# A multiscale agent-based model for the simulation of avascular tumour growth

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An agent-based paradigm for the simulation of complex systems is based on the modelling of the individual entities of the system. Given a chosen level of description, this implies modelling each and every entity of the system. When modelling biological systems at the cellular and/or molecular level, this results in the simulation of multitudes of agents, which raises performance issues. However, it is generally not necessary to have the same level of detail in every part of the system. In this paper, we propose to introduce dynamically an aggregated level in the simulation of avascular tumour growth. This model handles cells and PAI-1 molecules that are believed to play a key rôle in the amoeboid migration of cancerous cells. However, migratory events can only be triggered on the periphery of the tumour. The interior can therefore be modelled in an aggregated way by replacing the individual cells and molecules by a global agent. We show that this can be done without changing the global dynamics of the system, and gaining a linear increase of computing time while the number of cells and molecules increases exponentially.

## 1. INTRODUCTION

Complex systems are characterized by the dynamic interaction of numerous and heterogeneous entities, at various temporal and spatial scales, leading to nonlinear dynamics and emergent phenomena. Such emergent phenomena correspond to the appearance, at higher level of description, of structures and/or functions that are the result of the local activities and interactions of the entities at the lower level. To be able to model and study such phenomena one has to take into account the locality of the interactions and the multiple levels of description involved. Agent-based modelling is a paradigm that is well suited to tackle such a problem. By the modelling of the individual entities of the system, their behaviour and their interactions with other entities or with the environment, one can recreate an artificial system whose dynamics matches, as closely as possible, that of the real system. However, given a chosen level of description, this implies modelling each and every entity of the system at that level. When modelling biological systems at the cellular and/or molecular level, this results in the simulation of multitudes of agents, which immediately raises performance issues. It is therefore not reasonable to envision modelling a biological cell solely at the atomic or molecular level. Another difficulty is that biological knowledge is very sparse; therefore, while some parts of the system can be described at a given level of detail (where sufficient data are available to build a satisfactory model) other parts of the system are described at a less detailed level.

Depending on the biological question that the modelling work tries to address, it may be useful to model some parts of the system at the lower level, so as to gain new insights into the precise mechanisms at work at that level. The challenge is then to combine various levels of description inside a single model and be able to simulate entities at these various levels. Different approaches have been proposed to allow such multiscale modelling of complex systems, including hybrid models or multilevel formalisms (see Section 2). The approach that we propose consists in analysing, during an agent-based simulation, the structures that may arise from the interaction between the entities at a given level, so as to dynamically and automatically reify them as entities of the upper level.

Our proposed approach raises new issues that have to be addressed. The first problem is that the objects of a specific level do not necessarily have well defined and permanent boundaries. If we think of a traffic jam on a highway, we may wish to consider it as a higher level object, composed of a number of individual cars. As such, we may characterize its direction (opposite to that of the cars) and speed. Upon looking more closely at the object, we notice that cars aggregate to the object at the rear and escape from the front, therefore constantly modifying its very composition. The situation is analogous with biological cells, whose structures constantly exchange a lot of molecules with one another and with the outside of the cell. Another problem is the specification of the behaviour of such higher level objects. It generally cannot be simply deduced as the sum of the activity of the lower level entities since their effect is generally not purely

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additive. This is precisely one of the criteria that may be retained to state that a given phenomenon is emergent; that is, the fact that the behaviour of the global structure is quantitatively and/or qualitatively different from the sum of the activities of the entities comprising the structure (the whole is more than the sum of the parts).

The overall approach may be summarized by the following steps: 1. Automatic analysis and characterization of the structuring of the system; 2. Dynamic creation or deletion of higher level objects; 3. Computation of the aggregated behaviour of higher level objects; 4. Computation of the interactions with lower level objects (internalization/externalization/repulsion and so on); and 5. Computation of the new boundaries of higher level objects. While this process may be very powerful for leveraging simulation performances, it raises new validation issues because one has to be sure that the new model with aggregated agents remains qualitatively and quantitatively equivalent to the one without these higher level behaviours.

