Invasive cancer as an empirical example of evolutionary suicide

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Received 20 March 2014; Accepted 7 April 2014; Published online 1 June 2014

Abstract
In recent years, a large portion of the literature has focused on evolutionary suicide. Which is about the extinction of population via highly fit invasive mutation possessing a strategy favored by selection. "Darwinian extinction" or evolutionary suicide it is one of the most important findings in adaptive dynamics but unfortunately remains in need of more empirical examples. On the other hand, much literature has been published on somatic evolution and how carcinogenesis is an evolutionary process caused by mutation-selection, and how it competes on resources and space, and evades predation. Therefore, its micro-environment reflects most of ecological interactions in independent organisms. Today, there are many mathematical models describe this unique case of somatic evolution and show invasion fitness of tumor Clone cells as an unbeatable strategy leading to normal cell extinction and evolutionary stable strategy (ESS). When we combine the studies in these two lines of research, we almost inevitably arrive at the conclusion that evolutionary theory falls short of adequately explaining the phenomenon of life in its fullness and complexity. This is due to the fact that when we look at cancer as an empirical example for evolutionary suicide, we find that the latter is not a rare or special case and that it can occur in the most common ecological conditions. Therefore, it can be argued that in the absence of a mechanism for preventing evolutionary suicide, there will be no adequate explanation for life.

Keywords Darwinian extinction adaptive dynamics; tragedy of the commons; population dynamics; somatic evolution; invasion fitness; evolution theory; tumor progression.

1 Introduction
In simple terms, evolution as a theory aims to explain the phenomenon of life in its complexity and diversity via basic mechanisms such as genetic mutation and natural selection. According to the theory, such mechanisms are necessary and sufficient for life to occur as we know it. Logically speaking, a sufficient cause necessarily entails the occurrence of its result. So if it happens that the mutation-selection binary does not ensure the occurrence of its result, then it is not sufficient, and therefore is not a sound explanation of life.
According to EPP Susanna (2010), in other words, to say “r is a sufficient condition for s” means that the occurrence of r is sufficient to guarantee the occurrence of s.”

No one can deny the existence and impact of mutation/selection; however whether they are necessary and sufficient for explaining the existence of biological systems or not is a different question (Zhang, 2012). Moreover, what are we to do if it turns out that such mechanisms at the individual-population level may drive populations to extinction instead of survival? The eventuality of self-extinction, formally known as “evolutionary suicide”, has been confirmed in adaptive dynamic (Metz, 1996; Geritz, 1998; Dieckmann and Law, 1996; Geritz, 1997). According to Gyllenberg and Parvinen (2001), evolutionary suicide is an evolutionary process where a viable population adapts in such a way that it can no longer persist. Evolutionary suicide has been discovered in models of life-history evolution (Matsuda and Abrams, 1994; Ferrière, 2000; Gyllenberg et al., 2002; Webb, 2003; Parvinen, 2010; Rouset and Ronce, 2004) and in various other models (Zayed and Packer, 2005; Dercole et al., 2006; Hedrick, et al., 2006; Parvinen, 2007; Gandon and Day, 2009).

In fact, evolutionary biologist Haldane has observed that animals and plants are not quite such ruthlessly efficient strugglers as they would be if Darwinism were the whole truth…it does not pay a species to be too well adapted. A variation making for too great efficiency may cause a species to destroy its food and starve itself to death. It should be noted therefore that any gains that may be benefited from mutation-selection in the population will inevitably perish by one mutant drives population to evolutionary suicide.

Evolutionary suicide occurs because of evolution (mutation/selection) favors the genotype allele of invasive mutant whose phenotypic trait has higher adaptive fitness landscape, its adaptation progress to the point that a population no longer can exist. Fitness, furthermore, is defined by the ability to both survive and reproduce at the individual and group-level, even if we had to consider kin selection, group selection, and inclusive fitness (Maynard Smith, 1964; Hamilton, 1987). The model of evolutionary suicide follows the modern interpretation associated with Fisher's fundamental theory of natural selection (Parvinen and Dieckmann, 2013; Frank and Slatkin, 1992; Okasha, 2008). The occurrence of evolutionary suicide is a potentially possible event owing to the fact that mutant invasion fitness drives the population to extinction, even if we consider all of the above mentioned conceptions and principles. In fact, evolutionary suicide may occur even under the ideal situation of "Optimizing Selection" (Parvinen and Dieckmann, 2013). Moreover, evolutionary processes tend to promote suicide instead of preventing it, and when it occurs it will cause all of the adaptive benefits that it had once been acquired to disappear. Hence, we cannot accept a theory for life which not only fails to prevent evolutionary suicide but also promotes it. Our questions are

