Resource consumption, sustainability, and cancer

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Abstract

Preserving a system's viability in the presence of diversity erosion is critical if the goal is to sustainably support biodiversity. Reduction in population heterogeneity, whether inter- or intraspecies, may increase population fragility, either decreasing its ability to adapt effectively to environmental changes or facilitating the survival and success of ordinarily rare phenotypes. The latter may result in over-representation of individuals who may participate in resource utilization patterns that can lead to over-exploitation, exhaustion, and, ultimately, collapse of both the resource and the population that depends on it. Here, we aim to identify regimes that can signal whether a consumer-resource system is capable of supporting viable degrees of heterogeneity. The framework used here is an expansion of a previously introduced consumer-resource type system of a population of individuals classified by their resource consumption. Application of the Reduction Theorem to the system enables us to evaluate the health of the system through tracking both the mean value of the parameter of resource (over)consumption, and the population variance, as both change over time. The article concludes with a discussion that highlights applicability of the proposed system to investigation of systems that are affected by particularly devastating overly-adapted populations, namely, cancerous cells. Potential intervention approaches for system management are discussed in the context of cancer therapies.

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Introduction

The role of genetic and environmental variation has been well documented within the context of human genetics and animal/plant breeding [8]. Heritable variation that affects fitness makes evolution possible [9, 16]. The environmental landscape occupied by individuals within a population includes resources shared by members of cohabiting populations [39, 46, 47, 49] engaged in interference competition, i.e., the competition that emerges from variation within a population, guild (group of species that exploit the same resource), or some larger ecological unit. Selective pressures experienced by individuals within a population are thus directly a function of the group's heterogeneity. These selective forces generate and sustain feedback loops capable of altering, over different temporal, spatial, and multiple organizational scales, a population's interactions with the landscape in which such dynamics operate. Here, we explore the consequences of changes in population heterogeneity on overall system dynamics within a *conceptual* consumer-resource model. The heterogeneous population of consumers is assumed to be operating only under the influence of interference competition, i.e., the focus is on the dynamics of a *single* population. We study the impact of changes in population heterogeneity on resource viability and, consequently, on survival of a population that depends on this resource.

The perspective that natural and artificially induced reductions in heterogeneity may result in a population's collapse due either to loss in adaptive capacity or emergence of a critical number of over-consumers, is not new. It is known that both can lead to species extinction under conditions that correspond to excessive change, including those that result in the destruction of the species' habitat [51]. The case of an overly-adapted species potentially destroying their own habitat has become known as "evolutionary suicide" [24]. In host-parasite interactions, which are an extreme example of a resource-consumer system, evolutionary suicide is often seen as a natural consequence of tight co-evolutionary interactions, that is, the fate of the parasite is intimately connected to that of the host [35]. These systems are not unique to biology and have been documented in a variety of contexts, including social-economic systems [42] or in biological systems, where the resource may be defined as an ecological habitat [23]. Cases of biological control via introduction of invasive species fit the class of tight co-evolutionary interactions that may lead, often by design, to catastrophic events for the host; the case of *Myxomatosis* in Australia provides an example of such a system [13].

The specific nature of the immediate habitat is highly relevant. For example, in the case of host-

parasite interactions in diseases such as cancer, the habitat is confined to the body of the host [27]. In this paper, we restrict our attention to a subset of consumer-resource systems, where short-term adaptive success can lead to long-term system collapse (evolutionary suicide) under the assumption that the consumer species are unable to utilize alternative resources or find alternative homes within a viable time scale; examples include pika range land loss or isolated habitable lands [22, 50].

Managing consumer-resource systems that might be at risk for long-term collapse may demand an introduction of selective pressures that restrict or possibly eliminate the advantages of over-consumption (i.e., practices that reduce the advantages of over-consumers), but there are caveats. Management strategies aimed at rapidly increasing mortality of "undesirable" individuals within a population often have unintended consequences. One such consequence is the inadvertent selection of individuals highly resistant to control, which may or may not be directly connected to their ability to exploit the resource [13]. In agronomy, it is well documented that administration of toxic substances may result in selection of resistant individuals [6], while adding high toxicity costs to crops and consumers [12].

The resistance problem posed by pesticide spray regimes in agricultural systems is similar to issues encountered with treatment of bacterial infections, as administration of antibiotics may result in the selection for antibiotic-resistant microbes [7, 37]. Consequently, naturally rare "superbugs", which are otherwise suppressed or out-competed by non-resistant microbes, may suddenly thrive following the elimination of antibiotic-sensitive members of the bacterial population [6,10]. This may occur via the use of alternative, often dramatically distinct drug-use protocols that include random distribution or cycling of antimicrobials at the population level [7,37]. The fact that similar issues are critical to the development of effective cancer treatments is not surprising, particularly when aggressive treatment protocols are in place. Standard protocol for administration of chemotherapy, "maximal tolerated dose" or MTD, involves the administration of large doses of chemotherapeutic drugs for extended intervals of time. This practice allows only for the partial recovery of normal tissues (the 'under-consumers'), which are also severely affected by the therapy directed against cancer cells (the 'over-consumers'). The goal of MTD is to generate the highest possible level of cancer cell mortality, but by applying severe selective pressures on the population fo cancer cells, one predictably selects specifically for therapeutically resistant cell clones, which in turn can lead to metastatic disease and patient death [43].

While interventions are often a necessary evil, the aforementioned observations suggest that the focus of intervention or management strategies perhaps should not be driven by the goal of completely eradi-

cating undesirable members of a population. Instead, the focus should be on finding ways for controlled sustainable coexistence of the "consumer" and the "resource" over time. Intervention strategies that aim at reducing the likelihood, or altogether preventing, evolutionary suicide, must do so by maintaining some level of heterogeneity within a population. We highlight cancer because complete elimination of a sub-population may not be often the best policy. A similar counterintuitive result emerges when evaluating a population-level policy designed to maintain the viability of a limited supply of antimicrobials. This class of drugs has not undergone significant changes or increases over the past three decades, while the rate of population-level resistance has [7, 37].

