

The tragedy of the commons and prisoner's dilemma may improve our realization of the theory of life and provide us with advanced therapeutic ways

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Abstract

Maintenance of cooperative traits is a critical question in evolutionary theory, especially when the social dilemma, generated by the interface between cooperators and cheaters, is invoked. Since the 1960s, a large body of literature has focused on this topic and suggested various solutions. However, despite the great effort of evolutionary biologists, the arguments advanced are only partial and never seem to offer a conclusive answer. Nevertheless, it seems that the only generalizable solution is 'conscious intervention' as illustrated in the article. The findings implied by the following theoretical analysis have important therapeutic applications. They also represent a promising direction for future studies on invasive engineered 'cheaters' having plasmids carrying self-interested traits invading biofilms of pathogenic bacteria 'cooperators'. In fact, this perspective approach can be extended to the treatment of viral diseases and cancer

Keywords

Synthetic biology; Cooperation; Public goods; Plasmids; Social evolution

Introduction

Cooperation is a fundamental challenge to evolutionary theory (Leigh, 1977, 1983, 1999; Buss, 1987, 1999; Frank, 1995; Maynard Smith and Szathmary, 1995; Wilson, 1997; Michod, 1999; Reeve and Keller, 1999; Foster and Ratnieks, 2001). It is also critical for understanding transitions from unicellular organisms to advanced multicellular organisms according to

evolutionary theory (Maynard Smith and Szathmary, 1995; Hamilton 1996; Frank, 2003; West et al. 2007a; Pfeiffer and Bonhoeffer, 2003). Cooperative traits were found in the vast majority of biological systems. The unsolved questions are why do individuals appear to incur the costly altruistic behavior which decreases its fitness in order for other individuals to gain profit? And how can cooperative traits be maintained? (Frank, 1998; Frank, 2003; Sachs et al. 2004; West et al. 2006; Foster and Wenseleers, 2006; Lehmann and Keller, 2006). Microorganisms are particularly appropriate for study this problem (Elena and Lenski, 2003) due to several reasons: (1) the possibility of genetic manipulation; (2) they offer an opportunity to investigate evolutionary mechanisms; (3) their short generation time; (4) the relative easiness of creating transgenic cheaters.

Cooperative traits are widely present in microbes (Crespi, 2001) such as public goods production, which is usually costly, but at the same time available for utilization by neighbors in which case they will acquire higher fitness if they were non-productive. Therefore, such defectors will invest more in reproduction and will have more offspring than cooperators, thereby occupying the population and driving cooperators towards extinction. Examples of public goods in microorganisms include: (1) Production of digestive enzymes (Hase and Finkelstein 1993); (2) Production of the iron-scavenging siderophore (West and Buckling 2003); (3) Bacteriocins which kill competitors (Riley and Wertz 2002); (4) Chemical warfare against the predator (Gardner et al. 2004; Matz and Kjelleberg 2005) and (5) Quorum sensing (Williams et al. 2007). Examples of other collective actions in microorganisms include: (1) programmed cell death (Webb et al. (2003); (2) Fruiting body formation (Fiegna and Velicer, 2003); (3) Biofilm formation (Boles et al. 2005; Schooling and Beveridge, 2006) which account for over 99% of microbial life. Biofilms are ubiquitous, and adhere to both biotic and abiotic surfaces, including waste and nutrient channels and specialist cells. They are surrounded by an exopolysaccharide matrix (West et al. 2007b) which provides protection for embedded bacteria from the immune system and makes it more resistant to antibiotics. Biofilm could be briefly

described as a city of microbes (Watnick & Kolter 2000). However, the impact of Kin selection may be observed in biofilms initiated with one clone or lineage, but this is very rare in nature where biofilms normally include numerous species. For example, almost 700 bacterial species can be found in the oral cavity (Narayanan and Vaishnavi 2010)

