Cooperation among cancer cells: applying game theory to cancer

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Cancer cells cooperate in many of the hallmarks of cancer, within the tumor and with stromal cells in the microenvironment, via the secretion of diffusible factors. This cooperation cannot be explained simply as the collective action of cells for the benefit of the tumor, because non-cooperative clones can constantly invade and free-ride on the growth factors produced by the cooperative cells. A full understanding of cooperation among cancer cells requires methods and concepts from evolutionary game theory, which has been used successfully in other areas of biology to understand similar problems, but underutilized in cancer research. Game theory can provide insight into the stability of cooperation among cancer cells and the design of evolution-proof therapies by disrupting this cooperation.

Cooperation in cancer

Cells within a tumor compete for space and resources, but also cooperate with one another, by secreting diffusible factors that promote tumor growth and invasion[1-5]. Cooperative interactions between cancer cells and with their microenvironment are essential for cancer progression and crucial in driving resistance to therapies[6-8]. Many of the molecules responsible for these interactions, their genes and the signalling pathways they activate are known, but *why* cells within a tumor cooperate remains unexplained. The "why" here relates to the adaptive advantage[9-11] of cooperation: what selective advantage does a cell gain by cooperating (producing a growth factor)?

The idea that cells within a tumor cooperate for the benefit of the tumor – an appealing and apparently reasonable explanation – is a logical fallacy that has a parallel in the history of evolutionary ecology, where it is known as the "group selection" argument[12] – the idea, popular until the 1960's that the behaviour of individuals is driven by the success of their group or species, a logic that evolutionary biologists now agree is flawed[12-14]. A mutation making an individual cheat, for instance by free-riding on shared resources produced by other cooperative individuals, would confer a reproductive advantage to the cheating individual and its descendants. Thus, its type would increase in frequency in the population over time, irrespective of the consequences for the population in the long term – leading to what is generally referred to as "tragedy of the commons" [15]. In the original example, a group of herders whose cows graze a common land have a selfish short-term interest in putting as many cows as possible onto the land, even if the commons is damaged as a result, because the

benefit is private while the damage to the common land is shared with the entire group; if all herders make this selfish decision, however, the common will be degraded. Evolution is short-sighted, and nothing evolves for the benefit of the group, or the species, even if that may lead to inefficiencies and extinctions[14].

In the case of cooperation among cancer cells, a mutant cell that stopped producing growth factors would still benefit from the growth factors secreted by its neighbouring cells without paying the cost of producing it; hence that mutant clone would have a higher fitness and spread within the tumor. Over time, the clones originating from this non-producer cell should drive the original producer clone to extinction – a tragedy of the commons at the cellular level. Clonal selection[16-18], like natural selection in the wild, only promotes phenotypes that increase an individual cell's fitness, not the long-term benefit of the group it happens to belong to (the tumor). Nothing evolves for the benefit of the group – in this case, of the tumor.

How is cooperation maintained then? This question is the source of complex analysis and never-ending debates in other fields, from evolutionary biology[14,19-22] to economics[23-25], but is generally glossed over in cancer biology. A full understanding of cooperation between cancer cells requires the application of methods and concepts from game theory.

Game theory of cancer

Evolutionary game theory. Game theory is the study of strategic interactions, that is, situations in which an individual's payoff depends not only on its own behaviour but also on the behaviour of other individuals[26-29]. In other words, game theory is the study of optimization problems in which payoff functions are frequency-dependent, that is, when fitness depends not only on the (relatively stable) environment, but also on the changing frequencies of the other phenotypes in the population, which includes competitors and cooperators. Such problems are called "games", the individuals are called "players," and the behaviours are called "strategies" [**Box 1**].

In game theory applied to human behaviour, it is assumed that decisions are taken through rational decision-making and that payoffs corresponds to profit. In *evolutionary* game theory[30-33], payoff corresponds to Darwinian fitness, and there is no need to assume rationality or intention: the players are replicating individuals (in this case cells), and strategies are phenotypes produced by mutations that differentiate one subclone from another within the tumor. Optimization is achieved at the population level via natural selection (clonal selection), which changes the frequencies of the strategies over time in a manner proportional to their fitness.

While for an ecologist it is clear that natural selection in the wild is often frequency-dependent, in cancer research, the traditional view of carcinogenesis as a clonal population of cells developing all of the necessary genetic traits independently to form a tumor, might suggest that a genotype's fitness is independent of its relative abundance. Game theory does not offer new insight into hallmarks of cancer that are not frequency-dependent, such as the typical genome instability and limitless replicative potential of cancer cells. Most of the hallmarks of cancer, however, such as self-

sufficiency in growth signals, evading apoptosis and the immune system, neoangiogenesis and metastasis, depend on interactions between cancer cells or between cancer and stroma[6-8], which are frequency-dependent. Evolutionary game theory can help understand these interactions.

