GAME THEORY COMBINED WITH NETWORK ANALYSIS – GOOD APPROACH FOR ANALYSIS OF BRAIN TUMOUR GROWTH?

Franciszek Binczyk
Faculty of Automatic Control, Electronic and Computer Science, Silesian University of Technology, Data mining group, Akademicka 16, 44-100 Gliwice, Poland

Abstract

The paper is related to the idea of use of mathematical tools: game theory and graph analysis for the analysis of brain tumour behaviour. Author presents the main assumptions of both theories and describes what is the idea to use them in combination with Nuclear Magnetic Resonance data, such anatomical data as imaging T1, T2 and high resolution diffusion tensor imaging to obtain a possible way of answering the question: What determines different tumour behaviour (even in one family) such as rapid growth or silence.

1. Introduction

The brain tumours are one of the most deadly oncological diseases. Since they are invading the part of the body that is safely hidden inside a skull the may give no or just small symptoms in a long time and than rapidly expand. Since brain is a very sensitive structure the diagnostic techniques are limited. On possible non-invasive is to use Nuclear Magnetic Resonance (abr. NMR) Scanner to observe the change of behaviour of water molecules that can give non-direct information about the tumour and effects of its growth in a brain. With use of such information combined with biopsy it is possible to classify the tumour and detect its spread in the brain. However NMR gives only information about water molecules that may lead to the situation that in first scan the tumour is barely visible and in the next there is massive explosion and large volume is invaded. Because of that it is important to answer the question why and when tumour is likely to spread in days or stay in silence for months.
The idea that stands behind the project is to use mathematical tools: a game theory and elements of network analysis to define behaviour of the tumour and answer the question what are the most important factors that determines its behaviour.

2. The Game Theory

To start lets try to answer what is a game? One of the examples may be chess. The game is designed for two players that play together according to defined rules in order to accomplish the goal- win of the game. One may say that such a complicated game as chess requires lots of effort from the player but lets imagine that both players are using a tactics: peaceful oriented only at protecting own figures or aggressive that leads to eliminate as may enemy's as possible. Of course both tactics are limited by the rules of the game. Such a simplification may describe basis of nearly all games. However there even exists a separate branch of science called "Game Theory" that covers it all. The fathers of the Game theory are said to be Johan von Neuman and Oskar Morgenstern. In 1944 they described their thoughts and theories in the book of the title: The Theory of Games and Economic Behavior. Since that time many scientist worked on this topic, introducing new laws theories and improving original laws. One of them, John Forbes Nash jr. got for his breakthrough research one of the highest rewards, a Nobel Price. But the question is still opened what is the game in mathematical meaning? By means of game theory the Game could be defined as any conflict situation between two (or more) players. The player could be a man, company, animal cell (interesting from our point of view) or phenomenon. Every player in the game choses its strategy that determines a game result which is called an income of the player. Income of the player is measured in the units of usability such as money, chances of growth or simply satisfaction. In game theory, a result of the game is represented by a defined numerical value. The set of games could be divided into games that are:

- cooperative and non-cooperative,
- with zero and non-zero sum,
- simultaneous and sequential,
- symmetric and asymmetric.

Summarizing, game theory could be understood as the study of strategic decision-making or a mathematical model of conflict that includes the decisions done by decision makers. A very important factor that determines a result of a game is a strategy. A strategy, may be defined as one of the possibilities that player can pick at any time while playing the game. It is important to notice that the result of the game depends on the strategies that are chosen by both players. Strategies are divided into:

- pure and mixed (in which player may shift among strategies)
- or finite and infinite (when there exist a limit number of strategies or not).

It might be said that appropriate sets of strategy is crucial for the design solvable and meaningful game. In order to define proper strategy set (and its limits) one may use knowledge obtained about the given problem.

The last but not least important factor in game theory is an income of the player. It is a reward that is obtained by a player after each single game iteration. The amount of income depends on a strategy that was chosen by all players and on their decisions as well.

In normal form, game is may be represented as a 2 x 2 decision matrix. Each of two players of the game has two decisions that influence their income. In more general words, a game may be defined by set of equations that combines reward of the players and every possible of their choices.

In such a form of the game each player may chose between two strategies, which are represented by row and columns. The rewards are given in the cells of decision matrix. The first number in the cell represents the reward obtained by one player (row player) and second, reward obtained by second player (column player).

