The Effect of Cellular Interactions on Cancer Cell Growth Using Evolutionary Game Theory

Mihir Paithane, Student
Science, Technology, Engineering, and Math (STEM) Center at Mills E. Godwin High School

Abstract:

Cancer progresses through the spread of invasive malignant cells causing normal cells to decrease in proportions. The main reasons for these phenotypes are genetic mutations, but surrounding cells and microenvironments add to the inclination towards certain phenotypes. Game theory is a series of mathematical analyses that allow for the prediction of situations based on the outcomes of interactions between "players". The game theory can be applied to biological situations in the sense that they can attempt to predict the proportions of the phenotypes of cells after biological. The purpose of this experiment was to determine if interactions between cells had an effect on the phenotypic outcomes using the game theory.

In this experiment, game theory was used to assess the interactions between three cell phenotypes usually found in cancer. The three defined cells were autonomous growth cells, invasive and motile malignant cells, and cells that performed anaerobic glycolysis. Based on preset variables in the payoff matrix, analytical equations were deduced that allowed for the analysis of the proportion of autonomous growth and malignant cells in a tumor. *AnyLogic* was also used to simulate the interactions between cancerous and normal cells.

It was found that malignant phenotypes were more likely to appear in a tumor that contained high amounts of the phenotype of glycolytic cells. Inversely, autonomous growth cells were seen to decrease as the increase of glycolytic cell phenotypes was exhibited. This experiment could be elaborated on by increasing the number of phenotypes that interact within a tumor to add more applicable results to the real world.

Introduction:

Cancer is a pressing issue among the medical field. Its uncontrollable growth and hap hazard replication make it difficult to predict and attempt to cure. The rationale for this experiment was based upon the premise that current studies are hindering in advancements due to the fact that scientists are unable to predict what exactly cancer cells will do in the future. With applying the game theory to the behavior of these cells, this investigation hopes to better predict how cells in the body will react given certain interactions involving cancerous cells (Dingli *et al*., 2009).

Since the discovery of cancer, scientists have been in a constant search to find the cure for cancer. Major advancements have been made, but the cure still remains unknown. With this research, scientists will be able to better predict what phenotype will be a result of the "evolutionary game" that both malignant and benign cancer cells play. As a result of the help scientists will obtain from this experiment, they will also be able to prevent the cancer cells from spreading. According to Dingli, et al. (2009), "Besides providing an overall insight into what a patient's condition may be, our approach would provide important insights on therapies to ameliorate the patient's condition " (p. 1134). With these insights, scientists may be able to kill the cells that enhance cancer growth, hence slowing down the disease.

The independent variable for this experiment is the type of cell. Cancer's two main characteristics are uncontrollable growth of the cells in the body, and the ability for the said cells to migrate from their initial site of occurrence all the way to distant sites in the body (Learner *et al*., 2008, p. 742). Cancer tumors are observed as being one of two types: benign and malignant. A benign tumor is a slow growing tumor that does not affect surrounding tissues or cells. Whereas a malignant tumor continuously replicates and grows, affecting the surrounding tissues and cells. The driving force of a malignant tumor is the uncontrolled clonal spread of cancer

cells. Almost all cancer is caused by a mutation, or change in the DNA of a cell, and this stimulus is caused by outside environmental factors (Lerner *et al.*, 2008, p. 743).

Normal and cancerous cells are different from one another, but the most dangerous difference is that cancer cells do not respond to the signaling to halt replication. Additionally, cancer cells have stimulants that prevent them from sticking to other normal or malignant cells, giving them the ability to move throughout the body and affect other cells (Cancer Research UK, 2013). Coupled with their abnormal cell structure and behaviors, the proteins involved in regulating cell division events no longer appropriately drive progression from one cell cycle stage to the next, and in fact cancer cells increase the normal replication rate of a cell (Chow, 2010).

For the case of a cancer cell, genes mutate in the cell and become defective to the normal processes of cells. There are two types of gene mutations – dominant and recessive mutation. Dominant mutation is due to an abnormality in only one gene in a pair, and is characterized as a "gain of function" mutation. In this, a mutated gene will produce a defective protein that signals the cell to keep its growth factor receptor always "on". In a similar fashion, the recessive mutation works as a "loss of function" mutation; but decreases the certain function. In cancer, if both p53 genes, which are used to control cell growth, are mutated, then the "off" switch for cell division disappears and cell division is no longer under moderation (Coleman, 2006).

