Journal of Theoretical Biology ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Cooperation among cancer cells as public goods games on Voronoi networks

Marco Archetti

School of Biological Sciences, University of East Anglia, Norwich Research Park, Norwich NR4 7TJ, UK

HIGHLIGHTS

- Diffusible growth factors produced by cancer cells are a type of public good.
- Cell populations form networks that can be described as Voronoi graphs.
- The dynamics of public goods games is analysed on Voronoi graphs.
- The type of non-linear benefit is crucial, while the type of diffusion gradient is not.

ARTICLE INFO

Article history:
Received 28 July 2015
Received in revised form
13 January 2016
Accepted 19 February 2016

Keywords:
Game theory
Cancer
Growth factors
Cooperation
Diffusion
Voronoi

ABSTRACT

Cancer cells produce growth factors that diffuse and sustain tumour proliferation, a form of cooperation among cancer cells that can be studied using mathematical models of public goods in the framework of evolutionary game theory. Cell populations, however, form heterogeneous networks that cannot be described by regular lattices or scale-free networks, the types of graphs generally used in the study of cooperation. To describe the dynamics of growth factor production in populations of cancer cells, I study public goods games on Voronoi networks, using a range of non-linear benefits that account for the known properties of growth factors, and different types of diffusion gradients. The results are surprisingly similar to those obtained on regular graphs and different from results on scale-free networks, revealing that network heterogeneity per se does not promote cooperation when public goods diffuse beyond one-step neighbours. The exact shape of the diffusion gradient is not crucial, however, whereas the type of non-linear benefit is an essential determinant of the dynamics. Public goods games on Voronoi networks can shed light on intra-tumour heterogeneity, the evolution of resistance to therapies that target growth factors, and new types of cell therapy.

1. Introduction

1.1. Growth factors as public goods

At least five of the hallmarks of cancer (Hanahan and Weinberg, 2011) depend on the production of diffusible factors by cancer cells (Witsch et al., 2010): self-sufficiency in growth signals, evading apoptosis, sustained angiogenesis, immune system evasion and the initiation of metastases. Because most of the cytokines and growth factors that promote these processes diffuse in the extra-cellular matrix, their effect is not limited to the cells that produce them, and non-producing cells can use the factors diffusing from neighbouring producer cells. The production of such diffusible factor is, in other words, a form of cooperation between cancer cells (Jouanneau et al., 1994; Axelrod et al., 2006; Archetti et al., 2013a) and growth factors are a type of public good (the term "common goods" would be more appropriate because, "public goods" are often defined as being non-rivalrous, as well as non-excludable (Samuelson, 1954); this definition, however, applies to very few cases, and "public good" has been used more often in biology).

1.2. Public goods in evolutionary game theory

Public goods raise a collective action problem: why contribute to the production of a public good instead of free-riding on the goods (in our case growth factors) produced by other group members? The overexploitation of common-pool resources is a common outcome of such collective action problems (Hardin, 1968). Because of the strategic, frequency-dependent nature of the interactions, the most appropriate framework for the study of public goods is game theory. Evolutionary game theory (Maynard

E-mail address: m.archetti@uea.ac.uk

http://dx.doi.org/10.1016/j.jtbi.2016.02.027
0022-5193/

Smith, 1982), in particular, is appropriate because it does not assume rational behaviour; instead, the individuals (or cells), programmed to take the best decision have higher fitness and increase in frequency in the population by natural (clonal) selection. The study of cooperation has a long tradition in biology (Nowak, 2006). Public goods games in biology have been reviewed recently (for well-mixed populations: Archetti and Scheuring (2012); for spatially structured populations: Perc et al. (2013)).

1.3. Growth factors are non-linear public goods

For the study of growth factor production by cancer cells we must use assumptions that are rarely used in the study of public goods games. First, models of public goods often assume that fitness is a linear function of number of producers. For cancer cells this would imply that proliferation is a linear function of the amount of circulating growth factors, an assumption that is clearly not true; growth rates of cancer cells are typically a sigmoid function of the concentration of growth factors (e.g.: Valenzano et al., 1997; Karey and Sirbasku, 1988; Jourdan et al., 2005). We will assume different types of non-linear benefits here.

