Poster Presentation Abstract, The 7th International Conference on Systems Biology, Yokohama Japan, 9-11 October 2006 (ICSB-2006)

Study of Early Tumour Development and its Glycolytic Properties

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It is believed that the growth of tumours is mediated by an increase of acidity of the tumoral environment that is lethal to normal cells but still allows for the growth and duplication of tumoral cells[2, 3]. This acidity would be caused by a highly glycolytic metabolism of the tumoral cells that would be under selection during an anaerobic stage of tumour growth and cause an overproduction of lactic acid exported from the cell to the extra-cellular environment. Early studies of Pasteur and Warburg Effects[4] show that cells consume glucose and produce lactic acid differently depending on the oxygen availability and on the cell state (normal or tumoral).

In this work a tumour development model is created using Tsim (Tissue Simulator) in order to validate the acid-growth dependent hypothesis. Previous works have concentrated their models on the extra-cellular dynamics of diffusion of glucose, oxygen and lactic acid but in this work the glycolytic metabolism is also considered and represented by a set of differential equations obtained from literature[1].

The results are also compared to in vivo experiments that propose that tumour growth can happen due to other mechanisms other than lactic acid over-production[5].

This research is, in part, funded by Capes (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior).

Model Implementation:

This model was created using TSim (Tissue Simulator) and re-using the kinetics of glycolysis of Beta-cells model.

In this model we implemented two kinds of cells: the first one is healthy and generates a minor quantity of acid, most of the glycolytic flux goes into the Citric acid Cycle and very little is used to produce lactate.

The second type of cell is a tumoral cell. This cell has two differences when compared to a normal cell:

1. No negative feedback on the uptake of glucose from the Citric Acid Cylce. This feedback is believed to exist in normals cells to avoid over production of glucose derivatives and thus acidity;
2. 10% increase in the speed of the reaction that produces lactic acid from pyruvate;

Interestingly, the loss of negative feedback is not enough to generate acid-mediated tumour invasion in this model, thus the increase in the production of acid seems to be essential for tumour growth.

However the increase in the reaction speed of lactic acid generation cannot be higher than 20% otherwise the tumoral cells will generate too much acid and will die themselves.

Below we report the behavior of three models created for this study:

1. Model with 1 healthy cell, 1 tumoral cell and one blood vessel access;
2. Model with 4 blood vessel accesses, 8 healthy cells and 1 tumoral cell;
3. Model with 30 healthy cells, 10 blood vessel accesses and one tumoral cell;

In all these models, healthy cells are induced to apoptosis by low pH levels (6.8) while tumoral cells will resist until a lower pH (6.0).

As proposed by Gatenby et al[2] the acid-induced apoptosis mechanism can explain the invasion of healthy tissues by tumoral cells as well as the low pH in tumoral regions.

The higher glucose consumption of glucose from tumoral cells also copes with the theory of disabled negative feedback on glucose uptake.

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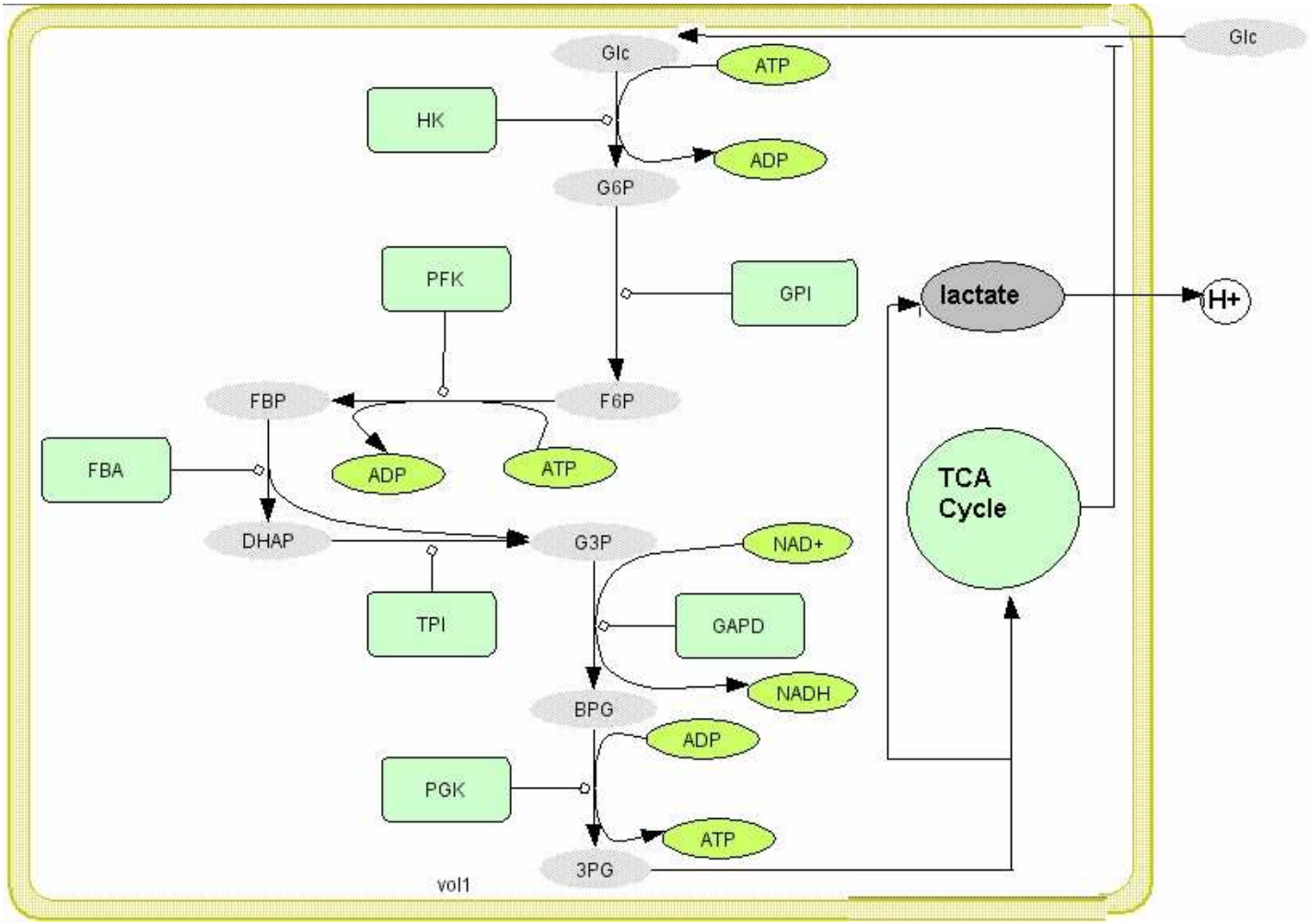

Figure 1: Model simulated, including a negative feed-back from Citric acid Cycle on the intake of glucose.

