



Investigation of Game Between Cells in Occurrence of Genetic Mutations Using EGT

Ali Bahraini^a, Madjid Eshaghi Gordji^{b,*}, Ali Ghaffari^c, Mahmoud Taheri^d

^{a,b,c}Department of Mathematics, Faculty of Mathematics, Statistics and Computer Science, Semnan University, P.O. Box 35195-363, Semnan, Iran.

^d Department of Medical, Tabriz University of medicine, Tabriz, Iran

(Communicated by Mohammad Bagher Ghaemi)

Abstract

In this paper, two games that play a role in creating a cancer tumor and suppression are studied using evolutionary game theory and its different modes are analyzed. The first game is the competition between a cancerous cell and a healthy cell to receive food through the blood. In the second game, the interaction between the two oncogenes Ras and Myc is examined for cellular deformation.

Keywords: Cancer, Genetics, Gene, Evolutionary, Game Theory.
2010 MSC: 26D15, 26D10.

1. Introduction

Cancer is a disease that remembers the human being's memory of chronic pain and chemical treatment. Just one mutation is enough to make a cell cancer. A serious illness that can easily kill a patient with negligence and timely treatment. Unfortunately, the disease is now widely seen worldwide, so researching and understanding it to find a cure for it has become one of the most important issues for researchers worldwide.

A cancerous tumor is an abnormal mass of cells. Tumor cells grow for reasons unknown so far, and they grow without regard to body requirements, and are often detrimental to the body due to the absorption of nutrients through the blood. Tumors are commonly called neoplasms or new growth and are divided into two types of benign and malignant tumors. Benign tumors grow slowly and

*Corresponding author

Email addresses: a.bahraini@semnan.ac.ir (Ali Bahraini^a), meshaghi@semnan.ac.ir (Madjid Eshaghi Gordji^{b,*}), aghaffari@semnan.ac.ir (Ali Ghaffari^c), razipathlab@gmail.com (Mahmoud Taheri^d)

do not invade other tissues. These tumors put pressure on adjacent tissues, but they may stop growing for some time and then remain unchanged. Malignant tumors grow exponentially and, if not prevented from growing, cause death in different ways. Malignant tumors usually spread to other body tissues. Malignant tumors spread by direct invasion of adjacent tissues as well as by the formation of secondary tumors called metastases. In general, most benign tumors grow slowly and within a few years, while most cancers grow at a surprisingly rapid rate and eventually spread, causing the death of the host. There are three ways cancer can be spread:

1. directly implanted in cavities or body surfaces
2. lymphatic spread
3. blood spread.

Cancer is a disorder of cell growth and behavior, its final cause having to be defined at the cellular and subcellular level. Studying cancers in populations, of course, can help fundamentally understand the origin of cancer. In other words, the influence of some factors related to the patient and the environment on the susceptibility to cancer is high. The likelihood of cancer in a person is expressed by the rate of death and national incidence, and is dependent on geographic and environmental factors, heredity and age [11]. Genetic damage is at the heart of carcinogenesis, such genetic damage (mutation) may be caused by environmental factors such as chemicals, radiation or viruses, or it may be inherited in a germ cell class. The genetic hypothesis of cancer states that a tumor mass is caused by the development of a single precursor cell progeny that has undergone genetic damage. Three classes of natural regulator genes are the major targets of genetic damage, including:

1. growth-promoting proto-oncogenes
2. cancer suppressor or growth inhibitory (antioxidant) genes
3. genes that regulate programmed cell death (apoptosis).

In addition to the three groups of genes listed, another set of genes that regulate damaged DNA repair can also be involved in carcinogenesis. Failure of DNA repair genes can lead to a mutation in the genome that results in neoplastic deformation.

In each DNA sequence, there is a set of instructions called genes. It is these genes that determine the physical properties of animals and humans. Genes are the same for all humans, so all humans inherit the same genes, but it is the alleles that determine how genes appear and manifest in one person. The allele is a gene that controls a trait located at a specific location on the chromosome. For example, having a species of eye color depends on the genes, but what color the eye inherits from the parents is determined by the alleles. Mutated alleles consider proto-oncogenes (natural genes) predominant because they cause cell deformation. On the contrary, both natural alleles of tumor suppressor genes must be damaged in order for cellular deformation to occur, so this family of genes is sometimes called recessive genes. Genes that regulate apoptosis may be predominant, such as proto-oncogenes, or may behave like cancer-suppressing genes.