Here, we first provide an overview of the work carried out in the study of a particular consumer-resource type system that incorporates the way that consumers interact with the shared resource (specific consumer level of heterogeneity). In this context, approaches for evaluation of the success of various intervention strategies are explored. We then introduce another metric for mathematically evaluating predicted health of the system, namely, changes over time in variance, in addition to changes in the mean values of parameter of (over)consumption, in order to evaluate whether this may help achieve successful population management while preserving sufficient levels of heterogeneity. We conclude with a discussion of the applicability of the results in the context of existing cancer treatments.

Mathematical Model

Model formulation

First, we evaluate the efficacy of intervention strategies while preserving a population's heterogeneity with respect to a consumer-resource system. In the proposed system, each individual is characterized by his or her own value of the intrinsic resource-consumption parameter, $c > 0$. A consumer characterized by a particular resource-consumption parameter is referred to henceforth as a c-clone.

Define $x_c(t)$ to be the number of c-clones within the population at time t. The total population of consumers is given by $N(t) = \sum_{\mathbb{A}} x_c(t)$ whenever c takes on discrete values, and $N(t) = \int_{\mathbb{A}} x_c(t) dc$ whenever c takes on a continuous set of values ($\mathbb{A}$ denotes the range of possible values of the parameter c). In general, application of the theory we apply here is insensitive to whether $\mathbb{A}$ is discrete or continuous.

We assume that the number of individuals $x_c(t)$ increases according to a logistic growth function, with the caveat that the carrying capacity is not constant but is a dynamic variable that depends on amount

of available resource. Each clone invests in resource restoration at a rate proportional to $(1 - c)$; a clone is considered to be an over-consumer if $c > 1$.

We start with a consumer-resource type model (see [33]) given by the following system of nonlinear equations:

$$\begin{cases} \dfrac{dx_c}{dt} = rx_c(t)\left(c - \dfrac{\sum_{\mathbb{A}} x_c(t)}{kz(t)}\right) \\ \dfrac{dz}{dt} = \gamma + \dfrac{e}{z(t) + \sum_{\mathbb{A}} x_c(t)}\left(\sum_{\mathbb{A}} x_c(t)(1 - c)\right) - \delta z(t). \end{cases} \quad (1)$$

The dynamics of the resource is determined by the constant natural restoration rate γ and the proportionate decay/loss rate $\delta z(t)$. The resource can also be depleted or restored by the $c-$clones. Specifically, consumer-induced resource depletion or restoration by a specific group of c-clones is captured by the term $e(1 - c)\frac{x_c/z}{1+N/z} = e(1 - c)\frac{x_c}{z+N}$. In other words, severe interference competition (over-consumption) and restoration is modeled as an additive, aggregate effect.

Overview of previous work

Full analysis of the parametrically homogeneous model, i.e., the case where the population is composed of a set of consumers characterized by a single average value of parameter c, was carried out in [28]. It was observed that as the parameter of over-consumption increased, the system went through a series of transitional regimes prior to collapse. Specifically, it was observed that the domain of attraction of the non-trivial equilibrium, which represents a state of sustainable coexistence of the population of consumers and their shared resource, shrank from global stability to being encircled by an unstable limit cycle. As the value of c further increased, population size started oscillating, until further increases in c eventually led to a complete collapse of both the population and the resource. From these results we hypothesized that transition into an oscillatory regime (emergence of oscillations as c increases in this example) serves as a predictor of collapse.

In order to visualize the evolutionary trajectories of an evolving system, where c would be able to change over time as a result of natural selection, we applied the Reduction Theorem, developed by G. Karev [26]. This technique allows studying the dynamics of a population that is composed of multiple clones, that is, a population that initially is heterogeneous with respect to c. The use of the Reduction

Theorem involves the use of a transformation carried out as follows:

Consider the equation for the rate of change of the population size over time:

$$x'_c = x_c \left(c - \frac{N}{kz} \right).$$ (2)

Introduce an auxiliary, 'keystone', variable $q_1(t)$ defined by

$$q'_1 = \frac{N}{kz}.$$ (3)

Then with

$$\frac{x'_c}{x_c} = c - q'_1.$$ (4)

Integrating the above expression leads to the following equation for calculating the size of each sub-population of clones x_c at time t:

$$x_c(t) = x_c(0)e^{ct-q_1(t)}$$ (5)

with the size of the total population calculated as:

$$N(t) = \int_c x_c(t)dc = N(0)e^{-q_1(t)} \int_c e^{ct} P_c(0)dc = N(0)e^{-q_1(t)} M[t],$$ (6)

where $M[t]$ is (by definition) the moment generating function (mgf) of the initial distribution of clones, and $P_c(t)$ is $P_c(t) = \frac{x_c(t)}{N(t)} = \frac{e^{ct}}{M[t]}$, in the population. The mean value of c can be simply calculated as

$$E^t[c] = cP_c(t) = c\frac{e^{ct}}{M[t]} = \frac{M'[t]}{M[t]}.$$ (7)

The dynamics of the parametrically heterogeneous population can now be fully described using the following system of equations:

$$\begin{cases} \frac{dq_1}{dt} &= \frac{N(t)}{kz(t)} \\ \frac{dz}{dt} &= \gamma + \frac{eN(t)}{z(t)+N(t)}(1 - E^t[c]) - dz(t), \end{cases}$$ (8)

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where $N(t)$ is calculated using Equation (6) and $E^t[c]$ is calculated using Equation (7). Full analysis of System (8) was carried out in [28].

Persistent selection for clones with the highest possible values of c in System (8), a predictable result, is observed. Numerical investigation of the transformed parametrically heterogeneous system allows explicitly plotting evolutionary trajectories that the population follows over time, as the expected value of c steadily increased; we see that trajectories generated as an increasing value of c "sweeps" through the aforedescribed domains of the parametrically homogeneous system.

