Selection-recombination-mutation dynamics: Gradient, limit cycle, and closed invariant curve

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In this paper, the replicator dynamics of the two-locus two-allele system under weak mutation and weak selection is investigated in a generation-wise nonoverlapping unstructured population of individuals mating at random. Our main finding is that the dynamics is gradient-like when the point mutations at the two loci are independent. This is in stark contrast to the case of one-locus–multi-allele where the existence gradient behavior is contingent on a specific relationship between the mutation rates. When the mutations are not independent in the two-locus–two-allele system, there is the possibility of nonconvergent outcomes, like asymptotically stable oscillations, through either the Hopf bifurcation or the Neimark-Sacker bifurcation depending on the strength of the weak selection. The results can be straightforwardly extended for multilocus–two-allele systems.

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I. INTRODUCTION

How a living being appears and behaves is inherently determined by the variety of genes located on the different loci of chromosomes. The entire genotype to phenotype map is very vast and complex, and it is further complicated by the environmental feedback effects. While the evolutionary dynamics, e.g., replicator dynamics [1–4], of simplified one-locus–many-allele systems exhibits quite rich dynamical behavior, the phenomenon of recombination during meiosis presents one with richer extension of the evolutionary dynamics in a population of sexually mating organisms. In the latter, the simplest nontrivial mathematical setup is that of a two-locus–two-allele (2L2A) system. While two different loci can determine two different phenotypic traits (e.g., seed color and seed color in the revolutionary dihybrid cross experiments of Mendel [5,6]), there are many examples where two loci control the same trait, and their interaction has a considerable effect on the phenotype. Some such examples that quickly comes to mind are comb types on the head of chickens [7], flower color in peas [8], wheat kernel color [9], blood groups in humans [10], age-related hearing loss resistance in the Japanese wild-derived inbred MSM/Ms mice [11], and eye color of humans [12].

Haldane [13] and Wright [14] were among the first to mathematically explore the evolutionary outcome when selection acts on more than one locus assumed statistically independent, i.e., a system is in linkage equilibrium. Later Lewontin and Kojima [15] worked on a general 2L2A model with both selection and recombination included and showed that strong epistasis together with linkage disequilibrium can lead to significantly different outcomes. Subsequently, many extensions [16–20] of the model were studied—starting from prediction and calculation of all possible fixed points and determination of stability condition for some special cases in a simplified fitness model to the occurrence of cyclic motion. For a continuous time model, Akin [21] and for a discrete time model, Hastings [22] and Hofbauer and Iooss [23], showed that periodic orbits can be a possible outcome when a system is in linkage disequilibrium; when the 2L2A model is in linkage equilibrium such complex behavior cannot occur and the system becomes gradient-like, as shown by Nagylaki [24]. Nagylaki also showed that for a multilocus system under weak selection—selection strength sufficiently smaller compared to recombination—linkage disequilibrium decays close to zero within a few generations and the dynamics of the entire multilocus system is governed by the dynamical outcomes of time-continuous multilocus system [25–27]. Very recently [28], Pontz and coworkers studied the 2L2A model in detail under weak selection limit and classified all possible equilibrium structure and phase portraits for different payoff structures.

Mutation is the most important and indispensable ingredient of the evolutionary processes. It is important to note that the relationship between mutations at different loci is often complex and can be influenced by a variety of factors. It is possible for a mutation at one locus to affect the mutation rate at another locus on the same chromosome [29,30] directly or indirectly. For example, a mutation in a gene that codes for a repair enzyme involved in maintaining the integrity of DNA could alter the mutation rate of other genes by affecting the efficiency of DNA repair [31]. Similarly, a mutation in a gene that regulates the transcription or translation of other genes can affect the rate of mutations in those genes. Mutation may not be always completely random: It can depend on environmental changes [32] and fitness [33], and organisms can have evolved mechanisms which can influence the timing or genomic location of mutation [34]. In view of the above, in this paper, we distinguish between the cases of mutations that occur randomly (independent of what mutations occur at the other loci) from the cases where mutations can be treated to

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have occurred independently and randomly at a locus. We call the latter independent mutations.

The effects of mutation was studied in a one-locus two-allele model for both overlapping and nonoverlapping generations, and the results are really interesting: Mutation can stop the extinction of cooperators by producing cyclic or chaotic outcomes and even can produce coexistence regions where both the cooperators and defectors can survive simultaneously [35–38]. Evolutionary dynamics were studied for the case of the 2L2A with mutation as well [39–45].

Another aspect of mutation is worth pointing out. The thought-provoking Fisher's fundamental theorem of natural selection [46–48] is famously known to allude to the conjecture that the average fitness of the population should always increase and ultimately settle down to a maximum value when natural selection is the only driving force. While it is in analogy with the second law of thermodynamics where the entropy of an isolated system never decreases, the conjecture is debatable owing to the practical impossibility of isolating an evolutionary system from environment as any modification of the environment includes the effects due to selection-driven changes in allele frequencies [49]. The situation is further complicated by the presence of mutation and recombination. Nevertheless, some special cases exist. For example, in the presence of both weak mutation and weak selection, it could be shown that the one-locus–many-allele model [50] becomes a gradient system when the mutation probabilities depends on the target gene only [51]; the potential function of this gradient system, which is a generalization of average fitness, is maximized in the course of evolution. Another example is that of the 2L2A model [28] in the presence of weak selection: the 2L2A model, even in the presence of an evolutionary force of recombination, turns out to be a gradient-like system.

In such contexts, the study of the 2L2A model in the presence of weak selection and weak mutation still, to the best of our knowledge, remains to be reported. Specifically, we are interested in whether the 2L2A model is always gradient-like or there is a specific condition on mutation for that to happen. Does the answer depend on whether the mutations at the two loci are independent? Furthermore, if and when the epistasis-induced dynamics in the 2L2A system is altered due to presence of mutation is also a question of interest because epistasis or interaction between different loci has important effects on dynamics, like occurrence of cyclic motion [22] and sustaining polymorphism [28].

Without further ado, we introduce the model in the next section (Sec. II), and then we present the gradient 2L2A system in Sec. III. Subsequently, we discuss the nongradient dynamics in Sec. III before concluding in Sec. IV.

II. THE 2L2A MODEL

We consider a generation-wise nonoverlapping, unstructured population of randomly mating diploid individuals. The population is assumed to evolve under the action of viability selection that acts on two diallelic, recombining loci. We, thus, have the standard two-locus–two-allele (2L2A) model with viability selection [16,28,52–57].

A. Dynamics of gamete frequencies

Let A_1 and A_2 be the alleles at locus A, and B_1 and B_2 be the alleles at locus B. Let G_1, G_2, G_3, and G_4 represent the four possible gametes, *viz.*, A_1B_1, A_1B_2, A_2B_1, and A_2B_2, respectively. Let the frequency of the G_i gametes be x_i (obviously, $\sum_{i=1}^{4} x_i = 1$). In these notations, the frequencies of allele A_1 and B_1 are, respectively, $x_1 + x_2$ and $x_1 + x_3$, which we henceforth denote as p and q, respectively. Defining $D \equiv x_1x_4 - x_2x_3$, the measure of linkage disequilibrium, the following identities follow:

$$x_1 = pq + D, \tag{1a}$$

$$x_2 = p(1-q) - D, \tag{1b}$$

$$x_3 = (1-p)q - D, \tag{1c}$$

$$x_4 = (1-p)(1-q) + D. \tag{1d}$$

Furthermore, let the fitness of the G_iG_j genotype be w_{ij}. For simplicity, we assume that the fitness is independent of which gamete is from the mother and which one is from the father, i.e., $w_{ij} = w_{ji}$. We also assume that $w_{14} = w_{23}$; the last assumption means that the corresponding fitnesses are the same regardless of whether A_1 and B_1 are on the same chromosome or opposite ones. Consequently, the following matrix suffices for fully representing the fitnesses of genotypes:

$$\begin{array}{c} \\ A_1A_1 \\ A_1A_2 \\ A_2A_2 \end{array} \begin{array}{c} \begin{array}{ccc} B_1B_1 & B_1B_2 & B_2B_2 \end{array} \\ \begin{bmatrix} w_{11} & w_{12} & w_{22} \\ w_{13} & w_{14} & w_{24} \\ w_{33} & w_{34} & w_{44} \end{bmatrix} \end{array}$$

