My Intel STS Research on "Modeling the Cooperative Role of Growth Factors among Partially Transformed Tumor Cells Using Evolutionary Game Theory"

Quanqun Liu

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1. Personal Involvement

I started my project during the summer before my senior year. However, the idea for my project actually came from a few thought experiments[1] I conducted while I was brainstorming various research ideas a few months before. They were not particularly useful in the practical[2] sense since the majority of these experiments were untestable in real life, and I lacked the mathematical knowledge required to describe imaginary situations. But they did allow me to informally shift through various ideas to see if they could lead to useful conclusions. I recommend to anyone who is looking for a research topic to think about existing theories in new ways, and, if possible, design an experiment. Often thinking about an experiment before conducting it can make the actual research process more productive.

In terms of my research idea, I started out knowing that I wanted to work on something related to game theory. During my sophomore and junior years, I had bounced back and forth between various math concepts, but I always came back to game theory because it can describe interpersonal interactions in mathematical terms, an idea that was very intriguing to me. However, I looked for something beyond game theory's most common applications, namely in

[1] What scientists call a "mental exercise" used to analyze a problem, hypothesis, or theory.
[2] To quote P.M.S. Hacker, *"…*A thought experiment is no more an experiment than monopoly money is money."

economics, social psychology, and evolutionary biology. While searching for this new application of game theory, I noticed that cells, especially cancer cells, can behave strategically[3]. The development of a malignant tumor requires the emergence of more aggressive subclones of cells. I imagined that during the development of malignancy, there must be some form of competition[4] and cooperation[5] among the tumor cells. Each individual cell can be a player with a strategy determined by its phenotype. With these thoughts in mind, I began researching the possibility of applying game theory to cancer.

Through my research, I found that this topic is a relatively new application of game theory. The first paper that attempted to model cancer using game theory [1] was published in 1997. So there was not too much background information for me to build my project on. However, one of the advantages of researching such a new topic is that there is a lot of room for development. But before I can formulate a mathematical algorithm, I must determine what I want to model. While looking to answer this question, I stumbled upon a paper written by Robert Axelrod et al. [2] that presented the hypothesis, simply stated, that tumor cells cooperate through the sharing of diffusible products to aid the development of malignancy. After reading this paper, I decided that I wanted to look further into growth factors. For the next few weeks, I read extensively on both cancer and game theory. The model itself required many hours spent sitting at my desk and manipulating variables until the algorithm described as accurately as possible the tumor conditions I was investigating. By the end of summer, I had a novel, working evolutionary game theory model intended to test Axelrod's original hypothesis along with my own extensions of the hypothesis.

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[3] Strategically used in this sense does not mean that the cancer cells have a conscious knowledge of what they are doing but that they are "pre-programmed" to act in certain ways based on their phenotypes.
[4] Competition may occur over available space and nutrients in the tumor.
[5] Cooperation may occur through the sharing of growth factors, which I looked into in my study.

One last piece of advice to future high school scientists: it is possible to have a homegrown topic that can succeed in these competitions. It was highly impractical for me to go to my mentor's lab since it was over 1000 miles from where I lived and since my project did not require the use of specialized lab equipment. Do not worry if others are working in a lab. Some projects need to be completed in a laboratory setting while most math projects can be completed both inside and outside the laboratory. I completed the majority of my project at my desk. The point is not the location but to choose a topic you would want to research. Though I did become an Intel semifinalist, the real reason why my experience was so rewarding was because I picked a topic I enjoyed researching and spending hours a day puzzling through.

2. My Research Explained

In this section, I will present a brief summary of the key ideas of the research report I submitted to the Intel competition. The basis for using evolutionary game theory to design my model is that the transformation of normal cells into cancerous cells is an evolutionary process because it requires the cells to develop a set of important mutational capabilities, often called the "hallmarks" of cancer [3]. The tumor develops through the evolutionary selection of subclones of cells that contain these "hallmarks." Traditionally, it is believed that malignant tumors form from the division and proliferation of a single subclone of fully transformed cells [4]. However, because tumors often become malignant much more rapidly than predicted, we bring in the suggestion that partially transformed[6] tumor cells can cooperate to compose a tumor that contains all the hallmarks of cancer. Experimental evidence shows that genetic instability in the tumor during its development allows for the existence of various subclones of cells, each with a distinct phenotype [2].