Kin selection

The altruistic cooperation has been explained by (Hamilton 1964, 1963) where cooperators will gain indirect benefits by increasing the fitness of the other relatives, which happen to have the same cooperative genes, thus leading to transmission of genes to descendants. These insights have come to be known as kin selection (Maynard Smith 1964) or Hamilton's rule. According to this rule altruism is favored when $(r b - c > 0)$, where (c) is the fitness cost to the altruist, (b) is the fitness benefit for the beneficiary, and (r) is their genetic relatedness. Kin selection and the new group selection are just different ways of conceptualizing the same process. Moreover, they are mathematically identical (West et al. 2006). The two mechanisms of Kin selection are: (a) kin discrimination, when individuals can distinguish their relatives from non-relatives and direct the benefits toward relatedness only (West et al. 2007b). This mechanism is common in macroorganisms, for example: breeding vertebrate (Griffin and West 2003), but rare in microorganisms except some cases such as specialized production of public goods when each strain produces highly specific molecules that other lineages could not utilize (Meyer et al. 1997); (b) limited dispersal (population viscosity) (Hamilton 1964, 1971, 1972, 1975; Pollock 1983; Murray and Gerrard 1984; van Baalen and Rand 1998; Mitteldorf and Wilson 2000; Rousset 2004; Killingback et al. 2006; Lehmann and Keller 2006; Ohtsuki et al. 2006; Traulsen and Nowak 2006; Taylor et al. 2007; Alizon and Taylor 2008; Grafen and Archetti 2008; Johnstone and Cant 2008; Lion and van Baalen 2008; Shaw and Gardner 2008) which provides a physical niche for relatives to keep close and stay together. Thus, cooperative traits will be directed indiscriminately toward all neighbors who normally tend to be relatives without reliance

on active kin recognition. This mechanism is common in microorganisms. However, limited dispersal generates local competition among relatives (Hamilton, 1971; Grafen, 1984; Kelly 1992; Queller 1992; Wilson et al 1992; Goodnight 1992; Frank, 1998; West et al., 2002). In other words, although limited dispersal allows cooperators to preferentially interact, it will increase competition between them. Hence, dramatic influences on spatial - temporal dynamics in microbial life ensue. Here, because local resource patches are short-lived and many new ones should be generated, kin competition will be fierce and high dispersal rates will have an advantage. Consequently, selection will favor against limited dispersal in this tradeoff between competition-colonization (Nadell and Bassler, 2011; Yawata, et al. 2014). Thus, the scale of competition should be taken into account given the fact that global competition provides a relative advantage for cooperators, The cumulative result of this is the emergence of subpopulations that may only contain cooperators, thus ending with cooperators that have enough advantage to overcome the costs of cooperation. Therefore, pure cooperator subpopulations may thrive and reproduce at significantly higher rates than pure cheater subpopulations owing to the acquisition of cooperation reward (Griffin, et al. 2004). Taylor (1992 a, b) predicted that in the simplest possible scenario. The effects of increased relatedness and local competition exactly cancel out. It should thus be noted that the dispersal pattern in small kin groups, rather than individuals, can favor cooperation because it combines relatively high relatedness and relatively low kin competition. This observation is termed 'Budding dispersal' (Goodnight 1992; Gardner and West 2006; Lehmann et al. 2006). We can divide the dispersal to three patterns: (1) individual dispersal within subpopulations (limited dispersal), (2) individual dispersal among subpopulations (high dispersal), (3) group dispersal among subpopulations (budding dispersal). Some experimental studies have examined the above predictions and suggested that cooperation will not be favored by limited dispersal or high dispersal, and that only budding dispersal would be favored by selection (Kümmerli, et al. 2009). This, in turn, has been observed in some species such as: social insects (Peeters

and Ito 2001), breeding birds (Williams and Rabenold 2005; Sharp, et al. 2008), Humans (Haldane 1932), Primates (Bradley et al. 2007) and Bats (Metheny et al. 2008). However, the question which may arise: do microorganisms in nature already could follow the pattern of budding dispersal? As far as I know, this is a topic that has not been addressed (Pion, et al. 2013). Yet if we consider biofilms as the most widespread life form of the microorganisms, we will find ourselves coming back to the limited dispersal pattern because biofilms are limited spatial structures.