We include two further phenomena in the model: recombination and mutation. While we let r denote the probability of recombination, the mutation from one gamete to another gamete is specified by the row stochastic matrix Q whose (i, j)th element Q_{ij} is the probability that an offspring with gamete G_j is born to a parent with gamete G_i. With this multiplicative [36,50] mutation that takes place during DNA replication process, the evolution of gamete frequencies is given by the following replicator-mutator equation [41,44,45,58]:

$$x_i' = \frac{\sum_j (x_j w_j - \theta_j r D w_{14}) Q_{ji}}{\bar{w}}, \tag{2}$$

where $w_i \equiv \sum_j w_{ij}x_j$, $\bar{w} \equiv \sum_j w_j x_j$, $\sum_j Q_{ij} = 1$, and $\theta_1 = -\theta_2 = -\theta_3 = \theta_4 = 1$. Here the prime is the tag for an immediately succeeding generation. We suppose that the mutation happens at the gametic stage [41,59].

We pause a bit to interpret Eq. (2) from a physicist's point of view. The nonlinear equation is essentially a mean-field equation of a stochastically evolving system of interacting agents whose number is held fixed over time. This is trivially achieved if one considers an infinite population to begin with, as has been considered in the 2L2A model. The agents are the gametes which can be in four possible states A_iB_j (given by various combinations of alleles at two loci). These four states appear with distinct frequencies, x_i's. There are transitions from one state to the others (and vice versa) via the process of mutation and recombination; there is also self-transition via replication (see Fig. 1). These probabilities of these transitions

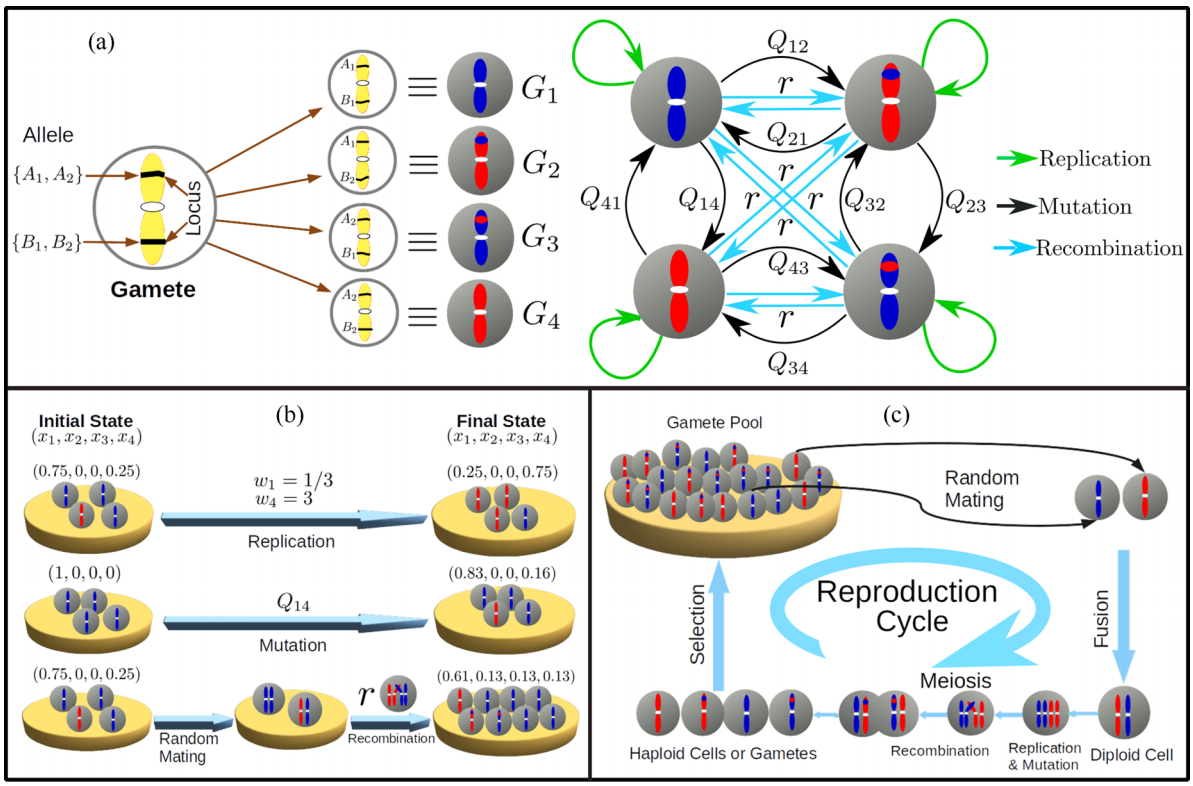

FIG. 1. Schematic representation of the 2L2A model. (a) Defining four different gametes and showcases, through a Markov chain representation, different evolutionary forces at play to change the state (x_1, x_2, x_3, x_4) of gamete population over time. We represent a gamete either as a circle containing yellow chromosomes and black lines for alleles or as a circle with red and blue chromosomes for easy visualization in later panels. (b) Illustratively clarifying the processes further at the population level. (c) The entire selection-recombination-mutation dynamics over one reproduction cycle. It should be noted that although the individuals are diploid organisms, the mathematical 2L2A model conveniently tracks the frequencies of the haploid gametes of organisms: The diploid organisms act only as carriers and facilitators of the evolutionary changes among the set of all gametes in the population.

are mathematically captured by parameters Q_{ij}, r, and w_i. Over time any initial frequency distribution over the states evolves and reaches a limiting stationary distribution. However, it must be emphasized that we do not solve for the aforementioned stochastic process in the population; rather, in this paper, we stick with the mean-field deterministic description of the evolutionary dynamics.

B. Dynamics of allele frequencies

It is well known [50] that recombination drives 2L2A model's phase space trajectories onto the Wright manifold in the absence of selection and mutation. The Wright manifold is a linkage equilibrium manifold (Λ_0), where $D = 0$; and a population in linkage equilibrium is restricted to be on the equilibrium manifold, i.e., Λ_0 is an invariant manifold.

As elaborated in the introduction to this paper, since our goal is to observe the effect of both weak selection and weak mutation on the dynamics of the 2L2A selection-recombination model, we introduce a small parameter s such that the fitnesses and the mutations can be recast as

$$w_{ij} = 1 + sm_{ij}, \tag{3a}$$

$$Q_{ij} = s\epsilon_{ij} \quad \text{for} \quad i \neq j. \tag{3b}$$

Thus, the limit of small s renders the dynamics of Eq. (2) to be that expected under weak selection and weak mutation.

In the presence of weak selection ($s \ll r$) and weak mutation, on using Eq. (3) in Eq. (2), we obtain

$$x_i' = x_i - \theta_i r D + O(s). \tag{4}$$

Interestingly, we find that the effect of mutation at this order is completely absent. Hence, the known results [26,27] for the case of the models without mutation (but with selection) hold in our case as well. Close to Λ_0, there exists a smooth invariant manifold, Λ_s, that is globally attracting for Eq. (2); for any initial values the linkage disequilibrium $D(t)$ becomes $O(s)$ asymptotically in time.