In order to make analysis of the game much easier there were introduced to important conditions that game could satisfy. The Pareto optimum is such a division of rewards in the game that any other change positive for one player may be only negative for the second player. The nice example of such a game may be: a man with bread and a man with water. At the first iteration a man with bread is thirsty while man with water is hungry. At that stage they are ready to exchange large amount of their goods with a rival but after few iterations they are both satisfied and don't want to exchange their goods for a low price. In such a case an income of one is a lost of the second and rule of Pareto Optimum is satisfied. Second important feature of the game is so called Nash equilibrium. In general, player one and two are in Nash equilibrium if player one is making the best decision that he can, taking into account players two decision. On the other hand player two is making the best decision, taking into account player one decision.

Example of the game- prisoners dilemma

These wells know game has a nice storyline. Two members of a criminal gang were arrested and imprisoned. Each prisoner refuses to cooperate with a police. Unfortunately the police have no evidence to put them in jail. The best case is that they would both spend one year in jail. At the same time, they were offered a deal. If one of them will testify against other, he will go free while the partner will go to jail for 3 years but if both will use this opportunity they will both spend two years in jail.

	Player 2 stay silent	Player 2 testifies
Player 1 stay silent	1,1	3,0
Player 1 testifies	0,3	2,2

Fig.1 Decision matrix of the Prisoners dilemma game

After simple analysis we see that such a game has one Nash Equilibrium when they both decides to testify.

3.Evolutionary Game Theory

Evolutionary game theory is the application of theoretical background introduced by von Neuman to biological populations. Important assumption is that such a population may evolve during the game. John Maynard Smith and Gorge Price proposed evolutionary game theory in 1973. The main difference between EGT and classical GT is the focus on the dynamics of strategy change/evolution that is a result of number of such a modified strategies that may be found in population. During the years concept of evolutionary game theory has proven itself to be extremely helpful to explain many complex phenomenon's that occurs in Biology. An example of such a game may be Hawks and Doves. Smith Price presented the game for the first time in their paper "The logic of animal conflict" published in 1973 in Nature. The traditional pay off matrix for the Hawk-Dove game is given below on figure 2. V is the value of the resource, and C is the cost of an escalated fight. It is (almost always) assumed that the value of the resource is less than the cost of a fight.

	Hawk	Dove
Hawk	(V−C)/2, (V−C)/2	V, 0
Dove	0, V	V/2, V/2

Fig.2 Decision matrix of the Hawk-Dove game

On of the important concept that was introduced with EGT is evolutionary stable strategy. It is a strategy that adopted by population in given environment cant be change to any other rare strategy. An evolutionary stable strategy may be

understood as a Nash Equilibrium that remains stable after a population chooses it. One may notice that population, due to the process of natural selection, rejects other strategies.
It is worth to notice that evolutionary game theory concept assumes that the players may evolve and pick better strategies that will result in better reward for them. Such a case may be illustrated by a modified version of Hawk-Dove game. The main difference from the original is existence of additional strategy - the Owl. Such an additional player "studies its opponent" in order to behaves as a hawk when meets weaker opponent or behaves as a dove while meets stronger opponent. It is worth to notice that concept of Owl is in fact an evolutionary stable strategy. The decision matrix for modified Hawk-Dove game is presented on figure 3. It can be noticed that Owl can invade as a mutant in both populations and can survive invasion of both.

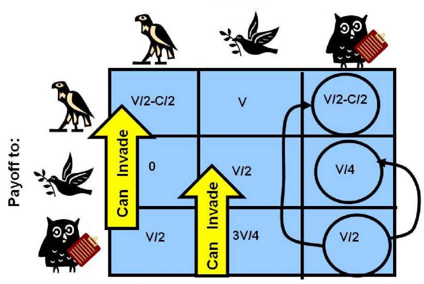

Fig.3 Decision matrix of the Hawk-Dove game

Replicators

In evolutionary game theory replicator is a structure that has ability of self-copying itself and tend s to create as many copies as possible.
That is why replicator may be a good description of player/population in an evolutionary game.
Behavior of the replicator might be described with use of differential equations and it's called replicator equations.

I. The first replicator equation describes proportion of population p playing strategy s in time t.

$$\frac{d}{dt}p_i(t) = \alpha\beta \cdot p_i(t) \cdot (\pi_i(t) - \bar{\pi}(t))$$

Where α is the rate at which critters learn about other strategies, β is their willingness to change strategies, π (t) is the expected reward in time and π (t) is average reward obtained by whole population.

II. If the strategies are in fact inherited in the population not learned, one may use simplified equation:

$$\frac{d}{dt}p_i(t) = p_i(t) \cdot (\pi_i(t) - \bar{\pi}(t))$$

,where π (t) is the expected reward in time and π (t) is average reward obtained by whole population.

