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An overview of recent applications of Game Theory to bioinformatics

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ABSTRACT

The goal of this work is to provide a comprehensive review of different Game Theory applications that have been recently used to predict the behavior of non-rational agents in interaction situations arising from computational biology.

In the first part of the paper, we focus on evolutionary games and their application to modelling the evolution of virulence. Here, the notion of *Evolutionary Stable Strategy* (ESS) plays an important role in modelling mutation mechanisms, whereas selection mechanisms are explained by means of the concept of *replicator dynamics*.

In the second part, we describe a couple of applications concerning cooperative games in coalitional form, namely *microarray games* and *Multi-perturbation Shapley value Analysis* (MSA), for the analysis of genetic data. In both of the approaches, the Shapley value is used to assess the power of genes in complex regulatory pathways.

1. Introduction

Game Theory is a mathematical theory dealing with models for studying interaction among decision makers (which are called *players*). Since the seminal book by John von Neumann and Oskar Morgenstern (1944) 'Theory of Games and Economic Behavior', it is usual to divide Game Theory into two main groups of interaction situations (which are called *games*), *non-cooperative* and *cooperative* games. Non-cooperative games deal with conflict situations where players cannot make binding agreements. In cooperative games all kinds of agreement among the players are possible.

In non-cooperative games each player will choose to act in his own interest, keeping into account that the outcome of a game depends on the actions of all the players involved. Actions by players can be simultaneous (the 'stone, paper, scissors' game or the 'matching pennies' game) or at several points in time (chess, backgammon).

Cooperative games deal with situations where groups of players (which are called *coalitions*) coordinate their actions with the objective to end up with joint profits which often exceed the sum of individual "profits".[1]

The terms *bioinformatics* and *computational biology* are often used interchangeably [17]. However, *bioinformatics* more properly refers to the creation and advancement of theory and of algorithms to solve formal and practical problems arising from the management and the analysis of biological data. In order to extract useful information from data produced by high-throughput biological techniques such as genome sequencing, bioinformatics uses mathematical tools. A representative problem in bioinformatics is the study of gene regulation to perform expression profiling using data from microarrays or

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[1] For game theorists, *utility value* would be more correct than the term profit. As for the ordinary language, we use for the moment the term profit with reference to something that is in the interest of the decision maker to be maximized.

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other technologies (see for instance, [8,16,42]). Other common problems are the analysis of mutations in cancer, the evolution of virulence and the HIV infection, etc.

In this paper, we review some applications of Game Theory to the analysis of biological data. Obviously, such applications are not aimed at answering normative issues, like giving an advice to a group of variables (e.g. genes) on how they should behave inside a biological cell. In this context, Game Theory is used to describe the behavior of variables and to predict the outcome of their interaction [35]. Of course, a critical issue of all these applications of Game Theory to experimental data is a meaningful definition of the notion of "profit". The possibility of extending the concept of profits, benefits, savings or whatever could be in the interest of each decision maker to be maximized on her/his own count, is a well-known feature of Game Theory applications. In Game Theory, the term "profit" usually is more correctly replaced by *utility value* of a *rational* player. We do not want to enter here the discussion of how an utility function is defined and why it is a numerical representation of the *preferences* of a rational decision maker. For introductions to this problem see for instance the books by Kreps [21].

In Section 2, we introduce evolutionary games and their application in modelling the evolution of virulence. Section 3 deals with coalitional games and their applications to gene expression data analysis. Section 4 concludes.

2. Evolutionary Game Theory

Evolutionary Game Theory originated as an application of the mathematical theory of non-cooperative games to biological contexts, based on the idea that frequency dependent fitness introduces a strategic aspect to evolution. It was in fact the publication of 'The Logic of Animal Conflict' by Maynard Smith and Price in 1973 [26] that introduced the concept of an *Evolutionary Stable Strategy* or ESS into widespread circulation. In 1982, Maynard Smith's seminal text 'Evolution and the Theory of Games' appeared [25], followed shortly by Robert Axelrod's famous work 'The Evolution of Cooperation' in 1984 [5]. Since then, evolutionary Game Theory has gained increased interest by economists, sociologists, and anthropologists – and social scientists in general – as well as by philosophers [39,43,41,4,3,22].

In the context of biology, evolution requires populations of reproducing individuals, in the sense that, under appropriate conditions biologic entities such as cells, viruses or multicellular organisms can make copies of themselves [32].

In general, an evolutionary process combines two mechanisms that have proven to be of utmost importance: a *mutation mechanism* that provides variety and a *selection mechanism* that favors some varieties over others. The role of mutation is highlighted by the idea of ESS, while the role of selection by the concept of the replicator dynamics. The replicator dynamic assumes that subpopulations playing a better than average strategy grow, while those associated with worse than average strategies decline. It should be noticed that ESS is a Nash Equilibrium which is "evolutionarily" stable, meaning that once it is fixed in a population, natural selection alone is sufficient to prevent alternative (mutant) strategies from successfully invading.

2.1. Evolutionary Stable Strategies

As said, a key concept in evolutionary Game Theory is that of an ESS. A population playing such a strategy is invincible by any other strategy. More specifically, suppose that the initial population is programmed to play a certain pure or mixed strategy profile x. Now, assume that a small population share, ϵ, where $\epsilon \in (0,1)$, plays some other pure or mixed strategy y. Hence, if an individual is drawn to play the game, then the probability that the opponent will play the mutant strategy y is ϵ, and the probability that the opponent will play the incumbent strategy x is $1-\epsilon$. Under these assumptions, the payoff in that match is the same as in the match with an individual who plays the mixed strategy $w = \epsilon y + (1-\epsilon)x$. The corresponding payoff to the incumbent and mixed strategy is $u(x,w)$ and $u(y,w)$, respectively. Stability for strategy x can be formally translated in the following inequality

$$u(x, \epsilon y + (1-\epsilon)x) > u(y, \epsilon y + (1-\epsilon)x). \tag{1}$$

More precisely, we have:

Definition 1. A strategy x is said to be *evolutionary stable* if for every strategy $y \neq x$ there exists some $\bar{\epsilon}_j \in (0,1)$ such that inequality (1) holds for all $\epsilon \in (0, \bar{\epsilon}_j)$.

There is also a weaker notion of evolutionary stability, called neutral stability. Instead of requiring that all mutants earn less than the incumbent strategy, neutral stability requires that no mutant prosper in the sense of earning a higher payoff than the incumbent strategy.

Definition 2. A strategy x is said to be *neutral stable* if for every strategy there exists some $\bar{\epsilon}_j \in (0,1)$ such that inequality

$$u(x, \epsilon y + (1-\epsilon)x) \geqslant u(y, \epsilon y + (1-\epsilon)x), \tag{2}$$

holds for all $\epsilon \in (0, \bar{\epsilon}_j)$.

Using linearity of expected utility in probabilities, relation (1) can be written as follows

$$\epsilon u(x,y) + (1-\epsilon)u(x,x) > \epsilon u(y,y) + (1-\epsilon)u(y,x). \tag{3}$$