Aggregation of Variables and System Decomposition: Applications to Fitness Landscape Analysis

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■ Abstract

In this paper we present general results on aggregation of variables, specifically as it applies to decomposable (partitionable) dynamical systems. We show that a particular class of transition matrices, namely, those satisfying an equitable partitioning property, are aggregable under appropriate decomposition operators. It is also shown that equitable partitions have a natural application to the description of mutation-selection matrices (fitness landscapes) when their fitness functions have certain symmetries concordant with the neighborhood relationships in the underlying configuration space. We propose that the aggregate variable descriptions of mutation-selection systems offer a potential formal definition of units of selection and evolution.

Keywords: Fitness Landscapes, Aggregation of Variables, Decomposability, Mutation, Selection

■ Introduction

Biological systems as a general rule consist of very large numbers of interacting, hierarchically arranged subcomponents. Every introductory biology textbook presents its reader with the statement that multicellular organisms often consist of a large number of cell types arranged into precise configuration in three dimensions, while each cell in turn contains a vast array of macromolecules. Conversely, individual organisms (often of differing genotype) themselves interact with one another in demes and populations which are faced with both intra and interspecific competition.

The resulting high dimensionality of most biological systems should make an exhaustive description of the state space (and thus the state dynamic) completely intractable. What makes dynamical system representation of biological models possible (and, for that matter, the conceptual identification of "units" of biological structure and function) is the fortunate fact that an exhaustive description of the state space is not necessary to predict the behavior of many biological entities and/or their components. Consequently, it is of fundamental importance to theoretical biology to understand why and under what circumstances a description of a complex system can be achieved with fewer macroscopic variables. Although this representation has conceptually informed philosophers of biology (Wimsatt 1981, Schank and Wimsatt 1988), concrete results on this representation problem have largely been obtained outside of biology, mostly in economics (Simon and Ando 1961, Ando and Fisher 1963), computer science (Holland 1975) as physical chemistry (Haken 1977). In this paper we summarize the current knowledge about aggregability of linear dynamical systems and put the existing results on a systematic basis. Finally we discuss the applicability of these results to models of genetic evolution.

A reduced variable description can be due to either of the two properties which we will discuss in this paper: system decomposability and aggregation of variables. As we will see, while the two concepts are often related to one another, they are in principle independent.

To make our definitions concrete, we start with a biological (or any complex, multivariable dynamical system) with a state space specified by vector x=$\{x_1 ... x_n\}$ and some discrete time-evolution operator ϕ(x(t))=x(t+1) which fully determines the distribution of the state variables in the next time step. In the most general case, x_i(t+1)=ϕ_i(x(t)), i.e. where each state variable is potentially dependent on the state of every other variable in the system. Indeed, one could conjecture that an "exact" representation of any biological system would require exactly such a scenario, since in a living organism or an ecosystem, every entity in some indirect way interacts with every other component.

Fortunately, it is often the case that biological systems are in some sense "modular", in that one can identify subsets of variables C=$\{x_1 ... x_m\}$, where for an appropriate ordering of variables, $C_1=\{x_1 ... x_{k_1}\}$, $...C_I=\{x_{\sum_{j=1}^{I} k_j - 1} ... x_{\sum_{j=1}^{I} k_j}\}$, $...C_m=\{x_{n-k_m+1} ... x_n\}$ with $k_J=|C_J|$ the number of elements in the Jth class. These subsets are chosen such that they interact strongly with one another and not at all (or sufficiently weakly) with members of other subsets. Exact decomposability also requires that $C_I \bigcap C_J = \phi$.

Consequently, the state dynamics of any variable $x_i \in C_I$ can be expressed as a function $x_i(t+1)=\phi_i(C_I(t))$, implying that the function ϕ:x(t)→x(t+1) itself is decomposable into functions $\phi_1 ... \phi_I ... \phi_m$, each of which acts only on the state variables within the corresponding partition C_I. From a computational standpoint, it follows that each partition is dynamically self-contained, and that we only need information about the state variables within the same partition to compute the frequency of the variable in the next time step.

As a straightforward example of decomposability, consider a general linear dynamical system x(t+1)=**A**x(t) where **A** is a constant valued square matrix of dimension n with coefficients A_{ij}. For an arbitrary matrix structure, we have $x_i(t+1)=\sum_{j=1}^{n} A_{ij}\, x_j(t)$. However, for a decomposable system, the transition matrix will have a block-diagonal form

$$(0.1) \qquad \boldsymbol{A} = \begin{pmatrix} A_1 & 0 & 0 & 0 & 0 \\ 0 & \ddots & 0 & 0 & 0 \\ 0 & 0 & A_I & 0 & 0 \\ 0 & 0 & 0 & \ddots & 0 \\ 0 & 0 & 0 & 0 & A_k \end{pmatrix}$$

where each square submatrix A_I of dimension k_I (the number of elements in the Ith partition) contains nonzero coefficients for (some) interaction terms A_{ij} for i,j∈C_I, and zero elsewhere, corresponding to the absence of cross-partition interactions. For a system described by a matrix of the above form, we have $x_i(t+1)=\sum_{j\in C_I} A_{ij}\, x_j(t)$ given i∈C_I. It therefore follows that the dynamics within each partition can be represented independently of one another as $C_I(t+1)=A_I\, C_I(t)$. Decomposable linear systems and approximately decomposable systems having this structure have been analyzed in some detail elsewhere (Simon and Ando, 1961).

While no biological system is probably perfectly decomposable in such a way, it is reasonable, at least as a first-order approximation, it is also true that a large degree of localization and modularity exist in organismal design. At any given time during development, gene networks can often be partitioned into regions of strongly interacting components, just as cells giving rise to specific tissue types and organ systems are often developmentally and functionally modular with respect to the rest of the organism. Another well-studied example comes from population biology - the so-called metapopulation (Levins 1969), in which most competition and other forms of interaction between conspecific individuals occur in localized demes rather than across an entire population. One even can argue that biology as a science would be impossible if there would not be a certain minimal degree of decomposability, at least in experimental situations.

The examples of organ systems and interdemic competition raises the related issue of aggregability. Apart from being relatively self-contained modules, organ systems are characterized by what complex systems theorists refer to as "emergent" properties, i.e. from a particular interaction of lower-order "microvariables" there arise identifiable "macrostate" variables which have interaction properties as state variables in their own right. For instance, even though organs are in some sense aggregates of cells, it is obviously useful to think of organs as having roles as individual entities within physiological

systems apart from being aggregates of cell types, just as interacting living organisms are obviously individuated entities rather than a collection of organs.

To formalize these notions of "emergence" and "macrostates," consider again a dynamical system with n state variables, x(t+1)=ϕ(x(t)). We define this dynamical system to be aggregable if there exists some transformation y=f(x) such that y has m<n state variables, and that there is some operator Φ such that y(t+1)=Φ(y(t)) gives a dynamically sufficient description of the dynamics of y (i.e. $y_1 ... y_m$ act as state variables for the aggregated system).

A familiar example of aggregation of variables comes from thermodynamics, where macrostate variables such as energy, temperature, and entropy can be derived from the distribution of molecular microstates in an ensemble, and that the macrostates themselves serve as dynamically sufficient state variables for the system. Aggregation of variables is also implicit in the identification of units of selection in evolutionary biology, in arguing that higher entities such as genomes (or under group selection scenarios, populations) act as units of transmission and selection while being themselves composed of such units (genes) at the lower level.

