Beating cancer at its own game

Game theory has been used to understand economics, ecology and evolution. It is now being used to try to help us outwit cancer. **Sophie Fessl** asks: will evolutionary game theory guide the way to a more strategic use of available cancer drugs?

Cancer isn't a game – but if we treat it that way for the purpose of developing therapeutic strategies, cancer may be beaten. This is the premise of a section of mathematical oncologists, who use game theory to analyse cancer progression and the impact of different strategies for treating it.

There are early indications that this approach could be making some headway. A pilot trial in the treatment of metastatic prostate cancer, for instance, indicated that the use of strategic drug holidays may be able to keep the disease in check for longer using a lower cumulative dose. Examples like this are now fuelling questions about whether we may already have the drugs needed to treat most cancers, but need to learn to use them in a way that plays to the cancer cells' evolutionary weaknesses.

Evolution – a process by which, as Darwin wrote, "from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved" – is also at play in cancer. Except that, in cancer, the 'endless forms' generated by the clonal evolution of cancer cells are frustrating and often deadly, holding as they do the key to cancer's ability to successfully outwit treatment.

The concept of cancer as an evolutionary process is one that has become fundamental to our conceptualisation of the disease in recent years. It has informed our understanding of why metastatic cancer so often responds to initial treatment but then almost invariably evolves resistance, eventually leading to treatment failure. What is hasn't yet done is effect any fundamental change to the treatment strategies we use, which remain largely reliant on using successive lines of treatment as and when resistance to the previous one develops.

David Basanta, Associate Member of the Integrative Mathematical Oncology Department at H. Lee Moffitt Cancer Center in Tampa, Florida, believes that cancer's ability to evolve will always give it the upper hand against this conventional approach to treatment. He argues that the answer lies in taking on cancer at its own game. For some years now he has been a leading member of a group of mathematical oncologists who are spearheading the application of game theory to studying cancer, an approach he summarises like this:

"Cancer treatment is a process of selection: sensitive cells die, while resistant cells are selected for and remain in the tumour. Treatment is one of those modifiers of the selection pressure exerted to shape tumour evolution. One tool to study this selection is evolutionary game theory. Evolutionary game theory focuses on interaction: It explains the interaction between cell types and how tumours and their cell composition change with selection pressure."

Using game theory to understand biology

Game theory is a mathematical tool that was originally used to understand conflict and co-operation in economics. It allows mathematicians to study games in which the outcome for one player depends not only on their own strategy but also on the strategies that the other players use. The 'prisoner's dilemma' is a popular example of a classic game theory model.

John Maynard Smith pioneered

"Evolutionary game theory explains the interaction between cell types and how tumours change with selection pressure"

the use of game theory for understanding evolution and its dynamics. Evolutionary game theory differs from classical game theory in that players are not rational. Players – or animals in an ecosystem or cancer cells in a tumour – use a variety of behaviours and features, a phenotypic strategy, to compete for the available resources. But the players do not decide on or choose a strategy. Instead, they inherit their strategy – their strategy is based on their genes. And the payoff, or consequence of interaction, is survival and proliferation. Which player (or animal or cancer cell) wins or loses is determined by their phenotypic strategy, the frequency of the players in a population and their interaction.

One early example of the use of evolutionary game theory in cancer was using a hawk–dove game to study the emergence of tumour invasiveness (see p 18). The model asked: when resources are scarce, what are the payoffs for a motile cell that moves away to a place where it doesn't have to share resources, and for a proliferative cell that stays to use the resource? Evolutionary game theory models have been used to analyse different aspects of cancer, from the steps along cancer progression, to how increasingly aggressive phenotypes arise, how cancer cells co-operate through the release of

Strategies of survival: the hawks and the doves

One classic example of an evolutionary game is the hawk–dove game. Individuals in a species have two ways to resolve fights over food: while hawks are aggressive, doves are meek.

When two doves chance upon food, they divide it into two equal halves. When two hawks have a dispute, they fight. The winner takes the food, while the loser is severely injured. When a hawk and a dove meet, the dove baulks and leaves the food to the hawk. While the hawk wins the food, the dove gets nothing but also avoids injury.