The dependent variable for this experiment is the phenotypic outcomes based on the game theory. Game theory is a mathematical approach to real-world situations that involve two or more decision makers, or "players" (Rosenthal, 2005). It also deals with the analysis of conflict situations. One underlying feature for all game theory situations is a conflict between two or more players resulting in a win for some players and a loss for others (Dingli *et al*., 2009). Each player has a certain set of actions, referred to as strategies, which it can use. The result of these strategies based on what each player selects is called an outcome. (Lerner et al., 2008, p. 1852).

A payoff matrix is a part of the game theory that shows the possible unique outcomes solely determined by which of the given alternatives a player might choose, and each state of nature which may occur in the future, after the alternative is chosen. Of the given alternative, only one will occur in the future, so the payoff matrix allows the player to see all possible outcomes with the given information. Once both the alternative and the future states have been set, the intersecting cells each display the possible outcomes each given scenario. (Kmetz, n.d.)

Evolutionary game theory is the application of game theory to evolving populations of populations in biology in the sense of which strategies prove to be inherited by populations the most. Equations and functions with multiple variables representing parameters in an environment are used to model how a population will evolve over time. The G-function is used to work with x amount of individuals using different strategies without having to write an exact function for each fitness of each cell (Vincent & Gatenby, 2005). Recent studies, by Vincent & Gatenby, have showed a model for the population dynamics of multiple cells in an environment to be:

$$G(v,u,x,R) = B(1 - \frac{1}{K(v)}\sum_{j=1}^{n_s} a_j(v,u)x_j)(\frac{E(v)R^2}{R_0^2 + R^2} - m)$$

given that B converts the substrate quantity of glucose to proliferation, $K(v)$ limits growth, $a_j(v,u)$ is the competition term, and a Michaelis-Menten uptake (with a constant R_0) minus a fixed consumption rate m representing the last term (2005). This paper has brought up the fact that even though drug dosage and attempts to cure cancer can affect the replication and fitness of the cells, their interactions among other normal cells also affect the proliferation rate of cancer cells as well as the normal cells (Vincent & Gatenby, 2005).

For this experiment, three different cells with different "fitness" levels were decided upon. One consists of normal growing cells (AG), one consists of cancerous cells (MAI), and one additionally type of cell that uses anaerobic glycolysis for energy production (GEP). The first

two types are implemented into this investigation due to their relevancy to the purpose of this investigation. The last type was added to depict another abnormal cell that may occur in the human body to allow for the results of this experiment to be more applicable to the real world. There is no control because the interactions between the cells cannot be compared to a "regular" interaction due to the nature of the cells. The constants set up are the analytical equations used the number of interactions occurring in the payoff matrix, the variable used to define the cell phenotypic outcome, the cost given to each type of cell respectively in each scenario of the payoff matrix and given for each variable, and the number of trials for each possible scenario.

The hypothesis for this experiment is if the autonomous growth cell and increasingly motile and invasive cell interact, then the phenotype outcome will be a greater amount of autonomous growth cells. This hypothesis reasoning is due to the greater fitness exhibited by normal cells as opposed to the decreased fitness exhibited by the malignant cells (Basanta, 2008). The purpose of this experiment is to determine if interactions between different types of cells have an effect on the phenotypic outcome of later generations in terms of cancer cells using the game theory.

Methods and Materials:

The number of possible phenotypic outcomes of a cell was set at three possible phenotypic outcomes. The first phenotypic outcome was set to autonomous growth and labeled for future analysis as AG. The second phenotypic outcome was set as a cell that can switch to anaerobic glycolysis for energy production and was label with GEP for future analysis. The final phenotypic outcome of the three cells was set to a cell that becomes increasingly motile and invasive and was respectively labeled MAI. During set up, no assumptions were made as to what genetic changes are necessary for mutation to occur.

Next, a payoff matrix, a component of the game theory, was set up to analyze the results of the different cellular interactions. Three variables were set to summarize the outcomes of the

interactions. The variables were set as g, m, and r respectively to characterize different components of the interaction. The variable g represented the fitness cost of switching to glycolytic metabolism. The variable m was used to represent the both the loss of fitness for a non-glycolytic cell to live in an acidic environment, as well as the gain of fitness for a glycolytic cell that increases the acidity of the environment. The last variable, r, was used to represent the cost of motility incurred by the MAI cells. Through game theory calculations, the calculations of the outcomes based on the different interactions between the different phenotypes were placed in each respective interaction cell in the payoff matrix. Additionally, using the *AnyLogic* Program, a mathematically simulated model was completed to visualize the proliferation of cancer cells as well as normal cells over time given certain parameters based on other experiments with parameters such as infection and curing probabilities and cellular interactions per step.