It should be noted that we make no assumptions about which variables contribute to any macrostate component y_I. In principle, each y_I could be a function of all of the microstates or any subset thereof, y_I=f($x_1 ... x_n$), hence the variables contributing to any two macrostates could contain any number of overlapping microstate variables. Thus, while aggregation of variables provides a reduced variable description of the system dynamics at the macrostate level, the individual macrostates need not be functions of non-overlapping partitions of microstates. Indeed, in the case of thermodynamics, each macrostate variable is a function of every microstate (gas molecule configuration). Consequently, aggregativity need not imply decomposability, nor vice-versa.

Dynamical systems which are both decomposable and aggregable constitute a special class of phenomena. In such systems, each macrostate variable y_I is a function of a partition $f_I(C_I)$, i.e. y_I(t+1)=Φy_I(t)=Φ($f_I(C_I(t))$). Model representations of such systems combine the computational and conceptual advantages of having on the one hand the smaller number of macrostate variables as a consequence of aggregativity and smaller, mutually exclusive subsets of microstates contributing to each variable.

We now turn our attention to the formal properties of decomposable and aggregable linear systems.

■ Aggregation and Decomposability of Linear Dynamical Systems

Consider again a generic, n-dimensional linear dynamical system x(t+1)=**A**x(t). We ask whether there exists an aggregation operator **Q** such that for y=**Q**x, there is a matrix $\hat{\boldsymbol{A}}$ specifying the aggregate dynamics y(t+1)=$\hat{\boldsymbol{A}}$y(t). In general **Q** can be any (mxn) linear operator that projects the n-

dimensional vector x into m-dimensional space for y.

It follows from the definitions of aggregativity that

$$(1.0) \quad \boldsymbol{x}(t+1) = \mathbf{A}\mathbf{x}(t),\ \boldsymbol{Y}(t+1) = \hat{\boldsymbol{A}}\,\boldsymbol{Y}(t)$$
$$\mathbf{Q}\mathbf{A}\mathbf{x} = \hat{\boldsymbol{A}}\,\mathbf{Q}\mathbf{x},$$

therefore, given an aggregation **Q** for a system defined by **A**, the operator for the aggregate dynamics $\hat{\boldsymbol{A}}$ has to satisfy the relation:

$$(1.1) \quad \hat{\boldsymbol{A}}\,\boldsymbol{Q} = \mathbf{Q}\mathbf{A}$$

Note that this relation has to hold for arbitrary aggregation and transition operators, though for the purposes of further analysis we restrict attention to linear operators.

If $\mathbf{Q}\boldsymbol{Q}^T$ is intertible, $\hat{\boldsymbol{A}}$ can be solved for explicitly:

$$(1.2a) \quad \hat{\boldsymbol{A}}\,\mathbf{Q}\mathbf{Q}^T = \mathbf{Q}\mathbf{A}\mathbf{Q}^T,$$
$$\hat{\boldsymbol{A}} = \mathbf{Q}\mathbf{A}\mathbf{Q}^T\,(\mathbf{Q}\mathbf{Q}^T)^{-1}$$

This implies that in cases where an exact aggregation of variables (defined by **Q**) exists, $\hat{\boldsymbol{A}}$ can be expressed in the above form. As will be discussed below, it does not imply that an exact aggregate dynamical operator $\hat{\boldsymbol{A}}$ exists for an arbitrary aggregation rule (though it will be argued that in some sense 1.2a is the best approximation to an aggregate dynamics operator even in cases where an exact aggregation in terms of **Q** doesn't strictly speaking exist).

Expressed in summation form and defining matrix $\mathbf{D}=\mathbf{Q}\boldsymbol{Q}^T$, (1.2a) is

$$(1.2b) \quad \hat{\boldsymbol{A}}_{\mathrm{IJ}} = \sum_{K=1}^{m}\sum_{i=1}^{n}\sum_{j=1}^{n} \boldsymbol{Q}_{\mathrm{Ii}}\,\boldsymbol{A}_{\mathrm{ij}}\,\boldsymbol{Q}^T{}_{\mathrm{jK}}\,\boldsymbol{D}^{-1}{}_{\mathrm{KJ}}$$

The product $\mathbf{Q}\boldsymbol{Q}^T$ in (1.2) is invertible if and only if **Q** is full rank. If **Q** is an orthogonal square matrix, this product is the identity matrix and we have a trivial diagonalisation as the aggregate $\hat{\boldsymbol{A}}=\mathbf{Q}\mathbf{A}\boldsymbol{Q}^{-1}$.

If the row vectors of $\mathbf{Q}=\{q_1 \ldots q_m\}^T$ are orthogonal to one another, $\mathbf{Q}\boldsymbol{Q}^{\boldsymbol{T}}$ is a diagonal matrix with entries $\boldsymbol{D}_{\mathrm{II}}=\sum_{\mathrm{k}\in\mathrm{I}} \mathbf{Q}_{\mathrm{Ik}}{}^2$ (which equals n_I for matrices of unweighted characteristic vectors, since each nonzero coefficient of **Q** is unity) with the inverse $\boldsymbol{D}^{-1}$ having reciprocal entries $\boldsymbol{D}_{\mathrm{II}}{}^{-1}=\frac{1}{D_{\mathrm{II}}}$. Thus, for aggregations of decomposable systems, the coefficients of $\hat{\boldsymbol{A}}$ are, expressed again as sums:

$$(1.3) \quad \hat{\boldsymbol{A}}_{\mathrm{IJ}} = \sum_{i}\sum_{j} \boldsymbol{Q}_{\mathrm{Ii}}\,\boldsymbol{A}_{\mathrm{ij}}\,\frac{\boldsymbol{Q}_{\mathrm{Jj}}}{\sum_k \boldsymbol{Q}_{\mathrm{Jk}}{}^2}$$

It can be shown that some aggregate description exists for any dynamical system specified by a square matrix **A**, albeit an often trivial one. It follows as a general consequence of the spectral theorem for matrices that we can always write an aggregation in terms of the eigensystem of **A**, i.e. for a matrix

of eigenvectors **Q** of **A** with a corresponding diagonal matrix of eigenvalues **Λ**, we have QΛ=QA, because every matrix **A** has at least one eigenvalue λ and at least one associated eigenvector **q**, since we can write **Aq**=λ**q**. We can treat **q** as a (column vector) matrix **Q**, thus the following holds with $\hat{\boldsymbol{A}}=(\lambda)$ and **Q**=**q**:

Result 1.1:
Every nxn matrix **A** with n≥2 has an aggregation of variables with m<n.

As a corollary, given eigenspace $\{\boldsymbol{q}_1 ... \boldsymbol{q}_m\}$ of **A**, associated with eigenvalue λ, the mxn matrix **Q** with rows q_i is an aggregation of variables for **A** with $\hat{\boldsymbol{A}}=\lambda I_m$, where I_m is the mxm identity matrix for some m<n.

If **A** is symmetric, we obtain a stronger result, i.e an aggregation for any m macrostates up to m=n can be constructed:

Result 1.2:

If **A** is symmetric it has an aggregation with every dimension m, 1≤m≤n.

Proof: A symmetric (or Hermitian) has n real eigenvectors. It suffices therefore to select any m of them for the construction of the matrix **Q** of eigenvectors.

The disadvantage of an eigensystem aggregation, of course, is that in order to compute each of the m aggregate variables one requires information about all n microstates, as eigenvectors are generally expressed as a linear combination of all n state variables of a system. Consequently, although the aggregation allows a reduced state variable description of system dynamics, the aggregate variables themselves often have no interpretation from the standpoint of macroscopic system properties. The main motivation behind aggregation of variables, after all, is to uncover dynamically sufficient variables at various levels and clusters of variables that act in a dynamically coherent manner. Identifying subsets of coherently acting variables ultimately allows one to determine the nature of any system's communication with other, similar systems (through interaction of macrostate variables, as in thermodynamics), as well as offering insight into the "emergent" macrostate variables that ultimately drive the relevant system dynamics.