The simplest game describing the problem of cooperation is the Prisoner's Dilemma[34] (PD) [**Box 2**]. There is a vast literature in evolutionary biology[14,19-22] and economics[23-25] about the PD and on how, in spite of its predictions, cooperation can evolve because of genetic relatedness[14,22] or repeated interactions over time[19,21]. In cancer research, game theory was introduced[35-36] using a version of the game of Chicken[37] [**Box 3**]. Subsequent papers using game theory in cancer research[40-49] were extensions of this game, and analogous games with pairwise interactions continue to be used. These, however, are simple models that do not capture fundamental features of cancer: most cases of cooperation in cancer are examples of multiplayer games, where payoffs are calculated from the effect of the collective interactions of many cells, rather than from the pairwise interactions of pairs of cells. This is because in most cases cooperation in cancer depends on the effect of diffusible factors.

Cooperation via diffusible factors. Game theory has been applied to cancer to explain a variety of situations in which cancer cells cooperate with each other: the production of diffusible growth factors is the most straightforward example[3,50-53] and the first empirical test[3] of game theory in cancer was performed on insulin-like growth factor (IGF-II), which promotes proliferation and evasion of apoptosis in neuroendocrine pancreatic cells; similar dynamics arguably applies to other growth factors in other types of cancer. Other examples include the role of IDH1 mutated tumour cells in secondary glioblastomas[44], prostate tumor growth under intermittent androgen suppression therapy[54], metabolic mutualism between hypoxic and oxygenated cancer[55], interactions between glycolytic acid production and angiogenesis[56] and the Warburg effect [43,57,58].

Cooperation can also be mediated by the stroma. Normal fibroblasts, for example, are recruited and activated by the tumor, becoming cancer-associated fibroblasts (CAF) and acquiring pro-tumorigenic functions, secreting growth factors and cytokines that sustain tumor progression[59]. This is a form of coercion, not cooperation, given that the stromal cells are recruited and activated by the cancer cells for their own advantage. Cancer cells, however, do cooperate with each other by secreting the diffusible factors that recruit and activate the fibroblasts. In other cases, the benefit for the tumor arises from growth factors, produced by the cancer cells, that promote neo-angiogenesis; or disable the immune system by activating or inhibiting a variety of cells[6]. In all these cases, cancer cells cooperate with each other, by producing diffusible factors that induce the stroma to provide a benefit to the tumor. Game theory has been used to describe tumor-stroma interactions in the production of matrix metalloproteinases and tissue inhibitors of metalloproteinases[60], in the dynamics of prostate cancer progression and treatments[41] and in the dynamics of multiple myeloma[46,61,62].

The Warburg effect[63] (the switch from aerobic energy production through oxidative phosphorylation to anaerobic energy production through glycolysis) is another

example of intra-tumor cooperation that depends on diffusible factors. In some cases, a glycolytic subpopulation of cancer cells under hypoxia will release lactate as a by-product, thus fueling a subpopulation of cancer cells producing energy through oxidative phosphorylation[64]. The Warburg effect, however, is not merely an adaptation to hypoxia, and can occur even under normal oxygen concentrations[65]. In fact, its main function may be the acidification of the microenvironment through its diffusible byproducts[66-69], which promotes the death of normal cells, facilitates tumour invasiveness, has immunosuppressive effects, and stimulates release of growth factors. The cooperative nature of the Warburg effect is clear: energy production through glycolysis is less efficient for a cell than through oxidative phosphorylation (when oxygen is not limited) but induces a beneficial effect for the tumour as a whole: the acidification of the microenvironment brought about by the diffusible metabolites produced by cooperative (glycolytic) cells[43,44,57,58]. Cancer cells can even promote the Warburg effect in neighboring CAFs, a process referred to as the "reverse Warburg effect"[70]; these CAFs then secrete metabolites that can be used by cancer cells and oxidized for energy production[71], promoting tumor growth and metastasis[72].

Cooperation among cancer cells, therefore, occurs whenever diffusible molecules, with autocrine and paracrine effects, affect the survival and proliferation of the tumor. The production of growth factors that promote proliferation or angiogenesis, or that help evade apoptosis or the immune system, are examples of cooperation, among the cancer cells or between tumor cells and stroma. Cooperation can also be brought about by other diffusible factors, other than growth factors, such as the metabolites produced by the Warburg effect (discussed above) or small molecules that promote tissue invasion and metastasis: macrophages and mesenchymal stem cells contribute to the epithelial-mesenchymal transition at primary sites by secreting molecules that allow tumor cells to separate from neighbouring epithelial cell-cell contacts and acquire a mobile and invasive phenotype[73]; macrophages also help intravasation[74]; in the circulation, platelets protect cancer cells from cytotoxic immune cell recognition[75] and at secondary sites the integrins they produce mediate attachment to the endothelium[76]; platelets produced by macrophages induce protection against apoptosis[77] and the fibronectin produced by the CAFs promotes extravasation[78]; at secondary sites, CAFs produce factors that help direct metastatic dissemination, while myeloid-derived suppressor cells and natural killer cells create a microenvironment that helps tumor colonization[79].