The oncogenes or cancer genes originate from proto-oncogenes, the cellular genes that stimulate natural growth and differentiation. DNA in spontaneously occurring cancers contains transforming sequences similar to the Ras proto-oncogenes that are the ancestors of the V-units present in H and K sarcoma viruses. Mutations in genes that encode growth factors can cause cancer. In most cases the gene itself is not the growth, alteration or mutation factor. The products of oncogenes such as Ras also cause overexpression of growth factor genes. While proto-oncogenes encode proteins that stimulate cell growth, the products of cancer-suppressor genes are a brake for cell proliferation. One of the protein products of tumor suppressor genes is the Rb protein, which, if absent (due to gene deletion) or its ability to regulate transcription factors is impaired by mutations, the molecular

brakes are released into the cell cycle[12]

Given the fact that the cancer is evolutionary disease and natural selection is seen in the cells involved in cancer, modeling of the cancer since 1997 has been the subject of much attention, the models presented for game theory in the field of cancer have tried to show interactions between different cell societies and usually in relation are relevant one of the behavioral characteristics of cancer cells. Some of the most important models offered in this field are: the Tamlinson model[13], the Tamlinson and Bodmer model [14] the Bach et al. Model[1] , Dingli et al. Model[4] , The Wu model et al.[15] , The Mansury et al model[7] , the Kianercy model et al. [5], Basanta et al. [2] .

To purpose survey cancer , two games are considered and analyzed using evolutionary game theory in the field of two-player games [9] . The two games analyze the states that lead to cancer or suppress it. The first game is the competition between a cancer cell and a healthy cell to receive food through the blood. In the second game, the interaction between the two oncogenes Ras and Myc is examined for cellular deformation.

2. Evolutionary Game Theory

Evolutionary Game Theory is the application of the game theory to include living things in biology. In the game theory model, the players' behavior isn't based on maximizing their reward , but based on the test and natural selection. In this strategy model, a calculated route of activities isn't but it is a phenotypic behavior. The reward in this game is the same Darwin competency (Average success in reproduction more). In fact, strategies that should generate more revenue will gradually increase over time, this subject is the same with a Darwin natural selection theory that emerge in the form of productive equations from the theory of evolutionary games. In fact, the game theory model consists of three components:

1. The population of each group of players
2. Rules of the game
3. Producer equations

In the evolutionary games theory, populations interact with each other and according to the rules of the game earn different incomes; these equations are in a form where populations with higher incomes will grow in the next generation. For to be a sustainable evolutionary strategy, it must be have property that none mutation creature can't do easily invasion in the society and defeat others (A creature that following other strategy) if almost all members of society follow it [8, 6, 2, 10] .

3. Game between a healthy cell and a cancerous cell

Nutrients such as oxygen and glucose are sent to the cells through blood vessels. If there is a cancerous cell vicinity to a healthy cell, then the two cells compete for nutrients, and the cancer cell is usually more appetite than the healthy cell for nutrients. The competition for these two cells to absorb nutrients follows the game model of the prisoner's dilemma game, with the players' matrix of earnings as table (1) and the interpretation of the table 1 results presented below.

- Cancer progresses when the cancerous cell is a greedy and healthy donor cell.
- Cancer is suppressed when the cancerous cell is generous and healthy cell is greedy.

Table 1: Competition matrix for nutrients

| Members of Game | Cancerous Cell | | |
|-----------------|----------------|----------|--------|
| | Condition | Gracious | Greedy |
| Healthy Cell | Gracious | (1,1) | (1,0) |
| | Greedy | (0,1) | (0,0) |

Table 2: Competition matrix for nutrients

| Members of Game | Oncogene Ras | | |
|-----------------|-----------------|---------|----------|
| | Condition | actives | Inactive |
| Oncogene Myc | Growth order | (1,1) | (1,0) |
| | Apoptosis order | (0,1) | (0,0) |

- When both are greedy, there is background for cancer suppression.
- When both are generous, the background is provided for the formation of a benign tumor.

