (5% bigger than the normal)
- Removal of `cells number 1, 7, 4 and 2` are all unproductive. The growth of the tumour will remain the same as the normal

Thereby, we are able to put light on the role that the death of each cell would have on the fate of the tumour. This allows to identify three types of cells within a tumour. Afterwards, we will rely on these results to characterize any tumour with respect to the type of cells that mainly composes it.

5 TUMOUR CHARACTERIZATION

Main tumours classification techniques are based on shape factors of tumours' regions and texture measures. For instance, (Ng and Bischof, 1992) proposed a method for the mammographic detection and classification of two types of breast tumours. The method identified them as follows: circular, bright masses with a fuzzy boundary and stellate lesions surrounded by a radiating structure of sharp. In (Rangayyan et al., 1997), it is highlighted the importance of combining lesion edge definition with shape information for tumours classification. The potential of acutance is used to quantify the sharpness of tumours' boundaries. An application of this technique is proposed to discriminate between benign and malignant mammographic

tumours. Our approach of virtual tumour classification places more emphasis to the cells of the tumour rather than its shape and texture. In the previous section, we highlighted the influence of the removal of certain cells in the tumour growth. We have shown that the choice of cells to be irradiated had utmost importance for effective and efficient radiotherapy.

Fair classification should give an insight of the nature of any tumour without repeating every time the same identification processes, so well that it may allow to determine more quickly therapies to apply. To classify a tumour, we simulate successively the irradiation of each of its cells and observe its evolution. Depending on the results of these simulations, we know what are the dominant cell types in the tumour, which allows us to classify it in one of the six categories we define in table 1.

The category of the tumour depends on the main response we can expect from its irradiation which :

1. does not influence, neither in good, nor in bad way the growth of the tumour
2. accelerates tumour growth
3. stunts the growth of the tumour
4. stunts the growth of the tumour or at least maintains it to its normal pace
5. accelerates tumour growth or at best maintains it to its normal pace
6. can either accelerate or stunt the growth of the tumour

We have in figure 4 an example of classification.

We also implement an algorithm such as for a given set of tumours, it classifies each tumour in a category and then gives the resulting statistical distribution. Assuming that the set to process is the all possible phenotypes after 3 division cycles of a single cell, the distribution is depicted in figure 5.

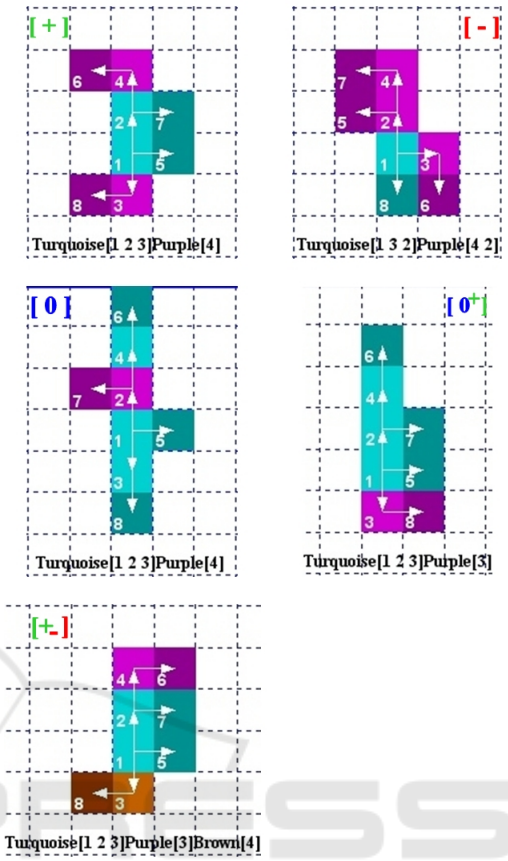

Figure 4: Example of 5 tissues classified each in a different tumour category. In figure 5, we show the entire distribution of the set of *8-cells* tumours in the six categories.