We propose to address these different questions in the context of the simulation of avascular tumour growth. We are particularly interested in studying the impact of the PAI-1 protein, which is suspected to be responsible for the transition between mesenchymal and amoeboid cell conformations [1]. PAI-1 molecules are thus believed to play a key rôle in initiating and sustaining amoeboid migration of cancerous cells. We first developed an agent-based model in which both cells and PAI-1 molecules were modelled individually. The behaviours that we took into account are the proliferation of cells (and their mutual repulsion) and the dynamics of producing and internalizing PAI-1 by the cells. We also modelled the fixation of PAI-1 to the extracellular matrix and the degradation of the matrix by mesenchymal cells. However, migratory events can only be triggered on the periphery of the tumour. The interior can therefore be modelled in an aggregated way, by replacing the individual cells and molecules by a global agent. We first present some related works in Section 2. We then develop our approach by explaining the initial agent-based model (in Section 3) and showing how it can be transformed so as to model some parts in an aggregated way (in Section 4). We present some results in Section 5 before concluding and presenting some perspectives in Section 6.

## 2. RELATED WORKS

Many works have addressed this issue of multiscale or multilevel modelling and simulation of a complex system, with different approaches. A first one consists in modelling the different levels by different formalisms in hybrid models, each of the formalisms being suited to the description of a particular level of the system. This kind of approach can generally be found in the modelling of systems where there is a difference of several orders of magnitude between the sizes or typical times of interaction of the largest and the smallest entities. This is the case in cardiac or cancer modelling, taking into account, in extreme cases, structures at the scale of organs under the control of regulatory networks at the molecular level. In the case of cardiac models, a very large number of research teams works at coupling different models (see the review of Southern et al. [2]). The models being coupled, mostly mathematical models based on differential equations, describe either the different scales involved (e.g., cell and tissue) or different types of physics involved (the electrical activity of the heart causes its mechanical contraction, which alters in turn the electrical activity and induces fluid movements in the cardiac chambers). In the field of tumour simulation, one can find models associating agent-based discrete models to account for cancer cells, and partial differential equation (PDE) approaches to account for molecular concentrations of the microenvironment and for the blood and lymphatic flows [3]. Further work will add Boolean automata to model the internal regulation network of the cell, thereby determining the progression of the cell in its life cycle [4, 5]. Still others associate PDEs at different levels to describe the dynamics of spatial growth of the tumour and the diffusion of some proteins [6].

A criticism that may be addressed to such approaches is the lack of coupling between different models. In some cases, it is indeed necessary to run a simulation of a first model before injecting its outputs as inputs of a second model. To limit this problem, alternative approaches have sought to propose formalisms to describe complex systems at different levels. Examples of such formalisms are L-systems, based on the description of topological structures thanks to a grammar and their transformation by means of rewriting rules [7], and their derivatives [8, 9]. More generally, one can consider that agent-based modelling approaches are naturally fitted to the multiscale description of complex systems: the notion of agent imposes no particular scale; one can mix agents at different scales within one model, and one can describe any complex system as the recursive nesting of agents at different scales. The Swarm simulation platform [10], for example, has been based on the notion of agent groups (swarms), each group having its own control and scheduling process, and each agent of a group being potentially considered recursively as a group in its own right. The language and simulation platform BioDyn [11] are based in turn on the notion of graph, enabling on the one hand the definition of membranes and compartments, enabling on the other hand the definition of composite agents that can bind, merge or divide.

The major disadvantage of an agent-based approach lies however in the need to model and thus simulate very many entities. For a simulation at the molecular scale, the agent-based approach will have to model each and every involved molecule, while a PDE-based approach will only have to model a limited number of regions characterized by the concentrations of the molecular species of interest. Both for considerations related to the observation and analysis of the system, and for performance issues, it may therefore be advisable to study dynamically the creation of higher-level structures inside such agent-based simulations, and to reify these structures as agents. This approach is the one adopted within the Epithelioma project [12], the disadvantage being that reification is, in this case, a modelling choice and not the result of observation of the simulation. Conversely one can find an example of automatic reification in hydrology [13] where runoff is modelled in the form of discrete volumes of water falling on the ground, and where higher-level objects such as ponds or gullies may dynamically appear by the observation of a continuous flow of agents over some areas of the environment.

## 3. THE INITIAL AGENT MODEL

### 3.1 The biological question

Cancer is characterized by complex processes governing proliferation and migration of cells. The importance of microenvironment in facilitating tumour cell growth and invasion has gained increasing interest [14] since it has been shown, using *in vitro* and *in vivo* models, that stromal signals and cell-to-cell interactions are critical determinants of tumour behaviour [15, 16]. These interactions include local influences on the primary tumour and the creation by the tumour itself of a permissive microenvironment for metastatic cells to grow, migrate and establish colonies in distant organs.