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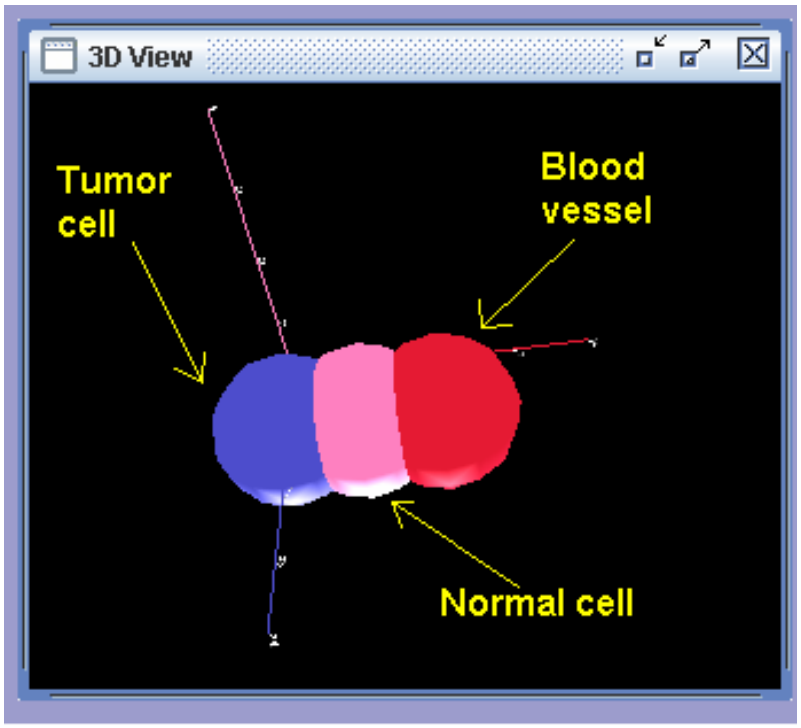

Figure 2: Model with one normal cell, one tumoral cell and one blood vessel access.

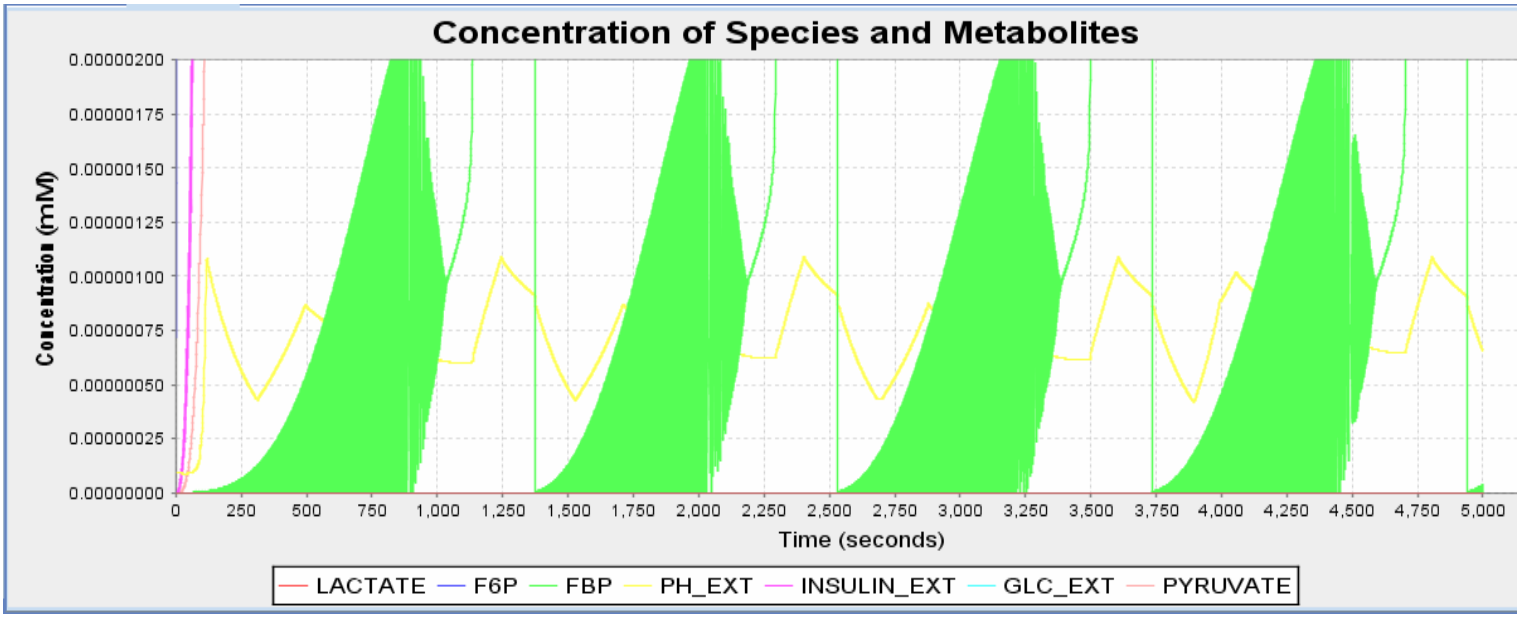

Figure 3: Progression of [H+] (pH in yellow) in the neighborhood of the cell marked as Normal Cell in Figure 1. The discontinuities are due to cell death (positive slope) or a new cell occupying the slot after mitosis of a neighbor cell (negative slope).