Results:

Table 1 is the summation of all the interactions between the three different cells using the stated variables. This table must be read using the columns and using the cells in those columns. For example, the fitness payoff for two AG cells interacting is ½ because AG cells have to share available resources. When an AG cell meets an MAI cell, the MAI cell will leave for another location, obtaining the base payoff minus the cost of motility 1 – r. When an AG cell meets a GEP cell, they both have to share the available resources; the AG cell loses fitness due to acidification of the environment. GEP cells never get the full base payoff because their metabolism is less efficient.

A standard EGT analysis has been used to study and analyze the differences in phenotypes in one scenario. The scenario is when mutations lead to invasive cells capable of motility in a tumor composed of autonomous growth cells. The first scenario analyzes the possibility of a tumor with AG cells that have the capability of becoming the MAI phenotype. By

theory, a population of AG cells will be immune to the invasion if the fitness of two AG cells is greater than one MAI cells from the invasion. If the fitness of an AG cell interacting with another AG cell is equal to the fitness of an MAI and AG cell interacting, then the AG cell may still stay immune to the invasion. The payoff matrix illustrates that if motility represents a non-negligible cost, then the only aspect required of a population of AG cells to be immune to invasion by an MAI phenotype is that the fitness payoff of two AG cells is greater than or equal to the fitness payoff for an MAI cell interacting with an AG cell. Essentially, the AG phenotype is only immune to an MAI cell invasion when $r \geq \frac{1}{2}$. p is the proportion of invasive cells in the tumor, and $E(X, Y)$ is the interaction between cell X and cell Y (Basanta, 2008).

$$pE(MAI, MAI) + (1-p)E(MAI, AG) = pE(AG, MAI) + (1-p)E(AG, AG)$$

$$p\left(1 - \frac{r}{2}\right) + (1-p)(1-r) = p + (1-p)\frac{1}{2}$$

$$p = \frac{1-2r}{1-r}$$

The mathematical simulation using the *AnyLogic* software is displayed in figures 1-7, as each show a different amount of interactions per step.

Discussions and Conclusions:

The research hypothesis of if the autonomous growth cell (AG) and increasingly motile and invasive cell (MAI) interact, then the phenotype outcome will be a greater amount of autonomous growth cells was supported based on Graph 1. Graph 1 illustrates a decrease in the proportions of AG cells as they interact with MAI cells, using the MAI cell's cost of motility variable – r. Essentially, Graph 1 is showing that as the cost of motility increases, the proportion of AG cells decrease as a result of the increase of GEP cells, the cells that decrease the fitness of AG cells. According to Graph 1, if the values of the cost of having the GEP phenotype and the

cost of a normal living cell next to a GEP phenotype are altered, then the proportions of MAI cells change. The lower values of g and higher values of m resulted in an increase of MAI cell proportions. The explanation that could be applied to this trend could be that the presence of GEP cells, cells that increase the acidity in the environment, reduce the costs of motility.

Table 1 describes the exact behavior of each type of cell with its possible interactions, which allow for an analysis of possible causes of the decrease in the proportion of AG cells. In the AG cell column of Table 1, the interaction with the GEP cell is shown to result in a decrease in fitness by $\frac{1}{2}$ and a decrease with the subtraction of the cost of switching to glycolytic metabolism. This large decrease could be the reasoning behind the decrease of the proportions since every interaction results in a loss for the AG cell's fitness. Supporting Table 1, Graph 2 similarly graphs a trend where the proportion of AG cells increase as the cost of glycolytic metabolism increases. Essentially, in scientific terms, an increase in g means that the cost of living in an acid environment decreases which in turn reduces the proportions of both MAI and GEP cells. The results display that MAI cells have the best chance of survival versus AG cells in a tumor filled with GEP cells, signified by graph 1. Based on graph 1, an increase in GEP cells also correlates to an increase in MAI cells. These simplified findings are in agreement with research done by previous scientists in which glioma cells that have been affected by cancer, exhibit similar trends (Basanta, 2008). Adding or possibly replacing the previous phenotypes with more extreme or a variety of phenotypes will allow for an increased holistic understanding of how exactly cancer cells work in all possible scenarios.

The *AnyLogic* Software simulation was used as a visualization tool using similar parameters as the paper by Vincent & Gatenby, but due to time constraints, their equations were simplified down to similar parameters (2005). Based on figures 1-7, it can be concluded that the

infection probabilities of the population will not change the amount of cancer cells, but rather the number of cellular interactions per step affect the amount of total cancerous cells as well as the speed at which all the cells in the population become cancerous. This finding should change the focus of the cure of cancer from honing in on the cancer cells itself, to reducing and hopefully isolating the cancer cells to decrease the interactions between the phenotypes. Figure 7 shows with zero cellular interactions the three randomly selected cancerous cells decreased within the first 20 steps, as compared to increases variably based on the number of cellular interactions.

