Speciation by Self-organizing Barriers to Gene Flow in Simulated Populations with Localized Mating

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ABSTRACT
Speciation caused by intrinsically forming barriers to gene flow is demonstrated using simulated populations. Although theory predicts that underdominance would be quickly eliminated from randomly mating populations, herein it is shown that when mating interactions are localized, mild underdominance can persist for long periods, as interbreeding populations self-organize into patches of compatible types separated by viable hybrid zones. Under certain types of even mild epistasis, hybrid zones will coalesce to create intrinsic barriers to gene flow between subgroups, resulting in speciation. Since underdominance, epistasis, and spatially localized mating/dispersal have all been observed in natural populations, the proposed mechanism is feasible and parsimonious. This model of speciation does not require any pre-mating isolation mechanisms, such as geographic isolation or assortative mating interactions due to niche differentiation or sexual selection. However, the presence of these would enhance the effects and reduce the time to speciation. It is probable that in natural systems, many mechanisms are operating simultaneously to cause speciation.

Categories and Subject Descriptors
J.3 Computer Applications [**Life and Medical Sciences**]: *Biology and genetics.*

General Terms
Experimentation, Theory.

Keywords
Speciation; self-organizing; evolutionary genetics; cellular automata; spatially-explicit model.

1. INTRODUCTION
Charles Darwin referred to speciation as the "mystery of mysteries" [6] and nearly 150 years later the mechanisms involved in speciation remain an important topic of debate in evolutionary biology. Various theoretical models of speciation have been proposed (for recent reviews of this topic, see [4],[5],[23],[13],[14],[9]). These models typically assume divergent evolution leading to speciation, subsequent to some form of pre-mating reproductive isolating mechanism. For example, disruptive natural selection toward use of different parts of the available resource spectrum [22],[11] could alter the timing and/or location of mating events, resulting in two or more effectively reproductively isolated subpopulations that then continue to diverge, despite continuing to share the same geographic range. Similarly, assortative mating (due to sexual selection, e.g., where like prefers to mate with like) has also been proposed as a pre-mating isolating mechanism [26],[16]. Several models employ a combination of these factors [41],[33],[34],[25],[7]. Chromosomal rearrangements, such as inversions, have been proposed as a mechanism that doesn't depend on pre-mating isolation in both plants [35] and animals [44]. This could permit rapid divergent evolution in genes linked to the rearrangements, despite continued interbreeding, ultimately resulting in speciation. Evidence suggests that this may have been an important mechanism in primate speciation [31].

Following Mayr's biological species concept [28], we define a species to be a group of actually or potentially interbreeding organisms that are reproductively isolated from other such groups. Thus, two groups are considered different species if hybrids are inviable. Although simple underdominance (where fitness of the heterozygote is lower than that of either homozygote, at a given locus) provides a logical mechanism for reproductive isolation that could lead to speciation, such models have been discounted because there is no evolutionarily reasonable mechanism by which two incompatible alleles could be maintained at a single locus in a panmictic population [8],[30],[38]. Bateson [1], Dobzhansky [8] and Muller [30] proposed an allopatric and epistatic solution to this problem. In their model, incompatibilities arise after a single ancestral population becomes geographically separated into two populations (each panmictic), and involves a minimum of two loci that are individually neutral or advantageous, but together interact negatively (epistatic underdominance). Relaxing the assumption of panmixia provides another possible explanation. Populations containing a strongly underdominant locus (where the heterozygote dies or is sterile) will self-organize into patches, when mating interactions are spatially localized [36],[37]. This suggests that sympatric speciation could occur if an

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environmental change causes a formerly neutral locus to become strongly underdominant, resulting in self-organization into patches separated by sterile hybrid zones [36]. Similarly, Kondrashov [24] considered the case where nearly simultaneous mutations cause Bateson-Dobzhansky-Muller (BDM) incompatibilities to arise in different parts of a single population with localized interactions. He used a deterministic model to show that locally beneficial mutations will spread like a wave through the population. If the heterozygote between the mutant alleles has reduced fitness, then a hybrid zone of reduced gene flow will occur where the waves collide, effectively separating the population into two parapatric subpopulations. Kondrashov [24] surmised, but did not demonstrate, that further BDM incompatibilities arising in one of the subpopulations would spread rapidly until the propagation wave collides with the boundary, further reducing the viability of the hybrid zone and could result in speciation through the accumulation of multiple incompatibilities at the boundary between the subpopulations.