(1) Is there an empirical example of evolutionary suicide?
(2) Is evolutionary suicide a particular case which occurs in very rare ecological conditions for mutant invasion fitness or is it possible through evolutionary processes in the most common ecological conditions and interactions known thus far?
(3) Are there any solutions which the theory of evolution can provide for this problem?

2 Is there an empirical example of evolutionary suicide?

The answer is 'yes'; among them are:

(1) Single-cell organisms (Fiega and Velicer, 2003)
(2) Multi-cellular organisms (Rankin and Kokko, 2006; Muir and Howard, 1999)
(3) Virulence parasite (De Roode et al., 2005)
(4) Plants (Gersani et al., 2001)
(5) Still, the present paper proposes a novel example represented in the case of invasive cancer, which in turn possess three important advantages:
(a) Cancer arises directly from evolutionary mechanisms (i.e., mutation, selection, genetic drift) thus supporting the results of the mathematical models which argue that evolutionary theory mechanisms cannot prevent the potential of evolutionary suicide.

(b) Cancer is the single empirical example of how evolution scenario of life on earth can occur (Casás-Selves and DeGregori, 2011; Merlo et al., 2006). Arguing that it is an empirical example of evolutionary suicide, one may plausibly argue that evolutionary suicide occurs at the heart of this scenario and therefore must not be ignored.

(c) Cancer has many and various ecological interactions (identical to the same ecosystem of independent organisms). This supports the main aim of this article, namely that evolutionary theory happens to be an insufficient explanation for the phenomenon of life because it fails to prevent evolutionary suicide. This becomes the more evident in the light of earlier evidence that it is not a rare or particular case but can occur in the most common ecological conditions.

3 Invasive malignant cancer is an evolutionary process and an empirical example of evolutionary suicide

3.1 Cancer is an evolutionary process
Since Peter Nowell has described tumor progress as an evolutionary fashion (Nowell, 1976) and many studies have supported it, evolutionary biologists believe cancer reflects species evolution (Casás-Selves and DeGregori, 2011).

The neoplasm is genetically and epigenetically heterogeneous. Inside it, the population of individual cells competes for space and resources. It evades predation by the immune system and can even cooperate, disperse and colonize new organs (Merlo et al., 2006).

3.1.1 Mutations
Cancer arises from genetic mutation such as mutations activating ontogenesis and inactivating tumor suppressor genes (Gatenby and Vincent, 2003a; Roth et al. 2001; Maley et al., 2006; Gonzalez-Garcia et al 2002; Frank and Nowak, 2004; Ibrahim et al., 2011) and epigenetic mutations such as hypermethylation (Weisenberger et al., 2006; Horie-Inoue and Inoue, 2006).

3.1.2 Genetic drift
Genetic drift plays a role in the co-existence of various colonies in the neoplasm and in neutral mutations fixation (Merlo et al., 2006).

3.1.3 Natural selection
Natural selection (NS) will favor neoplasm colonies because of the effective fitness strategies characterizing cancer as one of its major hallmarks (Hanahan and Weinberg, 2010):

(1) Sustaining proliferative signaling
(2) Evading growth suppressors
(3) Resisting cell death
(4) Enabling replicative immortality
(5) Inducing angiogenesis
(6) Activating invasion and metastasis
(7) Reprogramming of energy metabolism
(8) Evading immune destruction

Moreover, natural selection will also favor neoplasm colonies due to their genetic instability. Hence, cancer appears to invite all the conditions necessary for natural selection to act upon it. According to Ridley (1996): (a) reproduction. Entities must reproduce to form a new generation; (b) heredity. The offspring must tend to resemble their parents; (c) variation in the individual characters among the members of the population;
(d) variation in the fitness of organisms according to the state they have for a heritable character.