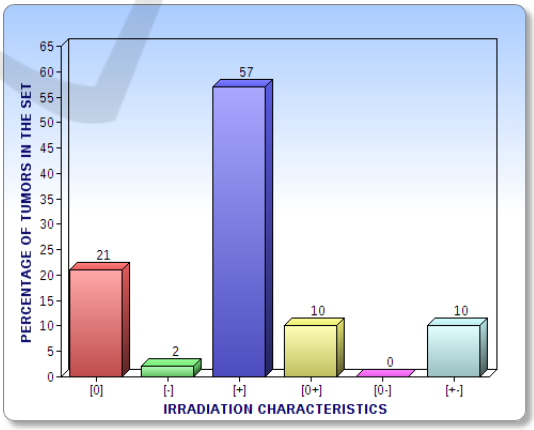

Figure 5: Distribution of the 61 *8-cells* tissues per tumour category. The cell division cycle for assessing the growth of the tissue after irradiation is set to 10. We can notice that there is no *[0-]* tumour in the studied set.

6 DISCUSSIONS AND CONCLUSIONS

We formalize in a mathematical model some generic features of cell division. Then using a cellular automaton whose rules capture the principles of that model, we propose a prediction method for tissue evolution. The interesting shapes predicted contribute to establish the reliability of our approach of morphogenesis. We applied this prediction method to deduce the latter states of a pathological tissue, given one of its previous states. Then, we highlight the importance of selecting suitable beams and energy intensities to fit properly the tumour size and shape in radiotherapy. However, we claim that it would be more interesting to find the most cost-effective scheme in terms

Table 1: The different categories of tumours and their description.

Category	Notation
Unproductive[1]	Zero : [0]
Dangerous[2]	Negative [-]
Effective[3]	Positive [+]
At Worst Unproductive[4]	Zero/Positive : [0+]
At Best Unproductive[5]	Zero/Negative : [0-]
Effective at Best and Dangerous at Worst[6]	Positive/Negative : [+-]

of cells to irradiate so as to ensure a slow growth of the tumour after shrinkage. If such method is taken into account by decision support tools for cancer therapy, it would more safeguard the healthy cells because the whole tumour will not be blindly irradiated. Indeed, it ensures that radiation is directed on specific cells within the tumour, relevant to be destroyed due to the fact that they are not or weakly linked to the aggressive cancer cells. For this purpose, the algorithm we implement does not randomly remove multiple cells in one fell swoop, as it could be simple to do, but it chooses each cell and determine its role in the growth of the tumour. Then, we found that it was more relevant to classify tumours according to their potential response to radiotherapy rather than to their shape and texture. Thereby, based on the growth we expected after radiotherapy, we were able to classify a tumour among six defined categories. We acknowledge that *in silico experiments* remain far from clinical applications but they allow to test and produce new assumptions in order to better understand the livings and control the disturbances they face. Hence, although the computational experiments we conducted in this paper remain up to now theoretical, they provide new avenues of research in the field of cancer therapy to be more effective. If such decision making methods and tools are validated and implemented, we are convinced that inadvertent use of imagery prior to treatment and some therapy drawbacks could be avoided. In future works, we aim to take into account the cellular neighbouring exchange in addition to the directions of division instructions. Indeed, due to what is called the *tumour microenvironment*, results obtained *in vitro* on the isolated cancer cells may dramatically differ from the observed behaviours of the tumour under *in vivo* radiation (Thompson and Maity, 2014). These discrepancies are induced by a complex constellation of extracellular and intracellular factors on the tumour. They are yet to be understood for fair *in vitro* experiments and even more so to be taken into account in *in silico* simulations. Besides the role and clinical implications of tumour microenvironment, it is also hard to predict in an accurate way, for a same cancer shape or type, the responsiveness of the radiation from a patient to another one. Depending on the degree of the individual susceptibility variation, the predicted results may be more or less far from the observed results, except predictive tests related to some clinical researches on blood lymphocyte.

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