Thus, in the weak selection and weak mutation limit, the linkage disequilibrium $D \to 0$ and, consequently, the dynamical equation is further simplified because of the fact that it can now be specified using only two variables p and q, for $t \geqslant t_1$. Specifically, in the set of Eqs. (1), D is replaced by $O(s)$ terms. Rescaling time $t(= 0, 1, 2, \dots)$ tagging generations as $\tau = st$, it is easy to see that as $s \to 0$, Eq. (2) approaches the following differential equations:

$$\dot{p} = q(1-p)\nu_1 + (1-q)(1-p)\nu_2 - qp\nu_3 - (1-q)p\nu_4 + p(1-p)\frac{1}{2}\frac{\partial \bar{m}}{\partial p}, \tag{5a}$$

$$\dot{q} = p(1-q)\nu_5 + (1-p)(1-q)\nu_6 - pq\nu_7 - (1-p)q\nu_8 + q(1-q)\frac{1}{2}\frac{\partial \bar{m}}{\partial q}, \tag{5b}$$

where, $\nu_1 \equiv (\epsilon_{31} + \epsilon_{32})$, $\nu_2 \equiv (\epsilon_{41} + \epsilon_{42})$, $\nu_3 \equiv (\epsilon_{13} + \epsilon_{14})$, $\nu_4 \equiv (\epsilon_{23} + \epsilon_{24})$, $\nu_5 \equiv (\epsilon_{21} + \epsilon_{23})$, $\nu_6 \equiv (\epsilon_{41} + \epsilon_{43})$, $\nu_7 \equiv (\epsilon_{12} + \epsilon_{14})$, $\nu_8 \equiv (\epsilon_{32} + \epsilon_{34})$, and

$$\bar{m} \equiv m_1 pq + m_2 p(1-q) + m_3(1-p)q + m_4(1-p)(1-q) \tag{6}$$

is the average fitness of the population wherein the marginal fitness of the gamete i,

$$m_i \equiv m_{i1} pq + m_{i2} p(1-q) + m_{i3}(1-p)q + m_{i4}(1-p)(1-q). \tag{7}$$

Since, at $p = 0$ and $p = 1$, $\dot{p} \geqslant 0$ and $\dot{p} \leqslant 0$ respectively; and at $q = 0$ and $q = 1$, $\dot{q} \geqslant 0$ and $\dot{q} \leqslant 0$, respectively, Eq. (5) is forward invariant in the p-q phase space—a closed unit square. It may also be noted that the dynamical equation remains invariant under addition (but not multiplication) of a constant matrix with the matrix M whose elements are m'_{ij}s.

III. 2L2A GRADIENT SYSTEM

If a dynamical system is gradient-like, then the nonconvergent solutions like periodic or chaotic solutions can be ruled out for the system. So it is very useful to find the condition on the mutation rates for which the 2L2A model becomes gradient-like.

It is of notational convenience to represent Eqs. (5) in the form

$$\dot{z}_i = \tilde{f}_i(\boldsymbol{z}) \equiv z_i(1-z_i) f_i(\boldsymbol{z}), \;\; i = 1, 2, 3, 4, \tag{8}$$

where $z_1 \equiv p$, $z_2 \equiv q$, $z_3 \equiv (1-p)$, and $z_4 \equiv (1-q)$ correspond to the four coordinates in the allele frequency space. The explicit expression of f'_is is obvious when compared with Eqs. (5). The phase space $\mathbb{P}$, hence, is $\Sigma^2 \times \Sigma^2$ embedded in $\mathbb{R}^4$; here Σ^2 is a one-dimensional simplex. We need to consider, e.g., the interior of $\mathbb{P}$, int$\mathbb{P}$; at any point $\boldsymbol{z} \in \text{int}\mathbb{P}$, let the tangent space be denoted by $\mathbb{T}_{\boldsymbol{z}}\mathbb{P}$.

Now for $\boldsymbol{z} \in \text{int}\mathbb{P}$ and $\boldsymbol{\eta} \in \mathbb{T}_{\boldsymbol{z}}\mathbb{P}$, the inner product

$$\langle \dot{\boldsymbol{z}}, \boldsymbol{\eta} \rangle_{\boldsymbol{z}} = \langle \tilde{\boldsymbol{f}}(\boldsymbol{z}), \boldsymbol{\eta} \rangle_{\boldsymbol{z}} = g_{ij}(\boldsymbol{z}) \tilde{f}_i(\boldsymbol{z}) \eta_j, \tag{9}$$

where (and henceforth) sum over repeated indices—Einstein's summation convention—has been imposed. g_{ij} is the metric in int$\mathbb{P}$. Considering the metric $g_{ij} = \delta_{ij}/[z_i(1-z_i)]$—reminiscent of the Shahshahani gradient [50,60,61]—and recalling Eq. (8), it is obvious that

$$\langle \dot{\boldsymbol{z}}, \boldsymbol{\eta} \rangle_{\boldsymbol{z}} = \frac{\partial U}{\partial z_i} \eta_i, \tag{10}$$

if there exists a continuous and differentiable scalar function $U(\boldsymbol{z})$ such that $f_i(\boldsymbol{z}) = \partial U(\boldsymbol{z})/\partial z_i$. Actually, since $\sum_{i=1}^{4} \eta_i = 0$ because $\boldsymbol{\eta} \in \mathbb{T}_{\boldsymbol{z}}\mathbb{P}$, even if a more general condition, *viz.*, $f_i(\boldsymbol{z}) = \partial U(\boldsymbol{z})/\partial z_i + \phi(\boldsymbol{z})$ (ϕ is a scalar function) is satisfied, Eq. (10) holds good (see Appendix A).

In summary, what we have found is that if $\dot{z}_i = f_i(\boldsymbol{z})$ is gradient system, then so is $\dot{z}_i = \tilde{f}_i(\boldsymbol{z})$. Consequently, for Eqs. (5) to be a gradient system, one requires

$$\frac{\partial f_1}{\partial q} = \frac{\partial f_2}{\partial p}. \tag{11}$$

This condition, on using the expression of f'_is, ultimately takes the form

$$\frac{1}{p}(\nu_1 - \nu_2) + \frac{1}{(1-p)}(\nu_3 - \nu_4) = \frac{1}{q}(\nu_5 - \nu_6) + \frac{1}{(1-q)}(\nu_7 - \nu_8). \tag{12}$$

As p and q are independent variables, the system is a gradient system if

$$\nu_1 = \nu_2, \;\; \nu_3 = \nu_4, \;\; \nu_5 = \nu_6, \text{ and } \nu_7 = \nu_8 \tag{13}$$

for all possible allowed values of p and q.

In the light of condition (13), Eqs. (5) take the form

$$\dot{p} = p(1-p)\frac{1}{2}\frac{\partial \bar{m}}{\partial p} + \nu_1(1-p) - \nu_3 p, \tag{14a}$$

$$\dot{q} = q(1-q)\frac{1}{2}\frac{\partial \bar{m}}{\partial q} + \nu_5(1-q) - \nu_7 q. \tag{14b}$$

It is interesting to note that with $V(p,q) \equiv \exp(\bar{m}) p^{2\nu_1}(1-p)^{2\nu_3} q^{2\nu_5}(1-q)^{2\nu_7}$, Eq. (14) can be recast as

$$\dot{p} = \frac{p(1-p)}{2V}\frac{\partial V}{\partial p}, \tag{15a}$$

$$\dot{q} = \frac{q(1-q)}{2V}\frac{\partial V}{\partial q}; \tag{15b}$$

here the interior fixed points (p^*, q^*) correspond to $\partial V/\partial p = \partial V/\partial q = 0$. In fact, it can be verified (see Appendix B) that $V(p,q)$ is the local Lyapunov function for the gradient system (14) because

$$\dot{V} = \frac{2V}{p(1-p)}\dot{p}^2 + \frac{2V}{q(1-q)}\dot{q}^2, \tag{16}$$

implying $\dot{V} = 0$ only at any $(p^*, q^*) \in (0,1)^2$ and $\dot{V} > 0$ always for all possible $(p,q) \in (0,1)^2$ other than the fixed points.