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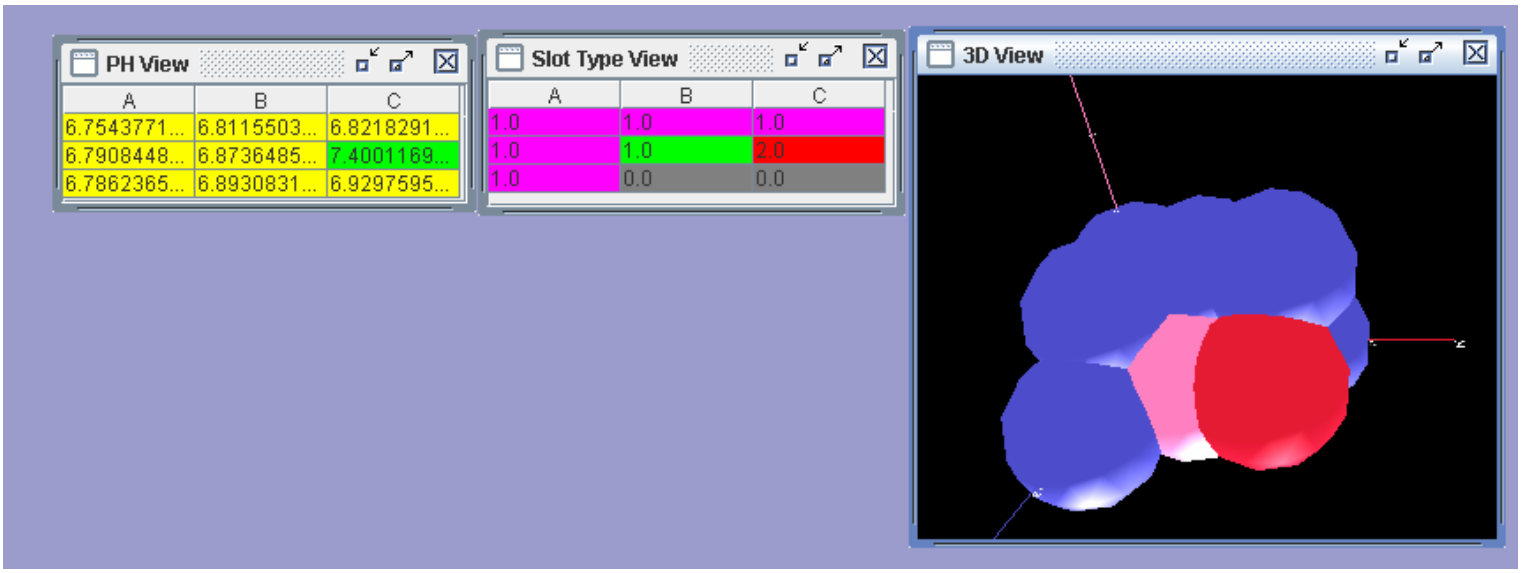

Figure 4: Invasive behavior of tumoral cell occupying the empty space and lowering pH in the vicinity.

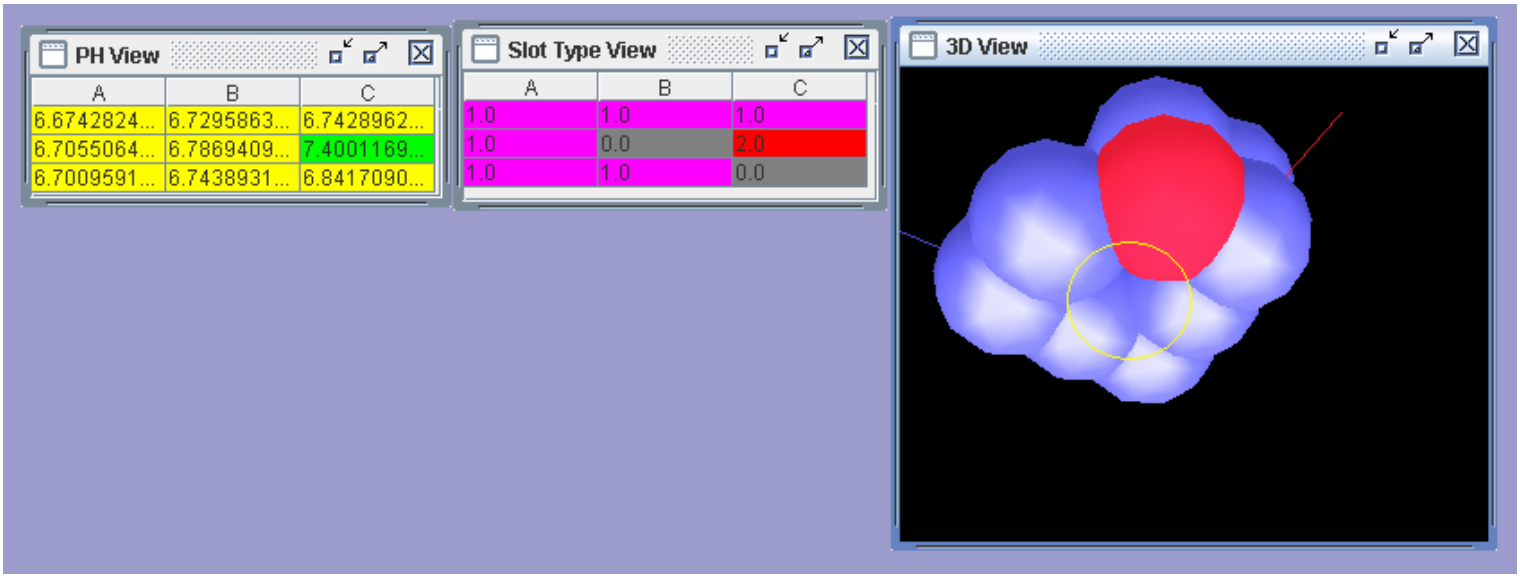

Figure 5: Low pH causes normal cell death by apoptosis, see the empty space between the tumoral cells and blood vessel where normal cell was located previously.