Remark. It is important to note that the initial form of the parametrically homogeneous system can significantly influence the final form of the parametrically heterogeneous system. For instance, if $x'_c = rcx_c \left(1 - \frac{N}{kz}\right)$, a variation on the form of the first equation in System (1), also used in [33], leads after applying the reduction theorem to an auxiliary equation of the form

$$q'_2 = (1 - \frac{N}{kz}),$$

from where it follows that

$$x_c(t) = x_c(0)e^{cq_2(t)},$$

$$N(t) = N(0) \int_c e^{cq_2(t)} P_c(0)dc, \, and$$

$$E^t[c] = \frac{M'[q_2(t)]}{M[q_2(t)]}.$$

The final system thus becomes

$$\begin{cases} \frac{dq_2}{dt} &= 1 - \frac{N(t)}{kz(t)} \\ \frac{dz}{dt} &= \gamma + \frac{eN(t)}{z(t)+N(t)}(1 - E^t[c]) - dz(t), \end{cases} \qquad (9)$$

with the corresponding expressions for $N(t)$ and $E^t[c]$ defined above.

Bifurcation diagrams of the parametrically homogeneous systems for $x'_c = rcx_c \left(1 - \frac{N}{kz}\right)$ and $x'_c = x_c(c - \frac{N}{kz})$ are qualitatively the same, up to a constant, in this particular case. However, parametrically

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heterogeneous systems are different, a fact that can be immediately grasped from the final forms of the transformed systems. Conceptually, if $x'_c = x_c(c - \frac{N}{kz})$, then the level of resource over-consumption affects solely the birth rates of each consumer. However, if $x'_c = rcx_c\left(1 - \frac{N}{kz}\right)$, then the system becomes self-regulating, since the value of c now affects both the birth and death rates of consumers.

We will focus on the investigation of System (1), since our interest lies in evaluating the efficacy of intervention strategies in a population of unregulated over-consumers. Due to the nature of the particular model given by System (1), the direction of the system's evolution over time can be anticipated. Specifically, the highest value of c is always favored, by construction. This property makes this particular system an excellent conceptual model for the study of the effect of intervention strategies on the overall long-term health of the system as a whole.

Population management strategies and their efficacy with respect to population composition

The goal of intervention strategies on this type of systems is to prevent population collapse, a potential outcome given the over-consumer induced resource overexploitation. One possible way of achieving this goal is to target the over-consumers directly. In [29], we studied the impact of a series of punishment-reward functions that target individuals within the population as a function their c-value. Specifically, we investigated the relative efficacy of punishment for over-consumption vs. reward for under-consumption, and concluded that in a system, where the reproductive success of an individual is determined solely by their ability to access and utilize shared resources, rewarding under-consumption is insufficient to prevent the tragedy of the commons; only the use of severe enough punishment can achieve this goal. Specifically, each individual can be punished or rewarded according to some function $f(c) \in C^1(\mathbb{R}^+)$, which directly affects fitness of each consumer-producer. With this function, each clone is immediately punished for over-consumption if $c > 1$, or rewarded for under-consumption when $c < 1$. (Note, that we only require that $f(c)$ be piecewise continuous and right differentiable in order to be able to apply the Reduction Theorem.) The system of equations that incorporates a punishment/reward structure becomes:

$$\frac{dx_c}{dt} = rx_c \left(c - \frac{b \sum_{\mathbb{A}} x_c}{kz} \right) + x_c f(c)$$

$$\frac{dz}{dt} = \gamma + \frac{e}{z + \sum_c x_c} \sum_{\mathbb{A}} x_c (1 - c) - dz. \qquad (10)$$

The study of the above system involved tracking not only the changes over time of the size of the population, $N(t)$ and the amount of the shared resource, $z(t)$, but also the change of the mean value of the parameter c and the overall distribution of clones over time. However, we haven't yet investigated the effects of $f(c)$ on a relevant metric for population heterogeneity which may be used as one of the predictors of the upcoming ecosystem crash. As we argued above, heterogeneity is the key factor in population adaptability. What is lacking is a specification of an adequate metric. The Reduction Theorem allows us to track the change in variance of c over time, which we use as a stand in for potentially more sophisticated measures. The following representative examples (see [29]) are highlighted here with the addition of the change in variance of c over time. The values of all the core parameters remain the same for all three cases unless otherwise specified. Noticeably, the goal of the following investigation is not to provide a comprehensive investigation of all the cases of various punishment-reward functions and initial distributions that were analyzed in detail in [29] but to expand the analysis through now additionally studying the change over time of variance of c within the population. This second moment could prove to be a potentially predictive measure of the health of the overall system.

In Figure 1, the initial distribution is taken to be truncated exponential with parameter $\mu = 10$. The parameters were taken to be $\gamma = d = e = r = k = 1$, $N_0 = 0.6$, $z_0 = 0.1$, $c \in [0, 2.5]$, and the punishment function is $f(c) = a\frac{1-c}{1+c}$ with $a = 1$. As one can see, around $t = 20$, we observe a decline in population size $N(t)$, decline in the amount of resource $z(t)$, rapid increase in over-consumption, as can be seen in the mean value of c. All this is accompanied by a rapid increase in variance, followed by a very sharp drop, as over-consumers "take over" the population, leading to its rapid collapse.