[6] They are cells that have acquired only some of the hallmarks of cancer.

While some researchers [1] chose to investigate the competitive side of tumor cell interactions, I wanted to look at the cooperative side because it might lead to a clearer picture of carcinogenesis. One of the more important hallmarks of cancer is the ability for the tumor cells to generate growth factors [3]. Growth factors regulate a variety of vital tumor processes, and successful tumor cells can respond to both paracrine and autocrine signals. The sharing of these growth factors allows for a method of cooperation among the phenotypically different subclones of cells. Because of the difficulties of studying cancer mechanisms in human patients, the purpose of this paper is to present a novel mathematical model to simulate and test the hypothesis proposed by Axelrod et al [2] that cancer cells cooperate through the sharing of growth factors to create a malignant tumor. In addition, I sought to investigate how the cooperation among partially transformed tumor cells affects the proportions of the three phenotypes[7] within the tumor. Furthermore, this study presents two different cases in which the type of growth factors secreted differs to see if cooperation still exists in the tumor. On a broader scale, I hope that this study will contribute to a better understanding of tumorigenesis and ultimately lead to new treatments for the disease.

To study tumor cell cooperation, I adopted an evolutionary game theory method to analyze the equilibria among three different phenotypes in two different cases. For both scenarios, the growth factor secreting phenotype is able to receive its own growth factor. In the first case, the three phenotypes that were present in the tumor are the GF (growth factor), the PRO (proliferative), and the INV (invasive) phenotypes. The phenotypes present were chosen because past experimental evidence showed they were representative of the typical phenotypic composition of most tumors [2, 5-7]. The INV phenotype is also traditionally associated with metastasis [5]. The GF phenotype secretes a growth factor that can be received by both the PRO

[7] I will elaborate on the phenotypes later on.

and the INV phenotypes via their growth factor receptors, the PRO phenotype proliferates at a rapid pace but does not migrate, and the INV phenotype does not proliferate as rapidly but actively migrates. From these descriptions of the tumor environment, I formulated a payoff table to simulate tumor conditions. Table 1 is the payoff table I used in this case:

		Payoff to		
		GF	**PRO**	**INV**
Encounter with	**GF**	$1-d-g+z$	$1-d+z$	$1-m+z$
	PRO	$1-d-g+z$	$1-d$	$1-m$
	INV	$1-g+z$	1	$1-m$

Table 1: Payoff table represents the change in fitness of a tumor cell with a given phenotype after interacting with another cell. The base payoff is 1, cost of sharing space is d, cost of producing the growth factor is g, cost of mobility is m, and benefit of receiving the growth factor is z. The table is read following the columns.

The fitness of each phenotype can be calculated after the cells hypothetically engage in all the possible interactions afforded by the payoff table. At equilibrium, the cells exist in a state where their fitnesses are all equal. From here, I calculated the proportions of each phenotype with regard to the cost and benefit variables. The actual derivation is present in my report, however for simplicity's sake, I will present to you only the final equations. Assuming *P* represents the proportions of each phenotype, I arrived at these equations:

$$P\ (\ GF\ ) = 1 - \frac{g}{z}$$

$$P\ (\ PRO\ ) = \frac{g}{z} + \frac{m}{d} - 1$$

$$P\ (\ INV\ ) = 1 - \frac{m}{d}$$

In the second case, the tumor environment remains the same except I replaced the GF phenotype with the SGF (specific growth factor) phenotype. Here, it is assumed that the SGF

phenotype secretes a specific kind of growth factor that can only be received by the PRO phenotype. Table 2 is the payoff table for this case:

		Payoff to		
		SGF	**PRO**	**INV**
Encounter with	**SGF**	$1-d-g+z$	$1-d+z$	$1-m$
	PRO	$1-d-g+z$	$1-d$	$1-m$
	INV	$1-g+z$	1	$1-m$

Table 2: Payoff table represents the change in fitness of tumor cells after interactions with other cells. The three phenotypes (SGF, PRO, and INV) are represented.