In this manuscript, computer simulations are used to demonstrate that, when mating is localized (referred to as *juxtamixia*), interbreeding populations with standing genetic variation comprising multiple weak (nearly neutral) incompatibilities can self-organize into reproductively isolated species, even when average effects in the initial population are identical for each allele and each locus.

2. METHODS

Populations of diploid individuals were modeled using two-dimensional stochastic cellular automata, wherein each lattice cell could be occupied by at most one individual at any discrete time step. Genotypes of individuals comprised $L \in \{2,4,6,8,10\}$ bi-allelic loci. The two possible alleles per locus are denoted by upper and lower case letters (e.g., *A* and *a*). Case does not imply dominance, but affects epistatic interactions, as described below. Since there are 3 possible genotypes per bi-allelic locus (e.g., *AA*, *Aa*, or *aa*), there are a total of 3^L possible distinct diploid genotypes. The normalized fitness f of each individual i was assessed as follows:

$$f_i = \frac{1 - U_i + E_i}{1 + E_{\max}} \qquad (2.1)$$

where a perfect fitness of 1 is reduced by an underdominance penalty U and increased by an epistatic bonus E, and then renormalized so that the maximum possible fitness is 1. The underdominance penalty U is computed as the proportion of loci that are heterozygous. Thus, the more loci in the genotype, the milder the underdominance; only genotypes heterozygous at all loci (e.g., *AaBbCc*) were inviable. The epistatic bonus E is computed as the product of an epistatic coefficient ε and the maximum of the number of homozygous loci with either upper case or lower case, such that only the two most genetically distinct homozygous genotypes (e.g., *AABBCC* and *aabbcc*) experience equal and maximal fitness. This simple fitness function was employed because it allows easy control of both the degree of underdominance (by changing the number of loci) and the degree of epistasis (by changing ε) being modeled, while still maintaining identical average effects for each locus and each allele. Example resulting fitness tables for a two locus genotype with $\varepsilon = 0$ and $\varepsilon = 0.1$ are shown in Fig. 1a,b, respectively. It

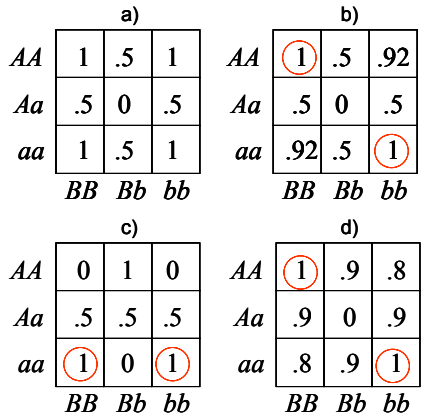

Figure 1. Sample fitness tables for two-locus, two-allele per locus, genotypes. a) Underdominance with no epistasis (Eq. 2.1 with $\varepsilon = 0$), b) underdominance with epistasis (Eq. 2.1 with $\varepsilon = 0.1$), c) additive by dominance epistasis (as proposed in [15], and d) within-locus additivity and between-locus epistatic underdominance (BDM incompatibility). Final reproductively isolated stable attractor states are circled.

should be noted, however, that the general conclusions reached herein are not limited to the particular fitness function described by Equation (2.1). Other forms of within locus interactions in the population genome will also result in self-organized speciation, if some form of epistatic underdominance exists. For example, in Figs. 1b,c,d, circled genotypes represent stable attractor states, to which a juxtamictic population will self-organize, resulting in two reproductively isolated species.

