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Agent Based Cancer Survival and Growth Simulation Utilizing Angiogenic and Hypoxic Environments

PROBLEM STATEMENT:

Ideal environments, in reality and modern science, are hard to come by. Resources and the lack thereof results in a need for a new modern way of testing and creating models that enable researchers to gain insights into how certain biological processes occur-in faster and more efficient ways. Through computational and systems biology, we have learned of how mathematical ideologies and biological processes intersect, creating scenarios where the mathematical modeling of these processes results in incredibly accurate simulations of reality. One area of research where these intersections meet is the simulation of tumor models utilizing the modeling technology of modern computer science. For our group project we decided to implement an Agent-Based model regarding the propagation of cancer cells in a layered petri dish with three types of cells (Capillary O2 suppliers, Cancer Cells, and Normal Cells). In order to measure the impact of O2 availability on human cancer utilizing Mesa, we had to determine how exactly cancer cells signaled capillary cells and O2 providers to create oxygen pathways for angiogenic tumor growth. In a study conducted by Dr. Carmeliat at the University of Leuven found that "Vascular endothelial growth factor (VEGF) is a homodimeric glycoprotein with a molecular weight of approximately 45 kDa. It is the key mediator of angiogenesis (the formation of new blood vessels), and binds two VEGF receptors (VEGF receptor-1 and VEGF receptor-2), which are expressed on vascular endothelial cells" (Carmeliat 1). In human cells, VEGF promotes embryonic cell growth and for tissue repair when the body is damaged. When a given cancer cell is under stress/duress (hypoxic in some cases) it may either die or create these VEGF angiogenic growth factors to provide new pathways for oxygen supplies. The production of

VEGF and other growth factors by the tumor results in the 'angiogenic switch', where new vasculature is formed in and around the tumor, allowing it to grow exponentially due to a boundless supply of oxygen and nutrients. Blood vessels are irregularly shaped, tortuous, have dead ends and are not organized into venules, arterioles and capillaries. They are also leaky and hemorrhagic, which leads to high interstitial pressure. These characteristics mean that tumor blood flow is suboptimal, resulting in hypoxia and further VEGF production. Thus, the study of VEGF propagation is vital in cancer therapy research as the inhibitions of these facts would make cancer cells hypoxic leaving them to be destroyed without the ability to increase in size further. Our model pushes to understand the connection between these angiogenic growth facts and tumor growth, and thus utilizing python mesa we have been able to create a model that shows how VEGF and oxygen consumption allows for tumor growth in a small petri dish simulated environment. This report aims to tell the reader how we have done this given the research and technologies mentioned.

BACKGROUND

In choosing our modeling software a paper done by Ghazal Tashakor and Remo Suppi titled “AGENT-BASED MODEL FOR TUMOR-ANALYSIS USING PYTHON+MESA” was incredibly useful with regards to determining how our approach would fare using this package. Dr. Tashkor found that using Python and Mesa allowed him to easily create biological networks that accurately modeled these phenomena. However, his research group's implementation simply showed how the agent based modeling software accurately showed how cell propagation worked utilizing graph networks. The group determined that “Since lumped models just provide a quantitative prediction of tumor size over time with only a few parameters and very low computational results, they would not be enough for an explicit investigation of many other events such as spatiotemporal dynamics of oxygen and nutrients or cell to cell interactions” (Suppi 4).

Due to this limitation, we implemented an In Silico model referring to “computational models of biology and it has many applications. It is an expression performed on a computer simulation. In Silico models are divided into three main categories (Thorne, Bailey, & Peirce 2007;Soleimani et

al., 2018): 1. Continuum based models which solve the spatiotemporal evolution problems of density and concentration of cellular population in the tumor microenvironment. 2. Discrete or agent based on a set of rules which change the cells' states and manage the cells' interactions within the tumor microenvironment. 3. Adaptive Hybrid models which integrate the above solutions." Specifically our environment modeled an adaptive hybrid model which integrated both solutions. With Oxygen distribution and VEGF propagation modeling we were able to encapsulate this interaction within a simulated petri dish environment using these specific modeling techniques.