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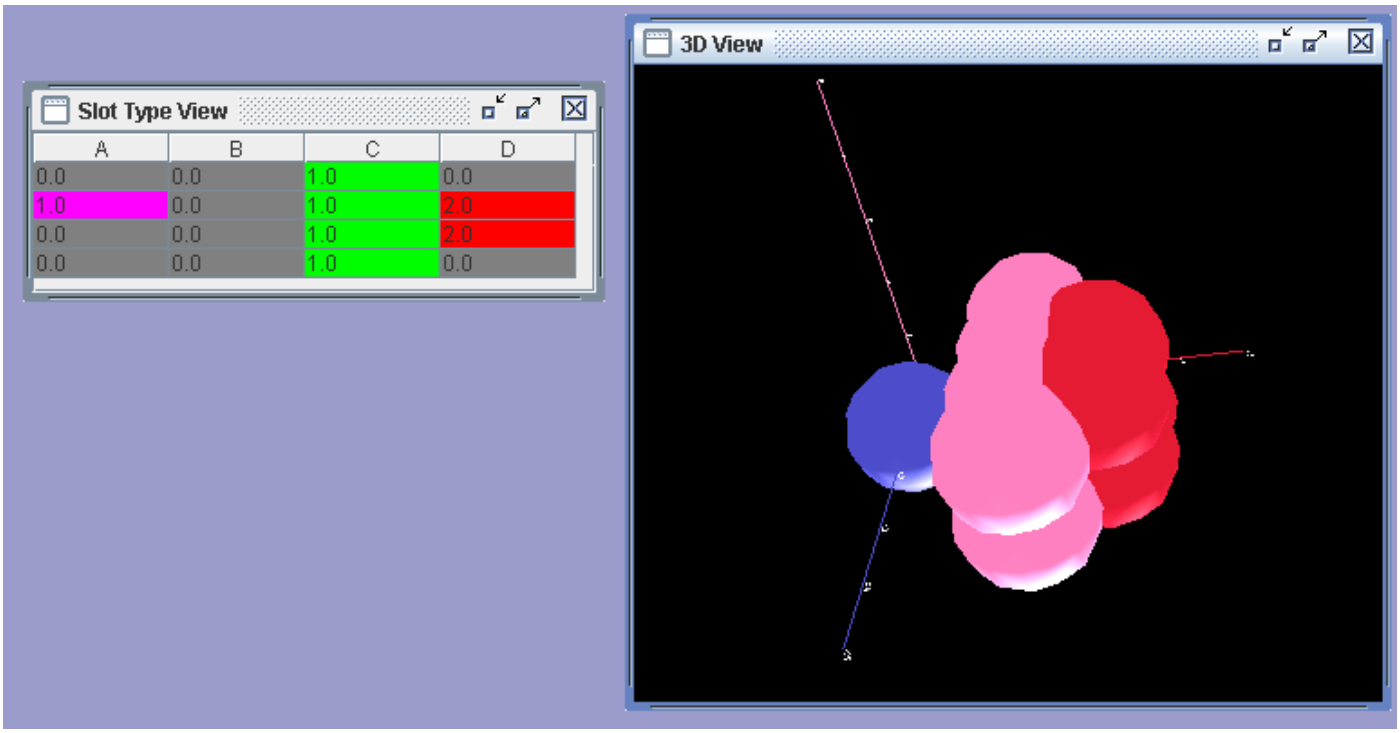

Figure 6: Model with 4 blood vessel accesses, 8 normal cells and one tumoral cell 2-cells away from blood access.

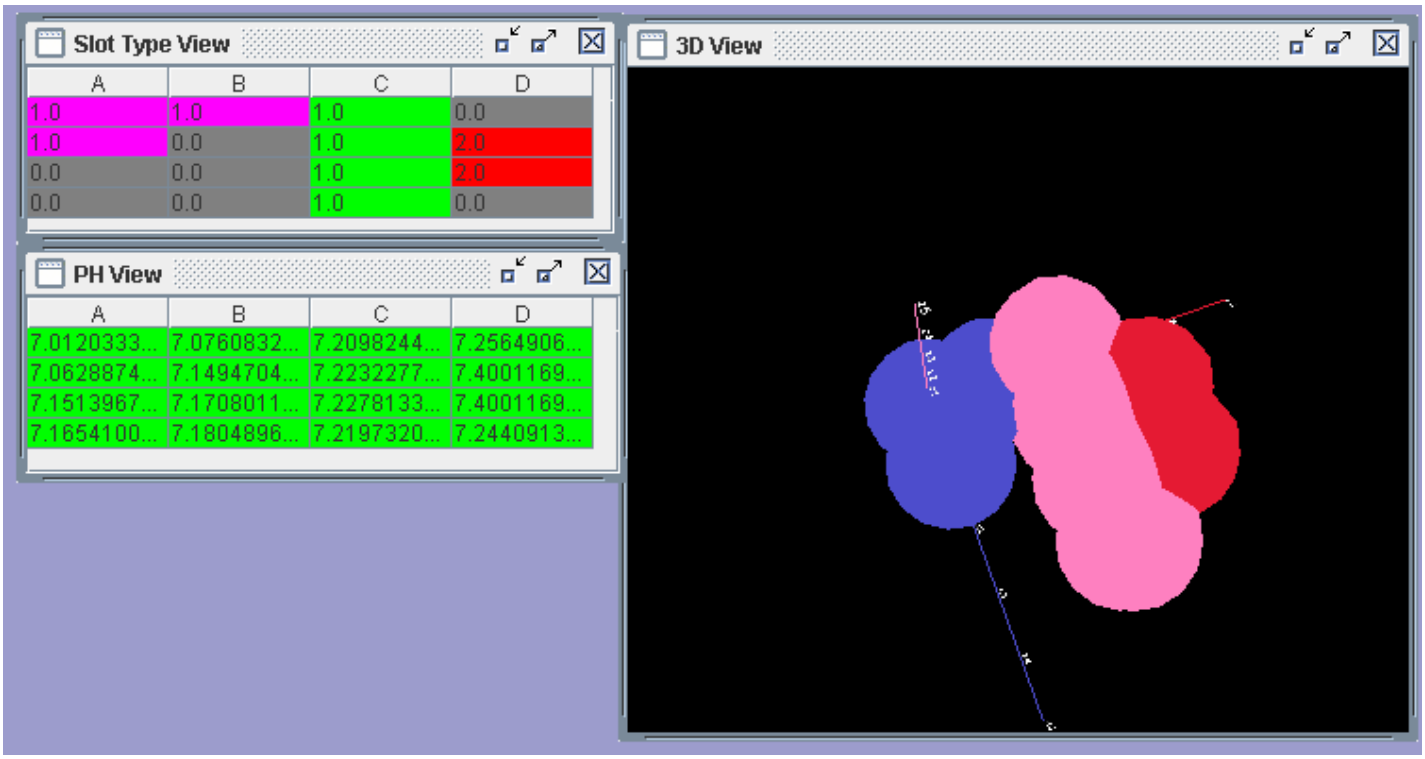

Figure 7: Tumoral cell duplicates into empty space and lowers pH in its vicinity.