Evolutionary game theory captures these interactions in a payoff table: what are the costs of each strategy for each interaction? Evolutionary game theory allows modellers to draw conclusions about the population. When modellers know how much an injury costs an individual and how much food helps in terms of reproduction, they can work out what the stable proportion of hawks and doves is in a given population. This is the evolutionary stable set of strategies: the ecosystem is at a point at which it cannot be easily disrupted.

Similar evolutionary games have been played with tumour cell populations.

growth factors, and how metastases get established in the bone.

Lessons to learn for cancer

What are the lessons that can be learned from studying cancer with such evolutionary games? One major conclusion drawn by Robert Gatenby, co-director of the Cancer Biology and Evolution Program at the Moffitt Cancer Center, who also headed the formation of the Integrative Mathematical Oncology program, is that focusing solely on destroying as many cancer cells as possible may not be the best option when dealing with metastatic, incurable cancer. "In metastatic prostate cancer, standard of care uses a simple strategy: we give the same drug at the maximum possible dose over and over again, until progression. But, when cancer is modelled as a game theoretic process in which the treating physician moves by applying therapy and the cancer cells play by deploying adaptive strategies, current treatment protocols represent a poor strategy.

"By repeatedly applying the same single drug, the physician imposes intense evolutionary selection pressure for resistance while removing all susceptible cells that are potential competitors. Before treatment, the resistant cell population is often small because the molecular mechanism of resistance comes with a cost in terms of their fitness.

"When susceptible cells are killed off with therapy, resistant cells can grow unopposed. With the maximum tolerated dose approach, we actually accelerate the growth of the resistant population. A high drug dose is good if it is curative, but not if it can't cure."

David Basanta cautions that in most aggressive tumours, tumour shrinking is only temporary, and the tumour grows back even bigger. "With treatment, we need to be careful what we leave behind. The resistant cells we leave behind are the reason why the tumour comes back: what we don't kill, we select for. The tumour gets bigger, as treatment options have been reduced and the cancer can keep growing."

From whack-a-mole to chess

The proponents of evolutionary game theory in cancer are ready with alternatives. Their models suggest that using available drugs

in a more strategic way may lead to a breakthrough in cancer therapy. The current maximum tolerated dose strategy resembles a 'whack-a-mole' approach, in which the cell populations that pop up are pushed back as they appear, but respite for the player is usually only short and the next cell population pops up again.

Using game theory, oncologists might be able to approach cancer therapy more like a game of chess, with a refined strategy reacting to the opponent.

This approach could, for example, help understand the impact targeted therapies have on heterogeneous tumours, where only some types of cell will be killed by the targeted therapy, leading to changes in the cell population, which may then respond differently to treatment – or not at all (see box).

"With treatment we must be careful what we leave behind. What we don't kill, we select for"

But if cancer progression is a game, can oncologists take the lead and control the direction in which it proceeds?

David Basanta hopes so. "By looking at cancer treatment as a game, we can change the dynamics. We need to change the rules of the game against cancer so that we can control how the cancer evolves in a different direction: either becoming treatable in the long term or more akin to a chronic disease that a patient can live with."

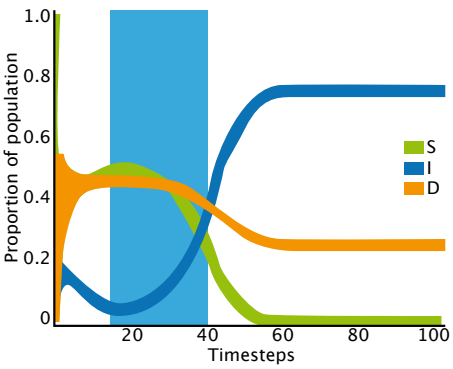
Evolutionary-informed therapy on trial

Several groups are trying to incorporate evolutionary thinking into developing a new strategy for treating prostate cancer. Gerhardt Attard, then clinician scientist at the Institute of Cancer Research, London, led a study in 2014 which tested a new option for treatment, namely using liquid biopsies to monitor for signs that drug-resistant cancer cells are emerging. Treatments could then be changed before the disease is (further) driven into a more aggressive form. However, this is more a case of detecting the mole early to whack it more quickly, rather than a strategy to play the mole.

Robert Gatenby is now testing just such a game-changing strategy. In a clinical trial of adaptive therapy in metastatic castrate-resistant prostate cancer, he is seeking to capitalise on the natural competition between susceptible and resistant cells by adjusting drug timing to account for the response of the tumour.