The models from this experiment can be applied to certain cancer observations. The model predicts that MAI and AG will coexist as long as the fitness costs of motility are not too high when compared to the fitness increase obtained by moving to a new location (Giese, 1996). Based on Schmidt *et al.*, "Malignant progression is common and more than 50% of low-grade tumors will eventually become malignant," (2003). In graph 2, the increase in the GEP phenotype is what the "malignant progression" can be compared to exemplifying that this experiment is in accordance with the said experiment of malignant progression.

Although real life implications and instances are much more complex and considered unable to be fully encompassed with mathematical models, this experiment aims to simply illustrate quantifiable values in which these situations can be attempted to be explained. This mathematical model unintentionally disregards spatial considerations (Basanta, 2008). In another words, this mathematical model may not take into account the decisions made by cells in terms of the changes in their environment – which is a source of error in the results. One possible improvement to this experiment would be to reconsider the reasoning behind each of the fitness payoffs. A more real world approach to this problem would be to change the now constant fitness payoffs, to variable functions in which certain changes in the environment are accounted for; for example the increase in the cost of motility when the populations of cells leave the area.

Works Cited:

Peer reviewed:

Basanta, D., Simon, M., Hatzikirou, H., & Deutsch, A. (2008). Evolutionary game theory elucidates the role of glycolysis in glioma progression and invasion. Cornell University Library. Retrieved from http://arxiv.org/.

Cancer Research UK. (July 24, 2013). How Cancer Grows. In Cancer Research UK. Retrieved August 28, 2013, from http://www.cancerresearchuk.org/cancer-help/about-cancer/what-is-cancer/grow/how-a-cancer-grows#moving.

Chow, A. (2010). Nature. In Cell Cycle Control by Oncogenes and Tumor Suppressors: Driving the Transformation of Normal Cells into Cancerous Cells. Retrieved August 29, 2013, from http://www.nature.com/scitable/topicpage/cell-cycle-control-by-oncogenes-and-tumor-14191459.

Dingli, D., Chalub, F., Santos, F., Segbroeck, S., & Pacheco, J. (August 1, 2009). Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells. British Journal of Cancer, 101, 1130-1136. doi:10.1038/sj.bjc.6605288.

Giese, A., Loo, M., Tran, N., Haskett, S. W., and Berens, M. E. (1996). Dichotomy of astrocytoma migration and proliferation. Int. J. Cancer, 67:275–282.

Kmetz, K. (n.d.). Business Consulting. In A Brief Review of the Payoff Matrix. Retrieved August 29, 2013, from http://www.buec.udel.edu/kmetzj/business_consulting/Payoff%20matrix.pdf.

Vincent, T. L., & Gatenby, R. A. (2005). Modeling cancer as an evolutionary game. *International Game Theory Review*, 7(3), 331-346.

Non-peer reviewed:

Coleman, N. (2006). *Understanding cancer: A patient's guide to diagnosis, prognosis, and treatment*. New York: Johns Hopkins University Press.

Lee Lerner K., & Wilmoth Lerner, B. (2008). Cancer. In Gale Encyclopedia of Science. (Vol. 1, pp. 742-751). Detroit, MI: Gale Encyclopedia.

Lee Lerner K., & Wilmoth Lerner, B. (2008). Game Theory. In Gale Encyclopedia of Science. (Vol. 4, pp. 1851-1852). Detroit, MI: Gale Encyclopedia.

Rosenthal, E. (2005). *The complete idiot's guide to game theory*. Penguin.

Appendix:

EDD:

Title: The Effect of Normal or Malignant Cancer Cells on the Cancer Phenotype Outcome Using Game Theory

Hypothesis: If the autonomous growth cell (AG) and increasingly motile and invasive cell (MAI) interact, then the phenotype outcome will be a greater amount of autonomous growth cells due to their greater fitness as opposed to the MAI cell.