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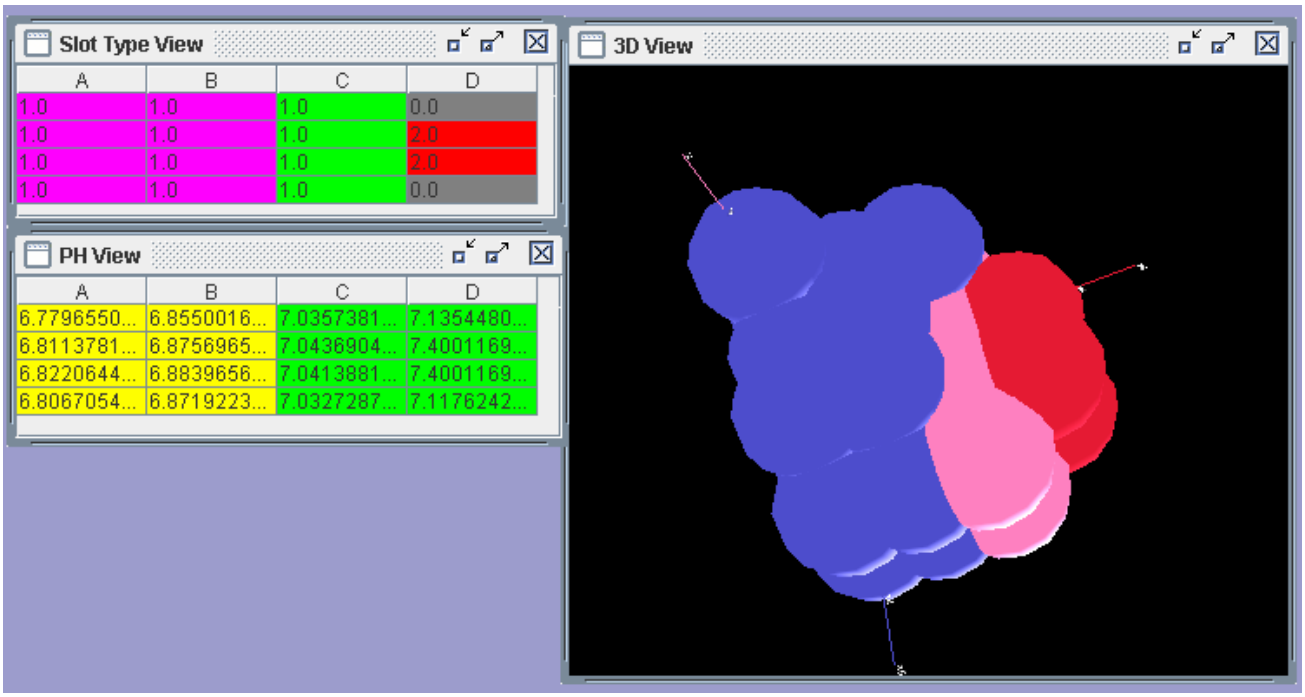

Figure 8: Tumor mass surrounds the healthy tissue imposing a reasonable amount of acid inflow lowering the healthy cells's environment.

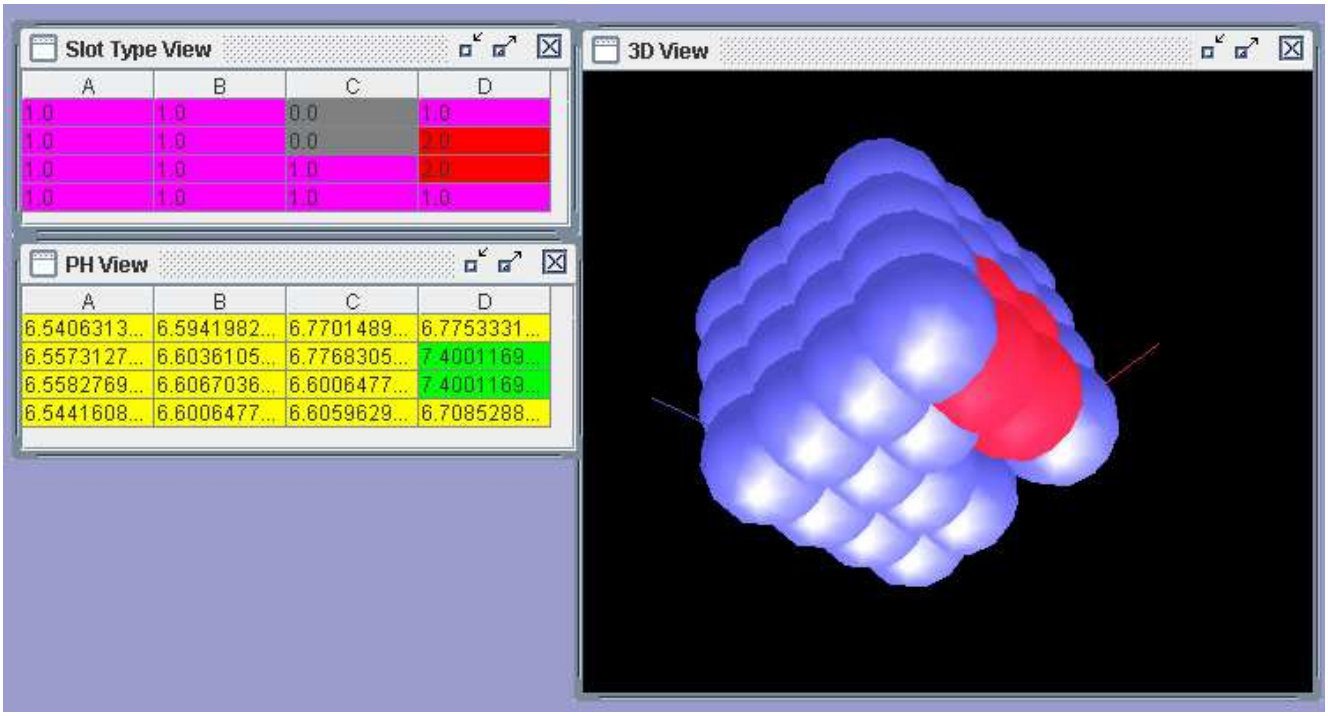

Figure 9: After reaching the apoptosis-inducing pH level, the normal cells die and the tumoral cells occupy their place.