The existence of the Lyapunov function leads to the conclusion for Eq. (2): for sufficiently small s and if all the equilibria of Eqs. (15) are hyperbolic, every solution of Eq. (2) converges to a fixed point. This is essentially an extension of a theorem due to Nagyalaki [26] and can be succinctly understood as follows. Substituting $w_{ij} = 1 + s m_{ij}$ and $Q_{ij} = s\epsilon_{ij}$ for all $i \neq j$ in Eq. (2), and assuming linkage equilibrium ($D = 0$) and condition (13), we arrive at

$$\Delta p = \frac{s}{\bar{w}}\left[\frac{p(1-p)}{2}\frac{\partial \bar{m}}{\partial p} + \nu_1(1-p) - \nu_3 p\right], \tag{17a}$$

$$\Delta q = \frac{s}{\bar{w}}\left[\frac{q(1-q)}{2}\frac{\partial \bar{m}}{\partial q} + \nu_5(1-q) - \nu_7 q\right], \tag{17b}$$

which reduce to Eqs. (15) as $s \to 0$. Here $\bar{w} = 1 + s\bar{m}$. It is straightforward to note that the fixed points of Eqs. (15) and Eqs. (17) and their stability properties for small enough s are the same. This means that if the fixed points of Eqs. (15) are hyperbolic, then due to the system being a gradient system, the initial conditions will be attracted to some stable fixed points; and so this is going to be the fate of the initial conditions under the map given by Eq. (2) whose corresponding fixed points are in the Λ_s manifold.

The search for which kind of replicator-mutator 2L2A system can be a gradient system interestingly stops at the most simple case of random point mutation, happening independent of what is happening elsewhere (e.g., at another locus). We call such mutations independent. It can be expressed in our setup as follows. Let the probability of mutation from A_i allele to A_j allele be given by μ^A_{ij}, and the probability of mutation from B_i allele to B_j allele is given by μ^B_{ij}. Naturally μ^A_{ii} and μ^B_{ii} correspond to the probabilities of no mutation from A_i and B_i alleles, respectively. So the corresponding mutation matrix Q representing the probability of mutation from one gamete to another gamete, when the mutations at the two loci are independent, can be represented by the following matrix:

$$\begin{array}{c} \\ A_1B_1 \\ A_1B_2 \\ A_2B_1 \\ A_2B_2 \end{array} \begin{array}{c} \begin{array}{cccc} A_1B_1 & A_1B_2 & A_2B_1 & A_2B_2 \end{array} \\ \begin{bmatrix} \mu^A_{11}\mu^B_{11} & \mu^A_{11}\mu^B_{12} & \mu^A_{12}\mu^B_{11} & \mu^A_{12}\mu^B_{12} \\ \mu^A_{11}\mu^B_{21} & \mu^A_{11}\mu^B_{22} & \mu^A_{12}\mu^B_{21} & \mu^A_{12}\mu^B_{22} \\ \mu^A_{21}\mu^B_{11} & \mu^A_{21}\mu^B_{12} & \mu^A_{22}\mu^B_{11} & \mu^A_{22}\mu^B_{12} \\ \mu^A_{21}\mu^B_{21} & \mu^A_{21}\mu^B_{22} & \mu^A_{22}\mu^B_{21} & \mu^A_{22}\mu^B_{22} \end{bmatrix} \end{array}.$$

Now note that condition (13) for the gradient system in more convenient notation is

$$\nu_1 = \nu_2 \Rightarrow \epsilon_{31} + \epsilon_{32} = \epsilon_{41} + \epsilon_{42}, \tag{18a}$$

$$\nu_3 = \nu_4 \Rightarrow \epsilon_{13} + \epsilon_{14} = \epsilon_{23} + \epsilon_{24}, \tag{18b}$$

$$\nu_5 = \nu_6 \Rightarrow \epsilon_{21} + \epsilon_{23} = \epsilon_{41} + \epsilon_{43}, \tag{18c}$$

$$\nu_7 = \nu_8 \Rightarrow \epsilon_{12} + \epsilon_{14} = \epsilon_{32} + \epsilon_{34}. \tag{18d}$$

This is trivially satisfied by the aforementioned mutation matrix for an independent mutation because of the fact that $\sum_{j=1}^{2} \mu^A_{ij} = \sum_{j=1}^{2} \mu^B_{ij} = 1$—the normalization condition of probability. In conclusion, *in the presence of independent point mutations at the two different loci, the 2L2A system always behaves as a gradient system in the weak selection limit,* and no complicated dynamics like oscillatory or chaotic dynamics can appear. It may be noted, however, that the converse of this result need not be true: Mathematically speaking, mutations that are not independent (mentioned in Sec. I) may or may not satisfy the gradient condition.

It is instructive to compare this result with the analogous one for the one-locus–many-allele model, represented by a dynamical equation: $x_i' = \sum_j x_j w_j Q_{ji}/\bar{w}$. The condition for it to be a gradient-like system in the weak mutation and weak selection limit [50,51] is that the mutation rates must depend on the target gene only, i.e., Q_{ji} does not depend on index j. Evidently, it is different from the 2L2A model's condition (13) that it is more general due to the two-loci character of the system; nevertheless, it may be observed that if the mutation rates are dependent on the target gene only, condition (13) is trivially satisfied. Of course, condition (13) may be satisfied for mutations are dependent on source gene as well, something not possible at all in one-locus–many-allele model. The reason behind the more general condition (13) is genetic recombination, which is not present in the one-locus–many-allele model. The recombination in the 2L2A model allows for the exchange of genetic material and, hence, changes in gametic frequencies. Also, linkage disequilibrium, which appears in the presence of recombination, approaches the invariant Λ_s manifold in the weak selection and weak mutation leading to condition (13).

IV. 2L2A NONGRADIENT SYSTEM

Now let us see some of the examples where nonconvergent dynamical outcomes are possible in the 2L2A model in the presence of mutation in the weak selection limit. As is clear from the preceding discussion, we have to consider nonindependent mutations as they can result in nongradient dynamics and hence oscillatory outcomes.

Let us consider a simple fitness matrix well studied in literature [15,22]:

$$\mathsf{M} = \begin{bmatrix} k & L_1 & k \\ L_2 & K & L_2 \\ k & L_1 & k \end{bmatrix}. \tag{19}$$

It basically says that a genotype homozygous at both loci has the fitness k, a genotype homozygous at A (B) locus and heterozygous at B (A) locus has the fitness L_1 (L_2), and a genotype heterozygous at both loci has the fitness K. Our aim is to illustrate the nonfixed point-type dynamics that can appear in such systems in the presence of mutation.

To this end, let us take a mutation matrix that does not satisfy condition (13), and hence the corresponding dynamics given by Eqs. (5) is not a gradient system. Specifically, let us take $\epsilon_{31} = \epsilon_{24} = \epsilon_1$, $\epsilon_{12} = \epsilon_{43} = \epsilon_2$, and other mutation probabilities as zero. Furthermore, in order to achieve analytical tractability, let us choose $\nu_1 + \nu_2 - \nu_3 - \nu_4 = 0$ and $\nu_5 + \nu_6 - \nu_7 - \nu_8 = 0$ (note that our choice of Q satisfies these) so that the internal fixed point (p^*, q^*) is conveniently located at $(1/2, 1/2)$.

