The model considered here makes a clear distinction between the primary locus and the evolvability modifier loci. In real organisms however, as well as in the most interesting artificial life systems, genes have emergent functions that are not pre-labeled as 'primary' or 'modifier' loci. Similarly, the phenotypes are not pre-labeled as 'good' or 'bad', but their effects on the short or long term survival of their carriers are emergent properties. These survival properties may not be inferable from a reductionist description of them. Hence, real organisms and artificial life systems may exhibit evolutionary pathologies as emergent phenomena that can only be observed retrospectively.

The suppression of evolvability for evolutionary pathologies becomes a possibility in evolutionary systems that contain structured populations. These abound in biological systems, and have been investigated in artificial life as well (D'haeseleer and Bluming (1994), Ray (1995)).

Because of the complexity of organismal phenotypes, the effect of one trait on another trait's evolvability may not be obvious, or even in principle predictable. Therefore, evolutionary pathologies may be suppressed in structured populations and yet not be known. If Nature, or the experimenter, changes the population structure from multiple demes to a single interacting population, the suppression of evolutionary pathologies may become known by its breakdown: genetic variability for pathological traits that had been suppressed under a structured population could be expected to emerge in a newly panmictic population. In biological and artificial life systems where phenotypes and evolutionary dynamics are emergent, the best methodology to explore the suppression of the evolvability of evolutionary pathologies may be through experimental alterations in population structure.

In conclusion, the model examined here demonstrates another circumstance in which evolvability can evolve (Altenberg (1995)). In the present case, evolvability evolves to be suppressed when the trait confers short term individual advantage and long term population disadvantage. The net effect is that evolution increases survival. But what evolves here is not an organismal phenotype, but the genome's propensity to generates variants.

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At generation 0, the plot of the population lies on the X-axis, i.e. there are an average of zero CHECKPOINT+ alleles per individual. Under mutation pressure alone, the population would equilibrate to the dotted line at $0.0625 = 1/16 = 8$ loci / 128 alleles per locus. After 100 generations of extinction and recolonization dynamics, however, almost all demes have an average of one CHECKPOINT+ allele per individual. By generation 200, most demes average two CHECKPOINT+ alleles per individual, with a few demes having more or fewer. As the generations continue, demes averaging just under 3 CHECKPOINT+ alleles increase to around half of the total number. A fraction of the demes average as many as 4 CHECKPOINT+ alleles per individual. The consequence of having multiple CHECKPOINT+ loci is that there is little likelihood that a deme will generate an individual with the pathological trait. Hence, the evolvability of the pathological trait has been suppressed.

It is notable that the distributions are concentrated around integral numbers of CHECKPOINT+ alleles. This occurs because each deme is recolonized by a single individual with a discrete number of CHECKPOINT+ alleles. As mutations accumulate, the distribution shifts downward toward the equilibrium line at 0.0625. Once a deme is recolonized, it 'ages' with the mutational loss of CHECKPOINT+ alleles. There is no dynamic to increase the number of CHECKPOINT+ alleles above the mutational equilibrium frequency of 0.0625 in an existing deme. As demes age and more individuals lose their CHECKPOINT+ alleles, the chance of generating the pathological trait increases and, along with that, deme extinction. Hence, deme extinctions are drawn predominantly from older demes, while deme recolonizations are a uniform sample of individuals in the deme neighborhood. The difference in the distributions of extinctions and recolonizations leads to the increase in the number of CHECKPOINT+ alleles per individual over the metapopulation.

Discussion

It might be argued that the 'checkpoint' genes modeled here (Figure 1) are not really evolvability modifiers, but are simply genes that epistatically interact with the primary locus to control the pathology phenotype. Indeed, the only distinction between the primary locus and the modifier loci is in the asymmetry between the number of alleles that allow the pathological trait to be expressed: in the primary locus, 1 out of 4 alleles allow the pathological trait; in the modifier loci, it is 127 out of 128 alleles. Loss of the pathological trait is the same whether due to a mutation at the primary locus, or a mutation at one modifier locus to CHECKPOINT+.