Spatial structure

Spatial structure is a widely acknowledged principle for averting the tragedy of the commons and also happens to be a key mechanism for promoting cooperative traits (Frank, 2010; MacLean, 2008; Hol, et al. 2013; Nadell, et al. 2010; Keymer, et al. 2006; Bachmann, et al. 2013). However, spatial structure does not guarantee cooperation stabilization and persists for the following reasons:

Mutation-Dispersal rate

Although, the spatial structure could rescue cooperators by preventing interactions among cheaters-cooperators, it couldn't avert the emergence of cheaters within a population of cooperators by mutations. Hence, hypermutation rate within these segregated microbial patches in the context of metapopulation models will violate protection provided by spatial structure (Harrison, and Buckling, 2005), thus bring us back to the social dilemma in well-mixed populations. Hence, the rate of mutations which may generate defectors within pure cooperators patches should be always lower than migration rate (colonization rate) of the same individuals which colonize new patches. But this is unlikely to be ubiquitous owing to the fact that no known mechanisms govern this equation. Moreover, high dispersal-colonization rate and the spatial structure pattern (Biofilms) are irreconcilable. In addition, high dispersal rate generates low relatedness and more opportunities for encounter cheaters. Furthermore, biofilms (Spatial structures) can be thought of as a limited dispersal regime ($d = 0$) (dispersal rate between

subpopulations = 0) whereby, cooperation is disfavored in biofilms due to Kin competition. Although cooperation may become fixed in some subpopulations due to random genetic drift in the short-term, cheaters, who arise from long-term mutations, will drive cooperators to extinction (Kümmerli, et al. 2009). To conclude this part, spatial structure is a double-edged sword, and it may not be as universally beneficial for cooperation as previously thought (Hauert and Doebeli 2004)

Dispersal-Extinction rate

The rate of cheater migration to cooperator patches must always be lower than the extinction rate of cheater patches so that spatial structure can facilitate rescuing of cooperators; but this is unlikely to be ubiquitous owing to foraging theory, which predicts that if rates of resource acquisition diminish with patch use, then shorter travel times between patches promote shorter patch residence times (Charnov 1976; Stephens and Krebs 1986). However, hypermotility allows bacteria to efficiently migrate to other patches (high dispersal rate between patches and low residence time within patches) whereas, hypermotility individuals frequently seem to be defective in collective traits (cheaters), especially in biofilm formation (Meng, et al. 2011). Hence, reversion to dynamics of a single well-mixed patch or unstructured populations.

Invasive plasmid

Biofilms are the embodiment of the spatial structure in microbes. It is believed that biofilms can provide strict spatial structures which have the capacity to rescue cooperative traits and explain their persistence. However, this conception of biofilms may not withstand encounter with depolymerizing bacteriophage (Harper, et al. 2014) or conjugal invasive plasmid (Krol, et al. 2013), which carries the selfish traits of the donor planktonic bacteria surrounding a mature recipient biofilm, in which case it could attach the outer layer of the biofilm then transconjugants plasmid into the biofilm. Therefore, like the bacteriophage, plasmid will invade the biofilm, but with an alternative mechanism. Normally, the conjugal pilus may reach 5–10 μm in length, and this is approximately compatible with the findings of shallow

inoculation (shallow inoculation is 1 μm below biofilm) reported in this study (see: (Merkey, et al. 2011) “For shallow inoculation, the plasmid spreads horizontally to a similar extent for all cases, but spread in the vertical direction is strongly affected by the type of growth dependence.” This availability of plasmid invasion has been intensively invoked in the interpretation of bacterial evolution. Generally, horizontal gene transfer (HGT) is the major source of genetic diversity of bacterial evolution (Thomas, and Nielsen, 2005). It has played a central role in bacterial evolution at least since the origins of the bacterial divisions (Gogarten et al., 2002). Therefore, although spatial structure seems at first glance like a key mechanism which prevents the tragedy via preventing cooperators-cheaters interaction and segregating both of them into two pure populations, thus restricting transmission of traits, this scenario should be altered after realizing the critical role of (HGT) in bacterial evolution. Ultimately, this is a key point that has important therapeutic applications to be explicated in the section: (6)