Gatenby and colleagues started by modelling treatment response to abiraterone, which inhibits CYP17A, an enzyme needed to produce testosterone. Simulations showed that standard dosing strongly selects for androgen-independent cells – cells for which this therapy does not work. Clinical trial data show that, with standard dosing, treatment fails at a median of 16.5 months after the start of therapy. Gatenby and colleagues used this information to develop an adaptive therapy regime that is designed to suppress proliferation of androgen-independent cells and is informed by each patient's response to therapy. Last year, they reported results from 11 patients in a pilot clinical trial. "We simply gave abiraterone treatment until PSA drops to half the pre-treatment value. Then we stopped treatment until PSA reached the pre-treatment level," Gatenby explains. "When the drug is taken away, the tumour grows, but there is no selective pressure for resistance.

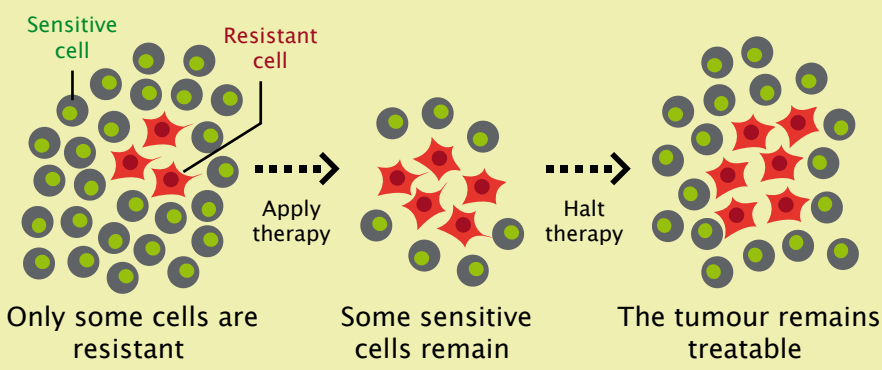
Stroma dependent vs independent cell game



A hypothetical tumour has two main clonal cell populations: one successful tumour population (D) that is dependent on support from stromal cells (S), and one less successful tumour population (I) that is independent of the stroma. Treatment was designed to kill as many cells as possible. In this case, the stromal cells are killed off, and population D is reduced. However, the growth potential of the remaining tumour cells (I) is unaffected. As these cells are not susceptible to the treatment, this initially treatable tumour has now become completely resistant.

Source: David Basanta and Alexander R A Anderson (2013) Exploiting ecological principles to better understand cancer progression and treatment. *Interface Focus* 3:20130020. Reproduced by permission of the Royal Society. Permission conveyed through Copyright Clearance Center, Inc.

Adapting for balance



Cancer-cell populations compete, so completely killing cells that are sensitive to a particular drug lets resistant cells grow unfettered. A pilot clinical trial in advanced prostate cancer led by Robert Gatenby and colleagues at the H. Moffitt Cancer Center in Tampa, Florida, is providing early evidence that adjusting dosage according to tumour response could extend time to progression by maintaining balance between the populations.

Source: Adapted from Cassandra Willyard (2016) Cancer, an evolving threat. *Nature News* 532:166–168. Reproduced with permission, © 2016 Springer Nature

In fact, the treatment-sensitive cells are fitter than the resistant cells and grow back more. At the end of the cycle, when PSA reaches pre-treatment level, we are basically back where we started. The tumour remains treatable."

> "We need to change the rules of the game against cancer so that we can control how the cancer evolves"

Mathematical models showed that, depending on a patient's starting conditions, this cycling between treatment and drug holiday could last for between two and twenty cycles, at which point the resistant cells finally take over and the tumour becomes untreatable. The cycle length also depends on the patient, as smaller populations of resistant cells lead to longer cycle times, because it takes longer for the PSA value to reach its pre-treatment value. Cycle length was calculated to lie between three months and more than one year, which was also seen in practice, says Gatenby: "Some of the patients in this trial received treatment less than once a year. So far, only one of the patients in the pilot trial progressed, at the end of two cycles." The other ten patients reported on in the publication have a median time to progression of at least 27 months. But this is not enough for Gatenby: "Ultimately, our goal is to control the tumour sufficiently long that it effectively becomes a chronic disease."