Consequently, we are interested in aggregations which also determine system decompositions (i.e. **Q** with orthogonal row and column vectors), or at least aggregation operators where the entries for any one row or column are a small subset of the total state space. While it follows from Theorems 1.1-2 that some aggregation always exists, it should be apparent that an aggregation with an arbitrary choice of **Q** (one computationally convenient or intuitively meaningful from the standpoint of system structure) need not necessarily satisfy $\hat{\boldsymbol{A}}$**Q**x=**QA**x for any vector x for $\hat{\boldsymbol{A}}$ defined in (1.2).

■ Interpretation of $\hat{A}$

In order for $\hat{A}$ to be an appropriate descriptor of the aggregate dynamics, both X=**Q**x and X(t+1)=$\hat{A}$**Q**x must be meaningful state variables. Ideally, one would want the defining dynamical properties of the original system to be conserved in the transformed, aggregate description. For example, if x describes a probability distribution and **A** is a transition matrix, we expect that X should also be a probability distribution under the action of $\hat{A}$.

In the above special case of **A** a stochastic matrix acting on distribution vectors, it is not necessarily the case that any aggregation of variables (acting on the original state vector x) should give a distribution or that the aggregate dynamics operator $\hat{A}$ is stochastic. For an arbitrary choice of weighted entries in **Q**, $\sum_J \hat{A}_{IJ}$ is not generally equal to unity given $\sum_i A_{ij}=1$ for all j.

Given a row-stochastic, irreducible matrix **A** (the same arguments apply to column stochasticity by transposition and left versus right multiplication), by assumption 1_n**A**=1_n. In order for $\hat{A}$ as to be row-stochastic, we also need to satisfy $1_m\hat{A}=1_m$. Because $\hat{A}$**Q**=**QA**, it follows that

$$\mathbf{1}_m \hat{A}\, Q = \mathbf{1}_m QA = \mathbf{1}_m Q$$

i.e. 1_m**Q** is an eigenvector of $\hat{A}$ with the eigenvalue λ=1. Since by the Perron-Frobenius Theorem this eigenvalue is unique, it follows that 1_m**Q**=1_n. This leads to Lemma 1.0:

Lemma 1.0:

For any positive-definite (and therefore irreducible) stochastic matrix **A**, $\hat{A}$ defined in (1.4) is stochastic if and only if 1_m**Q**=1_n

since $(1_m Q)_i=\sum_{j=1}^{m} q_{ij}$, i.e. the column sum of **Q**, this condition will always be fulfilled for a partitioning.

One often encounters a more fundamental problem than conservation of stochasticity in the transformation from **A** to $\hat{A}$. While (1.2) follows as a consequence of (1.1), the converse is not true, i.e. it does not follow that given a rate matrix **A** and an arbitrary aggregation **Q** there will be a dynamically sufficient description of the aggregate variables in terms of $\hat{A}$=$\mathbf{QAQ}^{\mathsf{T}}\left(\mathbf{QQ}^{\mathsf{T}}\right)^{-1}$. Otherwise it would be the case that any aggregation (at least those specified by full-rank aggregation matrices) would be possible for any linear dynamical system.

To see that given some transition operator **A** and a choice of aggregation **Q**, the matrix $\hat{A}$ in (1.2) does not in general satisfy (1.1),

$$\hat{A} = \mathbf{QAQ}^T\left(\mathbf{QQ}^T\right)^{-1} \Longrightarrow \hat{A}\,\mathbf{QQ}^T = \mathbf{QAQ}^T \Longrightarrow$$
$$\hat{A}\,\mathbf{QQ}^T Q = \mathbf{QAQ}^T Q$$

the last line cannot generally be rewritten as $\hat{\boldsymbol{A}}\mathbf{Q}=\mathbf{QA}$ because ($\boldsymbol{Q}^T\mathbf{Q}$) is not itself a full-rank matrix and is therefore not invertible.

On the other hand, it is the case that in some sense $\hat{\boldsymbol{A}}$ as defined in (1.2) is the best approximation to the aggregate dynamics given an arbitrary (not exactly aggregable) **A** and choice of aggregation **Q**. By "best approximation", we mean that for a defined set of state vectors x, we want to minimize the difference between the aggregation of the state vector after a time step, Y(t)=**QA**x(t) versus the approximation to Y(t) as $\hat{\boldsymbol{A}}\mathbf{Q}$x(t). To do this we compute the distances for some norm of

$$||\,Y(t)-\boldsymbol{Q}x(t)\,||=||\,\boldsymbol{B}^t\,Y(0)-\boldsymbol{Q}\,\boldsymbol{A}^t\,x(0)\,||$$

given a choice of aggregate dynamic matrix **B**, or equivalently, we ask which **B** minimizes ||**BQ**x-**QA**x|| for a set of x in the state space. From the following result, we can show that **B**=$\hat{\boldsymbol{A}}$ will on average minimize the difference:

Theorem 1.1:
The matrix **B**=$\hat{\boldsymbol{A}}$ minimizes $\min_B$||**BQ-QA**||, where the matrix norm ||X|| is the Frobenius (Euclidean) norm, i.e.

$$||X||=\left(\sum_{i,j}X_{ij}\right)^{1/2}$$

We derive the **B** that minimizes ||**BQ-QA**|| by differentiating and solving for the coefficients of **B** (here the indices I,J and K,L denote the m rows of **Q**, while i,j and k,l are used to index the n columns of **Q** and the rows/columns of **A**)

$$(1.6)\qquad \frac{\partial\,(\,||\,\mathbf{BQ}-\mathbf{QA}\,||\,)^2}{\partial\,\boldsymbol{B}_{IJ}}=$$

$$2\sum_K\sum_k\left(\sum_L\boldsymbol{B}_{KL}\,\boldsymbol{Q}_{Lk}-\sum_l\boldsymbol{Q}_{Kl}\,\boldsymbol{A}_{lk}\right)\left(\sum_L\boldsymbol{Q}_{Lk}\,\frac{\partial\,\boldsymbol{B}_{KL}}{\partial\,\boldsymbol{B}_{IJ}}\right)=0$$

The partial derivative $\frac{\partial\,\mathbf{B}_{KL}}{\partial\,\mathbf{B}_{IJ}}$ = 1 for K=I, J=L and is 0 otherwise. Hence, (1.6) can be rewritten as: $\sum_Y\,\delta_{KI}\,\delta_{LJ}\,\mathbf{Q}_{Lk}=\delta_{KI}\mathbf{Q}_{Jk}$. Substituting, we obtain

$$\sum_K\sum_k\sum_L\boldsymbol{B}_{IJ}\,\boldsymbol{Q}_{Jk}\,\delta_{KI}\,\boldsymbol{Q}_{Jk}=\sum_K\sum_k\sum_l\boldsymbol{Q}_{Xl}\,\boldsymbol{A}_{lk}\,\delta_{KI}\,\boldsymbol{Q}_{Jk}$$

$$\sum_L\boldsymbol{B}_{IL}\sum_k\boldsymbol{Q}_{Lk}\,\boldsymbol{Q}^T_{kJ}=\sum_L\boldsymbol{B}_{IL}\,\boldsymbol{D}_{LJ}=\sum_k\sum_l\boldsymbol{Q}_{Kl}\,\boldsymbol{A}_{lk}\,\boldsymbol{Q}^T_{kJ}$$

The last expression is equivalent to $\mathbf{BQ}\boldsymbol{Q}^T=\mathbf{QA}\boldsymbol{Q}^T$, therefore $\mathbf{B}=\hat{\boldsymbol{A}}$ minimizes the Euclidean norm $\|\mathbf{BQ-QA}\|$.