In Figure 2, the initial distribution is taken to be Beta, with parameters $[\alpha, \beta] = [2, 5]$. The punishment function is $f(c) = \rho(1 - c^\eta)$, where $\rho = 1.2$, $\eta = 0.5$, and $c \in [0, 3]$. This particular punishment function allows for separation of the effect of punishment for over-consumption (parameter η) and reward for under-consumption (parameter ρ). In this case, one can observe that the maximal population size is smaller than was in the previous case, and the rate of increase of $E^t[c]$ is much slower. However, we
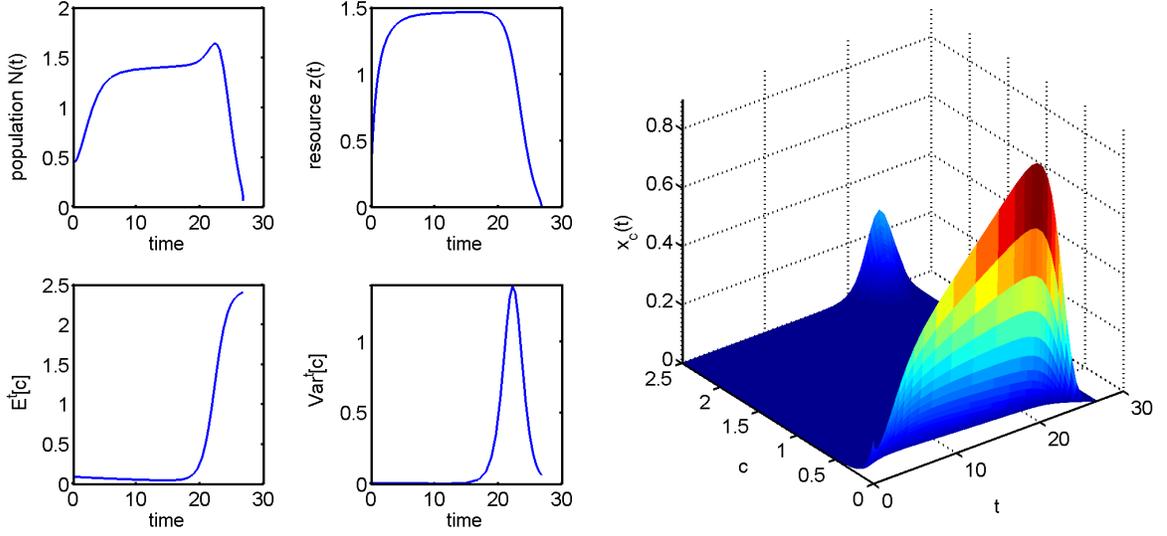
Figure 1. System (10), where initial distribution of clones in the population is taken to be truncated exponential with parameter $\mu = 10$. The parameters were taken to be $\gamma = d = e = r = k = 1$, $N_0 = 0.6$, $z_0 = 0.1$, $c \in [0, 2.5]$, and the punishment function is $f(c) = a\frac{1-c}{1+c}$ with $a = 1$.

once again observe a rapid increase in variance, followed by a rapid decrease, which precedes population collapse.

Finally, in Figure 3, the initial distribution is taken to be Beta with parameters $[\alpha, \beta] = [2, 2]$. The punishment function is $f(c) = a(1-c)^3$, with $a = 0.1$ and $c \in [0, 2.5]$. In this particular case, the maximal value of the population is smaller than in the previous two cases, which implies that the absolute number of over-consumers is in fact smaller as well. This could provide an explanation for why in this case the population survives for a longer period of time despite a high mean value of $E^t[c]$ at the early stages of population growth. Moreover, as one can see, in this case, where the population survives longer than in any of the other ones, the variance, while still decreasing, does so without spiking.

The differences in the shape of the curves of the change in variance of c over time could be connected to an observation, made by Gorban and colleagues [20]. Specifically, these authors have observed that *in a number of social, ecological and economical systems, rapid increase in variance, when coupled with increase in correlation between different components in the system, could be indicative of an approaching system collapse.* Sharp increase in variance is an indication of a rapid change in population composition, to which the system as a whole needs to adapt, as it is a stressor that comes from inside the system
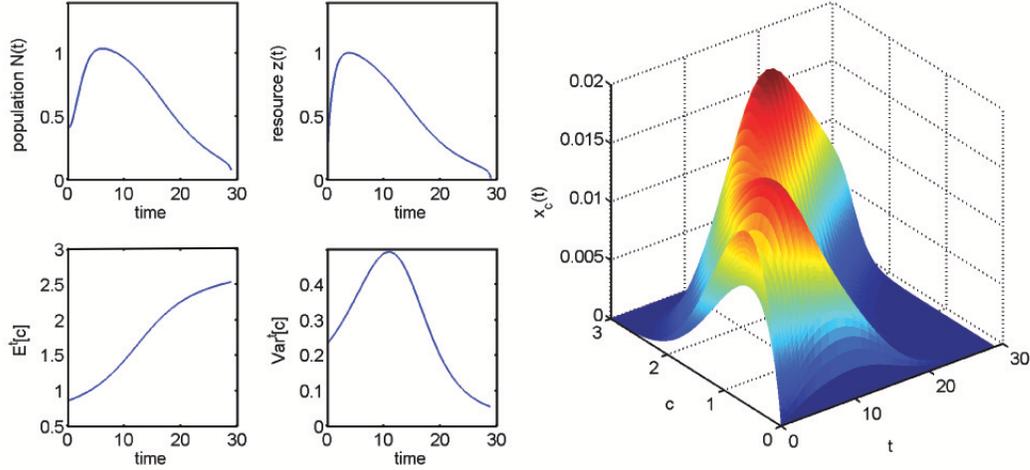
Figure 2. System (10), where initial distribution of clones in the population is taken to be Beta, with parameters $[\alpha, \beta] = [2, 5]$. The punishment function is $f(c) = \rho(1 - c^\eta)$, where $\rho = 1.2$, $\eta = 0.5$, $c \in [0, 3]$.
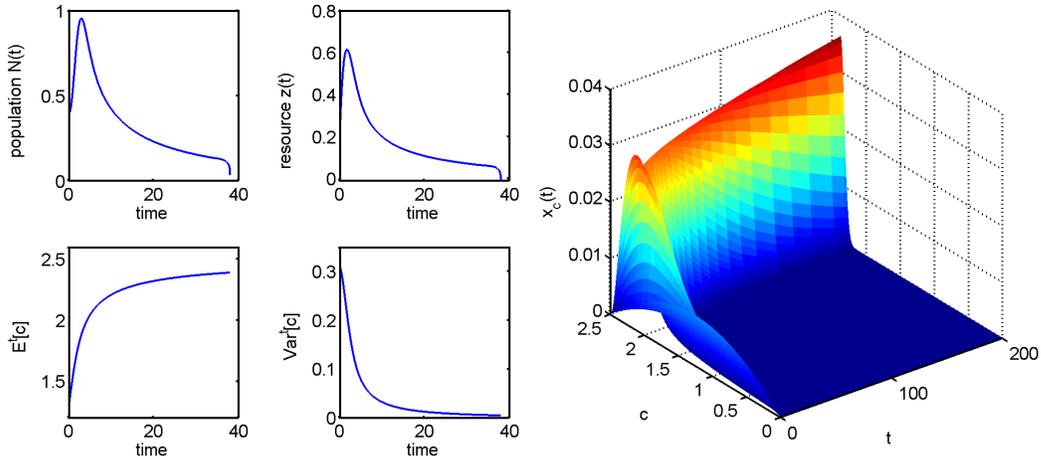