Evolution was simulated in non-overlapping generations. At each generation, each cell was repopulated by the offspring of two parents, stochastically selected using fitness proportionate selection from the parent population in the mating neighborhood centered on the cell. That is, the probability P_i of selecting parent i, from this neighborhood, was computed as:

$$P_i = \frac{f_i}{\sum_{i=1}^{n} f_i} \qquad (2.2)$$

where n is the number of individuals in the mating neighborhood. Selfing was not permitted. Here, we report on random mating neighborhoods comprising (a) the entire population (panmixia) and, (b) overlapping spatially-localized neighborhoods of contiguous cells centered on each cell in question (juxtamixia). Unless otherwise indicated, the size of the juxtamictic neighborhoods was 9 cells (3×3), for the results presented here. For each pair of selected parents, a single offspring was produced to occupy the cell in the next generation. Loci were unlinked, so parents donated alleles to their offspring via independent assortment (uniform recombination). If the offspring of selected parents was inviable ($f_i = 0$), then the cell was treated as empty for the subsequent generation.

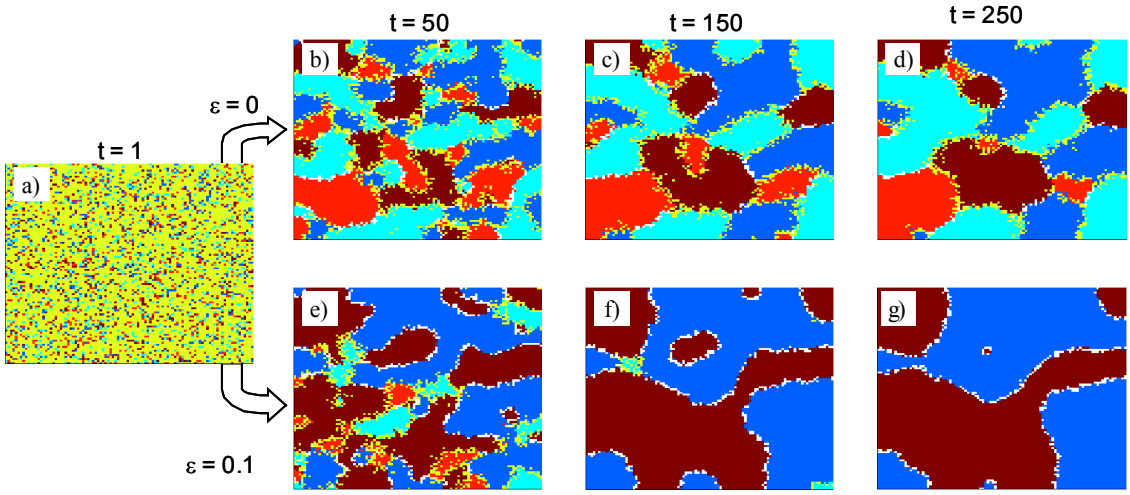

Figure 2. a) A representative two-locus, two-allele per locus, diploid population was initialized in Hardy Weinberg equilibrium. b-d) With no epistasis (per fitness table in Fig. 1a), the population self-organizes into clusters of the four possible homozygotes (indicated by color) separated by hybrid zones, most of which are permeable, so no speciation occurs. e-g) With epistasis (per fitness table in Fig. 1b), the boundaries coalesce into impermeable hybrid zones, leaving reproductively isolated populations (i.e., species) of the two most fit homozygotes (*AABB* and *aabb*). The variable *t* refers to the number of generations.