This does not mean that $\|\hat{\boldsymbol{A}}\mathbf{Q}x-\mathbf{QA}x\|$ is minimized for any choice of x (or even lower dimensional subspaces of the n-space of x), however, it does mean that over an $\nu \leq n$ dimensional region the vector space defined by the rowspace of $\mathbf{A}$, $\hat{\boldsymbol{A}}$ gives a minimum distance between $\hat{\boldsymbol{A}}\mathbf{Q}x$ and $\mathbf{QA}x$.

It follows because for any choice of a uniform state vector $\bar{x}=\{\bar{x}_1 ... \bar{x}_n\}$ where $\bar{x}_i=\bar{x}_j$ and an n-dimensional sphere $\xi(x)$ about $\bar{x}$, letting $\mathbf{G}=\mathbf{BQ-QA}$, $\psi=\mathbf{G}x=\mathbf{BQ}x-\mathbf{QA}x$ (with g_{ij} the coefficients of $\mathbf{G}$):

$$\psi_i = \sum_{j=1}^{n} g_{ij}\, x_j, \quad |\psi|^2 = \left(\left| \sum_{j=1}^{n} g_{ij}\, x_j \right| \right)^2 = \left(\sum_{j=1}^{n} g_{ij}\, x_j \right) \left(\sum_{j=1}^{n} g_{ij}\, x_j \right) =$$

$$\sum_i \left(\sum_j g_{ij}\, x_j \right) \left(\sum_k g_{ik}\, x_k \right) = \sum_j \sum_k x_j\, x_k \sum_i g_{ij}\, g_{ji} = < x\boldsymbol{G}^T\boldsymbol{G}x >$$

Computing the expected value of $|\psi|^2$, by integrating over $x=\{x_1 ... x_n\}$, we derive:

$$E[|\psi|^2] = \int |\psi|^2 \xi(x)\, dx =$$

$$\sum_i \sum_j \sum_k G_{ij} \int \xi(x)\, x_j\, x_k\, dx\, G^T_{ji} = \sum_i \sum_j \sum_k G_{ij}\, (\mathrm{Cov}(x_j, x_k) + \bar{x}^2)\, G^T_{ji}$$

For a distribution $\xi(x)$ with spherical symmetry around $\bar{x}$ (i.e. for all x_i, $\xi(\bar{x}+x_i')=\xi(\bar{x}-x_i')$), we have $\int x_i\, \xi(x_1 ... x_n)\, dx_i = 0$, therefore:

$$\mathrm{Cov}(x_j, x_k) + \bar{x}^2 = \int \xi(x)\, x_j\, x_k\, dx =$$

$$\int\int \ldots \int x_j \int x_k\, \xi(x_1 \ldots x_n)\, dx_j\, dx_k \ldots dx = \delta_{jk}\, \mathrm{Var}(x_j)$$

since by definition, spherical distributions have zero cross term covariances. Furthermore, we require that the radii in all orthogonal directions are equal, i.e. $\mathrm{Var}(x_i)=\mathrm{Var}(x_j)=\sigma^2$ for all i,j. Consequently,

(1.7)

$$E[|\psi|^2] =$$

$$(\sigma^2 + \bar{x}^2) \sum_i \sum_j g^2_{ij} = (\sigma^2 + \bar{x}^2)\, (||\boldsymbol{G}||)^2 = (\sigma^2 + \bar{x}^2)\, (||\mathbf{BQ} - \mathbf{QA}||)^2_{\min}$$

If for convenience we chose $\bar{x}=0$ and the variance (corresponding to the square of the n-ball radius) equal to unity, then the integral over the sphere gives us $(||\mathbf{BQ} - \mathbf{QA}||)^2_{\min}=\|\hat{\boldsymbol{A}}\mathbf{Q}-\mathbf{QA}\|$. Consequently, one can think of (1.2) as the best possible approximation to an aggregable system even

in cases where an exact aggregation is not possible.

Even for transition operators that are not aggregable with respect to a given **Q**, we can ask whether there exists a subspace of values x for which the system is exactly aggregable. We show that for systems where the aggregation matrix corresponds to a partition (decomposition) of variables, one can specify conditions on x and on **A** such that

$$\mathbf{QA}x = \mathbf{QAQ}^T\ (\mathbf{QQ}^T)^{-1}\ \mathbf{Q}x$$

holds exactly.

We restrict our attention to partitionings defined by **Q**, i.e. aggregations which are also decompositions. With a proper ordering of state variables, the partition matrix can be written in the form

$$\mathbf{Q} = \begin{pmatrix} q_1 & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & q_m \end{pmatrix}$$

If the aggregate variables are an unweighted sum $\sum_{i\in C_I} x_i$, each vector q_I is a characteristic vector defined such that q_{i_I}=1 for $x_i \in C_I$ and 0 otherwise. Because the aggregate variables for partitions are functions of non-overlapping subsets of variables, they tend to be more computationally tractable in determining conditions for aggregability.

We first compute the constraints on x for arbitary **A** and **Q** for which the aggregation is exact. Rewriting the matrix products in terms of sums, we have

$$(1.8\,a) \qquad (\mathbf{QA}x)_I = \left(\sum_i Q_{Ii}\,A_{ij}\right) x = \sum_j \left(\sum_i Q_{Ii}\,A_{ij}\right) x_j$$

for Q_I a characteristic vector, the above evaluates to

$$(1.8\,b) \qquad (\mathbf{QA}x)_I = \left(\sum_{i\in I} Q_{Ii}\,A_{ij}\right) x = \sum_j \left(\sum_{i\in I} A_{ij}\right) x_j$$

while applying (1.3) gives us for the general case

$$(1.9\,a)$$

$$\left(\mathbf{QAQ}^T\ (\mathbf{QQ}^T)^{-1}\ \mathbf{Q}x\right)_I = \sum_J \left(\sum_{i\in I}\sum_{j\in J} \mathbf{Q}_{Ii}\,\mathbf{A}_{ij}\,\frac{\mathbf{Q}_{Jj}}{\sum_{k\in J}\mathbf{Q}_{Jk}{}^2}\right) \sum_{k\in J} \mathbf{Q}_{Jk}\,x_k$$

which for matrices of characteristic vectors is

$$(1.9\,b)\quad \sum_{J}\left(\sum_{i\in I}\sum_{j\in J}\frac{1}{n_J}\,\boldsymbol{A}_{ij}\right)\sum_{k\in J}x_k$$

Setting (1.8b) equal to (1.9b) and solving for x given arbitary **A**, we have

$$(1.10\,a)\quad x_j=\frac{1}{n_J}\sum_{j\in J}x_j\;\; j\in C_J\implies x_i=x_j\;\;\forall\, i,\, j\in C_I$$

i.e. exact aggregation is satisfied whenever the within-partition distributions are uniform.

When the coefficients of **Q** are weighted characteristic vectors and thus not equal to unity, in order for (1.8a) to equal (1.8b), the entries of x must satisfy the relationship:

$$(1.10\,b)\quad x_j=\frac{\boldsymbol{Q}_{Jj}}{\sum_{k\in J}\boldsymbol{Q}_{Jk}^{2}}\sum_{j\in J}\boldsymbol{Q}_{Ik}\,x_k\;\;\forall\, j,\, k\in C_J$$

If the aggregate variables are an unweighted sum $\sum_{i\in C_I}x_i$, each vector q_I is a characteristic vector defined such that q_{i_I}=1 for $x_i\in C_I$ and 0 otherwise. Because the aggregate variables for partitions are functions of non-overlapping subsets of variables, they tend to be more computationally tractable in determining conditions for aggregability.