Time to progression – in this pilot trial – is increased, and remarkably, this is achieved with a lower cumulative drug dose, explains Gatenby: "On average, the men on our trial receive less than half the dose that they would have received otherwise, with standard of care. We see a longer response and use less drug, which for our patients also means avoiding toxicity. Drug holidays mean that the disease is easier to live with. Some patients have long breaks, of two to four months, in which they do not take abiraterone. This means we can prolong their lives and improve their quality of life."

It is probably little surprise that this pilot trial was carried out at the Moffitt Cancer Center: the centre has an Integrated Mathematical Oncology Department, with a faculty of six cancer researchers and mathematical modellers. And they are highly interconnected with the small and dynamic scene of researchers applying game theory – and other mathematical models – to understanding cancer.

But will adaptive therapy, if it lives up to its promise in larger trials, be confined to academic centres with access to an extensive mathematical background?

"Anybody could do this trial," assures Gatenby, "The planning is complex – we had a team of two oncologists, two mathematicians and one evolutionary biologist designing this trial. But we distilled this information into a simple trial that could be done anywhere. If you need a mathematician in the clinic to run a trial, it is just not going to happen." Another clinical trial of adaptive therapy with abiraterone for prostate cancer at the Moffitt has recently been approved; five more are being planned for melanoma, ovarian, thyroid, breast and lung cancer.

The sucker's gambit

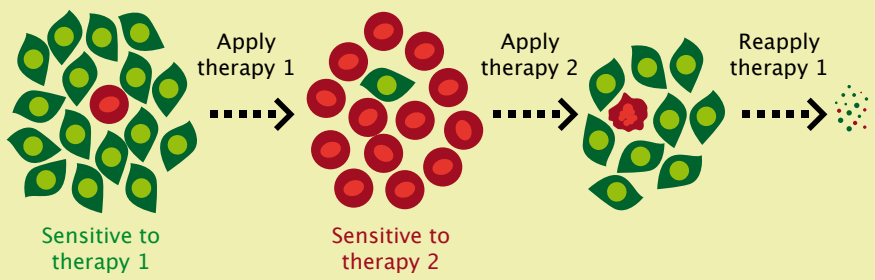
A different approach to exploiting evolutionary dynamics for cancer treatment is what is known as 'the sucker's gambit' or 'evolutionary double bind'. Taking a hypothetical example from ecology, if crows are introduced to control a population of mice, those mice that hide in bushes are better adapted and likely to survive. If snakes are now introduced, the snakes are more likely to pick off mice in bushes – the snakes now select in favour of mice in the open, which are in turn more vulnerable to crows, and so on. In cancer, an evolutionary double bind would mean that a first treatment makes the tumour more vulnerable to second treatment, which in turn makes the tumour more vulnerable to the first treatment – at best, wiping the tumour out, or at least controlling the disease by cycling between treatments.

> The snakes select in favour of mice in the open, which are in turn more vulnerable to crows, and so on"

The concept of an 'evolutionary double bind' could be the explanation for a curious observation in a clinical trial of p53 cancer vaccine and chemotherapy. In 2006, Scott Antonia and colleagues at the Moffitt Cancer Center ran a pilot trial on 29 patients with small-cell lung cancer, who had failed first-line chemotherapy. Just over half of vaccinated patients had a specific T-cell response to the p53 vaccine, but only one patient showed a (partial) tumour response. However, follow-up after the trial found a clinical response to second-line chemotherapy in 62% of patients who received it – while historical controls show a response of less than 5%. Patients who responded immunologically to the vaccine were more likely to respond to second-line chemotherapy (75%, compared to 30% of patients without immunological response).

How did this synergistic effect arise? Basanta has published an explanation based on evolutionary game theory: "Antonia and colleagues did not expect such a synergistic effect to happen, and previously no mechanism to explain the observation was found. Our model suggests that a double bind is behind the synergy. We are still testing how to explore this option further for cancer therapy." While the researchers do not know exactly how this evolutionary double bind proceeds, they speculate that patients' response to the p53 vaccine – perhaps by down-regulation of p53 – left the cells more vulnerable to chemotherapy. Alternatively, the chemotherapy may have made the tumour cells more vulnerable to immune attack, primed by the p53 vaccine.