While performing linear stability analysis of Eqs. (5) about fixed point $(1/2, 1/2)$, the Jacobian comes out to be

$$J = \begin{bmatrix} \alpha & \beta \\ \gamma & \delta \end{bmatrix}, \tag{20}$$

where $\alpha = (k - K)/4 - (\nu_1 + \nu_2 + \nu_3 + \nu_4)/2$, $\beta = (\nu_1 - \nu_2 - \nu_3 + \nu_4)/2$, $\gamma = (\nu_5 - \nu_6 - \nu_7 + \nu_8)/2$, and $\delta = (k - K)/4 - (\nu_5 + \nu_6 + \nu_7 + \nu_8)/2$; and the corresponding eigenvalues are

$$\lambda = \frac{(\alpha + \delta) \pm \sqrt{(\alpha - \delta)^2 + 4\beta\gamma}}{2}. \tag{21}$$

For the Hopf bifurcation to occur one must have $4\beta\gamma < -(\alpha - \delta)^2$, and it happens at $\alpha + \delta = 0$, which can be recast to read $(k - K) = \sum_{i=1}^{8} \nu_i$. For illustrative purposes, if we now fix $\epsilon_2 = 0.2$ and $(k - K) = 1$, and work with ϵ_1 as a variable parameter then at $\epsilon_1 = 0.3$, the Hopf bifurcation should occur (see Fig. 2).

We observe that in the setting in which we are working, the condition of the Hopf bifurcation is independent of any constraints on L_1 and L_2. This has an interesting implication that we now point out. The case $K > L_1, L_2$ and $k > L_1, L_2$ corresponds to strong epistasis in the literature [22], where it was shown that for oscillatory behavior to appear in the 2L2A model (without mutation), strong epistasis is a necessary condition. However, when nonindependent mutation is in action, the limit cycle can appear even in the absence of the

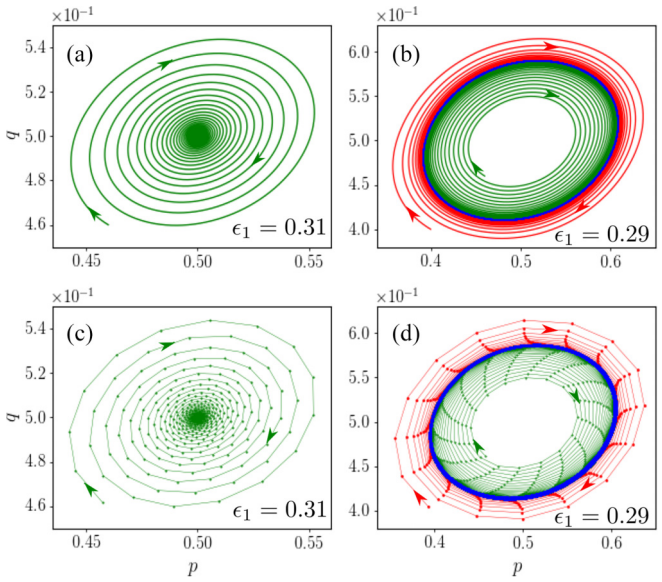

FIG. 2. Mutation drives oscillatory outcomes in nongradient 2L2A system. As discussed in Sec. IV, for illustrative purposes, we take $\nu_1 = \nu_4 = 0.3$, $\nu_6 = \nu_7 = 0.2$, $\nu_2 = \nu_3 = \nu_5 = \nu_8 = 0.0$, and $k - K = 1.0$. The Hopf bifurcation and the Neimark-Sacker bifurcation (in the time discrete version) occur at $\epsilon = 0.3$. Panels (a) and (b) depict the appearance of the limit cycle (blue closed curve) via Hopf bifurcation as ϵ_1 decreases. whereas panels (c) and (d) exhibit the birth of a closed invariant cycle (blue closed curve) via Neimark-Sacker bifurcation (we take $s = 0.01$). The red and green trajectories depict evolution of two separate initial conditions. (In the lower panel, the red and the green curves are a guide for the eye to follow the discrete orbit.)

strong epistasis because the corresponding Hopf bifurcation condition is dependent only on the values of k and K.

In this context, we recall that the 2L2A gradient system closely approximates the corresponding discrete-time dynamics of the 2L2A model in the weak selection limit. Each initial condition approaches a stable fixed point. A somewhat analogous effect is seen corresponding to the limit cycles in a discrete-time 2L2A nongradient system. For the same parameter values and sufficiently small s, an invariant closed curve is generated. However, in general, the orbits on the invariant curve need not necessarily be periodic with a finite number of periodic points as another possibility is that the orbit on the curve can be everywhere dense (may be due to quasiperiodcity or chaos). As long as s is sufficiently small [we can ignore $O(s^2)$ and higher order terms], it is easily seen that the time-discrete equation (which is effectively the Euler forward discretization of the continuous-time equation) under the same parameter values chosen above (while discussing the Hopf bifurcation) undergoes the Neimark-Sacker bifurcation. We do not present the calculations for the sake of avoiding trivial repetition. Numerical evidence of this is showcased in Fig. 2.

V. DISCUSSION AND CONCLUSION

Summarizing, we have mathematically investigated the two-locus–two-allele selection-recombination-mutation dynamics through the replicator equations in the limit of weak selection and weak mutation. We note that when selection and mutation are sufficiently weak, one can ignore linkage disequilibrium completely, and the system becomes a two-dimensional continuous-time differential equation which faithfully approximates the evolutionary dynamics when the dynamics is gradient-like. Our search for the cases of mutation for which the dynamics is gradient-like has led to the result that whenever the point mutation rate at one locus is not affected by what happens at the other, the dynamics is always gradient-like. When the dynamics is not gradient-like, we found that stable limit cycle or stable closed invariant curve can appear. The dynamics on the invariant curve can, in principle, sustain nonconvergent solutions like periodic, quasiperiodic, and chaotic orbits. We have also discussed how the dynamical manifestation of epistasis can completely change in presence of mutation.

As already mentioned in introduction, the dependent mutation is a widely observed phenomenon. What has been mathematically emphasized is that, within the paradigm of a deterministic replicator-mutator equation, it may facilitate oscillatory dynamics of gene frequency. However, we are not aware of any direct experimental instance verifying it explicitly, which may simply be because this result is not common knowledge in the literature. We recall that Eqs. (18), the condition for the 2L2A system to be gradient-like, is trivially satisfied when the mutation rates do not depend on which allele is mutating; i.e., if all the alleles mutate to a given allele at the same rate, then the 2L2A system is gradient-like. Interpreting differently, for oscillations to possibly appear, different alleles must necessarily mutate to a given allele at unequal rates. Whether dependent mutations should lead to an oscillatory outcome depends not only on the violation of condition (18), but also on the form of the fitness matrix as illustrated in Sec. IV. On a broader note, we understand that the presence of oscillatory outcomes, i.e., the fact that the corresponding systems are not gradient-like, indicates that there is no fitness-related quantity of the population that is maximized à la Fisher's fundamental theorem.

We would like to make a few points explicitly clear. First, the condition of the realization of gradient-like 2L2A replicator-mutator system is independent of the fitness matrix, making the result quite general. Second, it should be remarked that had the mutation been taken as additive rather than multiplicative [35,36], the form of the final dynamical equation in the limit of weak selection and weak mutation remains the same as Eqs. (5). Finally, we are tempted to claim that our results imply that, within the paradigm of replicator dynamics of an evolutionary process in the weak selection and mutation limit, an observation of oscillatory gametic or allelic frequencies in a 2L2A system with the possibility of mutations at both loci may be an indirect indication of the existence of mutations that are not independent. As an aside, we may mention that another theoretical model [62] shows that the interference of mutations at multiple points leads to oscillatory outcomes.