Most of these instances of cooperation among cancer cells and between tumor and stroma, brought about by diffusible factors, are examples of what game theorists call “public goods games”[80,81]: players (cells) can contribute (by secreting diffusible factors) to a public good. A public good is any good that leads to a benefit for a group – cooperators and defectors alike. In the case of cancer cells the benefit is proliferation, protection against apoptosis or the immune system, acidification of the microenvironment, or invasion and metastasis (**Figure 1**). The effect of the contributions can be direct or mediated by the stroma. A strategy, in this context, can be defined by the amount of diffusible factor produced by the cell.

A situation analogous to mutualism in ecology[82] can arise if two or more different clones produce one (or more) type of diffusible factor each and rely on each other for the provision of the other factor(s)[2,4]. But cooperation often evolves even when there is no interdependence, i.e., one clone produces one or more diffusible factors and another clone does not produce any, or a lower amount - the defector cells have a free ride on the diffusible factors provided by cooperative cells[3]. What prevents defector cells from spreading within the tumor? This is the essence of the problem we need to explain.

Direct interactions. Other types of interactions occur via transmembrane molecules, such as cell-cell adhesion, where fitness depends on a cell's own phenotypes, as well as the phenotype of their immediate one-step neighbours (the cells that are in direct contact). Cooperating for the production of cell-cell adhesion molecules enables cells to stick together, and even if one cell stops producing adhesion molecules it is kept in place by adjacent cells. Multi-cell interactions represent a public goods game, in which a cell interacts only with its immediate neighbours, rather than with other cells within a diffusion range, and a benefit (cell adhesion) is achieved if at least one cell cooperates, a game known as a Volunteer's Dilemma[83,84] (if the adhesion molecules produced by one cell are enough to keep a non-cooperative cell in place; if more than one co-operator is required, the game is a threshold public goods game[80,81,83,84]). While interactions in this case do not involve diffusible factors, the game is still a type of public goods game, in which a benefit is achieved with a threshold of one (or more) cooperator. Here, however, intra-tumor cooperation is clinically desirable (because it prevents metastases), whereas in most other cases of public goods, cancer therapy should aim at impairing cooperation.

In other cases, although more rarely, interactions can take the form of a pairwise game (a game with only two players). Cells within tumors do not normally interact in pairs simply because they are surrounded by more than one cell. Even in monolayers, the average number of neighbouring cells is 6 (fewer than 4 or more than 9 neighbours occurs rarely[51]), and the number of neighbours increases in three dimensions. A special case in which interaction are actually pairwise, but among multiple players (interacting sequentially in pairs), may occur in cell-cell competition[85,86] and in cell-induced apoptosis promoted, for instance, by FAS (CD95) ligands[87]. A common assumption is that a higher efficiency of FAS ligand production would always lead to an advantage in proliferation. Game theory suggests that this might not be necessarily true – the cells with the lowest efficiency could have a higher fitness, and different types could be maintained in the tumor – two results that seem counterintuitive and are difficult to grasp without game theory [**Box 4**].

The vast majority of the interactions we have discussed, however, are examples of multiplayer collective action problems for the production of public goods. How is cooperation possible here?

The logic of cooperation

Public goods games. In a public goods game[80,81], individuals in a group can decide to cooperate or defect; all members of the group receive a benefit from the fact that the group (the tumor) does well, but only the cooperators pay a small cost from contributing to the collective benefit, whereas defectors do not pay this cost (or pay less). One way to calculate how much each individual benefits from the enhanced group benefit, is to sum all the contributions, multiply the result by an enhancement factor, and then redistribute it equally to all players, including the defectors. In this game, which is called the N-person Prisoner's Dilemma (NPD) [90,91], it is easy to see that free-riding on the contribution of other group members (i.e. 'defecting') is the strategy most favoured by natural selection. Contributing cells do get their share of the group benefit, but defecting cells get their share plus the savings from not having contributed to the group benefit. Defecting cells thus enjoy a higher fitness and make up a larger proportion of the tumor in the next generation, resulting in fewer cells contributing to the group benefit until, eventually, only defecting cells are left, and nobody contributes to the group benefit. In short, the inexorable logic of the NPD is the extinction of cooperators – the "tragedy of the commons" [15].

There is a vast literature[19-25] in evolutionary biology and economics about how, in spite of this prediction, cooperation can evolve. Explanations fall into two main categories: genetic relatedness or repeated interactions. Genetic relatedness enables cooperators to provide benefits to their own kin, hence helping their own genes; repeated interactions allow reciprocation (punishment of defectors or rewards for cooperators). Essentially, both are forms of positive assortment: cooperation can evolve when a cooperative type interacts preferentially with other cooperative types.