While increased protease activity always indictes a negative prognosis, strategies to reduce invasiveness by protease inhibition have failed to show clinical efficacy [17]. Failure of traditional therapeutic approaches to treat this devastating disease may be due to our limited understanding of how the stromal cells present within tumours can facilitate the rapid progression of cancer. Therefore the rôle of matrix-bound PAI-1 (a strong and independent marker of bad prognosis) has been studied in mammary cancer cells, and it has been shown that a microenvironment enriched in PAI-1 is able to influence cell behaviour in terms of morphology, actin reorganization and migration [1].

### 3.2 The initial agent model

A first agent-based model has been prototyped using the Netlogo [18] platform in a preliminary study. In this model, three types of entities have been modelled, namely cells, PAI-1 molecules and the extracellular matrix, in a 2D environment.

Cells are modelled as agents that may proliferate, move, capture and release PAI-1. They are considered as semi-rigid circular agents of radius $r_c$. Cells are characterized by their age, an internal variable set to 0 when the cell is created or after it has divided. The age is incremented at each iteration of the simulation (it is a discrete time simulation). Cells may divide according to a probabilistic rule, division being more likely when age increases. A repulsive force is computed between neighbouring cells so as to avoid overlapping cells. A cell can be in three distinctive states [19]: active, quiescent or necrosed. In avascular tumours, nutrients diffuse from the edge of the tumour towards the center, which implies that cells too far away from the edge may not receive enough nutrients. Active cells are "normally" proliferating cells; quiescent cells are still alive but have stopped their proliferation; necrosed cells are dead because of starvation. In our model, dead cells remain in the simulation but are totally inactivated. Cells are also characterized by a number of uPAR membrane receptors, which can bind PAI-1 molecules, resulting in the internalization of both the receptor and the PAI-1 molecule. The receptor is then recycled on the cell membrane. The more such receptors a cell has on its surface, the more likely it will be to bind PAI-1 molecules in its immediate neighbourhood. Finally, cells may also spontaneously release PAI-1 molecules according to a fixed rate.

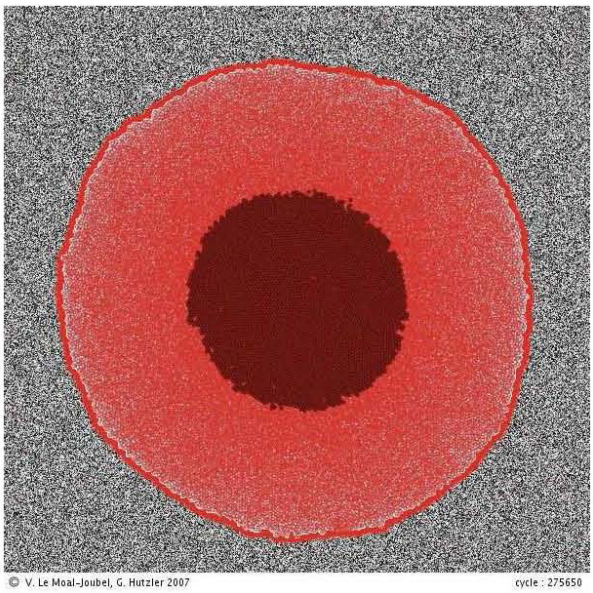


Figure 1. Screen capture of the simulation after 275 000 steps.

PAI-1 molecules can also be in three distinctive states: active, inactive or matrix-bound. PAI-1 molecules are released by the cells in the active state, and become inactive after a predefined number of simulation steps. When inactive, PAI-1 molecules can no longer bind to cell receptors and are internalized. Active and inactive molecules can bind to vitronectin, a receptor of the extracellular matrix, and become matrix-bound. Binding is modelled as a probabilistic event, depending on the local vitronectin concentration.

The matrix is modelled as a square grid of small regions, characterized by the amount of vitronectin available in the region. This amount is fixed randomly inside a chosen interval at the beginning of the simulation. Cells at the edge of the tumour, supposedly in a mesenchymal state, alter the matrix, which leads to a decrease of the quantity of vitronectin.

## 4. THE AGGREGATED MODEL

The agent model that we just presented very briefly is satisfactory in that it correctly reproduces the growth of an avascular tumour and the corresponding ring of matrix-bound PAI-1 that surrounds the tumour and that is usually considered as a sign of negative prognosis (see Figure 1). With that model, however, we quickly end up with thousands of cancer cells and hundreds of thousands of PAI-1 molecules, which is barely manageable using classical agent-based techniques. We therefore tried to introduce higher level abstractions in our model so as to reduce the computing load. Given that the zone that interests us most is the edge of the tumour, where matrix-bound PAI-1 is believed to induce the mesenchymal-amoeboid transition at the origin of metastatic escapes, the idea is to replace the inside of the tumour by an aggregated model (thereafter denoted as AggreM) in which individual cells and molecules would be replaced by a single agent, aggregating all the cells and molecules on its area. One can see the AggreM as a statistical model, defined by its area and by the number and types of cells and the number and types of PAI-1 molecules enclosed within it.