The tragedy of the commons and the Prisoner’s Dilemma

The tragedy of the commons (Hardin, 1968; Leigh, 1977; Frank, 1995; Michod, 1999; Hauert et al., 2002; Wenseleers and Ratnieks, 2004; Roopnarine 2013) is the situation where individuals selfishly exploit a common resource until the resource is reduced to the point that the individuals can no longer persist in it. Or when individuals destroy through competition the resource upon which they all depend on. In nature, the resources are abundantly available for everyone since no one has an exclusive monopoly or control over them. Therefore, each individual will be tempted to exploit the available resource in view of the fact that it will receive direct payoff from this attempt, whereas, it incurred a share of the costs resulting from overexploitation of the public good. Thus, open resources will always be vulnerable to rapacious consumption of selfish individuals, i.e. ‘cheaters or freeloaders’. Practically, all resources become susceptible to overexploitation by non-productive individuals who never seem to pay their share of production cost. It can be argued that the temptation to cheat is a nearly universal phenomenon

in biology (Axelrod 1985; Dugatkin 1997). Abstain from overexploitation does not have any advantages for individual which behaves as a prudent consumer ‘cooperator’, on the other hand, these individuals still incur the same costs. Therefore, virtually no benefit is gained from prudent consumption of resources and the selfish strategy will be always favored by selection as an ‘evolutionary stable strategy’. This further implies that it cannot be invaded by another strategy (Maynard-Smith, 1982; Geritz, et al. 1997). Ultimately, this will lead to entire resource depletion or drive cooperator individuals ‘as a social to extinction, which may also be followed by total population extinction ‘cheaters extinction’ if the social traits of the cooperators were essential to survival. In other words, individuals with self-interest strategies will sabotage the resource necessary for the whole population because evolution will always favor the selfish strategy until the resource (public good, cooperative traits, etc.) falls below the threshold resulting in extinction or depletion. Hardin’s example was a pasture shared by a number of shepherds, with each shepherd adding sheep and exploiting the pasture, thus reaping maximum payoffs while sustaining restricted consumption cost. The experimental examples of the tragedy of the commons (TOC) are: *Gadus Morhua*, (Olsen et al. 2004) *Oryzias latipes*, (Muir and Howard 1999) and *Myxococcus Xanthus* (Fiegna and Velicer, 2003) However, other numerous examples were reviewed in (Rankin, et al. 2007a). Similarly, examples of the public goods dilemma (see: Olson 1965) and also the prisoner's dilemma examples (PD) (see: Axelrod and Hamilton 1981; Dugatkin, 2002) (PD) should, in pursuit of more accuracy, be called N-person Prisoner’s Dilemma (NPD), as it will be played by more than two players (Archetti, and Scheuring, 2011). Many studies demonstrated examples of NPD, such as: sharing of large preys by groups of predators (Packer et al. 1990; Stander 1991; Creel 1997; Bednarz 1988), nesting and breeding in birds (Rabenold 1984), production of replication enzymes in viruses (Turner and Chao 1999), adhesive polymers in bacteria (Rainey and Rainey 2003), invertase in yeast (Greig, and Travisano, 2004), the formation of fruiting bodies in social amoebas *Dictyostelium discoideum*, (Strassmann, et al. 2000)

and cancer (Kareva, 2011). PD is an evolutionary paradox because, given the Darwinian perspective, 'survival of the fittest' selection should always favor selfish strategies in well-mixed population where ' $T > R > P > S$ ' (T, temptation to defect; R, reward for cooperation; P, punishment for mutual defection; S, sucker's payoff). In short, evolutionary theory predicts that cheating will always outcompete cooperate (Hamilton 1964; Trivers 1971). That is, in the long-term, cheaters will inexorably invade and take over the population, a process that eventually leads to average fitness decline and population extinction. Consequently, such findings undermine the assumption that natural selection (NS) always promotes survival by maintaining and increasing fitness (Fisher, 1930), in view of the possibility that (NS) may convert into a self-destroying mechanism.