Some results that already exist in the evolutionary game theory literature can be applied to game theory of cancer. For instance, theory predicts[92] that when cooperation affects the probability of reproduction, it evolves under less strict conditions than when it affects the probability of surviving death. In the context of cooperation among cancer cells, this would imply that cooperation for the production of growth factors that promote proliferation is more likely than cooperation for growth factors that promote resistance to apoptosis.

This and other existing results, however, are based on the NPD, and make a crucial assumption that is not valid in cancer biology: linear (additive) effects. Diffusible factors in tumors have, in fact, non-linear effects. In general, the effect of biological molecules, including growth factors, is a sigmoid function of their concentration[93]: the effect of each contribution is not simply added in a linear way, but it has synergistic effects at first and then diminishing returns, as observed in a logistic curve. Nonlinear games are notoriously difficult to analyse, but using linear games like the NPD can lead to misleading results[80], hence evolutionary game theory of linear public goods games cannot be simply applied to cancer biology. New methods[94,95] have been developed recently that enable analysis for many types of non-linearities, including sigmoid benefit functions encompassing the effect of most types of growth factors.

Predictions and tests. The theory of non-linear public goods suggests that clones that produce different amounts of growth factors can be maintained in a stable polymorphic equilibrium, even though defectors do not pay the cost of contributing to the public good, because at intermediate frequencies of producers, due to non-linear effects, cooperating confers a higher fitness than defecting [**Figure 2**][3,50-53]. It is important to notice that the maintenance of cooperation has nothing to do with the benefit of the tumor: players do not cooperate because cooperation improves the overall fitness of the group (indeed, the maximum benefit for the group is not at the achieved equilibrium but requires a higher fraction of producers[3] – the equilibrium is inefficient). Rather, self-interested players (cells) cooperate when that is convenient for them to do so, that is, when the marginal benefit of cooperating (the difference in benefit compared to a defector) is higher than its relative cost/benefit ratio (in **Figure 2**, where the fitness of cooperation is higher than the fitness of defection).

Note that, while a cooperative population can be invaded by defector mutants, a population of defector cells cannot be invaded by a cooperative mutant, because the benefit of cooperation is shared among all players, but the cost a cooperator pays is a private cost. Hence, both pure defection and a mixture of co-operators and defectors are stable outcomes, and their occurrence depends also on the initial composition of the population. Well-known features of cancer, like intra-tumor heterogeneity, the inefficiency of metastasis, the inefficiency of establishing cell lines from single clones, and the low plating efficiency of single cells are all compatible with this bi-stable dynamics.

The stable heterogeneous equilibrium can be achieved if the cost of producing the growth factor is low enough compared to the benefit it confers. The critical cost/benefit depends on the diffusion range of the molecules secreted and on the shape of its effect as a function of its concentration[3,50-53]. Not surprisingly, cooperation evolves more easily when the cost is low (and disappears entirely above the critical threshold). This prediction has been confirmed using experimental tests of the theory in pancreatic cancer cells[3], where the cost/benefit ratio can be manipulated experimentally by titrating the amount of exogenous growth factors available to the cells. The collapse of cooperation may be happening naturally all the time within tumors since only a tiny minority of cancers actually develop enough to become clinically relevant[96,97]. The few tumors that actually manage to develop stable cooperation may thus be the exception, rather than the rule.

Cooperation also evolves more easily if the diffusion range is low and if the benefit function is steep (more specifically, a steep function enables cooperation for a higher value of the critical cost, but it also makes cooperation less robust to random fluctuations[52,94]). These parameters can be estimated in cell populations, and the dynamics of the system – the number and types of equilibria and how the population changes in response to changes in these parameters – can be predicted. Other empirical results related to the theory, however, are still rare, and experiments done specifically to test the theory are even less common. The diffusion range of growth factors, a crucial parameter of the models, remains difficult to estimate. In addition, there is no comprehensive view of how important each growth factor is for each tumor type –

information about these combinations is scattered through the literature. With the development of new technologies to engineer cells, it is now easier to produce non-cooperative clones by knocking out genes for growth factors and use them in competition/cooperation experiments with their original producer cells[3].

More interactions between theory and experiments are also needed, to link the large amount of data already existing in cancer research, as well as the ability to manipulate and measure clonal selection in cancer cell populations, to models of evolutionary game theory. For example, a recent study showed interdependence between two clones within a tumor[4], which resembles mutualism for the exchange of diffusible goods between cells, while a model of essentially the same system (two types of players trading two different public goods)[98] was published almost at the same time in evolutionary biology. In this and other cases, clearly a mutual awareness between theoretical results in game theory and empirical results in cancer research would be beneficial.

Impairing cooperation

Many modern targeted therapies try to impair intra-tumor cooperation by neutralising growth factors or their receptors. However, even the most successful targeted therapies generally lead to relapse. While therapies that target the stroma, like immunotherapies, may be less susceptible to the evolution of resistance because stromal cells are not genetically unstable like cancer cells[7,99], mutants that are not susceptible to a therapy can arise in the population of cancer cells, and spread by clonal selection, even when therapies seem effective in the short term. Evolution-proof therapies – therapies not prone to the evolution of resistant clones – are needed. Unfortunately, considerations on equilibria and dynamics are rarely, if ever, taken into account in the design of therapies[100].