Oxygen is essential to all life and its biological processes, and for our modeling purposes we determined a structure where every cell was predetermined with an oxygen level and each cell would consume a certain amount of oxygen during each step. If a cell died it would still appear on the grid, however it would become a small dot and easily be replaced by a malignant tumor cell. Essentially the goal of the tumor cell would be to produce as much of itself as possible. Survival would be entailed entirely on oxygen levels, and capillary cells would be the provider of nutrients and proteins. Essentially the predicted behavior would be that cancer cells would be producing high levels of VEGF if under duress or probably hypoxia. This would lead to VEGF angiogenic factors being produced outward in order to search for an oxygen supply. If not found in a sufficient amount of time the cancer cell would undergo hypoxia. However if VEGF angiogenic factors manage to interact with capillary cells, it would result in capillary cells beginning to crop out to the source of the VEGF production creating a pathway for oxygen to the cancer cell leading to the creation of more cancer cells. According to a study conducted by the Abramson Family Cancer Research Institute at University of Pennsylvania, the research team stated that "Ambient air is 21% O2 (150 mm Hg); however, most mammalian tissues exist at 2%-9% O2 (on average 40 mm Hg). "Hypoxia" is usually defined as ≤ 2% O2, while severe hypoxia or "anoxia" is defined as ≤ 0.02% O2." (Bertout 1). The following pseudocode determines if a cancer cell begins generating VEGF given certain factors after a given number of "steps":

```
for t in targets:
    roll = r.random()
```

```
    if self.oxygen > ss.CANCER_OXYGEN_DUPLICATION_LIMIT and
    type(t).__name__ == "Empty" and roll <
    ss.CANCER_DUPLICATION_CHANCE:
        self.subtract_oxygen(ss.CANCER_DUPLICATION_OXYGEN_COST)
        coord = t.pos
        self.model.grid.remove_agent(t)
        self.model.grid.scheduler.remove(t)
        new_cancer = Cancer(coord, self.model,
        vegf_mutation=self.vegf_mutation)
        #Cell_Dict['cancer'] = Cell_Dict.get('cancer') + 1
        self.model.grid.place_agent(new_cancer, coord)
        self.model.grid.scheduler.add(new_cancer)
```

Cells are be considered hypoxic and have a chance of dying if the following code is executed:

```
if roll > 0.4 + (self.oxygen)* 0.1:
                new_empty_agent = Empty(self.pos, self.model)
                coord = self.pos
                self.model.grid.remove_agent(self)
                self.model.grid.scheduler.remove(self)

                self.model.grid.place_agent(new_empty_agent,
                coord)
                self.model.grid.scheduler.add(new_empty_agent)
                print(type(self).__name__, "died at" , self.pos)
```

According to a study conducted by Dr. Snyder at the Department of Medicine, Division of Pulmonary and Critical Care Medicine, Northwestern University Medical School, the researchers stated that “The BCL-2 family of proteins regulate cell death in response to anoxia (0–0.5% O2). By contrast, under hypoxia (0.5–3% O2), mitochondrial oxidative stress activates hypoxia-inducible factors (HIFs) to promote cell survival.” Using our prior research and the analysis of given models and factors we determined the percentage of each of these factors in the ***sim_settings.py*** file as shown below:

```
CELL_DEACTIVATION_MIN_STEPS = 350
MAX_OXYGEN_CAPACITY = 100
CAPILLARY_GROWTH_FRACTION = 0.85
# limit on the number of capillaries around the new one
CAPILLARY_GROWTH_DENSITY_LIMIT = 4
CANCER_OXYGEN_CONSUMPTION = 10
CANCER_OXYGEN_VEGF_LIMIT = 30
CANCER_OXYGEN_DUPLICATION_LIMIT = 30
CANCER_DUPLICATION_CHANCE = 0.5
CANCER_DUPLICATION_OXYGEN_COST = 20
CANCER_VEGF_SUPPLY = 40
CANCER_VEGF_CHANCE = 0.05
NORMAL_OXYGEN_CONSUMPTION = 1
CELL_OXYGEN_CONSUMPTION = 1
```

Desired values can be changed to fit other models and environments, but as this is given our model was generalized and the numbers were obtained from the papers cited, specifically “Mitochondrial regulation of cell survival and death during low-oxygen conditions.” , “The impact of O2 availability on human cancer.” and “ VEGF as a key mediator of angiogenesis in cancer” for VEGF properties.

DECOMPOSITION OF THE PROJECT:

Vishaal Yalamanchali did hefty research on the biology behind the problem statement and contributed to the data collection and creation of result data. In addition, Vishaal contributed towards the creation of this paper and created some slides for the oral presentation.

Pooya worked on literature review to come up with the research idea and problem statement. He further contributed to the implementations of the simulation and the code.

Raghav Verma worked on researching the project and found the initial code the project was forked from. He later contributed to the slides, final report and marginally to the code.

CODING THE PROJECT:

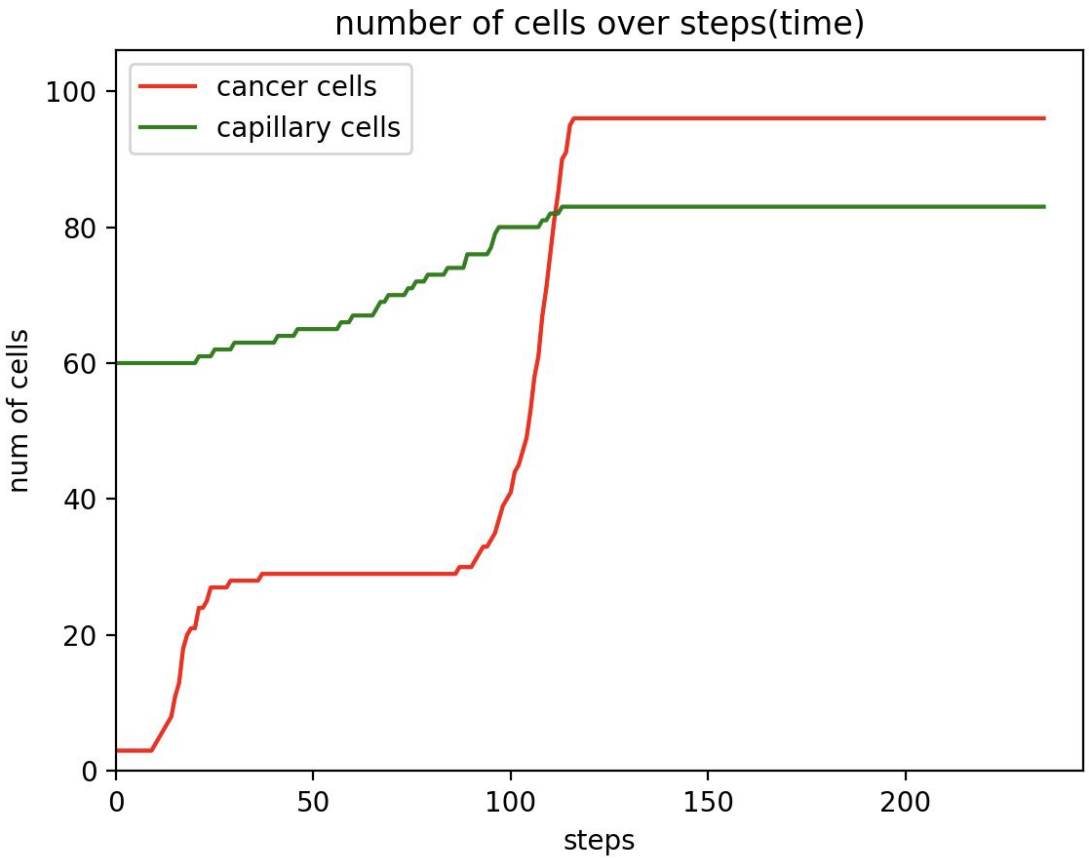
Initially, our group found this repo https://github.com/shippy/cell-activation-model which had a really simple model for cell activation in the python mesa environment. After forking the code from the repo, we modified the visualization to show an overlay of the model itself and the VEGF spreading throughout the other grid. Class hierarchy was created where there was the base class **Cell** and the following cells (**Capillary, Cancer and Normal)** were subclasses. During each step each cell is evaluated iteratively through the entire network where there is an evaluation done on the amount of oxygen within the cell and from there new states and new cells are determined based on these decisions. In this state space all cells consume oxygen, and capillary cells provide the nutrients required for tumor growth. Thus the problem becomes a graph search for the cancer cell to find the closest capillary cell and utilize VEGF growth factors in order to create the capillary tissue.

RESULTS:

After a series of tests and simulations we decided that placing the capillary wall to the right side and have the cancer cell begin its life on the left of the wall would be the best way to demonstrate the properties mentioned above. In our environment there are two grids, the top one containing the actual cell model with the cells colored red, green, and purple each indicating capillary cell, normal cell and cancer cell respectively. The placement of the initial cancer cell is

randomized, as is the layout of the normal cells and empty spaces. Approximately 30% of the remaining spaces are occupied by normal cells and 70% are unoccupied.

We found that the time taken for observing exponential growth in the number of cancer cells is directly correlated with the distance of the initial cancer cell from the capillaries. We also found that the number of cancer cells is inversely correlated with the number of alive normal cells, as both cells have to compete for the same amount of oxygen but cancer cells can multiply quickly.



The simulated behavior falls in line with our expectations from reading the aforementioned research papers, that when cancer cells are given enough time to produce high levels of VEGF, a sharp increase in the size of the tumor is observed, before it stabilizes to an elevated value. The size and reach of the capillaries gradually grows as the concentration of VEGF increases and the capillaries advance towards the cancer cell. Once the cancer cell begins receiving oxygen and stops producing VEGF, the rate of growth of the capillaries slows down and eventually they stop

growing. As the tumor is exposed to more and more oxygen and nutrients, the number of cancer cells grows exponentially, quickly occupying large parts of the petri dish before stabilizing.

CONCLUSION:

The results of our simulation indicate that VEGF plays a major role in the angiogenesis of cancer. Our results also demonstrate the presence of an 'angiogenic switch', allowing new blood vessels to quickly form around the tumor, leading to exponential growth. Although once tumors are sufficiently large enough they are not as dependent on deriving nutrients and oxygen from blood vessels, VEGF is key to early cancer growth (when tumors are 1-2 mm in diameter). This indicates that early VEGF regulation may be helpful in controlling the spread of cancer. Our findings are consistent with medical literature and indicate that our biological model is accurate.

By utilizing Python and Mesa, we have been successful in creating a computational representation of the propagation of cancer cells in a petri dish and simulating how VEGF and oxygen consumption leads to tumor growth. Our project delineates how the rapid growth of tumors can quickly overwhelm the body, drawing resources away from critical functions leading to eventual collapse of the larger biological system.

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