Figure 3. System (10), where initial distribution of clones in the population is taken to be Beta with parameters $[\alpha, \beta] = [2, 2]$. The punishment function is $f(c) = a(1 - c)^3$, with $a = 0.1$, $c \in [0, 2.5]$.

as opposed to being generated by external factors. Failure to adapt will mostly likely lead to eventual system collapse. It is possible that similar mechanisms underlie the dynamics in our model. However, this question requires further investigation.

The resilience metaphor

A natural question arises as to the *resilience* of systems such as (1). Resilience, defined in [4] as "...the magnitude of disturbance that can be tolerated before a [social or ecological] system moves to a different set of processes", may be undesirable within certain contexts. For instance, if the resource is desired and the clones are a nuisance (i.e., in case of management of parasites, or even cancer cells within a body), then we would wish for the population of clones to be unresilient, and for the resource (the body/host) to be resilient. From a parasite's perspective it is probably best that both the population and host are resilient. Our punishment/reward structure, $f(c)$, is not a "shock" in the classic sense; rather, it is a real-time, non-adaptive form of population control, which by construction favors clones with lower reproduction rates that might instead use their resources to invest in increasing the carrying capacity of the environment that supports them [44]. Investigations into the robustness of the logistic model as trade-offs between resisting shocks to growth (r) and shocks to capacity (K) in Social-Ecological Systems (SESs) have shown that when a species (in our case the population of clones) is more robust with respect to one strategy that the other suffers [25, 30, 45].

What we wish to do here is to investigate if it is not merely the absolute magnitude of change that the system has gone through, presumably assessed through $\mathbb{E}^t[f(c)] = \int_C f(c) \frac{x_c(t)}{N(t)} dc$, but also the "spread" of the disturbance, $Var^t[f(c)] = \int_C (f(c) - \mathbb{E}^t[f(c)])^2 \frac{x_c(t)}{N(t)} dc$, that may be used to define the resilience of a system. Secondly, whether the transitions shown in the preceding figures fit within the resilience metaphor of [4], and whether the latter can help elucidate new insights. By no means are we in a position to quantify the effect of the "spread" of the disturbance; however, this possible connection might provide an interesting avenue of research in both the field of resilience theory and that of investigation of parametrically heterogeneous dynamical systems.

First, we will summarize the metaphor introduced in [4]. Carpenter, *et. al.* describe a cycle of adaptation, either in terms of the biophysical/behavioral properties, of the population, or of adaptive selection of control strategies for a species, where essentially 4 stages of existence are defined: r, K, Ω, and

α. The SES first favors an r-strategy where rapid production of a species dominates the system. Then it transitions to a K-strategy solution as either equilibrium is attained, or if other species (potentially more robust to changes in environmental conditions) come to dominate. This robustness does not favor sudden shocks (i.e., forest fires), and the SES enters the Ω stage, where collapse, or near collapse, occurs. The α stage is described as "renewal or reorganization" of the SES preceding another r-stage. Typically, as the authors note, the Ω and α stages are characterized by very short time scales, which favor the existence of *some sort of* SES. The two stages of growth and persistence, r and K, may in contrast occur over much slower scales. We are now presented with a particular challenge of implementing this theory here, since we have an intrinsically coupled system (clone-resource), but we find this framework useful in describing the outcomes.

In each of the examples in the preceding section we showed how increase in $\mathbb{E}^t[c]$ can be followed by collapse of the resource, which would then lead to collapse of the population that is dependent on the resource. The transitional regimes that are observed in various cases studied could in fact be understood and formalized within the context of 4 stages described above. In Figure 1 our population of clones starts in the r-stage (as shown by the overall population growth from time $t = 0$ to $t = 8$) and then enters the K-stage (the relatively flat population growth from time 8 to 19). Throughout all this time very specific clones (under-consumers) got selected over time, as can be evaluated by the low value of $\mathbb{E}^t[c]$ and that $Var^t[c] \approx 0$. Furthermore, due to the prevalence of highly under-consuming clones, the resource reaches its carrying capacity (transitioning from its own r-stage to K-stage at time $t = 10$). The subsequent spike in both variance and mean of parameter c suggest that the system has entered the Ω-stage, a rapid decline in resource availability. Moreover, while trajectory-wise, the initial direction of overall population growth could be indicative of a new r-stage, a closer look at the distribution of c-clones indicates that in fact the under-consumers have undergone a crash (Ω-stage), and the clones have "reorganized" about a new phenotype of over-consumers (this "reorganization" being indicative of a rapid α-stage). The growth of the the now favored over-consumers (r) leads to exhaustion of the resource, which is followed by an eventual collapse of the entire population. In the absence of both actors there can be no second renewal, and the SES is dead.