IV: Type of Cell		
Autonomous growth (AG)	Anaerobic glycolysis for energy production (GEP)	Increasingly motile and invasive i.e malignant (MAI)
20 Trials of equations	20 Trials of equations	20 Trials of equations

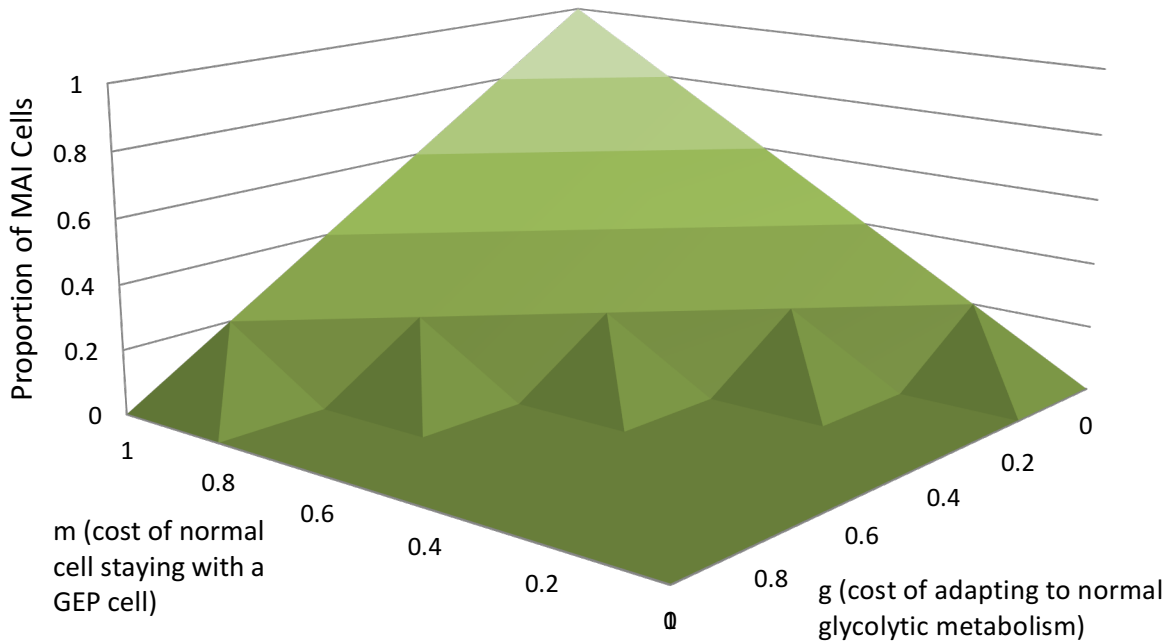
DV: Phenotype Outcome

Constants: Analytical equations used, number of interactions occurring in the payoff matrix, variable used to define the cell phenotypic outcome, cost given to each type of cell respectively in each scenario of the payoff matrix, number of trials for each possible scenario, the given value of cost in each variable

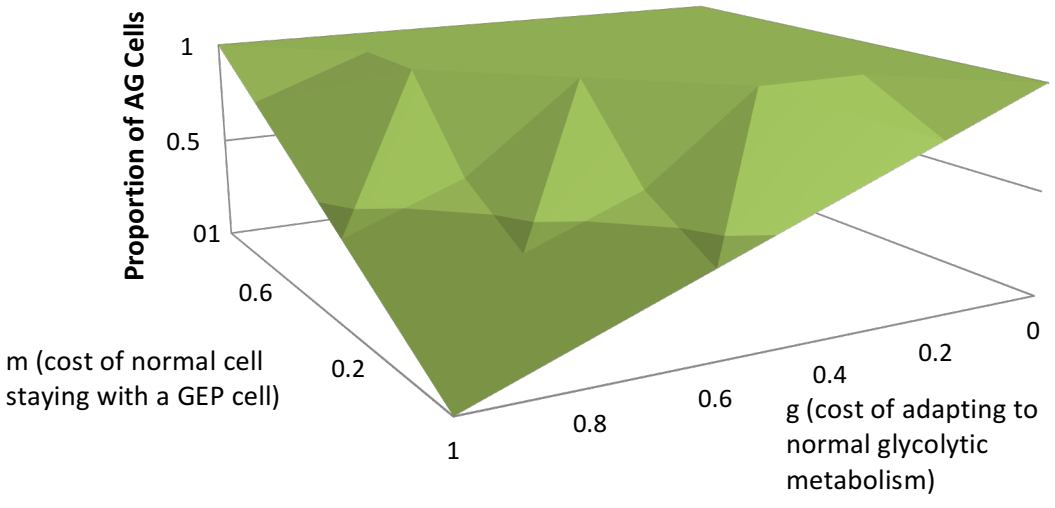
Table 1. Payoff Matrix of Interactions between three cells

	AG	MAI	GEP
AG	$\frac{1}{2}$	1 – r	$\frac{1}{2}$ + m - g
MAI	1	$1 - \frac{r}{2}$	1 - g
GEP	$\frac{1}{2}$ - m	1 – r	$\frac{1}{2}$ - g

Graph 1. Proportion of MAI cells in Tumor with Three Phenotypes



Graph 2. Proportion of AG cells in Tumor with Three Phenotypes



For the following figures, a pre-existing AnyLogic simulator for Influenza was used. However, the algorithm and mathematics behind the algorithm and simulation were different. The first and last figure shows a full screenshot of the simulation in action, and the subsequent images show the parameter that was changed – Phenotype Interactions per Step.