### 4.1 The selection of the agents to integrate

The first task to be tackled is to determine the agents that will be integrated in the AggreM. The aim is to integrate as many individual agents as possible so as to have the optimal computing gain, but without corrupting the initial model; i.e., with neither qualitatively nor quantitatively modifying the dynamics of the simulated tumour. Since the AggreM is defined in particular by the area it covers, cells inside the AggreM should not move too much.

Proliferating cells multiply and move due to repulsive forces and we therefore chose to exclude them from the AggreM because this would imply integrating elements with potentially complex dynamics. Moreover these are the outermost cells, in contact with the extracellular matrix, which is our zone of interest. Necrosed and quiescent cells on the other side are good candidates: they do not divide any more, hence the number of cells remains constant, nor do they move much any more because they are old cells that have found their place inside the tumour and are tightly packed. We chose to keep a ring of quiescent cells outside the AggreM because these cells can possibly switch back to the proliferative state. In addition, these cells will be used as a frontier line between the AggreM and the individual agents, thus making it easier to handle exchanges between them. The PAI-1 molecules located over the area defined by all the cells included in the AggreM will also be integrated into it.

### 4.2 Properties and behaviour of the aggregated model

The AggreM aggregates a number of cells of different types and a number of molecules of different types. It is therefore characterized by the number of agents of each type that it contains:

- $n_c$, the number of quiescent cells
- $n_n$, the number of necrosed cells
- $n_a$, the number of active PAI-1 molecules
- $n_i$, the number of inactive PAI-1 molecules.

In addition, although the AggreM is an abstraction (it does not correspond to a single physical entity in the real world), it remains a local and spatially anchored entity. It is therefore also characterized by the area that it covers, namely the union of the areas of all the cells included in the AggreM.

The behaviour of the aggregated model consists in the following elements:

1. Internal dynamics
   (a) updating of $n_c$ and $n_n$ due to the necrosis of quiescent cells as the tumour grows;
   (b) updating of $n_a$ and $n_i$ due to the capture and release of active PAI-1 molecules by quiescent cells and due to the inactivation of active PAI-1 molecules over time;
2. Molecular exchanges
   (a) internalize individual PAI-1 molecules that collide with the AggreM;
   (b) externalize the appropriate quantity of active and inactive PAI-1 molecules as individual agents;
3. Cell-cell interactions
   (a) repel the neighbouring cells when the density of

cells inside the AggreM implies compression of the cells;

(b) update the frontiers of the AggreM.

### 4.3 Proposed solutions

*Updating $n_c$ and $n_n$.* The calculation of the proportion of necrosed and quiescent cells inside the AggreM requires the ability to assess the proportion of the cells that are more distant from the periphery of the tumour than the threshold $D_n$ (the distance to the surface of the tumour beyond which cells become necrosed). The trouble is that the tumour is generally not circular but may have an irregular shape. These irregularities, however, can mostly be considered as a local flattening and the tumour can thus be globally approximated by an ellipse. We thus introduced a virtual transformation from the actual, ellipsoidal shape of the tumour to an idealized circular shape.

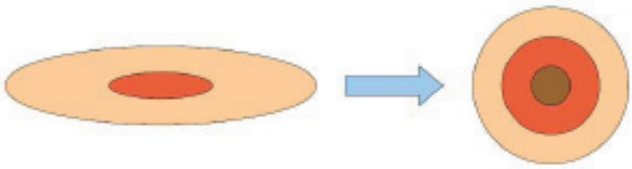

Figure 2. Direct transformation side effect: some internal cells become necrosed although they are less than $D_n$ away from the tumour surface.

The direct transformation from an ellipsoidal to a circular shape will have to preserve access to nutrients for the cells inside the AggreM. Indeed, the transformation from a very flat ellipse to a disk of the same area could provoke, among other undesirable side effects, the appearance of a necrosed core (see Figure 2). To avoid this phenomenon we introduced a virtual disk at the center of the tumour, void of cells. This virtual disk can be considered as a balloon inflated at the heart of the tumour so as to give it a circular shape. Access to nutrients and the area and circumference of the ellipse are therefore retained in this transformation (see Figure 3).