The model was implemented in Matlab (The Mathworks, Natick, MA). Reported experiments were conducted on a 100×100 cell lattice with non-periodic boundary conditions. For all runs, the population was randomly initialized in multi-locus Hardy-Weinberg equilibrium (with all alleles having initially equal frequencies and spatially uncorrelated random uniform distribution across the spatial domain), to preclude the introduction of initial bias in average effects or spatial organization. Experiments consisted of 10 random replications from each of 10 random starting domains. Prior experimentation showed that lattice size (at least for lattices of 100×100 or larger), boundary conditions (non-periodic, periodic), and crossover strategy (uniform, single point) did not qualitatively affect the results.

3. EXPERIMENTAL RESULTS

3.1 Emergence of self-organizing barriers to gene flow

Starting from a single population with standing genetic variation, repeatable emergence of self-organizing barriers to gene flow was observed in simulated populations of diploid digital organisms with spatially localized mating, resulting in speciation. With mild epistasis and juxtamixia, speciation into two reproductively isolated subpopulations consistently emerged. For simplicity, this is illustrated for the two-locus case with fairly strong underdominance in Section 3.1.1, but is extended to a more evolutionarily feasible model of *L*-loci with mild underdominance in Section 3.1.2.

3.1.1 Two loci

Populations of individuals with two loci, A and B, with the possible alleles *A, a, B, b,* were initialized in Hardy Weinberg equilibrium for the nine possible genotypes (Fig. 2a). Without epistasis (with fitness as in Fig. 1a), the population self-organizes into a patchy structure of the four possible homozygotes and coarsens over time (Fig. 2b,c,d). In this case, speciation does not occur since gene flow remains possible between all four homozygotes (Fig. 1a). In contrast, with directional epistasis present (with fitness as in Fig. 1b), the population self-organizes into reproductively isolated clusters of the two fittest genotypes (Fig. 2e,f,g), despite the absence of any environmental heterogeneity, externally imposed barriers to gene flow, or assortative mate preference. It should be noted that, if allowed to run indefinitely, stochastic events in these finite and homogeneous simulated spatial domains will ultimately favor one or the other species.

The effect of the degree of hybrid underdominance on gene flow of a neutral allele, between clusters of wholly or partially compatible subpopulations, is illustrated in Fig. 3. In these experiments, the left and right halves of a 4 cell wide domain were initially populated with two equally fit homozygous subpopulations, where the heterozygotes were less fit. The population was then allowed to evolve for two generations, and gene flow was assessed as the percentage of neutral alleles, at a separate locus, that were able to cross from one subpopulation into the other. Using linear fitness proportionate parent selection, the amount of gene flow across the hybrid zone is linearly proportional (R^2=0.87) to fitness of the heterozygote, for heterozygote fitness greater than zero (Fig. 3). However, there is a discontinuity when the hybrids become inviable, and gene flow

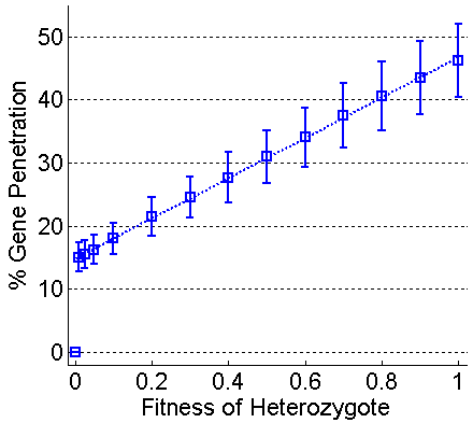

Figure 3. Permeability of hybrid zones as a function of the fitness of the heterozygote (see text for details). The relationship is linear for non-zero heterozygote fitness (R^2=0.87) but there is an abrupt discontinuity when the heterozygote fitness drops to zero and gene flow ceases. Each data point represents the mean of 100 trials (10 random runs from each of 10 random initial conditions), with vertical bars representing standard deviations.