The evolutionary theory and the conscious intervention

According to the evolutionary theory, it is conceivable that the tragedy of the commons should be found on a widespread level. Therefore, the fundamental question here is: why does life generally persist? (Parvinen and Dieckmann 2013). I have termed the mechanisms which prevent self-interest individuals from exceeding the threshold of resources as 'barriers'. They may exist by chance because there is no obligatory feedback associated with the threshold to create barriers to prevent cheaters from reaping benefits beyond resource threshold. However, the barriers will be useful only when they exist in suitable spatial - temporal circumstances. Only then selection will favor it. Therefore, evolution supports the existence of barriers. Hence, the emergence of barriers can be explained in Darwinian fashion. Still, and this is where the irony shows up, the fundamental evolutionary mechanisms (mutation\selection) will, as generally perceived, favor violation of such barriers on account of cheaters arising through mutations within cooperator populations. In this case, selection will always favor the selfish strategy owing to its contribution to higher fitness, as in the famous phenomenon termed 'the prisoner's dilemma'. Paradoxically enough, evolutionary mechanisms simultaneously enhance both the existence and violation of the barriers. I can illustrate this fact

by the following example: Coercion is one mechanism that has been widely suggested to avoid the tragedy of the commons (Clutton-Brock, and Parker, 1995; Frank, 1995; Wenseleers, et al. 2004) One potential simulation of coercion in microbes is the quorum sensing system (West et al. 2007b) which regulates the expression of genes for many traits in bacteria, i.e. plasmid transfer, bioluminescence, population mobility, biofilm maturation, virulence (Williams et al. 2007), and shuts growth genes, so that growth and division in the stationary-phase are ceased to avoid further consumption of rare nutrients necessary for protecting the public good and preventing resource depletion. By this way, bacteria can avoid the tragedy. Despite the fact that evolution supports the quorum sensing system as a barrier, evolution also supports the cheaters who violate this barrier. Thereby, Wild-Type is readily invaded and outcompeted by mutants in many bacterial species such as *Escherichia coli* (Zambrano et al. 1993), and this has happened in all tested media and conditions. These mutants neglect the signals of QS (system). Consequently, they have a growth advantage in the stationary phase, which means that their progeny will be increased and drive the wild-Type population into extinction in accordance with the prediction of the prisoner's dilemma (Vulić, and Kolter, 2001). Hence, we can not attribute any crucial solutions of this problem (Tragedy of the commons or the explanation of the existence and persistence of cooperative traits) to evolutionary theory because all mechanisms of evolution are entirely neutral when addressing this issue. Yet, one may also argue that the evolutionary process cannot be extremely biased for fixation of either barriers (solutions) or cheaters who violate these barriers (component Tragedy). Thus, there is something else which controls this competition and wildly induces cooperative traits in the long-term. In other words, evolutionary mechanisms have nothing to do with conflict between the causes of the tragedy and their solutions for it, whether the solution is that of outcompeting the tragedy or its contrary. Therefore, no evolutionary force can generally be assumed as a solution for this fundamental social dilemma which pervades in both Microorganisms and Macroorganisms. Even when considering barriers such as kin discrimination,

policing, pleiotropy (Foster, et al. 2004)... etc., no one can be generalized. Also, crucial solutions for the tragedy of the commons or prisoner's dilemma should have some form of awareness because there is no materialistic existence for resource threshold. This further implies that the threshold has no physical substance to deal with it, but instead a mathematical reality that requires consciousness to detect the value of the threshold. Consequently, the solutions require highly advanced skills like legal punishment or negotiation and so on. Hardin's own main solution to the tragedy of the commons was governance or privatization of the resource.

I suppose here an additional mechanism "conscious intervention" it is a metaphor of the knowledge and the choice. Regardless of determining the identity of this intervener. (we also don't know an independent entity for the other evolutionary concepts such as natural selection or mutation.)

Conscious intervention can control the rise of cheaters and their selfish degree in order to the maintenance of cooperation and avert tragedy. Hence, it may be the only general mechanism that could prevent the infinite theoretical likelihoods of cheaters emergence by migration or mutation (Mc Ginty, et al 2011) or horizontal gene transfer, and also could manipulate its degree in favor to cooperators. Moreover, the conscious intervention can accommodate other partial mechanisms like (Policing, Sanctions, Reciprocal Altruism, Reciprocity, Diminishing Returns (Foster, 2004), Feedback, Pleiotropy... etc.), in addition to the mechanisms which are relatively more general such as (Kin selection, spatial structure, Species-level selection (Rankin, et al. 2007b)). Hence, all these solutions could be incorporated into one mechanism, the mechanism of conscious intervention without running into a contradiction. Furthermore, conscious intervention has extra exclusive advantages such as the ability to address infinite theoretical likelihoods of cheaters emergence and the ability to detect the mathematical value of the resource thresholds. Thus, it provides an adequate explanation for cooperation persistence, the tragedy prevention, and also answers the question: why does life generally persist?