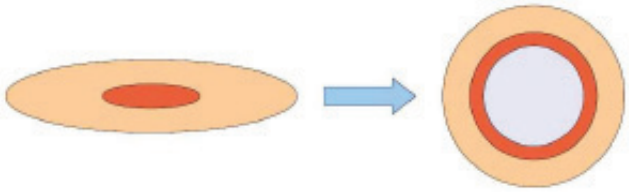

Figure 3. Transformation with the virtual disk.

Any point within the ellipse is distant from the edge of the ellipse by at most $b$ (the semiminor axis of the ellipse). The thickness of the resulting ring of cells should thus be equal to $b$. Mathematically, the transformation must verify the following three equations:

The area of the ellipse is given by:

$$A = \pi ab \tag{1}$$

where $S$ is the area of the ellipse, $a$ the semimajor axis, and $b$ the semiminor axis. The area of the tumour has to be preserved by the transformation. Therefore, the area of the ellipse has to be equal to the area of the whole disk minus the area of the virtual disk:

$$A = \pi(b + r_0)^2 - \pi r_0^2 \tag{2}$$

where $r_0$ is the radius of the virtual disk. The perimeter of the disk has to be equal to that of the ellipse:

$$c = 2\pi(b + r_0) \tag{3}$$

where $c$ is the perimeter of the ellipse.

From these equations, we can deduce the area $A_0$ of the virtual disk:

$$A_0 = \frac{c^2}{4\pi} - A. \tag{4}$$

Let $r_c$ be the radius of cells. If we take $r_c$ to be the length unit and $r_c^2$ to be the area unit, then we can transform eqn (4) to express $A_0$ as a function of the number of cells in the tumour:

$$A_0 = \frac{n_q^2}{\pi} - \pi n_s \tag{5}$$

where $n_q$ is the number of quiescent cells at the fringe of AggreM and $n_s$ is the number of cells inside AggreM. The radius of the tumour is then given by:

$$r_t = \sqrt{\frac{A_0}{\pi} + n_t}. \tag{6}$$

The number of necrosed and quiescent cells (respectively $n_n$ and $n_c$) can now be expressed as:

$$n_n = (r_t - D_n)^2 - \frac{A_0}{\pi} \tag{7}$$

$$n_c = n_s - n_n \tag{8}$$

with $D_n$ being the distance to the surface of the tumour beyond which cells become necrosed

*Updating $n_a$ and $n_i$.* At each simulation time step, the probability for an active PAI-1 molecule to remain free is:

$$P_{still} = (1 - P_c)^{n_r} \tag{9}$$

where $P_c$ is the mean probability for an active PAI-1 molecule to be captured by a quiescent cell inside AggreM and $n_r$ is the mean number of cells in the immediate vicinity of a PAI-1 molecule, thus being able to bind it. The number of PAI-1 molecules that are captured at each time step is then given by:

$$\Delta_a = n_a(1 - P_{still}). \tag{10}$$

A new value for $P_c$, denoted by $P_c'$, can then be computed, which is related to the mean number of uPAR receptors on the cell membranes:

$$n'_{upar} = n_{upar} - \frac{\Delta_a}{n_c} + 1 \tag{11}$$

$$P'_c = \frac{n'_{upar}}{M_{upar}} \tag{12}$$

where $M_{upar}$ is the maximum number of uPAR receptors that a cell can have, $n_{upar}$ is the mean number of uPAR receptors for cells inside AggreM, and $n'_{upar}$ is the new value of $n_{upar}$ for the current iteration (this value has to be maintained in the $[0, M_{upar}]$ interval).

The computation of the new value for $n_a$ is a little bit more complicated since we also have to take into account the inactivation of the oldest active PAI-1 molecules. If we denote by $n_{a,i}$ the number of active PAI-1 molecules inside AggreM of age $i$, and if active PAI-1 molecules become inactive at age $i_{max}$, then we first update the number of inactive molecules:

$$n'_i = n_i + n_{a,i_{max}}. \tag{13}$$

The update of active molecules is then done in the following way:

$$n'_{a,i} = n_{a,i-1} - \frac{\Delta_a}{i_{max}}, \text{ for } i = i_{max} \text{ down to 1} \tag{14}$$

$$n_0 = P_g n_c. \tag{15}$$

*Molecular exchanges.* The management of PAI-1 molecules entering AggreM is quite simple to handle since we can consider that any molecule diffusing into the area defined by AggreM (shown hatched in Figure 4) is integrated in AggreM. It is, however, much more complex to determine precisely how many molecules should be released by AggreM towards the active part of the tumour, and of what types (active or inactive molecules, of what age).