1.4. Decoupling the update and interaction neighbourhood

Another standard assumption in the study of public goods is that an individual can affects only the fitness of its one-step neighbours; more specifically, the assumption is that an individual belongs to multiple groups, each group centred on one of that individual's one-step neighbours, and that individual's fitness is the sum of all the payoffs accumulated by that individual in all these groups (Perc et al., 2013). While this assumption is reasonable for human interactions in social networks, growth factors typically diffuse beyond a cell's one-step neighbours. We must assume, therefore, that the payoff for an individual is a function of the number of producers within the diffusion range of the growth factor, which defines the interaction group. In other words, in order to study diffusible public goods, we must decouple the interaction neighbourhood (the group playing the public goods game) and the update neighbourhood (the one-step neighbours). This approach has been used to study a two-person game with a linear benefit function (the Prisoner's Dilemma) on a regular lattice (Ifti et al., 2004; Ohtsuki et al., 2007) and for non-linear public goods games on regular lattices with a fixed diffusion range (Archetti, 2013b).

1.5. Diffusion gradients

Given that growth factors diffuse beyond one-step neighbours, we must define the shape of the diffusion gradient. Because public goods games have typically assumed a one-step diffusion range, there has been little scope for analysing diffusion gradients so far. Four recent studies (Allen et al., 2013; Borenstein et al., 2013; Scheuring, 2013; Archetti, 2013b) have analysed diffusion gradients in the context of public goods, and have reached rather discordant conclusions because they used different assumptions, particularly on the shape of the benefit function. If the benefit function is non-linear, the shape of the diffusion gradient seems to be largely irrelevant for the dynamics, and can be approximated by a step function (Archetti, 2014a). This result may be limited, however, to the type of graphs (regular lattices) used in those studies.

1.6. Voronoi networks

The main departure from the standard approach analysed here is the use of Voronoi networks. Two topologies are usually considered in the study of spatial games: regular lattices, in which all individual nodes are topologically equivalent, and scale-free networks, in which different individuals have a distinct number of connections (reviewed in Perc et al. (2013)). While regular lattices neglect the importance of variation in connectivity, scale-free networks are not appropriate if players are distributed on a planar network. The

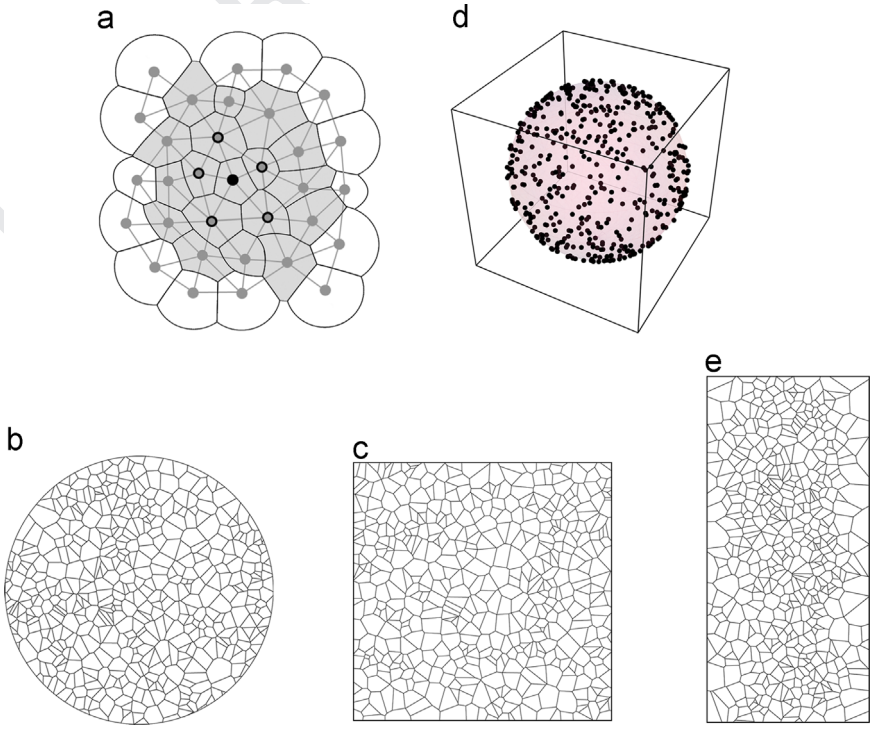

Fig. 1. Voronoi graphs. A monolayer of cells (a) can be described by a Voronoi tessellation of points on a plane, and the corresponding network by a planar graph (the grey lines) produced by a Delaunay triangulation of such points. An individual cell (black circle) is in direct competition with its one-step neighbours (grey circles with black edges); a group is defined by the diffusion range of the growth factor; here the diffusion range (grey cells) is $d=2$. Voronoi tessellations can be drawn on a circle (b), on a square (c) and on a sphere (d). Voronoi graphs on a sphere can be represented in two dimensions as parallelograms whose polygons on opposite edges are connected (e).

Please cite this article as: Archetti, M., Cooperation among cancer cells as public goods games on Voronoi networks. J. Theor. Biol. (2016), http://dx.doi.org/10.1016/j.jtbi.2016.02.027