3.1.4 Ecological interactions

(1) Competition: to compete on resources of nutrition and space, every competitor will have a negative effect on the others (Cagainard et al., 1985; Miller et al. 1980; Guba et al., 2001).

(2) Amensal: this has to do with partial competition having a partial effect as when a colony stimulates an immune response against its competitors only (Heppner et al., 1983).

(3) Predation: a tumor may use mechanisms which help it escape immune system predation (Seliger, 2005).

(4) Parasitism: when a colony benefits at the expense of other ones (Rundhaug, 2005; Nagy, 2004).

(5) Commensalism: when a colony increases other colonies' fitness without payoff (Heppner and Miller, 1998; Jouanneau et al., 1994).

(6) Mutualism: cooperation among all that benefits all (Axelrod et al., 2006; Ishiguro et al., 2006; Fukino et al., 2004; Mueller and Fusenig, 2004; Tlsty, 2001).

Ultimately, one finds that most of the important and common ecological interactions among independent organisms in the biological system are mirrored or present in cancer colonies with their micro-environments.

3.2 Invasive cancer is an empirical example of evolutionary suicide

A malignant cancer in the invasive phase (Vineis and Berwick, 2006) is a phenotype that has evolved by mutation/selection and one which possesses invincible strategies, (local) maximum adaptive fitness landscape, and evolutionary stable strategy (Gatenby and Vincent, 2003b). It therefore invades the population, leading to extinction of normal cells via competition (Gatenby and Gawlinski, 1996; Vineis and Berwick, 2006; Gatenby and Vincent, 2003b; Kareva, 2011a, b). Eventually, this leads to self-extinction following the destruction of resources (death of cancer patient). One may therefore argue that invasive cancer is an empirical example of evolutionary suicide. Contrary to Darwin's belief in natural selection “According to Darwin (1859) Natural selection will never produce in a being any structure more injurious than beneficial to that being, for natural selection acts solely by and for the good of each. ” Evolutionary suicide shows that adaptive traits can harm the population and drive it towards whole extinction. The same problem persists in neo-Darwinism, even when one takes into account 'inclusive fitness'; defined as (Bryden, 2007), the expected reproductive success of a trait/organism due to its phenotype and the frequency of the trait/related organisms in the population”. We can see cancer evolutionary dynamics as selfish behavior that prevents cooperation between cells in a tissue (Franziska Michor, 2005). Therefore, the mathematical dynamic models, which describe the invasion that follows from the selfish strategies, also describe the tumor progress and vice versa. As a result of competition between cooperator and defector strategies, Parvinen refers to what he calls the "Kamikaze-mutant" case in this model (Parvinen, 2010). I think this case of evolutionary suicide fully applies to tumor cells in the invasive phase since it appears to bear all the advantageous fitness traits unique to cancer. It is (ESS) and causes extinction of normal cells and the others genotypes colonies surrounding it. Below are some quotations from five important studies describing the ecological dynamics of the tumor progress (the competition among normal and invasive cancer, adaptive fitness landscape of normal and invasive cancer):

3.2.1 It should be noted that Kareva (2011a) showed cancer as a case of evolutionary suicide in this model, it "eventually entering the domain of attraction of the stable equilibrium of another, larger game, which can lead to evolutionary suicide ? Now glycolytic cells that have become numerous enough are cooperating, jointly increasing the toxicity of the surrounding microenvironment, and becoming more efficient competitors as a group, eventually killing the host and consequently killing themselves. In the model, this is captured through introduction of the additional toxicity term that captures increased mortality of aerobic cells proportional to the amount of lactic acid secreted by glycolytic cells. Indeed, one can observe that the cell population initially grows; peaks and then eventually collapses, going to extinction (see Figure 7). So, the either equilibrium
within the same game of prisoner's dilemma can become attracting not because of the changes in payoffs for each cell but due to different initial composition of the population of players, which happens solely through natural selection”.

3.2.2 According to Gatenby and Vincent (2003b), the tumor population can evolve to an ESS, driving the normal cells to extinction, resulting in an invasive cancer.