Figure 1.

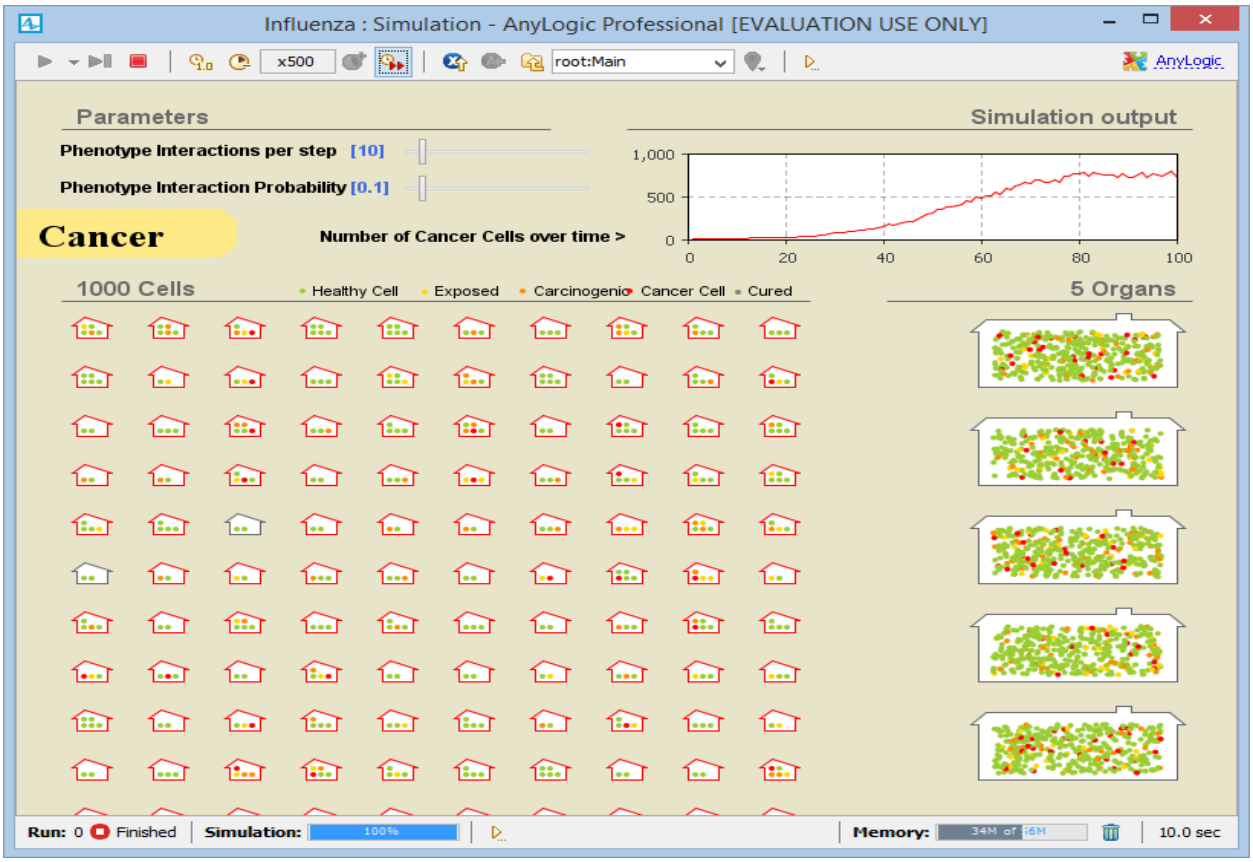


Figure 2.

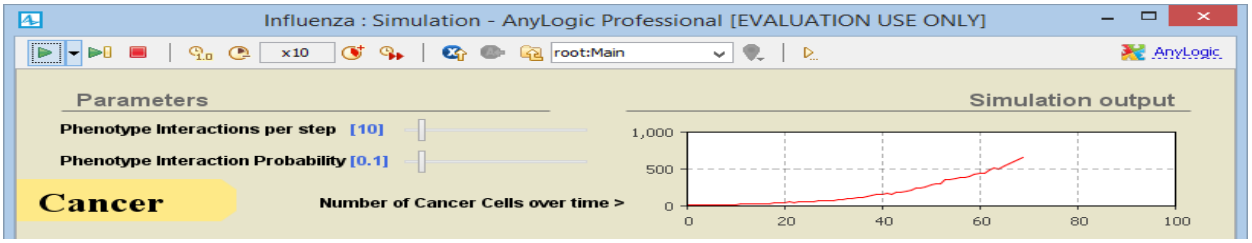


Figure 3.