We could view this all as a 4-tuple of stages for under-consumers, over-consumers, total clone population, and resource. Initially, we are met with a very favorable $(r, \emptyset, r, r)$ configuration (where $\emptyset$ denotes absence). The system reaches a seemingly stable $(K, \emptyset, K, K)$ configuration; however, a transition occurs

rapidly where the population of over-consumers undergoes an unintended renewal (K, α, K, K), presumably caused by the abundance of resource. This abundance facilitates temporary coexistence of both over- and under- consumers within the SES. There is no observable decay in the total population size because the growth of over-consumers overshadows the decline of under-consumers, and an unobservable set of transitions occurs: $(K, \alpha, K, K) \rightarrow (K, \alpha, \Omega, K) \rightarrow (K, \alpha, \alpha, K) \rightarrow (\Omega, r, r, \Omega)$. These transitions are characterized by a rapid growth in both the expected value of the parameter of consumption (the over-consumers entering r-stage), and its variance, indicating a transition of the the population as a whole, leading to the final set of transitions of the entire system, $(\emptyset, r, K, \Omega) \rightarrow (\emptyset, r, \Omega, \Omega) \rightarrow (\emptyset, K, \Omega, \Omega)$, eventually leading to evolutionary suicide, $(\emptyset, \Omega, \Omega, \Omega) \rightarrow (\emptyset, \emptyset, \emptyset, \emptyset)$.

Now let us examine another example, given in Figure 3. Here we can see what can be interpreted as two population regime shifts as the population as a whole undergoes two rapid shifts from Ω to α. The second regime is characterized by a long period of what can appear as stability. However, a closer look at the other characteristics of the system reveals a regime shift, selecting against under-consumers $(\Omega, r, \alpha, r) \rightarrow (\alpha, r, r, r) \rightarrow (\emptyset, r, r, r)$. This causes the highly varied system to lose diversity and select for highly over-consuming clones, $(\emptyset, r, \Omega, \Omega)$, which in turn once again results in eventual system collapse.

Analysis of these 4-tuples of interconnected stages points to several findings. Predictably, the absence of under-consumers leads to collapse of the system (i.e., $(\emptyset, \star, \star, \star)$ invariably led to system collapse). There must always exist a period when the over- and under-consumers coexist in order to allow the resource to grow to a level where the over-consumptive type may be selected for, (X, Y, α, r), where X and Y may represent any stage within which the clone type is present. Therefore, it appears that any intervention strategy needs to aim also at preventing an increase in consumptive variance in order to disallow the total population to undergo a strategy regime renewal, and hence prevent collapse through evolutionary suicide. One such possible strategy is discussed in the following section.

Intervention through adaptive control

Adaptive control is a method that can be of particular interest within the context of the proposed problem. Let us introduce a "central-planner", whose role it is to decide on the nature of the punishment function $f(c)$. The planner is faced with a vector of choice parameters $\vec{a}$ that affect the shape of the punishment function $f(c; \vec{a})$. Parameters in the vector $\vec{a}$ are implicitly dependent on the aspects within

the system that affect dynamics (e.g., state variables, parameters, etc.), and are chosen in such a way as to maximize the utility (a general measure of benefit) observed by the planner over time. This value could be a function of the outcomes desired by either the central-planner or by each individual. The current time utility can explicitly be written as $U_t(\vec{a}_t) = B_t(\vec{a}_t) - C_t(\vec{a}_t)$, where B_t represents anticipated benefits, and C_t represents the costs that are expected to be incurred depending on both the state of the system and the choices of the values of parameters in $\vec{a}$. Noticeably, $U_t(\vec{a}_t)$ reflects the discrete nature of implementation of interventions: the decision about the proposed mode of action is proposed based on the current state of the system and is executed over a time interval until new data is collected, and a new decision can be made.

The values of $\vec{a}_t$ are chosen in order to maximize $U_t(\vec{a}_t)$ over a planning horizon of length T via

$$V_t = \max_{\{\vec{a}_k\}_{k=t}^T} \left[U_t(\vec{a}_t) + \sum_{j=1}^T U_{t+j}(\vec{a}_{t+j})\delta^j \right], \tag{11}$$

where δ is some discount factor, a measure of how myopic the central-planner is in practice. A δ of one represents that each future utility gain is worth the same if gained in the future as it would be at the current time; a δ of zero indicates a purely myopic valuation of utility, where only the current time utility is considered. It should be clear that the more myopic the planner, the less likely the intervention strategy is to avoid future population crashes. In practice, a moderate discount between the two extremes is most likely.

For our particular system, it appears reasonable to assume the planner should value both the presence of the common resource $z(t)$, as well as the total size of the population of consumers $N(t) = \int x_c(t)dc$. We shall therefore consider a general form of the punishment function with the following specification. Let $p_c = \{c_i\}_{i=1}^p$ be a partition of the possible consumption levels within the system, i.e., $[0, c_{Max}]$. Define $f(c; \vec{a})$ to be the step function:

$$f(c; \vec{a}) = a_i \quad \text{for } c \in [c_i, c_i + 1). \tag{12}$$

Therefore, as the number of partition points grows, $p \to \infty$, so does the ability to approximate a large class of functions, $f(c; \vec{a})$. Noticeably, in order for the Reduction Theorem to be applicable, it is necessary that f be at least piecewise continuous and differentiable as $p \to \infty$.

Within the context of reward being a subsidy (perhaps monetary) and punishment a fine, we could

view them as a cost and benefit respectively. Given this control mechanism it is possible, for a given set of relative costs and benefits, that $\vec{a}$ could be chosen to follow either of the following three options: a) greatly favor under-consumers and punish over-consumers, assuming that value placed on persistence of resource and population are quite large compared to cost of under-consumer subsidy and benefit gained from punishing over-consumers; b) select for a distribution highly skewed toward over-consumers; particularly myopic planners (either because of a short planning horizon or high discounting on future returns) could see the large benefit gained from punishing over-consumers while not valuing the future collapse of the system; or c) induce a very small variance (or very slow growth in variance) within the population regardless of the mean consumption level. While not being valued directly, a small variance could likely be an unintended consequence for very forward-looking planners who can see the collapse that a large variance or rapid change therein may induce. Within the context of our model, it would appear that some combination of a) and c) would be the most preferable, as one would clearly wish to favor under-consumers. Additionally, in the case when rapid increases in variance are indeed correlated with increased likelihood of population collapse, managing variance in addition to population size would also be of importance. Therefore, if the value on $z(t)$ and $N(t)$ are relatively large when compared to the "revenue" gained from punishment (the benefit from $\int_1^{c_{Max}} x_c(t)dc$), and when both $\delta \approx 1$ and T large, then the central-planner would possess the foresight, and place adequate value on persistence, necessary to avoid population collapse while inadvertently selecting for narrow, slow growing variance.