We first compute the constraints on x for arbitrary **A** and **Q** for which the aggregation is exact. Rewriting the matrix products in terms of sums, we have

$$\sum_{J}\left(\sum_{r\in J}\sum_{i\in I}\boldsymbol{Q}_{Ii}\,\boldsymbol{A}_{ir}\,\frac{\boldsymbol{Q}_{Jr}}{\sum_{k\in J}\boldsymbol{Q}_{Jk}^{2}}\right)\boldsymbol{Q}_{Jj}=\sum_{i\in I}\boldsymbol{Q}_{Ii}\,\boldsymbol{A}_{ij}$$

Because Q is nonzero only for j∈J, the outer sum on the left-hand side evaluates to the term inside the parentheses multiplied by Q, giving us the constraint

$$(1.11\,a)\quad \sum_{r\in J}\sum_{i\in I}\boldsymbol{Q}_{Ii}\,\boldsymbol{A}_{ir}\,\boldsymbol{Q}_{Jr}=\frac{\sum_{k\in J}\boldsymbol{Q}_{Jk}^{2}}{\boldsymbol{Q}_{Jj}}\sum_{i\in I}\boldsymbol{Q}_{Ii}\,\boldsymbol{A}_{ij}$$

In the case of **Q** a matrix of characteristic vectors, both sides simplify to:

(1.11 *b*)

$$\sum_{i\in I} \boldsymbol{A}_{ij} = \frac{1}{n_J} \sum_{j\in J} \sum_{i\in I} \boldsymbol{A}_{ij} \Longrightarrow \sum_{i\in I} \boldsymbol{A}_{ij} = \sum_{i\in I} \boldsymbol{A}_{ik} \quad \forall\, j,\, k \in C_J$$

This corresponds to a matrix **A** where the within-partition column sums are equal to a constant. Matrices with this structure are said to be column-equitable (Tinhofer and Stadler 2001) and correspond to an equitable partition of state variables. From this we can conclude that an exact aggregation corresponding to equitable partitions are always satisfied for column (or row) equitable matrices. In the case of arbitrary coefficients in **Q**, the constraint can be interpreted as a weighted column-equitability.

Conditions (1.11) insure that **A** is aggregable under the constraints of **Q** for any choice of state vector x. While (1.10) suggests that for an arbitrary **A** there will always be some x which satisfy exact aggregability, it turns out that only for column-equitable matrices are aggregable solutions x invariant and stable under the action of **A**, (in other words, if x(t) is aggregable, x(t+1)=**A**x(t) will only be aggregable if **A** is column equitable), i.e.

Result 1.3:

If x is an exactly aggregable solution $\mathbf{Q}\hat{\boldsymbol{A}}$x=**AQ**x, then in general **A**x is also aggregable if and only if **A** is column-equitable.

In the case of **Q** a matrix of characteristic vectors, if x satisfies the aggregability conditions, then from (1.10) we know that $x_i = x_j$ for all i,j$\in C_I$. Since we have

$$(\boldsymbol{A}x)_i = \sum_k A_{ik}\, x_k = \sum_K \sum_{k\in K} A_{ik}\, x_k$$

and equality of x_{k_K} for all k within each partition K, in order for

$$\sum_K \sum_{k\in K} A_{ik}\, x_k = \sum_K \sum_{k\in K} A_{jk}\, x_k \Longrightarrow A_{ik} = A_{jk} \text{ for } i,\, j \in C_I .$$

In the case of real-valued coefficients of **Q**, the same reasoning shows that if x satisfies (1.10b), then **A**x will generally only be aggregable if the weighted-column equitability condition (1.11b) holds.

■ Equitable Partitions

Exact aggregability of a transition matrix **A** (with A_{ij} the transition rate from j to i) requires that given partitions C_I,C_J

$$\sum_{i\in I} A_{ij} = \sum_{i\in I} A_{ik} = S_{IJ} \quad \forall\, j,\, k \in C_J;\ i\in C_I$$

An intuitive interpretation of the constant column sum s_{IJ} is that every element i of the partition I has the same number (or, in the continuous case, magnitude) of connections to some element(s) of partition J. There is no requirement that the matrices be symmetric, therefore the sum of connections from all elements of J to any particular element i of I need not be constant. This corresponds to the special case of a column-equitable partition of a transition matrix.

An equitable partitioning of any set of vertices corresponds to a decomposition into subsets such that every element of each subset has the same number of connections (overall) to the elements of any other partition. The concept of equitable partitions was first developed in connection to graph theory (Schwenk 1974, McKay 1981, Godsil 1990) as a method of identifying graph invariance properties under within-partition perturbation.

The graph-theoretic definition of equitable partitions is given a graph G=(V,E) with vertex set V,E and a partition of vertices $\pi=(C_1 ... C_m)$ into m non-empty and mutually disjoint subsets C. The partition π is said to be equitable if for any i and j the number of neighbors (denoted by R_{IJ}) of any vertex $x_j \in C_J$ depends only on the partition indices I,J and thus independent of choice of vertex within a partition.

The equivalence classes defined by an equitable partition specify a reduced "quotient graph" G/π, a directed multigraph where each partition C_J is represented as a "reduced" vertex V_J with R_{IJ} connections to vertex V_I. Any partition π corresponds to a representation as a characteristic matrix **Q** such that $Q_{Ii}=1$ for $i \epsilon I$ and 0 otherwise.

Figure 0 illustrates equitable partitioning on a graph. Consider first the 12 vertex, 15 edge graph on the left hand side. The labeled graph on the right hand side codes each vertex by shadings and shapes in accordance to membership in equivalence classes (e.g. solid circles have one solid circle and two open circle neighbors, shaded squares are defined by having one open circle, one shaded square, and one open square neighbor, etc). The directed graph on the bottom represents the quotient graph for the equitable partitioning.

The number of edges R_{IJ} can be computed directly from the adjacency matrix of the original graph in Figure 1. Arranging terms so that members of the same equivalence classes are in the same partition blocks, we get the adjacency matrix, with $A_{ij}=1$ for vertices connected by an edge and 0 otherwise:

$$\boldsymbol{A} = \begin{pmatrix} 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 \end{pmatrix}$$

for which the quotient graph coefficients (corresponding to the number of edges connecting "aggregate" vertices in the lower graph of Fig. 1) are given by:

$$R_{IJ} = \sum_{i \in I} \sum_{j \in J} A_{ij} \; ; \quad \boldsymbol{R} = \begin{pmatrix} 0 & 2 & 1 & 0 \\ 1 & 1 & 0 & 0 \\ 1 & 0 & 1 & 2 \\ 0 & 0 & 1 & 0 \end{pmatrix}$$

The matrix **R** can be interpreted as an aggregation of variables representation of the adjacency matrix **A**, note that according to definition (1.2), **R** differs from $\hat{\boldsymbol{A}}$ only by normalization constants. Equitable partitioning can be interpreted as an exact aggregation of variables where the aggregation matrix specifies equivalence classes with respect to the number of neighbors in other subsets.

As with any subsets defined by an equivalence relation, equitable partitions can be interpreted as the orbits under the action of a permutation (group automorphism) on the vertex set. This basic property of vertex invariance within a partition can be described formally by defining equitable partitions as orbits of a group automorphism of a graph. If Aut[G] is the is the automorphism (permutation) group of all permutations of G, and H is any subgroup of Aut[G], then the orbits $O_1^H ... O_m^H$ of V under H define an equitable partition and correspond to $C_1 ... C_m$.