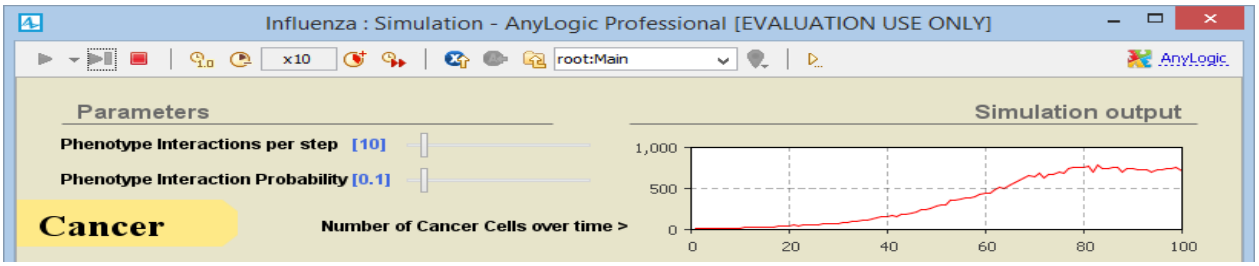


Figure 4.

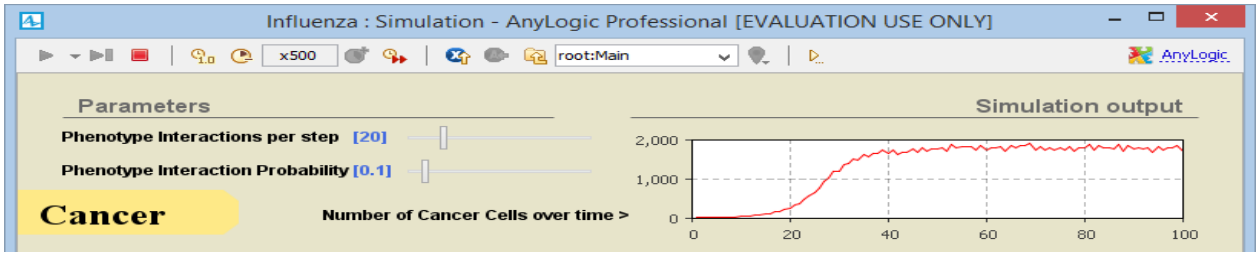


Figure 5.

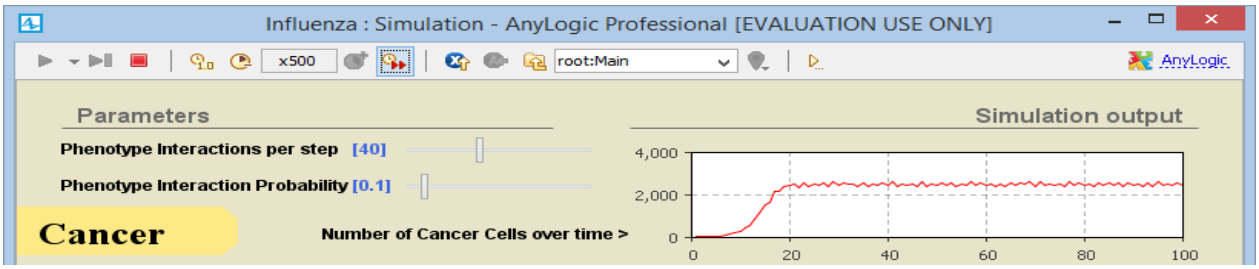


Figure 6.