Let us denote by $n_g$ the number of PAI-1 molecules leaving the aggregated model. The expression for $n_g$ is deduced from the hypothesis according to which PAI-1 molecules diffusing inside AggreM have a global dynamics similar to that of the molecules of an ideal gas. Indeed, the number of molecules released by AggreM will be proportional to the "pressure" inside AggreM, which is itself proportional, for a given temperature, to the ratio between the number of molecules and the volume in which they are contained. We recall that the ideal gas law is $pV = nRT$, where $p$ is the pressure, $V$ the volume, $n$ the number of moles of the gas, $R$ the universal gas constant and $T$ the absolute temperature. The pressure is then given by

$$p = \frac{nRT}{V} = \alpha \frac{n}{V}. \tag{16}$$

If we carry out a transformation from three to two dimensions in order to transpose this formula to our case, it becomes:

$$n_g = \alpha \frac{n_a + n_i}{r_c \sqrt{\frac{A_0}{\pi} + n_s}} \tag{17}$$

where $\alpha$ is a constant that we measured experimentally as having the value of 0.21. The measurement has been done by running the agent-based model and by evaluating, if the AggreM had been activated, the number of PAI-1 molecules that would have left the model.

To accelerate the computation we have made the hypothesis that these molecules are shared equally between the $n_q$ quiescent cells delimiting AggreM. Each of these cells thus receives $n_g/n_q$ PAI-1 molecules. For each molecule, a random draw chooses the quiescent cell in which the molecule is released, and another random draw determines whether the molecule should be active or inactive.

*Updating the frontiers of the aggregated model.* As the tumour grows, new quiescent cells have to be internalized. In practice, necrosed cells and quiescent cells that only have other quiescent cells in their immediate surroundings are integrated in AggreM, along with the PAI-1 molecules that are present over these cells (see Figure 4).

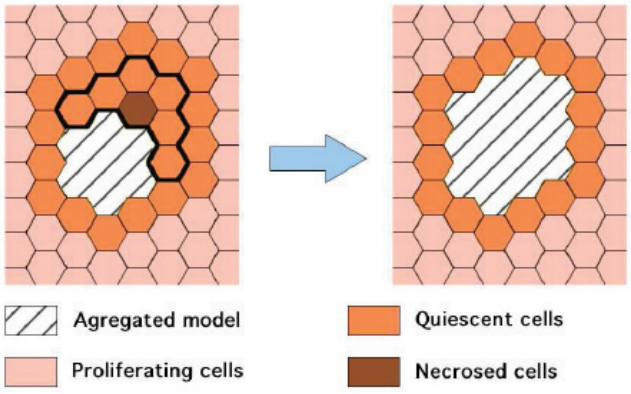


Figure 4. Integrating cells into the aggregated model: cells that are only surrounded by quiescent cells are integrated in AggreM.

Moreover, we have to handle the case when the volume $V_0$ of the virtual disk is negative. This is the sign that the cells in AggreM are compressed and mutually overlapping. It is then necessary to repel each of the quiescent cells of the border towards the closest proliferating cell, such that $V_0$ becomes positive or null again. Practically, we repel the quiescent cells of the border at a distance $\beta$ as soon as $V_0$ is below $\gamma n_s$. The two constants $\beta$ and $\gamma$ were both estimated empirically and set to 1.4, which appears to give good results; that is, provide a good correlation between the hybrid model and the agent model.

## 5. RESULTS

### 5.1 Validation of the aggregated model

A set of tests has been realized so as to measure the consistency between the hybrid multiscale model and the basic agent model. We made a set of 100 simulations for each mode over a period of 32 000 time steps. Figure 5 shows a comparison of the evolution of the different cell and molecule populations over time, showing a very good correlation. This result is confirmed by statistical measures made over the last 100 time steps to evaluate the relative distance between the two models, expressed as a percentage and computed with the following formula:

$$\frac{\left|val_{hyb} - val_{agt}\right|}{val_{agt}} \qquad (18)$$

where $val_{hyb}$ is a given value (e.g. number of cells of each type, number of PAI-1 molecules of each type, etc.) measured in the hybrid model and $val_{agt}$ is the corresponding value for the pure agent model. Results are shown in Tables 1, 2 and 3.