Thus, one might argue that the results seen here do not constitute an evolution of evolvability, but are simply metapopulation selection against the pathological trait itself, as seen in Kirchner and Roy (1999). This hypothesis, however, would explain the evolution of at most one CHECKPOINT+ locus. The evolution of additional CHECKPOINT+ loci has no effect on the phenotype, but rather, affects only the rate at which pathological variants arise by mutation—i.e. the evolvability of the pathological trait (Altenberg (1995)). We observe in the simulation that the metapopulation evolves to where most demes average from 2 up to 4 CHECKPOINT+ loci per individual. Thus, the strong mutation pressure toward CHECKPOINT- alleles is overcome by the metapopulation dynamics. The primary consequence is that evolvability of the evolutionary pathology is suppressed, and the rate of deme extinction is reduced because of evolution at the modifier loci.

The dynamics of this model is closely related to that of neutral network models of canalization. The concept of canalization was proposed by Schmalhausen (1949) and Waddington (1942). Canalization is defined as the accumulation of mutations that stabilize a phenotype against either genetic or environmental perturbations. The CHECKPOINT+ loci stabilize the non-pathological trait against mutations.

The usual condition that promotes canalization is stabilizing selection, when departures from the phenotype are deleterious (canalization thus lowers the mutational load). In the case of evolutionary pathologies, however, instead of stabilizing selection against the pathology phenotype, there is directional selection in favor of it. Only the presence of metapopulation dynamics prevents the immediately advantageous pathology phenotype from fixing in the population. Nevertheless, the metapopulation dynamics has the same long term effect as stabilizing selection would were it acting against the pathological trait.

Since all the different genotypes containing CHECKPOINT+ alleles have equal fitness, they comprise a neutral network (Fontana *et al.* (1993)). The population is forced by metapopulation dynamics to remain on this neutral network, since as soon as a genotype mutates off of the network to the pathology phenotype, its deme goes extinct. As in the case of stabilizing selection studied by van Nimwegen *et al.* (1999), evolution on the neutral network moves the population away from genotypes that are mutationally close to the deleterious phenotype. The mutational distance from the pathology phenotype grows with the number of CHECKPOINT+ loci.

A crucial element of the model that is necessary for CHECKPOINT+ loci to evolve is that demes be recolonized through extreme population bottlenecks. If recolonized demes were simple copies of a neighboring deme in their genotypes distribution, there would be no way to reverse the mutational pressure towards lower values of CHECKPOINT+ loci. Very strong genetic drift is required to produce occasionally higher numbers of CHECKPOINT+ loci, and the model here maximizes the force of drift by recolonizing with a single individual. Clearly, the magnitude of drift effects will be decreased by propagules with larger numbers of individuals, producing fewer demes with extreme numbers of CHECKPOINT+ loci. Consequently, large propagules will hinder the evolution of CHECKPOINT+ loci.

It is notable that multicellular organisms almost universally start as single individual cells. Michod and Roze (1999) point out that this prevents the spread of mutants that defect from multicellular cooperation. When the multicellular organism is taken as the deme, and its death as the extinction of the deme, then the dynamics can be seen to be homologous.

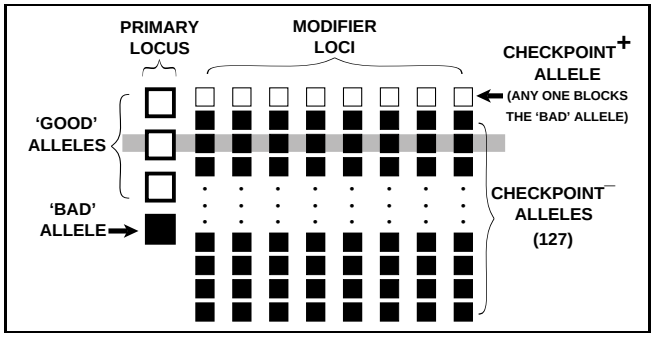

Figure 1: The evolvability checkpoint model.