And at equilibrium, I deduced:

$$P(SGF) = 1 - \frac{g}{z}$$

$$P(PRO) = \frac{z}{d} - \frac{g}{d} + \frac{m}{d} + \frac{g}{z} - 1$$

$$P(INV) = 1 - \frac{m+z-g}{d}$$

Then, I programmed the models into MATLAB to run simulations to see how varying the values of the costs and benefits could lead to different proportions within the tumor. Triple polymorphism exists for the majority of the time at equilibrium for both of the cases. Most notably in the first scenario, the PRO phenotype completely dominates the tumor through fixation[8] when all the costs and benefit variables are equal. However, fixation of the GF or the INV phenotypes never realistically occurs.

[8] The proportion of the PRO phenotype is 1 in this case.

Among the graphs showing my results, Figure 1 is particularly important, which is why I chose to explain it here, because it shows the relationship between the two cost variables, *m* and *d*, and the proportion of the INV phenotype in the tumor.

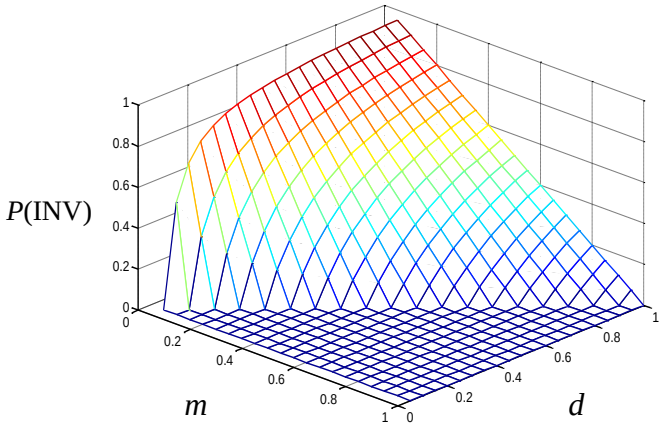

Figure 1: Proportion of cancer cell type PRO in the cell population with regard to variations in m and d.

Figure 1 shows that the proportion of INV cells in the population increases as the cost of sharing space increases and the cost of mobility decreases. The proportion reaches a maximum when *m* approaches 0.

Once again, in the second scenario, only fixation of the PRO phenotype can realistically occur. Interestingly, my results for the second scenario shows an inverse relationship between *z*, the benefit of receiving the growth factor, and the proportion of INV cells in the tumor. The results show that cooperation plays a universal role in the transformation of most tumors from benign tumors to malignant tumors. Therefore, the hypothesis proposed by Axelrod et al [2] is confirmed by my model. Since fixation of the INV phenotype never occurs, we can infer that the presence of other partially transformed phenotypes is crucial to its success. The final phenotypic compositions of the tumor in both cases follow a similar pattern which suggests that a secreted growth factor can indirectly affect those cells that cannot directly receive it. The results also suggest that under certain conditions, one phenotype (such as the INV phenotype) may be

completely eliminated from the population. This crucial finding could lead to new treatments that would manipulate the tumor environment to target one specific phenotype rather than attacking all phenotypes at once. By selectively eliminating fundamental players, the malignancy of the tumor itself can be lessened. In future works, I plan to take into account spatial and temporal considerations. This brief summary explains the most important parts of my findings and, hopefully, shows that evolutionary game theory has a very promising future in cancer research.

3. References

[1] I. P. M. Tomlinson, Game theory models of interactions between tumour cells, *European Journal of Cancer*. 33 (1997), pp. 1495-1500.

[2] R. Axelrod, D.E. Axelrod, K.J. Pienta, Evolution of cooperation among tumor cells, *Proceedings of the National Academy of Sciences.* 103 (2006), pp. 13474-13479.

[3] D. Hanahan and R. Weinberg, The Hallmarks of Cancer, *Cell*. 100 (2000), pp. 57-70.

[4] P. Nowell, The clonal evolution of tumor cell populations, *Science.* 194 (1976), pp. 23-28.

[5] A. Giese, M. Loo, N. Tran, S. W. Haskett, and M. E. Berens, Dichotomy of astrocytoma migration and proliferation, *International Journal of Cancer*. 67 (1996), pp. 275-282.

[6] N. M. Kumar and N. B. Gilula, The gap junction communication channel, *Cell.* 84 (1996), pp. 381-388.

[7] D. Basanta, H. Hatzikirou, A. Deutsch, Studying the emergence of invasiveness in tumours using game theory, *The European Physical Journal B - Condensed Matter and Complex Systems*. 63 (2008), pp. 393-397.