Table 1. Relative distance between the two models computed using eqn 18 for the different populations of cells.

| | proliferating | quiescent | necrosed |
|---|---|---|---|
| Mean | 1.18 | 3.30 | 1.44 |
| Standard deviation | 0.91 | 1.46 | 0.94 |

Table 2. Relative distance between the two models computed using eqn 18 for the different types of PAI-1 molecules.

| | soluble | matrix bound |
|---|---|---|
| Mean | 3.1 | 5.98 |
| Standard deviation | 0.89 | 0.93 |

Table 3. Relative distance between the two models computed using eqn 18 for the number of matrix bound PAI-1 molecules available on the fringe of the tumour.

| | min | mean | max |
|---|---|---|---|
| Mean | 21.79 | 10.76 | 4.65 |
| Standard deviation | 5.64 | 1.56 | 2.53 |

At the end of each simulation, a horizontal section of the model has also been obtained. This corresponds to a series of measures of the quantities of active, inactive and matrix-bound PAI-1 molecules present in the vicinity of regularly spaced points on a horizontal axis passing through the centre of the tumour. Also, we measured the mean quantity of matrix-bound PAI-1 molecules available to cells at the fringe of the tumour. Figure 6 shows both a comparative evolution of this last measure and a horizontal

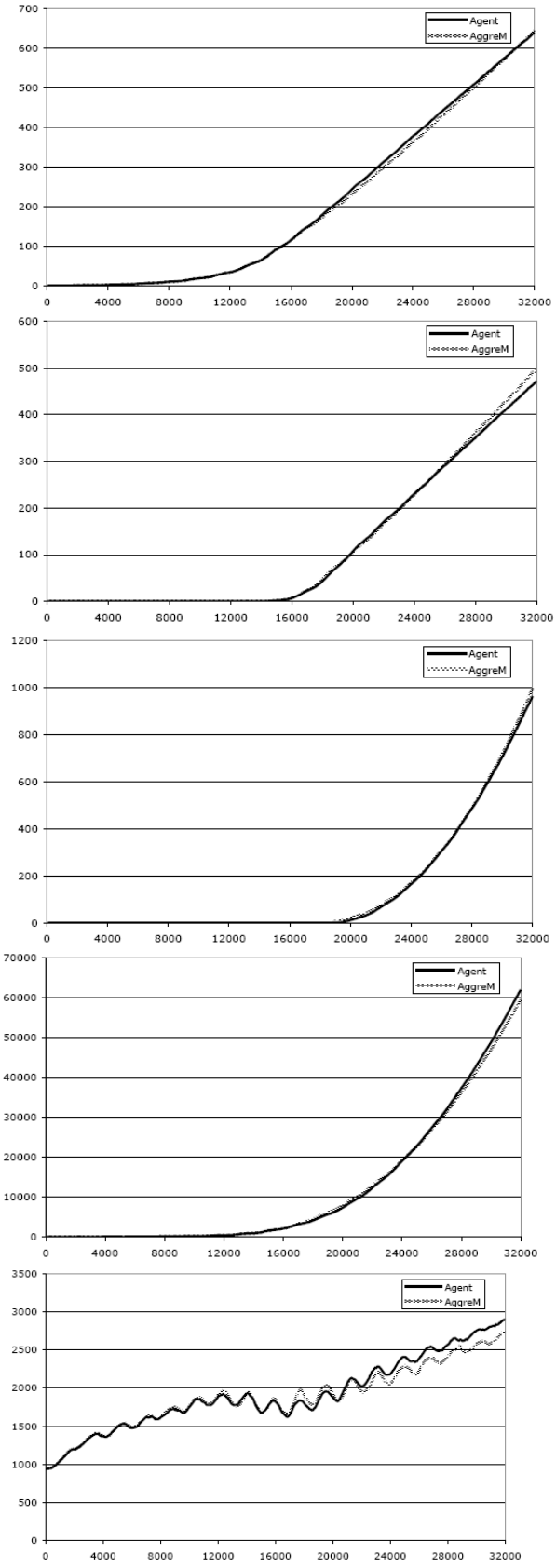


Figure 5. Comparison of the evolution of the number of (a) proliferating, (b) quiescent, (c) necrosed cells, (d) soluble and (e) matrix-bound PAI-1 molecules in the hybrid [AggreM] and agent [Agent] models; the abscissa corresponds to the number of simulation time steps while the ordinate corresponds to the number of cells (a,b,c) or molecules (d,e).

section for matrix-bound PAI-1. Again, this clearly shows a very good correlation between the two models, despite the stochasticity.