With proper use of above equations (and of course its modifications) it is possible to define evolution of nearly all populations using different strategies. It is worth to notice that one may define a structure that will influence the structural orientation of the played game. A so-called latice or grid may be introduced in order to define a constraint for population growth or evolution. In other words a player or replicator can only play (and in result duplicates) to the neighborhood that is available by means of a latice. It may be understood as a rule for replicator.

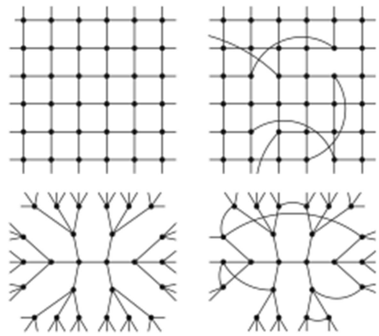

Fig.4 Examples of different possible connections in the grid.

4.Network analysis

Every graph is build of a set of two main components: nodes and edges that are connecting the nodes between themselves. There exists two kind of graphs: directed in which the direction of the flow from edge to edge has some matter and undirected, when the direction of the flow is not important. In analyzed case undirected graphs would be used since the networks that are under analysis such as: neural tracks or blood vessels in brain may carry information (tumor cells) in both directions. The edge of every graph may carry important information called weight that informs in non-direct way what is the strength of connection between the two nodes that is represented by such an edge. This property seems to be crucial while analysis of brain structures. Some of neural tracks and vessels are thicker than others. It means that they can carry more information and are more important for the graph itself. A graph /network theory is of course more complex and covers much more topics but for the purpose of this project author will use only simple graph/ network construction.

5.Data

In the project a large group of the patients with the same aggressive brain tumor but with different behavior in time was selected. For every brain, with use of information from diffusion tensor imaging, it was possible to define a network (neurons, vessels or combination of both). The different populations were obtained by manual segmentation of the image in order to divide brains into healthy (or better morphologically unchanged) parts and tumor tissue.

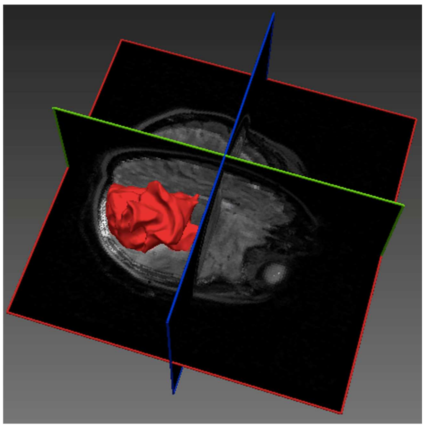

Fig.6 Exemplary segmented data set. 3D volume of tumor is marked with red color. It means that all inside red volume is treated as a population of tumor.

6.Preliminary conclusion

Since the project is new, no breakthrough results were obtained so far. The input data are prepared and the graphs are constructed. In the future research author plans to follow one of the two possible paths:

I. Perform evolutionary game on graph, use different strategies (mostly different values of coefficients) and observe the actual changes in order to guess the strategy that is used by a tumor.

II. Observe the „result of the game" to guess strategies and number of fenotypes in population (different parts of tumors), however this seems to be more difficult and maybe not solvable problem. Author plans to focus on this research in nearest future.

Acknowledgements

The work was partially financially supported by SUT grant BK219/Rau1/2013/t.3 and DoktoRis-Scholarship program for Innovative Silesia. Author is thankful to both of his supervisors and staff of Institute of Oncology in Gliwice and Deutches Krebsforschungszentrum for providing help, hints and access to the medical data.

References

1. Neumann J and Morgenstern O: *Theory of Games and Economic Behavior*, Princeton University Press (1944).
2. Nash, JF "Equilibrium Points in N-person Games". Proceedings of the National Academy of Sciences 36 (36): 48–9. (1950).
3. Maynard-Smith, J.; Price, G. R. :"The Logic of Animal Conflict". *Nature* 246 (1973).
4. Maynard Smith J, "Evolution and the Theory of Games", Cambridge University Press, (1982)
5. Szabo G, Fath G (2007) Evolutionary games on graphs. Phys Rep 446:97–216.
6. Bressler, S. L. Large-scale cortical networks and ▪ cognition. *Brain Res. Brain Res. Rev.* 20, 288–304 ▪ (1995).
7. Singer, W. Neuronal synchrony: a versatile code for the ▪ definition of relations? *Neuron* 24, 49–65 (1999).
8. Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev., Neurosci. 10, 186–198.

Information about author

MSc. Franciszek Binczyk
Institute of Automatic Control, Silesian University of Technology
ul. Akademicka 16 p.535
44-100 Gliwice
tel. (032) 237 11 66
franciszek.e.binczyk@polsl.pl