In summary:

Evolutionary thesis: a system of axioms "survival of the fittest,...etc."

Antithesis: there are facts "TOC and cooperation persistence" which cannot be explained using this system of axioms.

Synthesis: I add a new axiom "conscious intervention" to the system and obtain a better system.

The therapeutic applications

In this article, I demonstrated a theoretical analysis which concludes the necessary inclusion of 'conscious intervention' as a fundamental intrinsic mechanism that could guarantee an adequate explanation of cooperation persistence and tragedy prevention. These insights may be somewhat shocking and unusual, yet, fortunately, their predictions are testable, worthwhile it deserve the chance to be examined by future studies, particularly in synthetic biology for therapeutic purposes. This hypothesis predicts that there are overwhelming likelihoods for designing invasive engineered cheaters who could invade wild-types and drive the pathogenic bacteria to extinction, whether in the planktonic state or biofilms, cheaters would invade by invasive plasmids carrying the selfish traits. In similar approach, Brown and colleagues termed cheaters who carry medically beneficial alleles as 'Trojan horse' (Brown, et al. 2009). I believe it will be an important therapeutic trend in the future, particularly for chronic diseases caused by biofilms and virulent infections caused by collective actions in bacterial and viral diseases, or even treatment of disease caused by selfish strategies of cells like high growth rate, instead of high biomass yield or inefficient, as opposed to efficient resource consumption (Kreft, 2004; Bachmann, et al, 2013) as in the case of cancer (Anderson, et al. 2001). This could be achieved if we developed a classified categorization of the impacts and degrees of selfish and cooperative strategies in various environments to manipulate the selective pressure at any niche (Korolev, et al. 2014) .

In the context of bacterial diseases, some studies suggested that plasmids can only transfer to peripheral cells in biofilm microcolonies and that plasmids do not easily invade the deeper layers due to lack of nutrients and insufficient of oxygen in deeper cell layers, thus effecting an impact on transconjugants (Krol, et al. 2011; Krone, et al. 2007). However, plasmid invasion is higher in biofilms than in well-mixed liquids (Krol, et al. 2013) because, bacterial cells in biofilms stay in close contact. Moreover, biofilm formation enhances transconjugants in many ways (See: Madsen, et al. 2012). It is worth noting that plasmids do not need to invade the entirety of recipient biofilms and, instead, only need to initiate the selfish trait within the biofilm. Cheater lineages could then dominate and outcompete cooperator one's (wild-type).

Indeed, this has been documented in long-term infections, caused by bacteria, such as *Pseudomonas aeruginosa*, isolated from Patients with Cystic Fibrosis (Lee, et al. 2005) despite the fact that some environmental factors - such as thick mucus - can influence bacterial motility and prevent cheaters from rapidly taking over the whole population (Salunkhe, et al. 2005; Matsui, et al. 2006). However, hypermotility mutants will need shorter time for the invasion. In general, hypermotility allows efficient bacterial migration whilst, it is normally associated with deficiency in biofilm formation, for example: the *motN* mutant *Ralstonia solanacearum*, (Meng, et al. 2011), or full inhibition of biofilm formation, such as inactivation of *lsr2* gene in non-pathogenic bacteria *Mycobacterium smegmatis* (Arora, et al. 2008). Similarly, *Pseudomonas aeruginosa* hyperswarming mutants are caused by single-point mutations in the flagellar synthesis regulator, *FlaB*, which locks the natural mono flagellated bacteria.