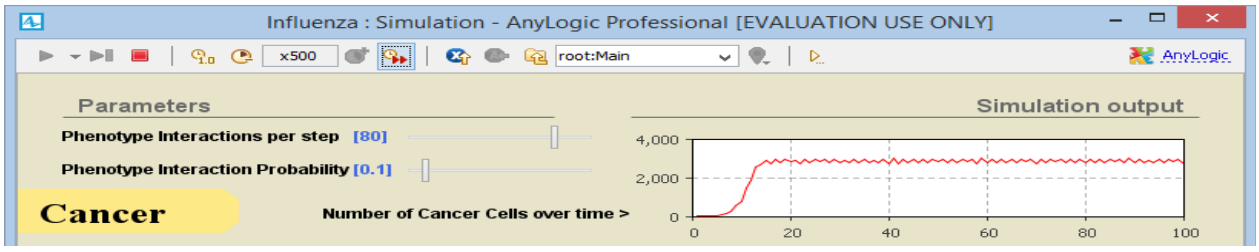
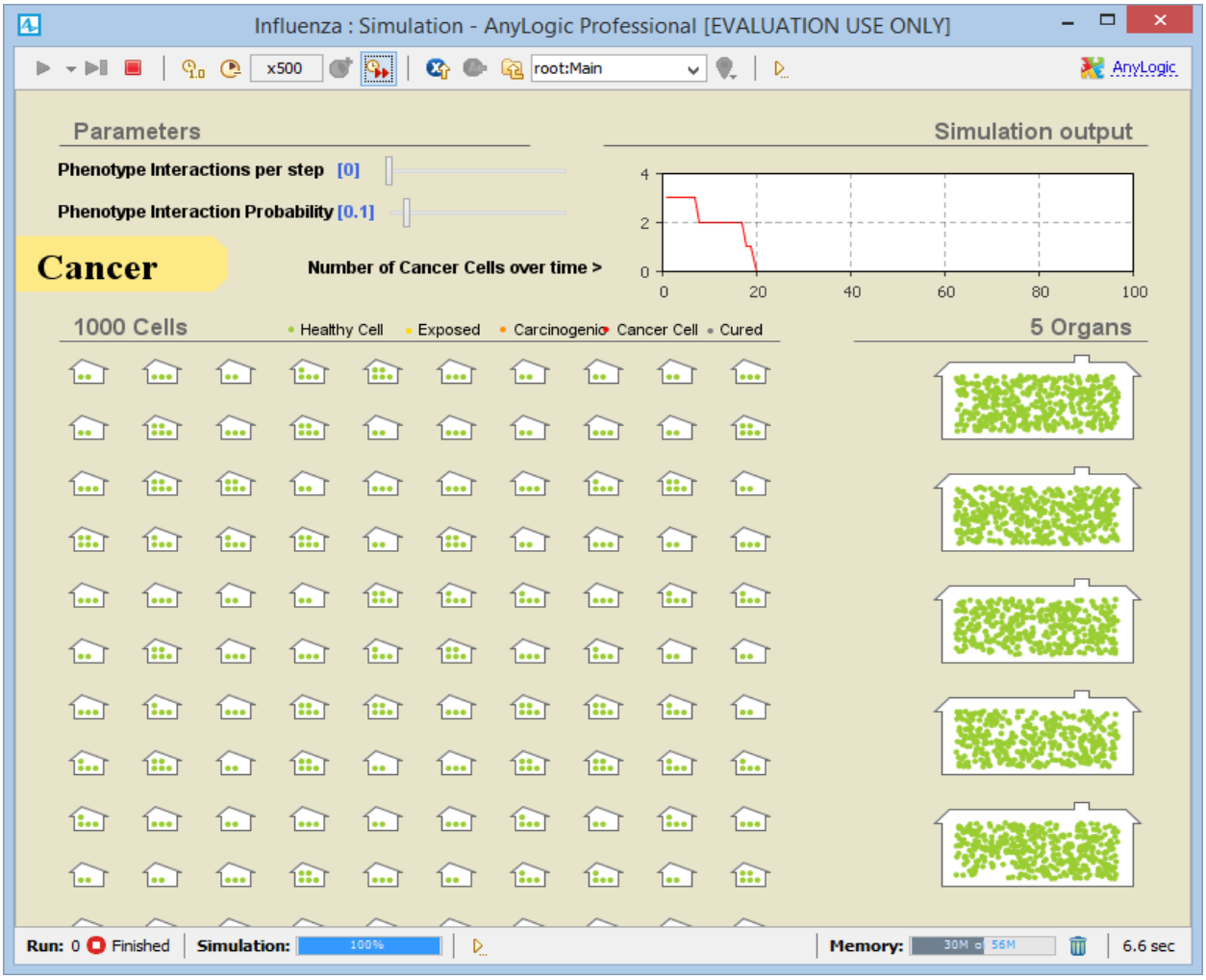


Figure 7.


Influenza : Simulation - AnyLogic Professional [EVALUATION USE ONLY]
x500
root:Main
AnyLogic
Parameters
Phenotype Interactions per step [0]
Phenotype Interaction Probability [0.1]
Cancer
Number of Cancer Cells over time >
Simulation output
4
2
0
0
20
40
60
80
100
1000 Cells
Healthy Cell
Exposed
Carcinogenic
Cancer Cell
Cured
5 Organs
Run: 0
Finished
Simulation:
100%
Memory:
30M of 56M
6.6 sec