The definition of equitable partitions is readily generalized to transition matrices with non-discrete coefficients. Stadler and Tinhofer (2001) define a row and column equitable matrices, respectively, such that given any partition π (and corresponding aggregation matrix **Q** with row vector q_I),

$$(2.1) \quad \boldsymbol{A} q_I = \sum_{J=1}^{m} \boldsymbol{R}_{JI} \, q_J \; ; \quad q_I^T \boldsymbol{A} = \sum_{J=1}^{m} \boldsymbol{S}_{IJ} \, q^T{}_J$$

where

$$\boldsymbol{R}_{IJ} = \sum_{j \in J} \boldsymbol{A}_{ij} \; ; \quad \boldsymbol{S}_{IJ} = \sum_{i \in I} \boldsymbol{A}_{ij}$$

The matrix is row-equitable if for some real-valued matrix **R** (referred to as the structure matrix of an equitable partition G/π) such that all rows of the submatrix $\boldsymbol{A}_{\mathrm{IK}}$ (a rectangular submatrix of dimension $|C_I|$x$|C_K|$, i.e. the submatrix where all entries of $\boldsymbol{A}_{\mathrm{ij}}$ with i$\in C_I$ and j$\in C_J$) sum to the same value $\boldsymbol{R}_{\mathrm{IJ}}$. Column equitability requires that the every column sum within block I,J is equal to $\boldsymbol{S}_{\mathrm{IJ}}$.

Matrices which satisfy both the row and column equitability relationships are said to be "equitable." This is a stronger condition than is necessary for exact aggregation, but it does not require matrix symmetry or identity of all A_{ij} for all i,j$\in C_I, C_J$. An equitable matrix has the property:

$$(2.2) \qquad \boldsymbol{S}_{\mathrm{IJ}}\, n_I = \boldsymbol{R}_{\mathrm{IJ}}\, n_J$$

where $n_I = |C_I|$, etc. Equitable matrices have a number of significant spectral properties (Stadler and Tinhofer 2000), which are briefly summarized by the following theorem:

Theorem 2.1 (Stadler and Tinhofer, 2000):

If **R** and **S** are the row and column structure matrices for **A**,π, and q_I is the characteristic vector partition C_I, then for matrix eigenvalues λ and eigenvectors x,

a) Spec(**R**)=Spec(**S**)$\subseteq$Spec(**A**)

b) **A**x=λx and q_Ix$\neq$0 for some i $\Longrightarrow \lambda\in$Spec(**S**)

c) $\chi_R(x)=\chi_S(x)$; if **A** is diagonalizable, then **R**,**S** are diagonalizable and $\chi_R(x)$ is a factor of $\chi_A(x)$.

Computing the aggregation matrix $\hat{\boldsymbol{A}}$ for an equitable partition is straightforward using (1.2), for **A** a column equitable matrix, we have

$$(G/\pi)_{\mathrm{IJ}} = \hat{\boldsymbol{A}}_{\mathrm{IJ}} = \left(\mathbf{Q}\mathbf{A}\mathbf{Q}^T\,(\mathbf{Q}\mathbf{Q}^T)^{-1}\right)_{\mathrm{IJ}} = \sum_{i\in I}\sum_{j\in J}\frac{1}{n_J}\boldsymbol{A}_{\mathrm{ij}}$$

which is simply $\frac{1}{n_J}$ **S**.

Because the aggregate matrix is simply a normalized structure matrix, it follows from the above Theorem that any eigenvalues of the aggregate matrix $\hat{\boldsymbol{A}}$ will also be eigenvalues of the adjacency matrix **A**, while the characteristic polynomials of $\hat{\boldsymbol{A}}$ will be factors of the characteristic polynomial of **A** provided that **A** is a diagonalizable matrix.

It was shown above that the concept of equitable partitioning can be extended to aggregation matrices **Q** whose nonzero entries are arbitrary positive real numbers rather than unity. While the column-equitable partition constraint (1.11b) follows from aggregation by characteristic vectors (1.8b), a more general criterion (1.11a) describes the conditions on **A** consistent with weighted characteristic vectors. We will refer to such systems as "weighted" equitable partitions, i.e. systems where the aggregated variables also correspond to a decomposition.

A special case of weighted equitable partitioning is that of the decomposable systems discussed in Simon and Ando (1961). For a dynamical system specified by a matrix of the form (0.1), over a timescale sufficient such that every state vector subset x_I whose dynamics are given by submatrix $\boldsymbol{A}_I$ is

within some error ϵ of its equilibrium distribution, there exists an aggregation of variables given by **Q** such that $q_I = \tilde{v}_I$ (the first eigenvectors of $\boldsymbol{A}_I$) and a corresponding aggregate dynamics operator $\hat{\boldsymbol{A}}_{\mathrm{II}} = \lambda_{I_1}$ (the leading eigenvalue of $\boldsymbol{A}_I$).

Aggregation of variables in Simon-Ando type systems, where the row vectors of **Q** are the first eigenvectors of each submatrix, represent a limiting scenario for equitable partitions, namely one where the membership of any variable $x_{i_I} \in C_I$ is determined not by symmetries of interaction but simply by whether there is any interaction with another state variable at all. Because there is no symmetry requirement for within-partition interactions, each coefficient of **Q** has a real-valued term, $q_{i_I} = \tilde{v}_{i_I}$.

■ Equitable Partitions on Fitness Landscapes

Introducing equitable partitions from a graph theoretic perspective makes a number of biological applications intuitive. Many biological systems, including metabolic and gene networks, are represented as (edge or vertex-weighted) graphs. Perhaps the best-studied graph representation in biology is the model of a fitness landscape, or more generally, a genotype configuration space. We propose that equitable partitioning may prove to be a powerful tool for analyzing complex fitness landscapes, in that it offers both an aggregate-variable description of system dynamics and the identification of self-contained decomposable entities that serve as building blocks of fitness functions.

A "fitness landscape" (Wright 1932, Stadler 1994) consists of a configuration space (V,ξ) of entities (genotypes, phenotypes, etc) and a real-valued function $f(V) \to \mathbb{R}$ mapping each vertex to a fitness value. The configuration space itself is defined by some neighborhood relationship between vertices, most often defined in terms of transition probabilities between different genotypes via mutation. If we define genotypes as length n strings where each "locus" has one of a k-letter alphabet, the vertex set consists of k^n genotypes. The neighborhood relationship is specified by positing a per-locus point mutation rate μ.

Because mutations at each locus are independent of one another, the mutation matrix can be represented recursively as a Kronecker product of per-locus mutation matrices (Rumschitzki 1987, Eigen et al 1989), i.e. an n-locus mutation matrix **M** is constructed as follows (assuming equal mutation rates at all loci and equal rates between alleles at any locus):

$$(3.1)\quad \boldsymbol{M} = \begin{pmatrix} M_{n-1} & \mu M_{n-1} & \cdots & \mu M_{n-1} \\ \mu M_{n-1} & \ddots & \mu M_{n-1} & \mu M_{n-1} \\ \vdots & \vdots & \ddots & \vdots \\ \mu M_{n-1} & \mu M_{n-1} & \cdots & M_{n-1} \end{pmatrix} = \begin{pmatrix} 1 & \mu & \cdots & \mu \\ \mu & \ddots & \mu & \mu \\ \vdots & \vdots & \ddots & \vdots \\ \mu & \mu & \cdots & 1 \end{pmatrix} \otimes M_{n-1}$$

If we posit a sufficiently low point (per locus) mutation rate $\mu << 1$ such that the probabilities of multiple mutants per generation scale in proportion to $\mu^d \approx 0$ for $d \geq 2$, then a reasonable first-order approximation of the mutation space is as a Hamming graph (V,E), where E is an edge connecting any two vertices (x,y) whose Hamming distance d(x,y)=1.

Constructing a transition (weighted adjacency) matrix for mutation on a Hamming graph is straightforward. For an n-locus system with point mutation, as a first order approximation (with column normalization) the mutation matrix **M** is specified by:

$$M_{ij} = \mu \text{ if } d(i,j) = 1; \quad M_{ij} = 1 - n\mu \text{ if } d(i,j) = 0$$
$$M_{ij} = 0 \text{ if } d(i,j) \geq 2$$

with the transmission dynamics fully determined by x(t+1)=**M**x(t).