The 2L2A model is a stripped-down mathematical abstraction of a real biological evolutionary process in a sexually reproducing population. Hence, the claims through the lens

of the replicator-mutator equation are justified only when observed in the real world. We must admit that we are, unfortunately, not trained in biological experiments to be able to make practical and authoritative remarks on how experiments should be done to detect the effect of nonindependent mutations in a real biological setting—this is something experimentalists have to ponder.

An immediate future work that builds on the present paper is to find how the aforementioned results manifest themselves in a finite population where stochastic effects can no longer be ignored. Also, in this paper we have exclusively focused on viability selection. The results can, thus, change nontrivially in the presence of fertility or sexual selections because they introduce higher-order interactions like allele-genotype and genotype-genotype interactions. Moreover, in general, there can be different modes of inheritance, like polyploidy, sex linkage, and cytoplasmic inheritance. An important future work is to find under what conditions the results of this paper hold for such general scenarios. Furthermore, many characteristics like our body size [63], height [64], and shape of different organs like the ear [65] are controlled by more than two loci of a chromosome. So understanding the evolutionary dynamical outcome of multilocus systems [66,67], in the presence of a mutation, is still another natural direction to investigate. While our main result—occurrence of a gradient system in the presence of independent mutation—is valid for multilocus–two-allele systems (see Appendix A), the condition for general multilocus–multi-allele systems' becoming gradient-like remains an open problem.

Before we conclude, we would like to emphasize that while our results are restricted to the scenarios where the deterministic replicator-mutator equation is relevant, the set of such scenarios is not restricted to merely genetics. The 2L2A deterministic dynamics finds application in evolution of learning [68], cultural evolution [69], neuroscience [70], and signaling systems [71]. Furthermore, we also remark that the 2L2A dynamical model is not just a mathematical endeavor; e.g., with some more additional features, it was used to explain a very high level of amino acid divergence between human *RHCE* and *RHD* genes in a short region around exon 7 [72].

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APPENDIX A: MULTILOCUS–TWO-ALLELE GRADIENT SYSTEM

Let there be a total $n+1$ loci and at the lth ($l = 0, 1, 2, \ldots, n$) locus two possible alleles be denoted by $A_0^{(l)}$ and $A_1^{(l)}$. The gametes—each represented by a sequence, $A_{\varsigma_0}^{(0)}A_{\varsigma_1}^{(1)}A_{\varsigma_2}^{(2)}A_{\varsigma_3}^{(3)}\cdots A_{\varsigma_j}^{(j)}\cdots A_{\varsigma_n}^{(n)}$, where $\varsigma_j \in \{0,1\}\ \ \forall j$—are mathematically sorted in a fashion such that ith gamete (G_i) is listed at position $i = (\varsigma_0 \times 2^0) + (\varsigma_1 \times 2^1) + (\varsigma_2 \times 2^2) + \cdots + (\varsigma_n \times 2^n)$, thereby helping us to directly associate a gamete number with a gamete. Let the frequency of G_i be x_i.

Furthermore, let the fitness of the G_iG_j type of genotype be w_{ij}. Assuming that the fitness is independent of which gamete is contributed by which parent, the equality, $w_{ij} = w_{ji}$, follows. The fitness of the ith gamete and average fitness of the population are, thus, given by $w_i \equiv \sum_j w_{ij}x_j$ and $\bar{w} \equiv \sum_j w_j x_j$, respectively.

Now for the multilocus system the selection-recombination evolutionary equation [25,26] for the gametes' frequency in the presence of multiplicative mutation which occurs during the gametic stage [58], takes the form

$$x_i' = \frac{1}{\bar{w}}\sum_{j=0}^{2^n-1}(x_j w_j - D_j)Q_{ji}, \tag{A1}$$

where Q_{ji} corresponds to the probability of mutation from the jth gamete to the ith gamete. The symbol D_i is understood as follows.

Let us decompose the set of loci $l = \{0, 1, 2, \ldots, n\}$ into two disjoint sets, I and J. Let the probability of recombination with the loci in I inherited from one parent with the loci in J inherited from the other parent be r_I. Now $D_i \equiv \sum_j \sum_I r_I(w_{ij}x_i x_j - w_{i_I j_J, j_I i_J}x_{i_I j_J}x_{j_I i_J})$ represents the measure of linkage disequilibrium for the ith gamete. $x_{i_I j_J}$ denotes the frequency of gametes consisting of the genes i_I located in I and the genes j_J located in J inherited from two different parents, where i_I (or j_J) corresponds to a vector with component i_l (or j_l) for every $l \in I$ (or $l \in J$). In passing, note that D_i ultimately boils down to $\theta_i w_{14} r D$ for the two-locus two-allele scenario, when $w_{14} = w_{23}$, as used in the main text. In consistent notation, $w_{i_I j_J, j_I i_J}$ is the fitness of the genotype formed by the two gametes—one whose frequency is $x_{i_I j_J}$ and another one whose frequency is $x_{j_I i_J}$.

Here again we are interested in an evolutionary outcome under weak selection and weak mutation. So let us take the form of the fitness and mutation as we have taken for the two-locus case (3). Under weak mutation, à la Nagylaki [25], we can show that under weak selection linkage disequilibrium in Eq. (A1) goes to quasilinkage equilibrium within a few generations ($t > t_1$). So we can write Eq. (A1) after $t > t_1$ as

$$x_i' = \frac{1}{\bar{w}}\sum_{j=0}^{2^{(n+1)}-1} Q_{ji}x_j w_j. \tag{A2}$$

Rescaling time $t(= 0, 1, 2, \ldots)$ of generations as $\tau = st$ and taking the limit $s \to 0$, we ultimately come up with the following differential equation [50]:

$$\dot{x}_i = x_i[m_i - \bar{m}] + \sum_{j=0}^{2^{(n+1)}-1}(\epsilon_{ji}x_j - \epsilon_{ij}x_i). \tag{A3}$$

We now want to rewrite this equation in terms of the frequency of the alleles.

We denote the frequency of the allele $A_0^{(l)}$, i.e., the frequency of the 0th allele at the lth locus by z_l and the frequency of the first allele at the lth locus by z_{n+l}. Since each locus contains two alleles, it is obvious that $z_{n+l} = 1 - z_l$. At the linkage equilibrium manifold, the gamete frequency is given by just the product of the corresponding allele

frequencies [26],

$$x_i = \prod_{l=0}^{n} z_{l+\varsigma^l n}, \tag{A4}$$

where $i = \Sigma_{l=0}^{n} \varsigma_l 2^l$, in our notation. z_l can be easily calculated by taking the sum over all possible gametes in which the lth locus contains the zeroth allele. Again, by virtue of the numbering convention of the gametes introduced in the beginning of this Appendix, one can write the allele frequency in terms of gamete frequency explicitly as follows:

$$z_l = x_0 + x_1 + \cdots + x_{2^l-1} + x_{2.(2^l)} + \cdots + x_{3.(2^l)-1} + x_{4.(2^l)} + \cdots . \tag{A5}$$

Taking the time derivative of Eq. (A5) and using Eq. (A3), we ultimately get the evolution equation for allele frequency:

$$\dot{z}_l \equiv \tilde{f}_l(\boldsymbol{z}) \equiv z_l(1-z_l)\left[\frac{1}{2}\frac{\partial \bar{m}}{\partial z_l} + \nu_{l_0}\frac{x_0}{z_l(1-z_l)} + \nu_{l_1}\frac{x_1}{z_l(1-z_l)} + \cdots + \nu_{l_{2^n}}\frac{x_{2^n}}{z_l(1-z_l)}\right] \equiv z_l(1-z_l)f_l, \tag{A6}$$

where $\bar{m} = 1 + s\bar{w}$,
and $\nu_{l_0} \equiv -[\epsilon_{0,(2^l)} + \cdots + \epsilon_{0,2(2^l)-1} + \epsilon_{0,3(2^l)} + \cdots + \epsilon_{0,4(2^l)-1} + \cdots]$,
$\nu_{l_1} \equiv -[\epsilon_{1,(2^l)} + \cdots + \epsilon_{1,2(2^l)-1} + \epsilon_{1,3(2^l)} + \cdots + \epsilon_{1,4(2^l)-1} + \cdots]$,
$\cdots \equiv \cdots$
$\nu_{l_{(2^l-1)}} \equiv -[\epsilon_{(2^l-1),(2^l)} + \cdots + \epsilon_{(2^l-1),2(2^l)-1} + \epsilon_{(2^l-1),3(2^l)} + \cdots + \epsilon_{(2^l-1),4(2^l-1)} + \cdots]$,
$\nu_{l_{(2^l)}} \equiv +[\epsilon_{(2^l),0} + \cdots + \epsilon_{(2^l),(2^l)-1} + \epsilon_{(2^l),2(2^l)} + \cdots + \epsilon_{(2^l),3(2^l)-1} + \cdots]$,
$\cdots \equiv \cdots$.