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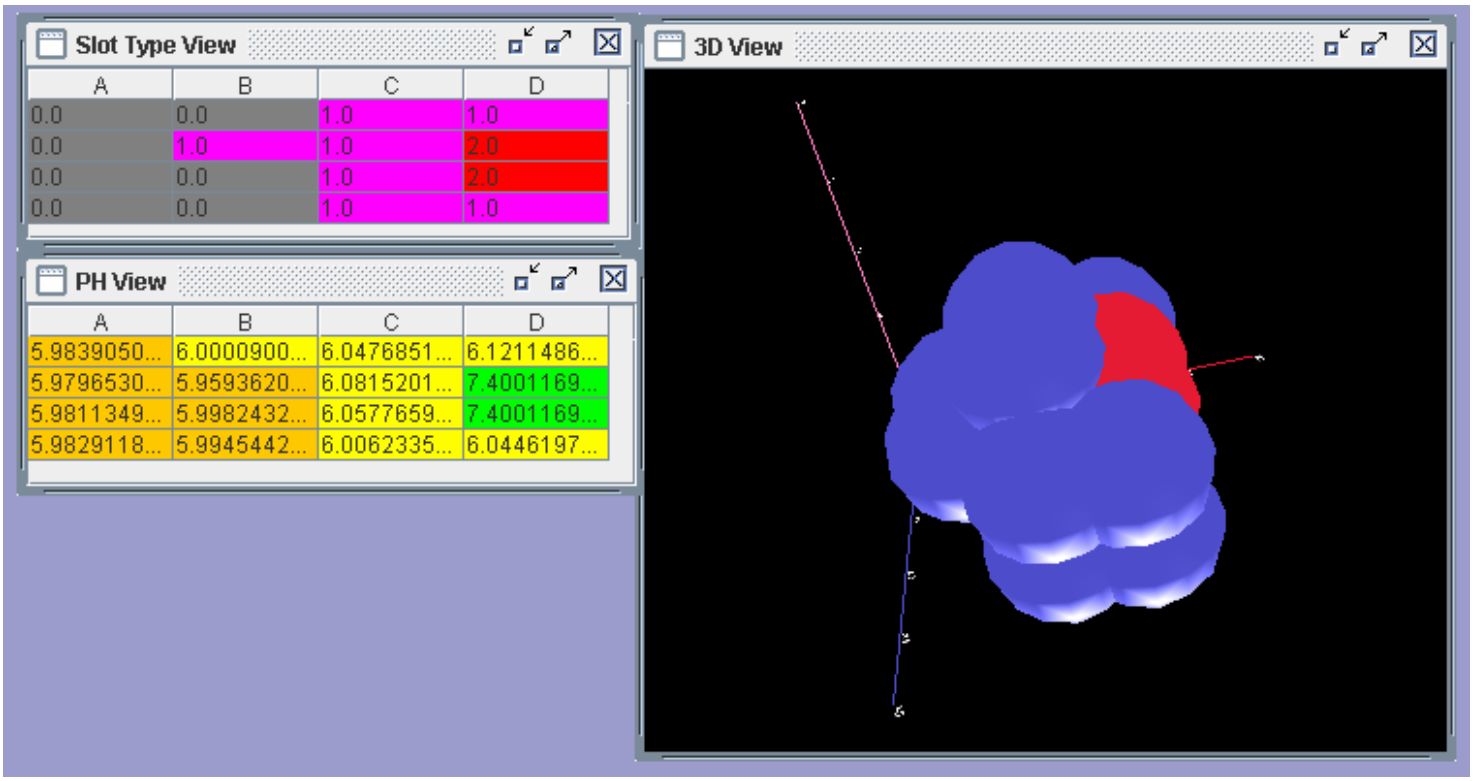

Figure 10: As tumour continues to produce acid, the cells that are more far away from blood vessels will die due to unbearable acid levels and then tumour will shrink. After acidity is dispersed in the environment the tumour will grow back again.