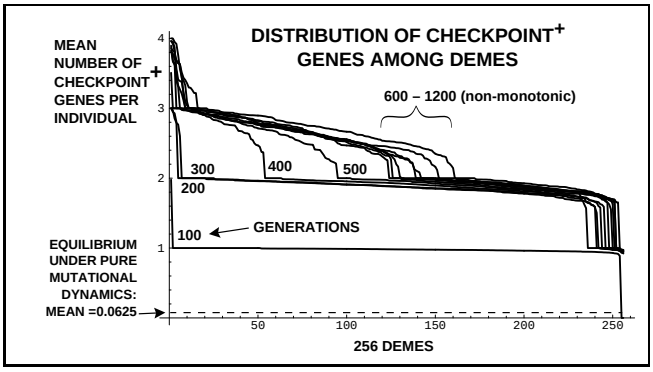

Figure 2: Evolution of evolvability suppression. The mean number of CHECKPOINT+ alleles per individual in each deme is calculated, and the demes sorted by this value along the X-axis, and the value plotted.

pathologies. Such a mechanism would be an example of selection on evolvability (Altenberg (1995))—in this case, selection against evolvability. Suppose that the organism could be mutated so that it could no longer generate the pathological traits. Would such variation in the evolvability of the pathology come to predominate in the population?

The Model

To investigate whether the evolvability of evolutionary pathologies can evolve, I construct the following model. There exists a primary locus, which has one allele (out of a total of 4) that produces the pathological trait. In addition, there exists a set of modifier loci which each have one allele that blocks the expression of the pathological trait, and 127 other 'permissive' alleles that do not. I will call them 'CHECKPOINT+' and 'CHECKPOINT−' alleles, respectively, because of their analogy to the 'checkpoint' genes in metazoan organisms that protect cells against evolution into cancer cells (Nojima (1997)). I have chosen these allele numbers so that mutation pressure alone produces the CHECKPOINT− genotype at the modifier loci, and the non-pathological genotype at the primary locus.

The genetic structure is illustrated in Figure 1. All genotypes are selectively neutral except the one that expresses the pathological trait, which has a selective advantage within the deme. The population structure consists of a 16 by 16 array of demes (with periodic boundaries).

• 1 primary locus, 8 modifier loci • 128 alleles per modifier locus: 1 CHECKPOINT+, 127 CHECKPOINT− • 4 alleles at the primary locus: 1 BAD, 3 GOOD • 0.01 mutation rate per replication per locus • 16 X 16 demes in the metapopulation • 2000 individuals per deme • Initial population: all individuals have the 'GOOD' primary gene and are all CHECKPOINT−

Table 1: Parameters of the model.

The demes are filled initially with genotypes that have a non-pathology allele at the primary locus, and permissive CHECKPOINT− alleles at the modifier loci. Other parameters of the model are given in Table 1.

The population reproduces in discrete generations. Organisms are asexual. The Wright-Fisher model of multinomial sampling is used for reproduction: 2000 offspring for each deme are sampled i.i.d. (independently, identically distributed) from the offspring genotype distribution of the parent population of the deme. The offspring genotype distribution is generated under the assumptions that:

- mutation rates are equal for all loci;
- mutation rates are symmetric between all alleles; and
- each locus mutates independently of the others.

These 2000 offspring replace the 2000 parents in the deme.

The deme size remains constant unless the pathological trait appears. I assume that that the pathological trait grows in frequency within the deme fast enough to be considered instantaneous relative to the other time scales in the model. Therefore, as soon as the pathological trait appears in a deme, the deme goes extinct, and is recolonized by a single individual from a neighboring deme.

This model is designed to be as simple as possible, yet demonstrate the evolution of evolvability in the case of evolutionary pathologies. Clearly there are several avenues in which greater biological realism could be captured, with accompanying increases in the number of free parameters and dynamical variables. These elaborations include intra-deme dynamics of the pathological trait, specific ecological bases for the pathology, variation in the size of propagules during recolonization, sexual reproduction, recombination, and migration. Also, the model could be extended to include modifier variation that is not neutral. These elaborations are deferred to treatments more extensive than the present work.