Here we have put a comma in the subscript of ϵ_{ij} merely for the visual clarity in reading the subscripts.

We know that the Shahshahani metric in the gametic space (a simplex of dimension $2^{n+1}-1$) is $g_{ij}(x) = \delta_{ij}/x_i$. Now we are interested to calculate the corresponding metric (e.g., $\bar{g}_{ij}$) in the allelic space, $(z_1, z_2, \ldots, z_{2n})$. Transformation of the coordinates yields

$$\bar{g}_{ij}(z) = \frac{\partial x^\rho}{\partial z_i}\frac{\partial x^\sigma}{\partial z_j} g_{\rho\sigma}(x). \tag{A7}$$

Evidently, for $i \neq j$, the metric elements $\bar{g}_{ij}(z)$ is zero, and for $i = j$ the metric is nonzero such that the metric can eventually be written as

$$\bar{g}_{ij}(z) = \frac{\delta_{ij}}{z_i(1-z_i)}. \tag{A8a}$$

Recall that the allelic phase space $\mathbb{P}$ is $(n+1)$-dimensional space, $\Sigma^2 \times \Sigma^2 \times \cdots \times \Sigma^2$, embedded in $\mathbb{R}^{2(n+1)}$; here Σ^2 is one-dimensional simplex.

We need to consider, e.g., the interior of $\mathbb{P}$, int$\mathbb{P}$; at any point $\boldsymbol{z} \in$ int$\mathbb{P}$, let the tangent space be denoted by $\mathbb{T}_z\mathbb{P}$. Now for $\boldsymbol{z} \in$ int$\mathbb{P}$ and $\boldsymbol{\eta} \in \mathbb{T}_z\mathbb{P}$, the inner product

$$\langle \dot{\boldsymbol{z}}, \boldsymbol{\eta}\rangle_z = \langle \tilde{\boldsymbol{f}}(\boldsymbol{z}), \boldsymbol{\eta}\rangle_z = \bar{g}_{ij}(\boldsymbol{z})\tilde{f}_i(\boldsymbol{z})\eta_j. \tag{A9}$$

Considering the metric $\bar{g}_{ij}$, it is obvious that

$$\langle \dot{\boldsymbol{z}}, \boldsymbol{\eta}\rangle_z = \frac{\partial U}{\partial z_i}\eta_i, \tag{A10}$$

if there exists continuous and differentiable scalar functions $U(\boldsymbol{z})$ and $\phi(\boldsymbol{z})$ such that $f_i(\boldsymbol{z}) = \partial U(\boldsymbol{z})/\partial z_i + \phi(\boldsymbol{z})$. In other words, this form of f_i is the condition for $\dot{\boldsymbol{z}} = \tilde{\boldsymbol{f}}$ to be a gradient system.

Now, consider the bilinear form $\boldsymbol{H}_z\tilde{\boldsymbol{f}}$:

$$\boldsymbol{H}_z\tilde{\boldsymbol{f}}(\boldsymbol{\xi}, \boldsymbol{\eta}) \equiv \sum_{i,j=1}^{2n} \frac{1}{z_i(1-z_i)}\frac{\partial \tilde{f}_i}{\partial z_j}\xi_i\eta_j, \tag{A11}$$

where $\boldsymbol{\xi}, \boldsymbol{\eta} \in \mathbb{T}_z\mathbb{P}$. We find that

$$\frac{\partial \tilde{f}_i}{\partial z_j} = \delta_{ij}(1-2z_i)f_i + z_i(1-z_i)\frac{\partial f_i}{\partial z_j}. \tag{A12}$$

Putting this relation in Eq. (A11) and imposing $f_i(\boldsymbol{z}) = \partial U(\boldsymbol{z})/\partial z_i + \phi(\boldsymbol{z})$, we find that $\boldsymbol{H}_z\tilde{\boldsymbol{f}}(\boldsymbol{\xi}, \boldsymbol{\eta})$ is symmetric, which, in turn, implies

$$\sum_{i,j=1}^{2n}\left(\frac{\partial f_i}{\partial z_j} - \frac{\partial f_j}{\partial z_i}\right)\xi_i\eta_j = 0 \tag{A13}$$

for all possible tangent vectors $\boldsymbol{\xi}, \boldsymbol{\eta} \in \mathbb{T}_z\mathbb{P}$. With $\boldsymbol{\xi} = \mathbf{e_i} - \mathbf{e_k}$ and $\boldsymbol{\eta} = \mathbf{e_j} - \mathbf{e_k}$ ($\mathbf{e}'$s are the unit basis vectors of $\mathbb{R}^{2(n+1)}$), we obtain

$$\frac{\partial f_i}{\partial z_j} + \frac{\partial f_j}{\partial z_k} + \frac{\partial f_k}{\partial z_i} = \frac{\partial f_i}{\partial z_k} + \frac{\partial f_k}{\partial z_j} + \frac{\partial f_j}{\partial z_i}. \tag{A14}$$

As an aside, one notes that this general condition for 2L2A reduces to the simpler condition, $\partial f_0/\partial z_1 = \partial f_1/\partial z_0$, as observed in the main text, making the presence of $\phi(\boldsymbol{z})$ redundant in the condition.

We now show that just like the fact that an independent point mutation renders the 2L2A model a gradient system, the multilocus–two-allele model in the presence of an independent point mutation is also a gradient system. To this end, it suffices to ignore $\phi(\boldsymbol{z})$, meaning we have as a special case of Eq. (A14):

$$\frac{\partial f_i}{\partial z_j} = \frac{\partial f_j}{\partial z_i}, \quad \forall j \in \{0, 1, 2, \ldots, n\}, \tag{A15}$$

at all values of z. Thus, we explicitly have

$$\frac{\partial f_i}{\partial z_j} = [(\nu_{i_{2^j}} - \nu_{i_0})(x_0 + x_{2^j}) + (\nu_{i_{2^j+1}} - \nu_{i_1})(x_0 + x_{2^j+1}) + \cdots + (\nu_{i_{2^i}} - \nu_{i_{2^j+2^i}})(x_{2^i} + x_{2^j+2^i}) + \cdots]\frac{1}{z_i(1-z_i)} + \frac{1}{2}\frac{\partial^2 \bar{m}}{\partial z_j \partial z_i}, \tag{A16a}$$

$$\frac{\partial f_j}{\partial z_i} = [(\nu_{j_{2^i}} - \nu_{j_0})(x_0 + x_{2^i}) + (\nu_{j_{2^i+1}} - \nu_{j_1})(x_0 + x_{2^i+1}) + \cdots + (\nu_{j_{2^j}} - \nu_{j_{2^i+2^j}})(x_{2^j} + x_{2^i+2^j}) + \cdots]\frac{1}{z_j(1-z_j)} + \frac{1}{2}\frac{\partial^2 \bar{m}}{\partial z_i \partial z_j}. \tag{A16b}$$