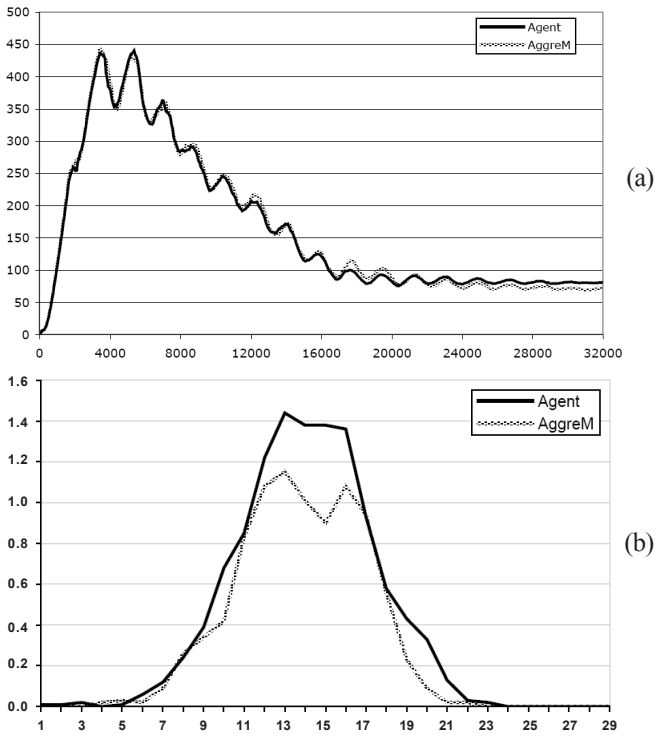


Figure 6. (a) Comparison of the evolution of the mean number of matrix-bound PAI-1 molecules during a simulation (time steps in the abscissa); (b) cross-section of the number of matrix-bound PAI-1 molecules (in the ordinate) available at the fringe of the tumour (abscissa: distance from the centre of the tumour in arbitrary units).

### 5.2 Computing cost improvement

We also evaluated the efficiency of the two models with respect to the computing time necessary to run simulations. The simulations have been sliced in 1600 time steps intervals, and we have measured the time necessary to execute each of these intervals. Figure 7 shows the comparative results for the two models.

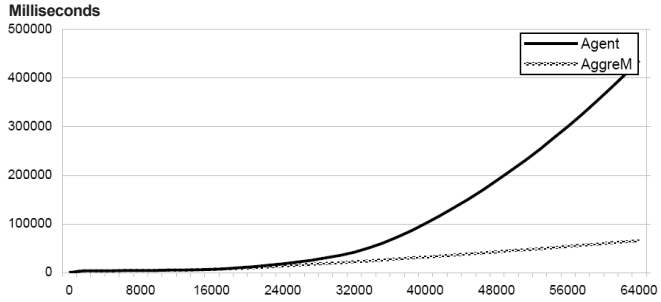


Figure 7. Comparative evolution of the computing time (ordinate) needed to run successive simulation intervals of 1600 time steps (abscissa: simulation time steps).

We notice that, while the growth of computing time related to the agent model is purely exponential due to the exponential increase of the number of cells and molecules, the growth of computing time when the aggregated model is activated appears to be linear.

At iteration 64000, for a total of nearly 13500 cells, the performance is already almost 7 times faster. This thus allows us to envision huge gains of computation time for simulations where the number of agents increases further. Indeed, because of the linear rather than exponential increase of the computing time with the size of the tumour, the gain is all the more important when the system is large.

## 6. CONCLUSION

We have shown in this study that it is possible to introduce higher level abstractions into agent-based models. This enables, with modifying neither qualitatively nor quantitatively the dynamics of the system, to very significantly reduce the computing load necessary to run simulations. This is very important because it opens the way to several crucial modelling perspectives. The first one is to be able to run larger simulations; that is, simulations of bigger tumours. The second is to run simulations with greater details, for example by improving the modelling of the extracellular matrix or by modelling the reorganization of the cytoskeleton of cells at the border of the tumour under the action of matrix-bound PAI-1. The third one is to enable a better calibration of the model by reducing the time necessary to evaluate a given set of parameters, thus allowing the testing of many more parameter sets.

The work on the hybrid model can be extended in several directions. The first one is to further improve the coherence between the two models by calibrating more precisely the values of the constants $\alpha$, $\beta$ and $\gamma$, either empirically or by automatic methods. One may argue that this is very *ad hoc* and could not be transposed easily to other kind of models. This issue is real and this is why we are developing a parallel research focused on detecting and characterizing emergent structures so as to automatically reify these structures as higher-level agents.

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