Results

The trajectory of a typical run of this model is shown in Figure 2.

Evolvability Checkpoints Against Evolutionary Pathologies

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Abstract

The opportunistic character of adaptation through natural selection can lead to 'evolutionary pathologies'—situations in which traits evolve that promote the extinction of the population. Such pathologies include imprudent predation and other forms of habitat over-exploitation or the 'tragedy of the commons', adaptation to temporally unreliable resources, cheating and other antisocial behavior, infectious pathogen carrier states, parthenogenesis, and cancer, an intra-organismal evolutionary pathology. A condition that can prevent the evolution of evolutionary pathologies is population fragmentation, with local extinctions and recolonizations—i.e. metapopulation dynamics. Can metapopulation dynamics suppress not only the occurrence of the pathological trait, but its rate of generation by mutation, i.e. its evolvability? A model is constructed in which one locus controls the expression of the pathological trait, and a series of modifier loci exist which can prevent the expression of this trait. It is found that multiple 'evolvability checkpoint' genes can evolve to prevent the generation of variants that cause evolutionary pathologies. The consequences of this finding are discussed.

Introduction

Adaptation through natural selection is an opportunistic process in that it is driven by the selective forces of the immediate moment. The long term consequences of a particular response to selection are not influential in this response. In the field of heuristic search, this would be known as a 'myopic' or 'greedy' algorithm, and it is well known that such algorithms can lead to outcomes that are suboptimal in the long run. In biological evolution, the myopia of natural selection makes it possible for traits to evolve that nevertheless systematically bring about their own long run extinction, and the extinction of the population that carries them (Wright (1959)). When the process of 'survival of the fittest' instead results in extinction, I wish to call such a paradoxical outcome an 'evolutionary pathology'.

The common property of evolutionary pathologies is that the trait under consideration gives its carriers a viability or reproductive advantage, and genetic variation for the trait tends to increase in frequency in the population; yet, once it becomes common, the trait has ecological properties that increase the rate of extinction of the population. Examples of evolutionary pathologies include:

- cancer (the organism being the population) (Stoler *et al.* (1999)).
- imprudent predation and other forms of habitat over-exploitation, the 'tragedy of the commons',
- adaptation to temporally unreliable resources,
- cheating and other antisocial behavior,
- infectious pathogen carrier states (Kirchner and Roy (1999)),
- parthenogenesis (Griffiths and Butlin (1995)),
- meiotic drive (Lewontin (1962)).

Many of these 'evolutionary pathologies' are just the flip side of phenomena that classically were paradoxes for simple Darwinian dynamics—altruism, prudent predation, sex—i.e. traits which decrease the fitness of their carriers, but which provide long term survival advantages for populations that carry them. The mechanistic answer found to these paradoxes is some form of structuring of the population, including group selection, kin selection, and structured demes (Wilson (1997)).

The same answer—population structure, and in particular metapopulation dynamics (Levins (1968; 1970)), where frequent local extinction and recolonization of demes occurs—comprises a mechanism that prevents evolutionary pathologies (McCauley (1993)). One example of an evolutionary pathology was considered by Kirchner and Roy (1999), based on the observation that longer life spans can increase the parasite burden of a species. The situation modeled by Kirchner and Roy (1999) is one in which longer life spans increase reproductive output, but also increase the parasite burden in a population, and consequently decrease the population's survival. They find that in a fragmented population, metapopulation dynamics can prevent the evolution of longer life spans, reduce the parasite burden, and improve the population viability.

The existing theoretical solutions to the problem of evolutionary pathologies all take a classical approach: conditions are found that prevent the persistence of genetic variation for the pathology when it is introduced into a population. But suppose that evolution could find a way to prevent the generation of the pathological traits in the first place. This would provide another mechanism to prevent evolutionary