The double bind



Developing resistance to one treatment can leave tumours vulnerable to others. This phenomenon may help explain the surprising findings of a trial looking at the impact of p53 vaccine on patients with small-cell lung cancer, which showed minimal direct impact on tumour growth, but was associated with a heightened response to subsequent chemotherapy, particularly among patients who had shown a strong immunological response to the p53 vaccine. Evolutionary modelling can suggest the best way to apply multiple therapies to almost eradicate resistant cells.

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Exploiting co-operation

Cancer cells not only compete, they also co-operate, for example by secreting growth factors. These not only benefit the producing cells but also their neighbouring cells. The cells producing no growth factor are at an advantage when surrounded by producing cells; they can free-ride on the growth factors and increase their frequency in the population.

Marco Archetti, lecturer in evolutionary theory at the University of East Anglia, in Norwich, UK, studies co-operation via growth factors using public goods games – a type of game theory model. "The problem we ask is: why don't the non-producing cells take over in a tumour, and drive the growth-factor-producing cells to extinction?"

As evolution is about the survival of individual cells, he explains, nothing can evolve for the benefit of the group, so the prospect that the tumour would eventually die off without growth factors is not going to deter non-producing cells from free-riding. "Non-producing cells can, in fact, drive producing cells to extinction. But if the cost of growth factor production is low enough, and the benefit of producing growth factors is non-linear, a stable equilibrium is reached, and the two cell populations co-exist in a tumour. When the level of 'cheating' cells is high, however, they drive out the growth-factor-producing cells."

"When the level of 'cheating cells' is high, they drive out the growth-factor-producing cells"

Archetti is attempting to use his insights on co-operation between cancer cells to devise more evolution-proof therapies, currently using a mouse model. "We are trying to devise therapies that are not prone to relapse, using genetically modified cells. In this approach, we take cells from a tumour and remove the genes they need for producing growth factors. We then reinsert the cells in the tumour. The modified cells spread, as they do not pay the cost of growth factor production, but free-ride on producing cells. These extra cheating cells drive the original clone to extinction."

As Theodosius Dobzhansky famously said, "Nothing in biology makes sense except in the light of evolution." It appears to hold true for cancer biology; how to carry that over to the clinic remains the big challenge.

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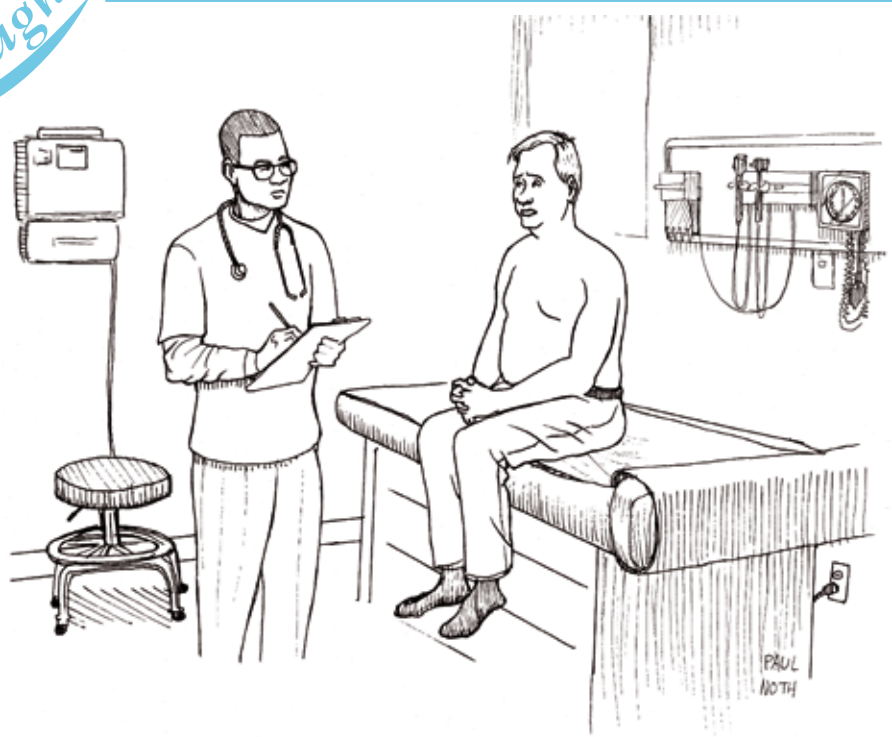
For a laugh



"Will I still be able to not exercise?"