Game theory deals with the core problem of the evolution of resistance: the stability of equilibria and the dynamics of perturbations. *Mechanism design*, or reverse game theory, in economics and ecology generally aims at devising ways to improve efficiency among rational self-interested individuals. In cancer research, the equivalent of mechanism design is the design of an effective therapy.

An example of the use of concepts from game theory in the design of therapies is the idea of changing the dosage of drugs in order to enable or promote cell-cell competition. Rather than targeting a tumor with the highest dose tolerated by the patient, it might be beneficial to reduce the dosage to enable competition between cancer clones, which can prevent or slow down the development of resistance – an idea ("adaptive therapy"[101-104]) that has parallels in the field of infectious diseases[105-109]. Other ideas include changing the selection pressure in a tumour such that the more benign (or easier to treat) clones within the tumor would be selected for ("sucker's gambit"[110]); or to use two therapies with synergistic effects such that cancer cells evolving to elude one will become more susceptible to the other ("double bind" [111-113]).

While these approaches suggest exploiting the interactions between different clones within the tumor (and highlight the importance of finding the right balance of

attack and the right sequence of treatments), they do not specifically target cooperation. An example of the use of game theory of cooperation in the analysis of the stability of therapies, is the case of tumor-stroma interactions in multiple myeloma, where osteoblasts, osteoclasts and malignant plasma cells are players in a public goods game[46,61,66]. It has been shown that reducing the amount of malignant plasma cells (the current approach to treating multiple myeloma) is not an evolutionarily stable strategy, whereas changing the parameters of the game, for instance by targeting the growth factors produced by the stroma and by the tumor, could lead to the extinction of the malignant cells and re-establish a healthy osteoblast-osteoclast balance.

Targeted therapies aim at impairing cooperation among cancer cells by targeting growth factors or their receptors. It has been suggested that therapies that target diffusible factors are a more evolutionarily robust approach (less susceptible to the evolution of resistance) than conventional drugs that target cells directly[114-117] because growth factors do not confer a private advantage to a mutant, resistant clone but to the whole population of cells. Although this is a valid point, resistance against targeted therapies, does evolve. Game theory shows[50,53] that an effective targeted therapy must be extremely efficient in order to be evolutionarily stable. A therapy that reduces the amount of available growth factor increases the amount of growth factors that cells must produce to achieve the pre-treatment fitness level (because some of the ligands are impaired by the therapy); in the short term this makes tumor growth decline because there is not enough ligand available; but in the long term, the dynamics of the system changes: unless the speed and efficacy of the initial reduction is high enough, the population will evolve to a new equilibrium with an even higher production of growth factor[50,53].

Rather than targeting the ligands or receptors, one possible alternative, inspired by the very logic of the dynamics of growth factor production, is to use cell therapy: engineering tumor cells by knocking out the genes coding for essential growth factors; when re-inserted within the original tumour, these modified cells would have a proliferation advantage, because they could free-ride on the growth factors produced by the original cells ("autologous cell defection"[53,118]) and would therefore spread by clonal selection, like a tumour within the tumour. Eventually a tumour made of all defector cells would collapse for lack of essential growth factors, or at least reduce the deleterious effect of cytokine overproduction – which is among the immediate causes of death for a patient[119].

This approach would harness clonal selection to our advantage: rather than leading to relapse, clonal selection would lead to the spread of the non-growth-factor-producing clone, leading to the collapse of intra-tumor cooperation – a tragedy of the commons at the cellular level. (This may be happening naturally all the time within tumors since only a tiny minority of cancers actually develop enough to become clinically relevant[96]; the few tumors that actually manage to develop stable cooperation may thus be the exception, rather than the rule). By harnessing the power of clonal selection, autologous cell defection would be self-promoting. In contrast, current forms of therapy have the opposite effect because they confer a proliferation advantage to clones that are

immune to the treatment, and hence eventually enable the tumor to grow again and lead to relapse.

There would be, of course, difficulties to overcome. The constitutive activation of a downstream pathway could make a growth factor irrelevant (like with current targeted therapies), although this would be a problem only for growth factors that affect proliferation, not other hallmarks of cancer, and could be mitigated by knocking out multiple growth factors (hence multiple pathways). The cost of growth factor production must be high enough to drive producer cells to extinction, and the knockout clone must expand quickly within the tumor; cooperation is more susceptible to collapse when growth factors have a high diffusion range and when they affect proliferation rather than apoptosis. Game theory can be used to predict the critical costs and speed necessary to achieve the collapse of cooperation, and these predictions can be tested in vitro[3]; similar tests in vivo must be developed.

In spite of all the incredibly challenging and inevitable technical difficulties, these are examples of how thinking in terms of dynamics and equilibria may lead to alternative approaches that have not been fully considered so far. There are certainly more.