Subsequently, multi-flagellated hyperswarmers emerge. Hence, the hyperswarmers will be able to get out in front of the wild-type and reach nutrients first. This will increase proliferation rate. Therefore, hyperswarmers will outcompete the wild-type (PAO1) and have more offspring. However, hyperswarmers are poor biofilm formers (van Ditmarsch, et al. 2013). This *per se* can reduce bacterial resistance up to 1,000

times compared with efficient biofilm formers (Boles, et al. 2004). It is conceivable that this general correlation between hypermotility and defective biofilm formation, can be utilized for therapeutic purposes. Likewise, quorum sensing because it controls biofilm formation and development (Davies, et al. 1998; Hammer, and Bassler, 2003; Waters, et al. 2008), it also controls many other essential traits reviewed in (Li, and Tian, 2012). Exploitative individuals can avoid the cost of producing the QS signal 'signal-negative' or the cost of both producing and response 'signal-blind'. Subsequently, cheaters will spread and outcompete the wild -type (Diggle, et al. 2007). Not only QS system can be useful and effective in these therapeutic purposes, but also any other public goods, because they constitute the vast majority form of social behavior in microbes, and they are always vulnerable to overexploitation by defectors (reviewed in West et al. 2007b).

It is also worth noting that some theoretical studies have suggested a shifting perspective for some altruistic traits from a mutualistic point of view. They refer to benefits gained by the altruistic individual, such as: secretion of the extracellular polymeric matrix (EPS), because the producer cells of (EPS) will reap the advantage by push descendants into a more oxygen-rich environment. Moreover, this mode of growth will suffocate the non-producing neighbors (Xavier, and Foster, 2007). If these predictions have been confirmed, we should avoid utilizing of such cheaters for therapeutic purposes because they will not able to invade the wild type strain. In addition, we should avoid utilizing of cheaters who possess advantages influenced by density-dependent processes and changes to unprofitable strategies in lower population density. In other words, if there is feedback between selfish competition and population density or when the selective advantage of investing in competition decreases as a function with population density (Rankin, 2007), then selfish traits will not become permanently beneficial - such as harassment in multicellular organisms - (Kokko, and Rankin, 2006). On the other hand, we should avoid targeting the cooperative traits which impose low costs on individuals such as metabolic prudence (Xavier, et al. 2011) because incurring of low costs

cannot do the required significant dynamic within the population.

Finally, this approach should be excluded if the intervention will lead to the volunteer's dilemma, where the ESS is a negative frequency-dependent selection. In this case, the defector is less fit than the cooperator when it becomes more common but fitter when it becomes less common. Then, the PD which we attempt to create, will be lost and converted to the Chicken game (Hawk-Dove, snowdrift (SD)) where, cooperators and cheaters can coexist. Permanently, both strategies can invade when rare (Gore, et al. 2009). This coexistence will happen if and only if the cooperative traits yield a direct benefit to the actor as well as to the opposing player (where $b > c > 0$). Then, cooperation will be the better strategy when being rare and can invade the cheaters because $S = (b - c)$, $P = (0) : (S > P)$. Therefore, it is better to adopt cooperation strategy when the opponent is a defector (defection is common). But when cooperation is common, defection will be the better strategy, because it is better to adopt defection strategy when the opponent is a cooperator. Because $R = b - c/2$, $T = b$ Therefore ($T > R$) (Doebeli, and Hauert, 2005). Consequently, mutant defector can invade the population of cooperators and so on.

Conclusion

The goal of this article was twofold: (1) to highlight the fact that the conflict between different strategies in nature has infinite theoretical likelihoods and the outcomes of such conflict will be inevitably against cooperation. (2) This problem cannot be addressed without a general mechanism which promotes cooperative traits and avoids tragedy everywhere. The ideal mechanism for this function is 'conscious intervention', provided that there is no physical embodiment of resource threshold in nature. This is why, given the nature of consciousness, mathematical language is the only way to detect resource threshold. In the light of what has been discussed thus far, one may confidently argue that this is the only mechanism that can guarantee tragedy prevention and address all possible likelihoods. The present

article has also emphasized the conclusion that evolutionary mechanisms have nothing to do with conflict between the elements and causes of tragedies on the one hand and their solutions on the other, and that they are entirely neutral. Hence, we cannot attribute any general or partial solutions of this problem to evolutionary mechanisms. Still more, such insights are testable because it have therapeutic applications in the field of synthetic biology via genetically engineered invasive cheaters who can invade wild-types 'cooperators' of pathogenic bacteria until cooperator populations go to extinction or overall population 'cooperators and cheaters' go to extinction, such empirical experiments could support or refute my predictions. Finally; the same therapeutic approach can also be applied in the treatment of viral diseases and cancer.

Competing interests

The author declares that he has no competing interests.

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