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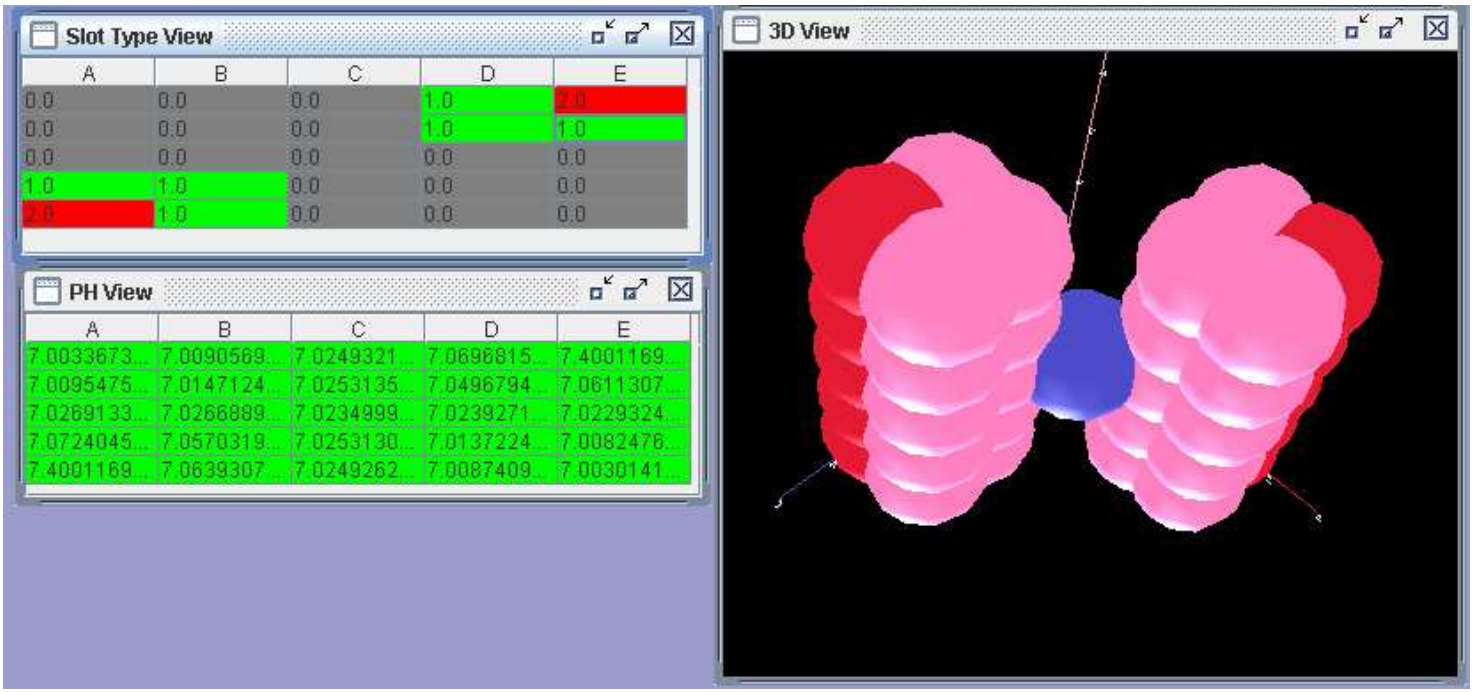

Figure 11: Model with 10 blood vessel accesses, 30 healthy cells and one tumoral cell.

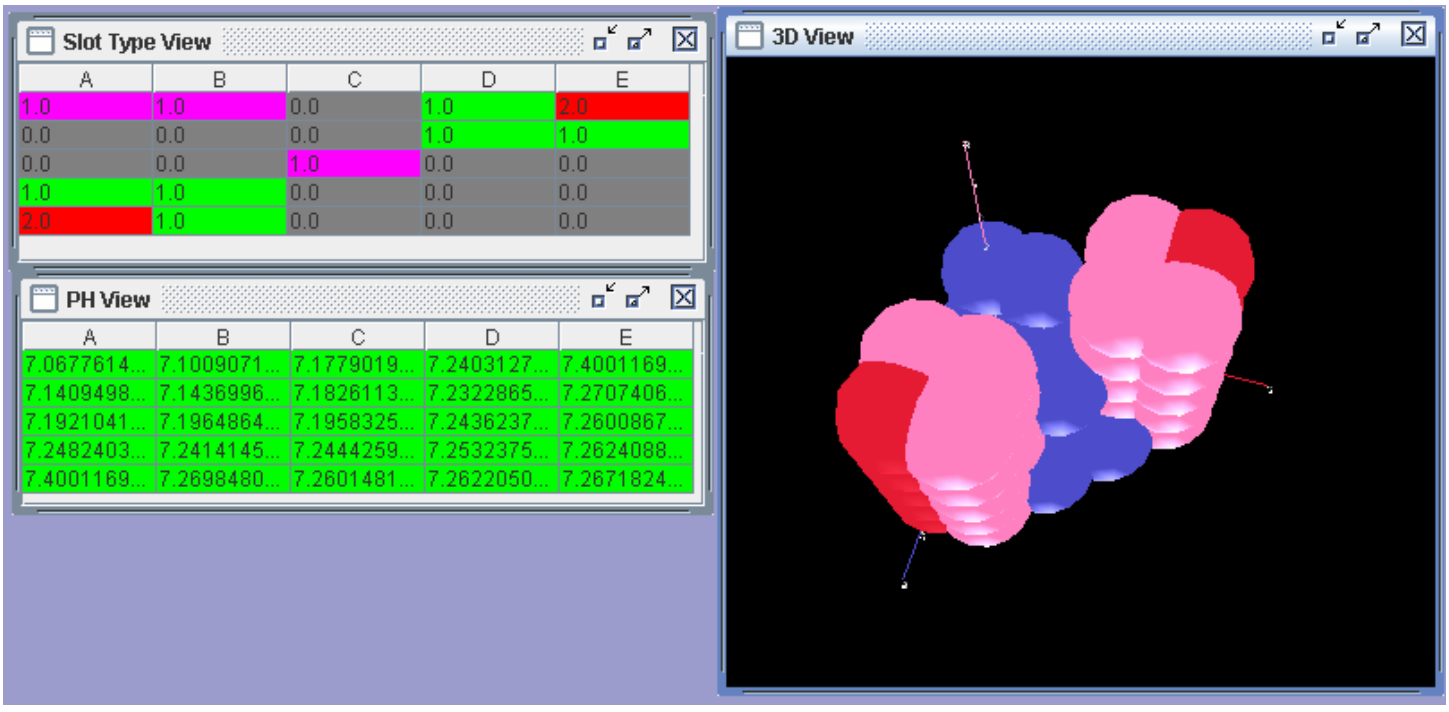

Figure 12: Initially the tumour mass is not capable of generating enough acid to promote apoptosis in the neighboring cells so the tumour will only grow into the empty region.