Conclusion

Cooperation is a fundamental force in populations subject to natural selection, including clonal selection, and it has been noted[120] that the major transitions in evolution are different ways of overcoming the problem of cooperation between self-interested entities, from cells within a body to individuals in a society. Cooperation, however, is not inevitable – indeed, stable cooperation between selfish individuals is rare and fragile[14,15]. Only a small minority of cancer cells develop into malignancies[96], and it stands to reason that these are the ones that have successfully managed to evolve cooperation. Understanding how to impair cooperation and harness clonal selection can provide insight into the design of evolution-proof therapies.

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Figure 1. Cooperative interactions within the tumor and with the stroma. **A:** Two cancer clones (blue and cyan) exchanging mutually beneficial growth factors. **B:** One cancer clone providing a growth factor to itself and to another, non-producer clone (yellow). **C:** Cancer cells providing cytokines to the stroma (pink), which becomes activated (purple) and provides growth factors to the tumor. **D:** Cancer cells producing growth factors that trigger the formation of new blood vessels (red), which provide oxygen to the tumor. **E:** Cancer cells producing or not producing (grey) adhesion molecules.

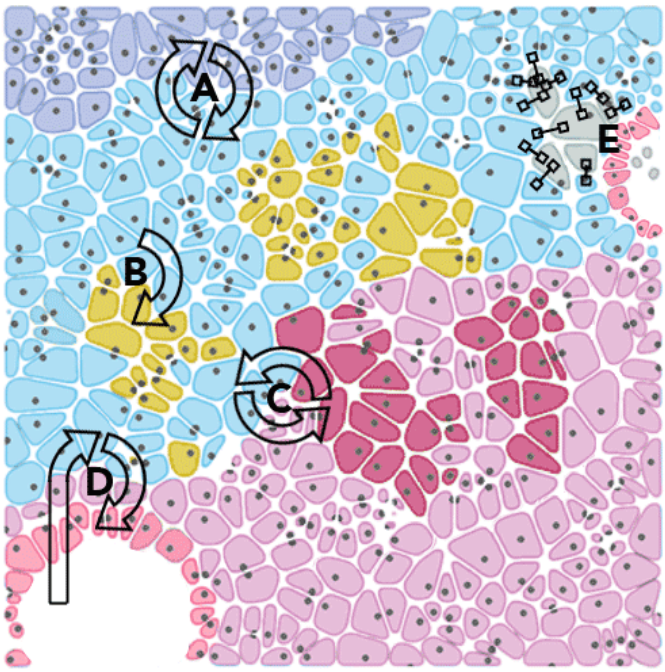
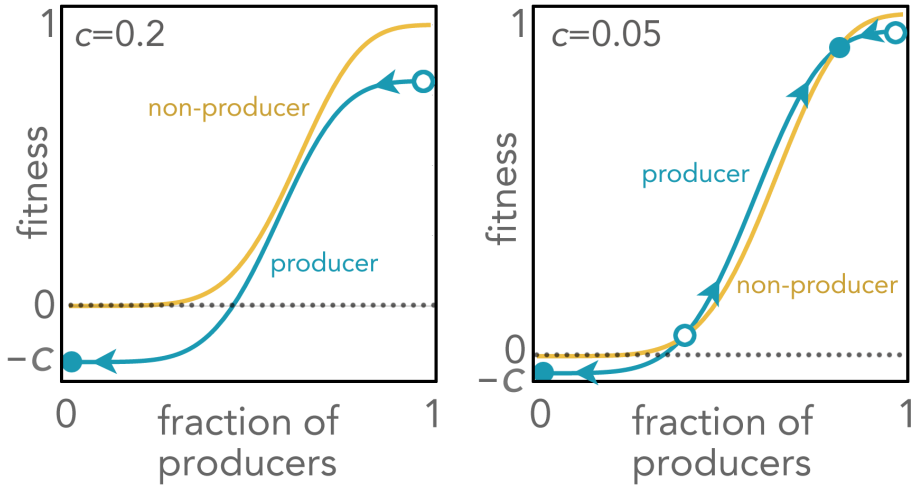


Figure 2. Non-linear dynamics. Fitness of producer and non-producer cells as a function of the fraction of producer cells for different costs of growth factor production *c*. Equilibria (full circles: stable; open circles: unstable) and the direction of the dynamics (arrows) are shown. When the cost/benefit ratio of growth factor production (*c*) is high (*c*=0.2), non-producer cells have a fitness advantage for any fraction of the two types, hence their frequency increases over time until the producers are eliminated from the population. When the cost is low enough (*c*=0.05), however, the small advantage of having an extra producer (itself) in the group can be enough to confer a net fitness advantage to producers when they are at intermediate frequencies; in this case, the population can converge to a mixed equilibrium of the two types.