Owing to the independence of x_i's, from Eqs. (A16a) and (A16b), one can easily say that the condition (A15) is satisfied when

$$\nu_{i_{2^j}} = \nu_{i_0}, \quad \nu_{i_{2^j+1}} = \nu_{i_1}, \ldots, \quad \nu_{i_{2^i}} = \nu_{i_{2^j+2^i}}, \ldots \tag{A17}$$

and

$$\nu_{j_{2^i}} = \nu_{j_0}, \quad \nu_{j_{2^i+1}} = \nu_{j_1}, \ldots, \quad \nu_{j_{2^j}} = \nu_{j_{2^i+2^j}}, \ldots. \tag{A18}$$

Now let the probability of mutation from $A_i^{(l)}$ allele to $A_j^{(l)}$ $(i, j \in \{0, 1\}$ and $i \neq j)$ allele at locus l be μ_{ij}^l. In independent point mutations, the probability of mutation from one gamete to another gamete is just the product of the corresponding allelic mutation probabilities. So we can write the explicit expressions of ν_{i_0} and $\nu_{i_{2^j}}$ $(\forall j < i)$:

$$\nu_{i_0} = -\big[(\mu_{00}^0\mu_{00}^1\cdots\mu_{01}^i\cdots\mu_{00}^{n-1}\mu_{00}^n) + \cdots + (\mu_{01}^0\mu_{01}^1\cdots\mu_{01}^i\cdots\mu_{00}^{n-1}\mu_{00}^n) + (\mu_{00}^0\mu_{00}^1\cdots\mu_{01}^i\mu_{01}^{i+1}\cdots\mu_{00}^n) + \cdots\big], \tag{A19a}$$

$$\nu_{i_{2^j}} = -\big[(\mu_{00}^0\cdots\mu_{10}^j\cdots\mu_{01}^i\cdots\mu_{00}^n) + \cdots + (\mu_{01}^0\cdots\mu_{11}^j\cdots\mu_{01}^i\cdots\mu_{00}^n) + (\mu_{00}^0\cdots\mu_{10}^j\cdots\mu_{01}^i\mu_{01}^{i+1}\cdots\mu_{00}^n) + \cdots\big], \tag{A19b}$$

and similarly all the other ν's in terms of the multiplication of mutation probabilities at each locus. One can check from the above expressions that both ν_{i_0} and $\nu_{i_{2^j}}$ ultimately boil down to $-\mu_{01}^i$. An intuition behind it may be gained by noting that ν_{i_0} (and $\nu_{i_{2^j}}$) contains terms which are (apart from an overall negative sign) the addition of the probabilities of mutation from the zeroth (and 2^jth) gamete to the gametes which do not contribute to the allele frequency, z_i. Actually, the sum of the latter gamete frequencies gives $1 - z_i$. Consequently, we can effectively consider the sum under question as the probability of mutation from the $A_0^{(i)}$ allele to the $A_1^{(i)}$ allele at the ith locus. Likewise, other conditions [(A17) and (A18)] are also satisfied trivially in the presence of independent mutations. So we can conclude that in the presence of independent point mutations, the multilocus–two-allele system is gradient-like.

APPENDIX B: LOCAL LYAPUNOV FUNCTION

Here we show that the function, $V(p, q) \equiv \exp(\bar{m})p^{2\nu_1}(1-p)^{2\nu_3}q^{2\nu_5}(1-q)^{2\nu_7}$, is a local Lyapunov function for the gradient system (14). First, we note that the value of the function $V(p, q)$ is always positive for all values of p and q in int$\mathbb{P}$. Next we show below that the function has local maxima (minima) at the stable (unstable) fixed points of Eqs. (14).

Considering the alternate form of Eqs. (14), *viz.*, Eqs. (15), we see that every fixed point $(p^*, q^*) \in$ int$\mathbb{P}$ corresponds to $\partial V/\partial p = \partial V/\partial q = 0$. For later use, we write below the explicit expressions of the second derivative of $V(p, q)$:

$$\left.\frac{\partial^2 V}{\partial p^2}\right|_{(p^*,q^*)} = \frac{2V[m_A - \nu_1 - \nu_3]}{p^*(1-p^*)}, \tag{B1a}$$

$$\left.\frac{\partial^2 V}{\partial q^2}\right|_{(p^*,q^*)} = \frac{2V[m_B - \nu_5 - \nu_7]}{q^*(1-q^*)}, \tag{B1b}$$

$$\left.\frac{\partial^2 V}{\partial p \partial q}\right|_{(p^*,q^*)} = V\bar{m}, \tag{B1c}$$

where $m_A \equiv \frac{\partial}{\partial p}[\frac{p(1-p)}{2}\frac{\partial \bar{m}}{\partial p}]|_{(p^*,q^*)}$ and $m_B \equiv \frac{\partial}{\partial q}[\frac{q(1-q)}{2}\frac{\partial \bar{m}}{\partial q}]|_{(p^*,q^*)}$.

Now, in the process of the linear stability analysis, the Jacobian of the linearized system at (p^*, q^*) is given by

$$J_1 \equiv \begin{bmatrix} m_A - \nu_1 - \nu_3 & 2p^*(1-p^*)\bar{m} \\ 2q^*(1-q^*)\bar{m} & m_B - \nu_5 - \nu_7 \end{bmatrix} \equiv \begin{bmatrix} a & b \\ c & c \end{bmatrix}, \tag{B2}$$

and the corresponding eigenvalues are

$$\lambda = \tfrac{1}{2}[(a+d) \pm \sqrt{(a-d)^2 + 4bc}]. \tag{B3}$$

Obviously, a necessary condition for the fixed point (p^*, q^*) to be stable is $(a + d) < 0$, which implies

$$\text{either} \quad \nu_1 + \nu_3 > m_A, \tag{B4a}$$

$$\text{or} \quad \nu_5 + \nu_7 > m_B. \tag{B4b}$$

This condition in light of Eqs. (B1) means that

$$\text{either} \quad \left.\frac{\partial^2 V}{\partial p^2}\right|_{(p^*,q^*)} < 0 \tag{B5a}$$

$$\text{or} \quad \left.\frac{\partial^2 V}{\partial q^2}\right|_{(p^*,q^*)} < 0. \tag{B5b}$$

Finally, the sufficient condition for the stability of the fixed point is $(a + d)^2 > (a - d)^2 + 4bc$, which boils down to

$$[m_A - \nu_1 - \nu_3][m_B - \nu_5 - \nu_7] > 4p^*q^*(1-p^*)(1-q^*)\bar{m}^2, \tag{B6}$$

which in light of Eqs. (B1) implies that

$$\left[\left.\frac{\partial^2 V}{\partial p^2}\right|_{(p^*,q^*)}\right]\left[\left.\frac{\partial^2 V}{\partial q^2}\right|_{(p^*,q^*)}\right] > \left[\left.\frac{\partial^2 V}{\partial p \partial q}\right|_{(p^*,q^*)}\right]^2. \tag{B7}$$

Conditions (B5) and (B7) together imply that the stable fixed point corresponds to the local maximum of the function $V(p, q)$. A similar calculation shows that the unstable fixed point corresponds to the local minimum, and the saddle fixed point corresponds to the saddle point of the function $V(p, q)$. Furthermore, we already know from Eq. (16) that $\dot{V} > 0$ except at the fixed points where it vanishes. Hence, it qualifies as the local Lyapunov function.

Actually, in the more conventional sense [73], the local Lyapunov function near a stable fixed point, (p^*, q^*), is $V(p^*, q^*) - V(p, q)$ and near an unstable fixed point, (p^*, q^*), is $V(p, q) - V(p^*, q^*)$.

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