Managing cancer as a heterogeneous consumer-resource type system

In addition to evident applications in biological systems and resource management [42], the reported results are also highly applicable in the field of cancer therapeutics, where inter- and intra-tumor heterogeneity plays a key role in the identification of treatments for cancer [3].

One of the possible ways to view cancer is as a type of a consumer-resource system, where both normal and cancerous cells rely on the resources provided by the host for survival and reproduction. Similarly to the proposed conceptual model, the immediate selective advantage of over-consumption of shared resources, such as glucose [18], glutamine [11], phosphorus [14], etc., by cancer cells selects for over-consumers at the expense of normal cells (the "under-consumers"). This in turn can eventually lead

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to the tumor committing evolutionary suicide via exhaustion of the shared resources, in this case its host. Noticeably, regardless of the specific reasons for what drives resource over-consumption, the final result is exhaustion of the "shared resources" at the expense of healthy tissues. In the terminal stages of the disease we indeed often observe nutritionally irreversible decrease in body mass (cachexia), which precedes death.

Most clinically available treatment strategies, and specifically chemotherapy, target the most rapidly dividing cells at different stages of the cell cycle [52]. Such an approach, while often effective in reducing the overall tumor burden in the short term, in fact highly efficiently selects for therapeutically resistant clones. If the highest rate of resource consumption translates to the highest growth rates, then chemotherapy administration translates directly into targeting individuals, or in this case cells, with the highest value of the parameter c. Unfortunately, in a clinical setting, such interventions are typically highly toxic to the host, and their long-term effectiveness is highly limited for most cancer types, including sarcomas, breast, prostate, pancreas and lung cancers [48].

Our results suggest that interventions that maintain heterogeneity within the population are in fact more effective long term. In cancer therapy, one strategy is administration of chemotherapy at lower doses but more frequent time intervals, also known as metronomic chemotherapy. In contrast to MTD, which administers maximally tolerated doses of cytotoxic drugs at largely spaced time intervals, metronomic regimen allows more gradual reduction in tumor burden, without severe selection for resistant clones, as is frequently observed with MTD [21, 31, 43].

Moreover, Gatenby and colleagues [17] have evaluated the efficacy of what has been termed "adaptive therapy", where the goal of the therapeutic intervention is not to cause maximal cell mortality but to maintain a fixed tumor burden. Such approach, which conceptually is similar to aforedescribed adaptive control, has been successful in producing long-term survival in mouse models. Perhaps a combination of the two approaches (strategies a and c in the previous section), namely, frequent administration of low dose chemotherapy in combination with adaptive control, would create an "adaptive metronomic chemotherapy" that could lead to most beneficial results.

Perspectives on sustainability within host parasite systems

In this article, the similarities between resource-consumer type systems, in the presence of a particularly devastating overly-adapted population (e.g., cancerous cells) have been highlighted. Cancer dynamics under the selective forces of treatment belong to a class of non-traditional examples, for which implementation of approaches that sustain some level of heterogeneity may be critical even if they seem counterintuitive. Other systems that can benefit from a consumer-resource perspective include disease transmission systems, particularly systems that are responsible for generation and spread of antibiotic resistant agents. For instance, management of the limited number of available antimicrobials that are currently being used to fight nosocomial infections is likely to have dramatic consequences at higher levels of organization. The need to embrace nontraditional policies in situations, where 'common sense' might dictate otherwise, must be seriously evaluated. The following observations on sustainability and slowing down the growth antibiotic resistance are based on [5].

The complex dynamics of emergent and re-emergent diseases within landscapes living under the tinkering effects of evolution, adaptive human behaviors, and public health policies that include treatment, vaccination or both, are used to highlight the dynamics of antibiotic resistance in the context of sustainability. On March 11, 2013, the British Chief Medical Officer Dame Sally Davies, [38], noted that "the problem of microbes becoming increasingly resistant to the most powerful drugs should be ranked alongside terrorism and climate change on the list of critical risks to the nation ... Yet while antibiotic use is rising – not least in agriculture for farmed animals and fish – resistance is steadily growing and the 'pipeline is drying up' of new drugs which can replace those becoming useless. [In fact] No new classes of antibiotics have been developed since 1987, and none are in the pipeline." Professor Nigel Brown, president of the Society for General Microbiology, remarks that immediate action by scientists is required if we are going to identify and mass produce new antibiotics; this kind of effort needed to tackle the problem of antimicrobial resistance and its transmission, particularly in the context of nosocomial (hospital) infections [38].

Mathematicians use contagion or epidemiological models to study the evolution, dynamics and control of diseases, including nosocomial or hospital infections, i.e., infections most often responsible for transmission of resistant pathogens in hospitals [7, 37]. The most celebrated epidemic model was introduced by a medical doctor W.O. Kermack and a statistician A. G. McKendrick [32]. Both researchers modeled

disease dynamics under the assumption that transmission depends on the intensity of hosts' interactions (handshakes, kisses, and more) and the frequency of encounters between susceptible and infected individuals.

In 1994, Malcolm Gladwell, a journalist writing for the New Yorker magazine, re-discovered a plausible explanation for the growth or decay of a different kind of disease, the 'disease' responsible for epidemics of crime in New York City [19]. He observed that the side of the tipping point that a system was 'on' determined whether or not crime was a problem. Hence, the direction of the crossing, as parameters were varied, could determine the difference between "night and day" when it came down to the level of success of criminal activity. Gladwell saw crime as a contagion process, recognized the existence of a threshold, and understood and appreciated the significance of crossing such a threshold. The insights that he gained from understanding models of contagion led him to the writing of several books. It is precisely within the classical contagion framework introduced by Kermack and McKendrick that the exploration of the impact of nosocomial infections in the presence of the selective pressures resistance generated by antimicrobials that evaluation of policies that manage disease levels, while limiting the spread of resistance disease strains, have been studied [7, 37].