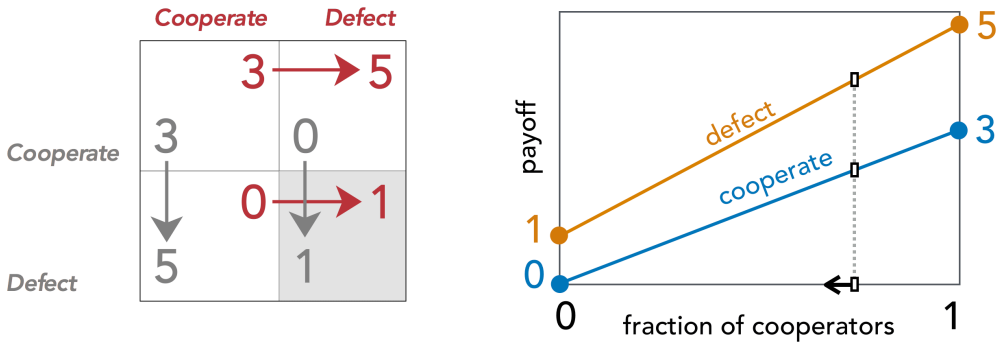
Box 1: Glossary

Game theory: the study of strategic interactions
Strategic interaction: a situation in which the optimal decision depends on the decision of some other player (frequency-dependent optimization problems)
Optimization: the choice of the best set of actions to maximise a payoff function
Game: the formal description of a strategic interaction; it includes the definition of the players, strategies and payoffs.
Players: the individuals (or cells, or other entities) that adopt strategies and obtain payoffs
Strategy: the decision or type adopted by a player (in biology, the phenotype)
Payoff: the reward from the outcome of the interaction (in biology, fitness)
Frequency-dependent selection: natural (clonal) selection in which fitness depends on the frequency of other phenotypes in the population
Clonal selection: natural selection (the preferential survival or the fitter phenotypes) within populations of cells
Evolutionary game theory: game theory applied to evolutionary processes (rational decision making is replaced by natural selection; conscious strategies are replaced by genetically determined phenotypes).
Evolutionary dynamics: the change in frequency of strategies over time, possibly leading to an equilibrium
Evolutionary stability: the property of being immune to invasion by a mutant strategy
Equilibrium: an evolutionarily stable state to which a population converges over time
Cooperator: a player that pays a cost to produce a benefit for its opponent, or contribute to a public good (for example, a growth factor producer)
Defector: a player that does not produce a benefit for its opponent, or does not contribute to a public good (for example, a growth factor nonproducer)
Pairwise game: a game with only two players
Multiplayer game: a game with multiple players (which can be made of multiple pairwise interactions or a single public goods game)
Public good: any good that leads to a benefit that can be exploited by cooperators and defectors alike.
Public goods game: a multiplayer game in which the payoff depends on the collective decision of multiple players rather than their pairwise interactions.
Linear benefit: the effect of cooperation on fitness when the sum of the contributions is additive (each contribution produces the same increment in benefit)
Nonlinear benefit: the effect of cooperation on fitness when the sum of the contributions is not additive but has increasing or diminishing returns, or both or a more complex non-linear function

■

Box 2: The prisoner's dilemma

Pairwise games can be described by payoff matrices that list the payoffs of all the possible interactions between the two players. In the figure below, two players (red and grey) must decide, simultaneously, to either cooperate or defect: mutual cooperation rewards both with 3 points, whereas mutual defection leads to only 1 point each; if only one player cooperates he gets 0 points and the defector gets 5 points. The actual entries of the matrix do not matter as long the ranking of the payoffs is conserved – this type of payoff matrix defines what is generally called the Prisoner's Dilemma (PD)[34].



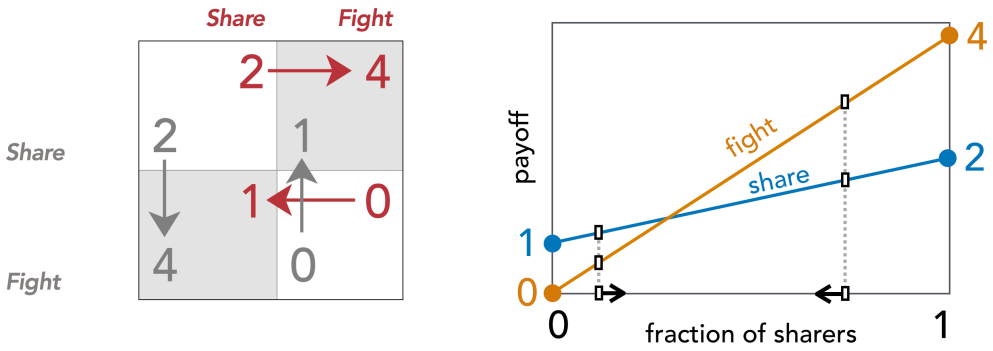
Mutual cooperation is better (payoffs are higher for both players) than mutual defection; hence, one might think, the players should cooperate (this is the traditional – but erroneous – explanation of cooperation between cancer cells). If the first player cooperates, however, the second player is better off defecting (getting 5 points instead of 3); and if the first player defects, the second player is better off defecting too (getting 1 point instead of 0). So actually, no matter what the other player does, the only rational strategy is to defect (the stable outcome of the game can be found simply by looking at where the arrows, which describe an increase in payoff for each player, converge). However, both players would be better off by choosing mutual cooperation. Hence the dilemma.