The factorization of mutation matrices into individual loci suggests an immediate application of equitable partitioning to **M**. Since the ordering of genotypes is arbitrary, we can arrange them into equivalence classes defined by the allelic identity at any given locus. For example, we write down the possible genotypes hierarchically by allelic identity at each locus for a 2 locus, 3 allele system, 000,001,010,011,100,101,110,111, the mutation selection matrix is

$$M_3 = \begin{pmatrix} 1-3\mu & \mu & \mu & 0 & \mu & 0 & 0 & 0 \\ \mu & 1-3\mu & 0 & \mu & 0 & \mu & 0 & 0 \\ \mu & 0 & 1-3\mu & \mu & 0 & 0 & \mu & 0 \\ 0 & \mu & \mu & 1-3\mu & 0 & 0 & 0 & \mu \\ \mu & 0 & 0 & 0 & 1-3\mu & \mu & \mu & 0 \\ 0 & \mu & 0 & 0 & \mu & 1-3\mu & 0 & \mu \\ 0 & 0 & \mu & 0 & \mu & 0 & 1-3\mu & \mu \\ 0 & 0 & 0 & \mu & 0 & \mu & \mu & 1-3\mu \end{pmatrix}$$

It can be seen that there are several decompositions of **M** consistent with equitable partitioning. The first and obvious one is that a partition into 4x4 blocks (corresponding to equivalence classes identical at the first locus 0** and 1**) is equitable. If we use right multiplication such that x(t+1)=**M**x(t) for a genotype distribution x, then the column structure matrices S_{II}=1-2μ should be proportionate to the exchange rates within equivalence classes while S_{IJ}=μ should give a measure of cross-partition exchange rates.

Generalizing this result is straightforward because every point mutational neighbor except for the one at the reference locus lies within its respective partition, therefore for an n-locus mutation system, S_{II}=1-(n-1)μ and S_{II}=μ. Furthermore, under the assumption of equal forward and reverse mutation rates, the matrix is symmetric, so that **R**=**S** for any mutation matrix of this form. Consequently, all of the results of Theorem (2.1) apply, including part c (because **M**=$\boldsymbol{M}^T$, **M** is diagonalizable).

Another consequence of the factorizability of **M** is that the matrix is characterized by "nested" equitable partitions. Within an equivalence class defined as 1**, for example, there are additional equivalence classes defined by 10* and 11* and so forth. For a partition with equivalence classes defined on a pair of loci, the structure matrices have the form R_{II}=1-(n-2)μ, with off-diagonal entries R_{IJ} equal to μ when IJ are members of the same equivalence class with respect to the first locus and 0 otherwise.

This can be repeated over equivalence classes defined over an arbitrary number of loci, i.e. for

k-locus equivalence classes, there are 2^k partition blocks with structure matrix entries R_{II}=1-(n-k)μ and $R_{IJ}=\mu$ for IJ members of the same equivalence class with respect to (k-1) reference loci, otherwise R_{IJ}=0.

Equitable partitioning immediately becomes problematic when we introduce fitness values and have a mutation-selection matrix instead. Using absolute rather than relative measures of frequency and fitness allows a linear representation of mutation-selection systems (Jones 1976, Thompson and McBride 1974, Hermisson et al 2001) i.e.

$$(3.2) \quad x_i(t+1) = x_i(t)\, w_i + \sum_{j=1}^{k} (\mu_{ij}\, w_j\, x_j - \mu_{ji}\, w_i\, x_i)$$

or in matrix form, x(t+1)=**A**x(t) where **A**=**WM** and **W** is a diagonal matrix of fitness values for each genotype, i.e. $W_{ii}=w_i$ and 0 elsewhere.

It should be clear that in general (for instance, the case where all genotypes have different fitness values), there is no symmetry in **A** and thus the mutsel matrix will not be equitable (as every row or column sum within any block partition will be different from every other). However, the same arguments that allow equitable partitioning on a mutation matrix allow it in cases where the fitness function is also factorizable.

If the fitness function of any genotype can be expressed as a product of the fitness contributions of each individual locus, then the mutsel matrix can be constructed recursively given an existing matrix **A** for n-1 loci and an nth locus which at which the 1...ν alleles contribute fitness values w_i^n (nth locus, ith allele),

$$(3.3) \quad A_n = \begin{pmatrix} w_1^n & w_1^n\,\mu & \cdots & w_1^n\,\mu \\ w_2^n\,\mu & \ddots & w_2^n\,\mu & w_2^n\,\mu \\ \vdots & \vdots & \ddots & \vdots \\ w_k^n\,\mu & w_k^n\,\mu & \cdots & w_k^n \end{pmatrix} \otimes A_{n-1}$$

Consider the special case where the fitness contribution at any locus depends only on its allelic state (for instance, in a Boolean genotype, each 0 or 1 has an equal contribution to fitness regardless of its position), which reduces the above recursion to matrices with identical $w_1^1=\ldots w_1^n=w_i$ for all loci. This is analogous to the assumption we made in constructing the mutation matrix, i.e. transition rates being equal at all loci.

Under the assumption of multiplicative effects at each locus (or, in the case of a log transform, additivity), the fitness landscapes corresponds to a single-peak "Fujijama" landscape (sensu Kauffman 1993). To give a concrete example, consider a fitness landscape for an n-locus, 2-allele system where the optimum is chosen for convenience to be x_0={00...0}. We construct a multiplicative fitness function $W(x)=W_0(1-s)^{d(x,x_0)}$, where W_0 is the fitness of the optimum (the same arguments apply for any fitness function which can be expressed as W(x)=f(x_0,d(x,x_0)).

This immediately suggests equivalence classes with respect to fitness measure, defined as all genotypes with the same Hamming distance to the optimum. There are (n+1) such classes, $C_d = \{C_0 ... C_n\}$ where $C_0 = \{x_0\}$ and C_d is the set of $\binom{n}{d}$ vertices of Hamming distance d with respect to the optimum.

An aggregation operator for a Hamming distance-based equitable partition **Q**x=X (with X_d the frequency distribution within the class C_d) is given by a matrix of characteristic vectors (given an arrangement of vertices starting with the optimum down through the various Hamming distance classes 1...n) such that $\boldsymbol{Q}_{\mathrm{dj}}=1$ (or some nonzero coefficient in the case of a weighted aggregation operator) if j is Hamming distance d from the optimum and 0 elsewhere. This gives us:

$$X_d = \sum_{i \in C_d} x_i = \sum_{i=1}^{\binom{n}{d}} x_i$$

Following (1.2), given mutation the mutation-selection matrix **A**, we derive the expression for the aggregate dynamics matrix $\hat{\boldsymbol{A}}$, summed over I,J classes of different components

$$\hat{\boldsymbol{A}} = \sum_{i \in C_I} \sum_{j \in C_J} \frac{1}{n_J} \boldsymbol{A}_{ij} = \sum_{i \in C_I} \sum_{j \in C_J} \frac{1}{\binom{n}{J}} \boldsymbol{A}_{ij}$$

From the definition of equitable partitions each element i of equivalence class I has a constant fitness value, W_I, and all mutation rates μ_{ij} must equal a constant-valued μ_{IJ} for all i,jϵI,J. An additional constraint is imposed by the structure of the hypercube if we hold to the assumption that multi-site mutations are negligible. Because each partition C_I is defined by Hamming distance I between its elements and an optimum genotype, it can be seen that the members of each equivalence class do not communicate with one another apart from the trivial $\boldsymbol{A}_{ii}=W_i(1-n\mu)$ retention rate for each vertex. For instance, if in a 4-locus system {0000} is the optimum, there is no point mutation that will take {1000} to {0100} etc.