3.2.3 According to Gatenby and Vincent (2003b), only after evolving strategies that allow for increased substrate uptake will the system come to equilibrium with complete destruction of all normal cells, i.e., an invasive cancer. Because its strategy is at a maximum on its adaptive landscape, the cancer population cannot be dislodged through the introduction of other mutant strategies (Derived from same G-function) this prediction of a decline in somatic evolution and, therefore, decreased Cellular heterogeneity in an established invasive cancer has been observed.

3.2.4 According to Gatenby and Vincent (2003b), a genotype allowed to evolve to an ESS will invade and destroy adjacent non-ESS populations. Furthermore cellular strategy at an ESS it will have no further pressure to evolve at least within the current microenvironment. Thus, the transition from a premalignant state to an invasive cancer should be accompanied by a transition from heterogeneous cellular population to one that is comparatively homogeneous.

3.2.5 According to Vineis and Berwick (2006), the effect of normal cells over cancer cells becomes negligible.

3.2.6 According to Gatenby and Gawlinski (1996), for aggressively invasive cancers there is no region of coexistence between tumor and normal tissues and therefore the Lotka-Volterra competition has no effect on the structure and dynamics of the tumor-host interface.

3.2.7 According to Kareva (2011b), another consequence of tumor heterogeneity is the possibility of so-called evolutionary suicide —in their quest for higher growth rates, lower death rates, and increased competitiveness and with their ability to migrate out and colonize distant organs, cancer cells defy “cooperation” with somatic tissue, eventually killing the host and thus killing themselves. This evolutionary experiment is run within each cancer patient, sometimes leading to cancer cells committing evolutionary suicide at the expense of the host. From an ecological perspective, one can look at this process as an attempt of new species (cancer cells), which have different metabolic and reproductive strategies compared with the “resident” population (somatic cells) to invade a new habitat (tissue). Successful invasion will result in the formation of a primary solid tumor.

4 Is evolutionary suicide a particular case that occurs in rare ecological conditions or is it possible through evolutionary processes in the most common ecological conditions and interactions that we know?

In the light of the ecological interactions of our empirical example (cancer), (i.e. Competition, Amensal, Predation, Parasitism, Commensalism, and Mutualism.), it can be argued that evolutionary suicide may indeed occur in the most important and common ecological conditions and interactions of life biological system

5 Are there any solutions which the theory of evolution can provide for this problem?

This problem is similar to the other problem known as "the tragedy of the commons" (Hardin, 1968) and which is defined as (Rankin et al., 2007): a situation in which the selfish actions of individuals result in the complete collapse of the resource over which they are competing. It thus appears that the solution heavily requires a great deal of "intelligence" in order to solve the dilemma and protect the biological system. According to Rankin et al. (2007), the lesson drawn from these studies is that solving the dilemma often requires negotiation and sanctions on disobedient individuals. This Changes the payoffs, so that group-beneficial behavior also becomes optimal for the individual” Kin selection, group selection, and so on may explain how natural selection opts for certain useful strategies such as cooperative and altruistic behaviors but
cannot prevent a phenotype which is fit and which has actually been favored by selection.

6 Discussion
6.1 Are there differences between cancer evolution in single organism and independent organism’s evolution?
Yes, there are differences and asexual reproduction may be the major one. However, this should not negatively impact the findings of this paper since cancer was cited as an empirical example for evolutionary suicide in the various and most common ecological conditions and interactions. Moreover, there are other empirical examples for evolutionary suicide in sexual reproduction (Rankin and Kokko, 2006; Muir and Howard, 1999). In spite of such differences, cancer still remains the only empirical example of how the evolutionary scenario of life on earth may occur.

6.2 Conclusion
Since the occurrence of evolutionary suicide in most populations and various ecological conditions is theoretically (adaptive dynamics) and empirically (cancer) possible, and since such an occurrence leads to full population extinction, then every extant population at the cellular and organismal level is a phenomenon which no theory may sufficiently explain without accounting for a mechanism which has the capacity to prevent evolutionary suicide. Since the theory of evolution does not account for such a mechanism, then it can be argued that the theory is inherently insufficient as an explanation of the phenomenon of life.

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