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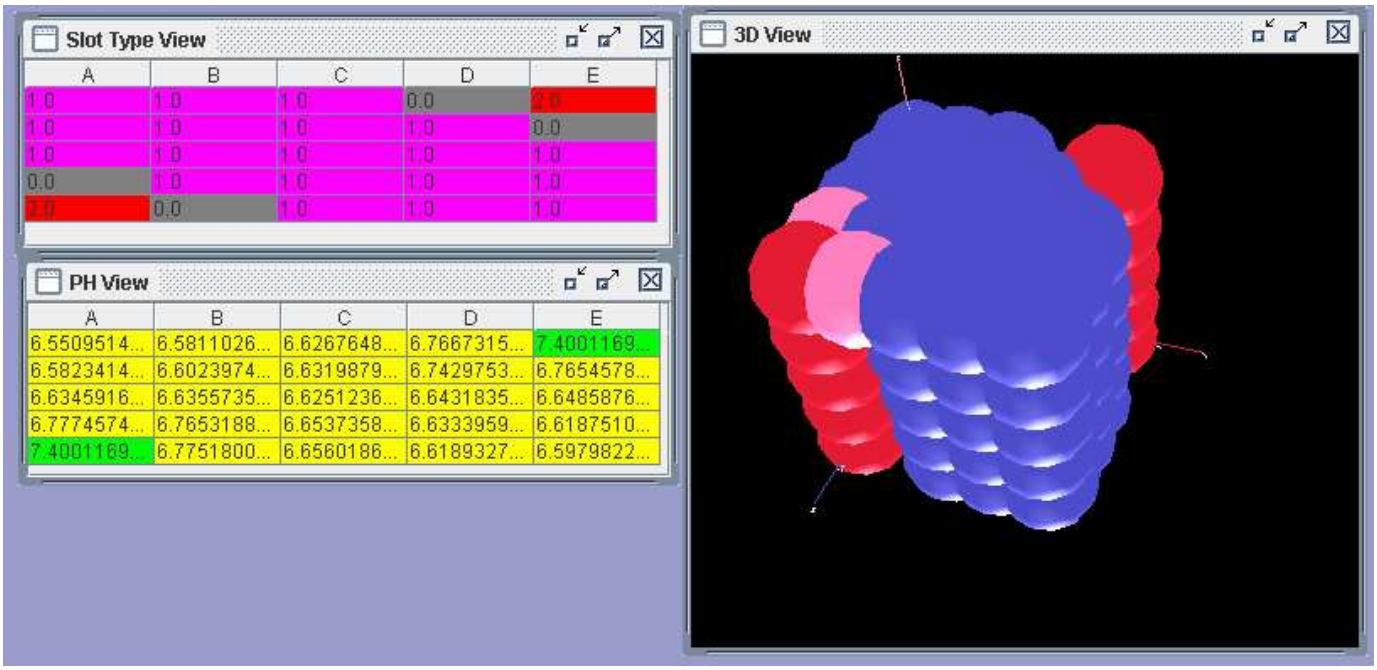

Figure 13: After reaching a critical mass, the tumour lowers the pH enough for causing apoptosis in most healthy cells. Notice that the center of the tumour has the lowest pH and is a candidate to host the necrotic core of the tumour.

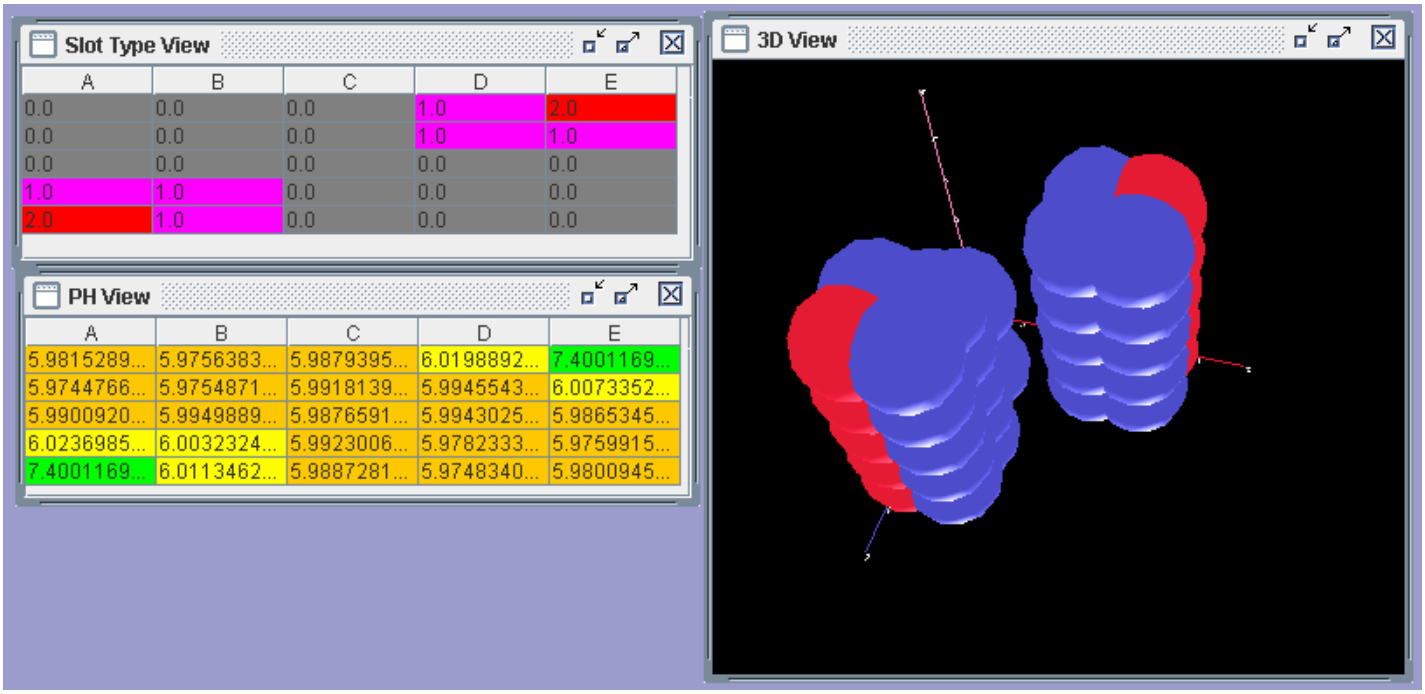

Figure 14: Because of the vertical conformation of the blood vessels, instead of forming a necrotic kernel, there is a formation of a vertical gap between the two tumoral masses.

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Next Steps:

Our models still do not include the process of "anaerobic glycolytic selection" proposedby Gatenby et al[2]. This process would explain how the cells with higher glucose uptake and higher production of acid would proliferate faster than cells without these mutations.

In order to implement this selective process our new models will include a pO2 gradient that will create areas where there's not enough oxygen for the cells to use the Citric acid Cycle to produce energy. The cells in this region would then suffer a selective pressure that would favor those that have a disabled glucose uptake negative-feedback mechanism.

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