4. Game between two oncogenes

Malignant tumors are caused by a regular sequence of events. Tumor formation can be divided into two separate stages of onset and progression. Studying the evolutionary game of oncogenes and tumor suppressor genes provides the molecular basis for understanding the concept of multi-stage carcinogenesis. Infection experiences in laboratory environment show that no oncogenes Ras, Myc alone can completely induce cellular deformation, but Ras and Myc can together cause deformation of fibroblasts (a type of active construction cell). This cooperation is essential because each oncogene is assigned to induce part of the phenotype for complete deformation. In other words, when the Myc oncogene sends a growth signal and the Ras oncogene is activated, fibroblast deformation occurs. It should be noted that oncogene Myc not only regulates cell growth, but can also induce apoptosis through cell death (programmed cell death to prevent cancer). The payoff matrix between these two oncogenes is shown in table (2).

5. Conclusions

In this article, Cancer Disease, one of the most dangerous diseases known to many people around the world annually, has been studied using game theory. By examining the competition between the cancer cell and the healthy cell, it was found that when the cancer cell is greedy, and the healthy cell donates, the cancer progresses. It was also concluded that the interaction between the two oncogenes required the cooperation of two oncogenes to form a cancer cell.

References

- [1] L. A. Bach, S. M. Bentzen, J. Alsner, and F. B. Christiansen, "An evolutionary-game model of tumour-cell interactions: possible relevance to gene therapy," *Eur. J. Cancer*, vol. 37, no. 16, pp. 2116-2120, 2001.
- [2] D. Basanta, M. Simon, H. Hatzikirou, and A. Deutsch, "Evolutionary game theory elucidates the role of glycolysis in glioma progression and invasion," *Cell Prolif.*, vol. 41, no. 6, pp. 980-987, 2008.
- [3] J.-P. Benoit and V. Krishna, "Finitely repeated games," 1984.
- [4] D. Dingli, F. A. da C. C. Chalub, F. C. Santos, S. Van Segbroeck, and J. M. Pacheco, "Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells," *Br. J. Cancer*, vol. 101, no. 7, p. 1130, 2009.
- [5] A. Kianercy, R. Veltri, and K. J. Pienta, "Critical transitions in a game theoretic model of tumour metabolism," *Interface Focus*, vol. 4, no. 4, p. 20140014, 2014.
- [6] A. McAvooy and C. Hauert, "Autocratic strategies for alternating games," *Theor. Popul. Biol.*, vol. 113, pp. 13-22, 2017.
- [7] Y. Mansury, M. Diggory, and T. S. Deisboeck, "Evolutionary game theory in an agent-based brain tumor model: exploring the 'genotype-phenotype' link," *J. Theor. Biol.*, vol. 238, no. 1, pp. 146-156, 2006.
- [8] M. J. Osborne, *An introduction to game theory*, vol. 3. Oxford university press New York, 2004.
- [9] M. J. Osborne and A. Rubinstein, *A course in game theory*. MIT press, 1994.
- [10] W. H. Press and F. J. Dyson, "Iterated Prisoner's Dilemma contains strategies that dominate any evolutionary opponent," *Proc. Natl. Acad. Sci.*, vol. 109, no. 26, pp. 10409-10413, 2012.
- [11] G. Roshandel et al., "Cancer incidence in Iran in 2014: Results of the Iranian National Population-based Cancer Registry," *Cancer Epidemiol.*, vol. 61, pp. 50-58, 2019.
- [12] M. S. Salamat, Robbins and cotran: *Pathologic basis of disease*. American Association of Neuropathologists, Inc., 2010.
- [13] I. P. M. Tomlinson, "Game-theory models of interactions between tumour cells," *Eur. J. Cancer*, vol. 33, no. 9, pp. 1495-1500, 1997.
- [14] I. P. M. Tomlinson and W. F. Bodmer, "Modelling the consequences of interactions between tumour cells," *Br. J. Cancer*, vol. 75, no. 2, p. 157, 1997.
- [15] A. Wu, D. Liao, T. D. Tlsty, J. C. Sturm, and R. H. Austin, "Game theory in the death galaxy: interaction of cancer and stromal cells in tumour microenvironment," *Interface Focus*, vol. 4, no. 4, p. 20140028, 2014. related results, *Journal of Inequalities and Applications*, 2012, O:238.