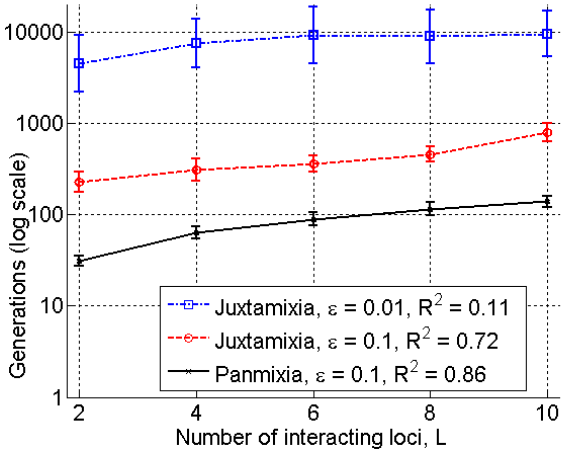

Figure 4. The number of generations until either speciation (with juxtamixia, shown for two levels of epistasis, ε = 0.01 and ε=0.1) or fixation of a single genotype (with panmixia, shown for ε=0.1). Each data point represents the mean of 100 trials (10 random runs from each of 10 random initial conditions), with vertical bars representing standard deviations.

abruptly ceases (Fig. 3). Thus, in this model, gene flow between clusters of like genotypes persists unless the hybrids forming at cluster boundaries are completely inviable. In the results here, speciation is defined as occurring when the population has converged on two genotypes that are reproductively isolated (zero gene flow between them).

These results are consistent with the symmetry breaking and pattern formation shown by disruptive selection in simulated two-locus haploid populations [36],[37], which are essentially equivalent to single-locus diploid populations with inviable hybrids. The primary argument against such models of speciation is that strong underdominance could not persist long enough in a population to result in a speciation event [8][30][38]. One counter argument is that neutral mutations could become fixed in a population, but then environmental change renders them underdominant, with subsequent disruptive selection [36]. Another counter argument is that epistatic interactions between loci could cause an allele to experience overdominance in certain combinations and underdominance in others. For example, consider the fitness table for two loci shown in Fig. 1c. A population with only *A*, *B*, and *b* alleles, will experience stabilizing selection, since the hybrid *AABb* genotype is the most fit. As long as randomly interbreeding populations remain in Hardy-Weinberg equilibrium, introduction of an *a* allele will be selectively neutral. However, any deviation away from a frequency of 0.5 at the B locus will result in directional selection towards *aaBB* or *aabb*, as originally proposed by Goodnight [15], because the marginal effects due to the B locus alone will then favor whichever is most prevalent of either *B* or *b*. The relatively small mating neighborhoods in a juxtamictic population thus result in likely establishment of both *aaBB* and *aabb* in different parts of the population, causing disruptive selection and subsequent self-organizing reproductive isolation (speciation) of these two genotypes. In the following section it is shown that nearly neutral (with only mild underdominance and epistasis) alleles at multiple loci can similarly interact to result in speciation.

3.1.2 Extension to multiple loci

Experiments were performed with between 2 and 10 epistatically interacting loci, where the only inviable genotype was heterozygous at all *L* loci. With nearest neighbor juxtamixia, speciation was always observed for all positive values of epistasis tested, (e.g., Fig. 4, top two lines). As the number of loci increases and/or epistasis decreases, the fitness valleys of heterozygotes at each locus become less pronounced, allowing increasingly easy traversal of fitness valleys and enabling underdominance to persist longer in the population. For example, with mild epistasis (ε = 0.1), the number of generations to speciation events increased exponentially (R^2 = 0.72) with the number of interacting loci *L* (Fig. 4, middle line). Decreasing the epistasis coefficient by an order of magnitude (to ε = 0.01) increased the mean of the log of time to speciation by an order of magnitude ($p < 0.0001$, ANOVA) but also increased the variance ($p < 0.0001$, O'Brien's test), with a corresponding drop in correlation (R^2 = 0.11, Fig. 4, top line).