Kermack and MacKendrick were indeed well aware of the ideas popularized by Gladwell. In fact, both had gone further by establishing mathematical results for infectious diseases in 1927. Contagion/contact models are now routinely used in the study of population-level questions in evolutionary biology or public health. The direct use of the Kermack-McKendrick 1927 model or its modifications, in the study of the dynamics of antibiotic resistance at the population level is therefore natural. The simplicity of the Kermack-McKendrick Susceptible-Infected-Recovered or SIR model has increased its popularity and helped establish the field of mathematical epidemiology [1, 2]. The following short synopsis using the transfer diagram in Figure 4 will highlight the essence of the contagion modeling approach. A population has been divided into three categories: susceptible or S, infected or I (assumed infectious) and recovered or R (assumed immune); there are no births or deaths. That is, we have selected a specific (short) temporal scale to study the dynamics of contagion in order to highlight the contagion modeling approach in as simple a setting as possible. It is assumed that all individuals are identical and that the population is large so that the use of differential equations is acceptable. It is further assumed that deaths from the disease under consideration are negligible and that there are no births. Hence, the population is constant and therefore it can be (and has been) normalized to one. It is assumed that infections arise from
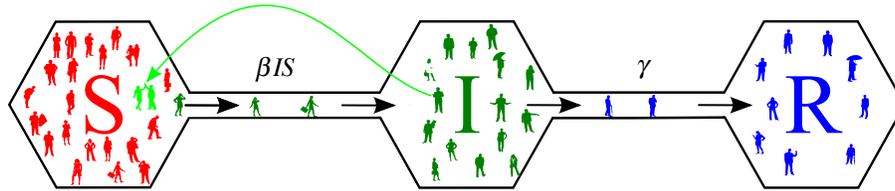
Figure 4. A phenomenological flow diagram for the transmission of a disease with susceptible, infectious, and recovered/immune stages.

interactions between susceptible and infective individuals (modeled via the mass action law) and that recovered individuals cannot get this disease again. Several things can be deduced from this particular model: if the assumptions outlined above are satisfied, then 1) for an outbreak to occur an infectious individual must be introduced (within a purely susceptible population); 2) over his/her infectious period $\frac{1}{\gamma}$, individuals that recover gain permanent immunity (moving to R), and 3) the "infection success rate" is actually β, and when it is applied over the window of opportunity $\frac{1}{\gamma}$, one can obtain the quantity known as the basic reproduction ratio $R_0 = \frac{\beta}{\gamma}$. An outbreak is possible if $R_0 > 1$ and the disease eventually collapses if $R_0 < 1$.

It is in variants of the above setting (variants that include births and deaths and disease-induced mortality) that the issues of the persistence, evolution and the expansion of resistance to antimicrobials are being studied under the shadow of the fact that the number of drugs is limited since no new ones have been brought to the market for nearly three decades [2, 7, 37]. The need for identifying ways of reducing the prevalence of resistant strains while maintaing our antimicrobial supply viable are obvious in light of the words stated by the British Chief Medical Officer Dame Sally Davies and a year earlier by the Director General of the World Health Organization, Dr. Margaret Chan on the pressing criticality of managing resistance. In fact, the head of the WHO, while addressing a meeting of infectious disease experts in Copenhagen, noted that we are facing a global crisis in antibiotics, the result of "rapidly evolving resistance among microbes responsible for common infections that threaten to turn them into untreatable diseases ... every antibiotic ever developed was at risk of becoming useless. 'A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill ... Antimicrobial resistance is on the rise in Europe, and elsewhere in the world. We are losing our first-line antimicrobials.' " [34].

Trying to identify implementable ways of slowing down the evolution of resistance or finding ways of

limiting the most powerful outcomes of tight coevolutionary interactions, like evolutionary suicide, are central to war on diseases like cancer, or tuberculosis, or nosocomial infections. Maintaining, for example, a sustainable pool of antimicrobials available for treating infections over long-time scales or identifying drug protocols that allow us to live with low-levels of cancer are but some of the topics that emerge in the study of models that address the importance of maintaining heterogeneity as a critical foundation for the development of policies.

Further, complications arise because in the study of sustainability one must account for processes that interact over multiple temporal and spatial scales as well as several levels of organization. Each particular system requires us to consider different units of selection, since as Lewontin has observed, [36], "As seen by present-day evolutionists, Darwin's scheme embodies three principles ... : 1. Different individuals in a population have different morphologies, physiologies, and behaviors (phenotypic variation). 2. Different phenotypes have different rates of survival and reproduction in different environments (differential fitness). 3. There is a correlation between parents and offspring in the contribution of each to future generations (fitness is heritable)...The generality of the principles of natural selection means that any entities in nature that have variation, reproduction, and heritability may evolve. For example, if we replace the term individual with the term population and then Principles 1, 2, and 3 describe a process by which one population may increase its proportional representation in the species relative to other populations. Similar reinterpretations of these principles could be made for species rather than populations and even communities rather than species." Consequently, what may be beneficial to an individual may be detrimental at a higher level of organization. This can become of utmost importance when a population as a whole is forced to respond to environmental shifts, which in turn may result in response as a unified group, or create a divide within the population [41]. Furthermore, when it comes down to human behavior, our ability to adapt is often linked to personal interests [15, 40]. These personal interests may at times conflict with and occur on a discordant temporal scale with the "public" goals. The presence of diverse and changing classes of individual behaviors present unique challenges to our ability to build policies capable of managing heterogeneity in the absence of well-formulated and implemented incentives and rewards within frameworks that adapt to changing (multi-level) landscapes. The implementation of cancer therapies that keep chemotherapies viable or policies that increase the life-span of antimicrobials must at the end not only account for the tinkering role of evolution but also for the complexities of human behavior.

Acknowledgments

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