In terms of evolutionary game theory, the plot on the right shows the dynamics of the process in a population: the two lines show the fitness of the two strategies (cooperation and defection) as a function of the fraction f of cooperators in the population. At the extremes, interactions are always either with a cooperator (at f=1) or with a defector (at f=0), hence the value of the two functions at those values of f can be taken from the matrix on the left. The intermediate values show the frequency-dependent fitness of the two types. Because the fitness of a defector is always higher than the fitness of a co-operator, at the next generation there will be fewer cooperators in the population; hence the fraction of cooperators in the population will always decline irrespective of the current fraction (the arrow show the direction of the dynamics) and the final outcome will be the extinction of cooperation: all players will defect and have fitness equal to 1.

■

Box 3: The game of chicken

In the game of Chicken[37], also called Snowdrift[38], or Hawk-Dove game[39], two players must decide to either share a resource or fight to have exclusive control over it. Sharing confers 2 points to each player, whereas if both fight they both get 0 points (for instance because the benefit of the resource is offset by the cost of fighting – note that the zero here does not mean that the costs and benefits exactly cancel each other; as usual the actual values only matters in relation to each other's rank); but if one player fights and the other doesn't, the fighter gets most of the resource and neither player has a cost (the fighter gets 4 and the other player gets 1); hence here it is better to fight if the other player does not, and vice-versa – which is the equilibrium of the game.



One can find the fraction of fighters at equilibrium by equating the payoff of the two strategies (the equilibrium is, by definition, the status in which the frequencies of the two types do not change). If s is the fraction of sharers in the population, the fitness of a sharer is $s(2)+(1-s)(1)=1+s$ because a sharer has payoff 2 when interacting with another sharer and 1 when interacting with a fighter; similarly, the fitness of a fighter is $s(4)+(1-s)(0)=4s$; hence at equilibrium (we must have $1+s=4s$) we have $s=1/3$. As we can see in the plot on the right above, this is where the fraction of sharers converges in the population dynamics of the game: at high frequencies of sharers the fitness of a fighter is higher, so fighters will increase in frequency; at low frequencies of sharers, however, fighters have lower fitness, hence the sharers will not be eliminated from the population.

A similar logic applies to public goods games that describe the production of diffusible growth factors in multi-player interactions with nonlinear benefit effects.

■

Box 4: The truel

The most general principle of evolution by natural selection, Darwin's "survival of the fittest", does not necessarily apply to interactions between more than two players. Consider a duel in which two individuals, A and B, shoot at each other, with accuracies (probabilities to hit the opponent) a and b respectively. If they shoot at the same time and $a>b$, clearly A has a higher probability of winning the contest. Even in a sequential, repeated duel (at the beginning, and after each shot, who shoots next is chosen at random) again clearly A has a higher probability of winning the contest. In duels between more players, however, this is not necessarily the case. Consider a 3-person version of the duel (a "truel"[88]). Three individuals, A, B and C, shoot at each other with accuracies a, b and c respectively (with $a>b>c$) in a sequential, repeated truel. Who will be the most likely to win?

The answer here is not so simple as in the 2-person duel; one must take a strategic decision: whom to shoot at? It is easy to see that one should shoot at the opponent whom one prefers not to face in the 2-person duel, because facing a weaker opponent confers a higher payoff in a duel: A would prefer a 2-person duel against C than against B, hence A should shoot at B; B would prefer a 2-person duel against C than against A, hence B should shoot at A; C would prefer prefer a 2-person duel against B than against A, hence C should shoot at A. In synthesis, in a 3-person duel, the best strategy is to shoot at the strongest opponent: if all three players are still in the game, both B and C will shoot at A; A will shoot at B; nobody will shoot at C.

Given these considerations, one can calculate the probability of ultimately winning the contest for the three types. Straightforward algebra shows that this probability is highest for C and lowest for A, unless the differences in skills are extremely large. For example, with a=0.8, b=0.6 and c=0.4 the probabilities of winning for A, B and C are respectively 30%, 33% and 37%. What seems paradoxical (the weakest type can have the highest fitness) is actually the result of rational, strategic considerations (it is better to shoot at the strongest opponent). The logic of the theory is indisputable, but the result is not intuitive – that is why game theory can help us understand complex strategic interactions.

Extensions of this game to evolving populations with clonal selection has shown[89] that three (or more) types can be maintained as a mixed population, potentially explaining stable heterogeneity in the absence of fluctuating selection for characters that affect direct competition abilities.

■