The results of these experiments demonstrate that, with localized mating and mild underdominance, clusters of like genotypes spontaneously form. With even a small amount of disruptive epistasis (where the most fit genotypes are genetically incompatible with each other), leaky genetic boundaries between these clusters tend to coalesce over time to form impermeable genetic barriers to gene flow, even when individual traits are

nearly neutral. Thus, speciation can occur as an emergent property from standing genetic variation in locally interbreeding populations.

There is no question that natural populations do maintain a great deal of genetic variation, and both underdominance [10],[43],[12] and epistasis [40],[1] are commonly observed. Indeed, the etiology of many diseases has recently been shown to require epistatic interactions at several loci [29],[39], and epistatic underdominance of unlucky mates can result in hybrid sterility [32]. Thus, while the model employed herein is highly idealized, it nonetheless manifests properties observed in natural populations, while removing the confounding effects of differences in average effects of different alleles or different loci, heterogeneity in the environment, or pre-mating isolation of similar genotypes due to mate selection. How such genetic variations become established in the population is another issue. If individual traits are nearly neutral this could be possible due to random processes, or changes in the environment could alter genetic interactions in an existing genome. In panmictic populations, the likelihood of fixation of underdominant alleles decreases exponentially with the product of the population size and the degree of underdominance [14]. Exact quantification of the probability of fixation is difficult to generalize for a population with localized mating, since it depends on the size and shape of the local mating probability kernel (which may be spatially non-uniform), as well as on boundary conditions. However, when mating is localized, the effect of population size will be significantly mitigated, therefore increasing the likelihood of fixation of new mutants in local neighborhoods. Furthermore, within-locus underdominance such as employed in this study is not *necessary* for self-organizing speciation. For example, consider the simple two-locus fitness table shown in Fig. 1d, which contains BDM type incompatibilities. Directional selection makes it easy to introduce and fix both *a* and *B* alleles into a juxtamictic population initially containing only *A* and *b* alleles [24] (since $f(Aabb) > f(AAbb)$ and $f(AABb) > f(AAbb)$, where f is the fitness according to Fig. 1d) with subsequent speciation into reproductively isolated populations of *AABB* and *aabb*. This model is trivially extendible to multiple loci, where the epistatic underdominance could be mild or even absent (neutral) on a pair-wise basis. Thus, juxtamixia permits multiple BDM incompatibilities to arise and persist within spatially continuously interbreeding populations, with subsequent self-organization into reproductively isolated species. Empirical evidence suggests that epistasis may be an important factor leading to speciation [32] and some form of epistasis is a common assumption in theoretical models of speciation [8],[30],[25],[7]. Epistasis is not a strict theoretical requirement for speciation in juxtamictic populations that exhibit underdominant loci. Drift alone could result in adjacent clusters being reproductively isolated, especially if more than one genotypic combination were inviable. However, adding epistatic directionality and/or epistatic underdominance dramatically increases the probability that this occurs, making speciation events more likely.

3.2 Effects of size of mating neighborhood

In the previously described results, mating was spatially localized. This is a necessary condition for cluster formation and subsequent speciation in this model. When mating was panmictic, the population quickly converged on a single genotype in all trials, as predicted by mean-field approximations. For example, in a two-locus panmictic system without epistasis (fitness as in Fig. 1a), the population converged on one of the four double homozygotes with equal probability, within a maximum of 55 generations. With epistasis (fitness as in Fig. 1b), panmictic populations converged on one of the two optimal double homozygous genotypes (*AABB* or *aabb*) with equal probability, within a maximum of 51 generations. The number of generations to fixation of a single genotype grew exponentially (R^2=0.86) with increasing number of loci (Fig. 4, bottom line), however speciation was never observed in any run when mating was panmictic. Additional experiments on larger domains confirmed that the probability of speciation in this model (with positive epistasis) is determined by the ratio of juxtamictic neighborhood size to domain size, rather than absolute neighborhood or domain size. As the size of the mating neighborhood increases relative to the size of the domain (i.e., as juxtamixia approaches panmixia), the size of the initial clusters formed also increases, and thus the probability of speciation decreases and the probability of fixation of a single genotype increases.

Juxtamixia may be a better approximation of the spatial aspects of mating strategies in many real populations than is panmixia. For example, pollen dispersal in various plant communities is known to remain fairly localized [27]. In animal populations, the existence of genetic clines that are incompatible at adjacent extremes of so-called “ring species” [42],[17],[18],[19],[20] is also consistent with assumptions of both spatially localized breeding strategies and the evolution of hard barriers to gene flow within continuous but spatially structured populations.

As with other spatially explicit models of evolutionary dynamics, such as lattice structured individual based models [36],[37],[24] and meta-population models [21],[3] the results presented here underscore the importance of taking spatial aspects of interactions into account. While analytical mean field models are certainly more tractable and are easier to generalize from than simulation-based speciation models [13], it has been observed that they cannot capture essential evolutionary dynamics that emerge as a consequence of localized spatial interactions [36],[9]. This observation is further supported by the current work.

3.3 Causes of speciation

Numerous models of speciation have been proposed in the literature [8],[30],[44],[33],[34],[22],[26],[16],[7],[25],[11]. The model presented herein illustrates an additional mechanism by which speciation can occur (and under some circumstances may even be an expected outcome) in interbreeding populations, due to self-organizing barriers to gene flow caused by localized mating in a population with certain types of epistatic genetic variation. This speciation model does not require any external barriers to gene flow, such as environmental heterogeneity or pre-mating isolation due to mate preference, nor does it require differences in average effects of any given allele or locus. In natural populations, it is likely that many of these forces exist simultaneously and that both intrinsic and extrinsic barriers to gene flow interact synergistically resulting in speciation. For example, self-organizing barriers to gene flow will have a tendency to coalesce with even mild external (e.g., geographical) barriers to gene flow, as in [37], therefore enhancing the disruptive effects of both.

4. SUMMARY

Speciation was repeatedly demonstrated in spatially structured digital diploid populations evolving in homogeneous environments. The initial populations included standing multi-loci genetic variation exhibiting mild within-locus underdominance and between-locus epistasis. Such populations self-organize into patchy continua of self-similar genotypes with reduced gene flow between patches. The interesting result shown herein is that, although these boundaries are initially independent of each other, over time they become aligned. Thus, leaky genetic boundaries coalesce to form hard genetic boundaries, and speciation is an emergent property in this model, arising as the result of the genetic recombination events between individuals interacting locally without any geographic, niche-based, or mate preference pre-mating isolating mechanisms. The self-organizing process demonstrated herein is not limited to the particular fitness model employed (used for simplicity), but emerges from a variety of epistatic fitness models (such as those shown in Figs. 1c and 1d, illustrated for clarity with 2-locus epistasis).

When mating was panmictic, speciation did not occur. However, when mating was juxtamictic (occurring in localized overlapping neighborhoods), speciation was the expected outcome. There is ample evidence in many natural populations that mating interactions exhibit spatial structure. While the uniformly structured topology employed in this study is clearly a simplification of the spatial nature of biological interactions, these simulations underscore the sensitivity of evolutionary processes to spatial aspects of interactions and the limitations of mean field models in predicting outcomes.

All speciation events are unlikely to be attributable to the same mechanism, or even to one mechanism operating alone. Divergent selection and drift following pre-mating isolation, whether due to allopatry, niche differentiation, or mating preferences, are all possible contributors to genetic divergence within species. Chromosomal rearrangements provide one possible explanation for how genetic divergence can occur in the absence of pre-mating isolation. The model presented in this work, in which recombination of many nearly neutral alleles can lead to emergent intrinsic barriers to gene flow, offers another feasible and parsimonious mechanism for genetic divergence without pre-mating isolation. This model shows one way that emergent properties in complex biological communities can drive evolutionary change. It is probable that in natural systems, many of these mechanisms are operating simultaneously to cause speciation.

6. Acknowledgments

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