This means that for a sufficiently low mutation rate, the aggregate transition rates are in proportion to the cross-term sums

$$\hat{\boldsymbol{A}}_{II} = \frac{1}{n_I} \sum_{i \in I} \sum_{j \in I} \boldsymbol{A}_{ii} \simeq W_I \, (1 - n\mu_{II})$$

$$\hat{\boldsymbol{A}}_{IJ} = \frac{1}{n_I} \sum_{i \in I} \sum_{j \in J} \boldsymbol{A}_{ij} \simeq W_J \, \mu_{IJ} \, n_I \, n_J$$

The coefficients of $\hat{\boldsymbol{A}}$ can be interpreted as "aggregate" mutation rates and fitness values. Because the fitness values of each genotype within any partition are equal, the aggregate fitness value W is equal to that of any its elements w for all iϵC_I. The aggregate mutation rates M_{IJ} represent the collective transi-

tion rate from partition C_I to partition C_I, i.e. $\mu_{IJ}=\sum_{i\in I}\sum_{j\in J}\mu_{ij}$.

As for mutation matrices, the mutsel matrix for a multiplicative single-peaked landscape is both row and column equitable, as a consequence of all genotypes within a partition (distance class) having equal fitness. From Theorem (2.1a) it follows that the eigenvalues of $\hat{\boldsymbol{A}}$ are a subset of those of **A** for a multiplicative landscape.

To illustrate, consider a mutation-selection matrix **A** for a five locus system with a per-locus mutation rate μ=0.1 and fitness values W_{00000}=1 at the optimum genotype and $(1-s)^d$ for any genotype of Hamming distance d, with s=0.1. Figure 1a shows a plot of the spectrum of **A**. It can be seen in the graph that the multiplicity of every eigenvalue corresponding to each distance d class is $\binom{n}{d}$, e.g. λ=0.7366 has a multiplicity of 5, λ=0.6295 has a multiplicity of 10, and so forth.

The spectrum of the aggregated mutsel matrix $\hat{\boldsymbol{A}}$ (Fig. 1b) consists of the same eigenvectors as that of the original matrix, only with multiplicities of unity because each Hamming class is represented as a single variable. The leading eigenvalues of **A** and $\hat{\boldsymbol{A}}$ (in this case λ_1=0.8564) corresponds to the equilibrium mean fitness of the population (Moran 1976, Buerger 1998, 2000), and the same leading eigenvalue characterizes the equilibrium of the aggregate description. This is to be expected, as for any exact aggregation, if $\hat{\boldsymbol{A}}\mathbf{Q}x=\lambda\mathbf{Q}x$, then $\mathbf{A}x=\lambda x$.

Eigen et al (1989, pgs 200-202) implicitly took advantage of equitable partitioning and aggregativity to compute leading eigenvectors (their "quasispecies" distributions) and error-thresholds on a single-peak landscape. While our aggregation operators follow a different scaling and formalization, we essentially replicate Eigen et al's results to illustrate the utility of aggregation methods in calculating mutant-class equilibrium frequencies and estimating error-threshold values.

The leading eigenvector for a single-peak mutation-selection matrix can be interpreted as the mutation-selection equilibrium about the global optimum. Because of the fitness and mutational distance equivalence relations inherent in the system, computing the aggregate frequencies within equivalence classes is as informative about the structure of the system as computing the entire distribution (i.e. we are interested in the frequencies of the optimal fitness genotype, the total number of mutant class 1 neighbors, etc).

Mutation-selection matrices are computed for the same fitness function as in Figure 1, for different per-locus mutation rates. For each mutational value, the mutsel matrix **A** and the aggregate matrix $\hat{\boldsymbol{A}}$ is computed. The stationary distributions derived for each $\hat{\boldsymbol{A}}$ are shown in Figure 2. For low mutation rates of course, the equilibrium distributions are of course concentrated near the optimum, with fairly low probability density about the error one neighbors and negligible probability density elsewhere. In contrast, as $\mu\rightarrow$0.1 (as shown by the lower curves in Fig. 2, with the mutation rate being nμ where n=5 loci), the probability densities at and near the optimum are not necessarily greater than elswhere, illustrating the familiar "error threshold" phenomenon. If individual genotype frequencies rather than aggregate class frequencies were plotted, every frequency would tend towards $\frac{1}{32}$ at the error thresshold. In the case of these plots of aggregate frequency, each class d tends towards $\frac{1}{32}\binom{n}{d}$.

That error threshold estimates can be done on the aggregate representation illustrates that subsets of genotypes defined by distance classes from the optimum are evolutionarily equivalent under point mutation and selection. Hence, there are several implications of an equitable partition representation of a single-peak landscape. On the one hand, by replacing the state variables x_i with $X_I=(\mathbf{Q}x)_I$, we have reduced a 2^n dimensional system to one of n+1 dimensions (with the Hamming class d partition having $\binom{n}{d}$ members). Secondly, in by defining equivalence classes in terms of common fitness values and neighborhood relations to members of other fitness classes, we have identified the entities the selection and transmission process "sees" at a macroscopic level. Because X=**Q**x is a dynamically sufficient description of mutation-selection process, one can regard each aggregate variable X_I rather than each genotype as a unit of evolution.

We next inquire whether equitable partitioning can be generalized to describe more complex landscapes, namely, those where the fitness values of each genotype are defined by distances to multiple local optima.

■ Aggregation of Multipeaked Landscapes

By extension of the model for a single-peaked landscape, we construct a fitness function where the fitness of any genotype depends only on the Hamming distance to a set of k reference vertices, W(x)=$F_w(d_1,d_2...d_k)$, where d_j is the distance of genotype x to the jth vertex. An example of such a fitness function would be one where each reference vertex corresponds to a local optimum, and the fitness of any genotype is determined by how far it deviates from any or all local optima. Again, because the system is defined in terms of Hamming distances, there is the assumption of equivalent effects at each locus.

In order for equivalence classes determined by Hamming distances to be dynamically sufficient entities with respect to mutation and selection operators, both the fitness values and number of mutational neighbors in each class must be fully determined by the Hamming distance values. While fitness-value equivalence classes are well-defined for an arbitrary number of reference vertices, as we will show below it is not necessarily the case that equivalence classes based on fitness are also equivalence classes with respect to the number of mutational neighbors. In other words, unlike the case of a single reference vertex (or, as we will see, two) for three or more reference vertices Hamming distances alone are not sufficient descriptors of neighborhood equivalence classes.

Consider (again on an n-locus, 2 allele configuration space) a fitness function $F_w(d_1,d_2)$ determined by the Hamming distances with respect to two reference vertices x_1,x_2. We define D_{12} as the Hamming distance between the two reference vertices. If D_{12}=n (for example, x_1=00...0 and x_2=11...1), it should be obvious that the equivalence classes are identical to those defined by a single reference vertex, because d_1 is fully determined by d_2=n-d_1.

When the reference vertices are not mirror images, some loci are identical and others are oppo-

site, giving us $0<D_{12}<$n. Taking advantage of the symmetries in this situation, we divide the loci into those that are identical at both reference vertices N_{fix} and those that differ N_{var}=n-N_{fix}. For any genotype x_j, the distance to both reference vertices $D_{(\text{fix}),j}$ on the subset N_{fix} loci is of course the same. The subclass Hamming distances $D_{(\text{fix}),j}$ together with $D_{(\text{var})\,j,2}$ and $D_{(\text{var})\,j,1}$ define equivalence classes with respect to neighbors, because for any choice of genotype the Hamming distance over the fixed subset to both reference genotypes is identical while the subset of variable loci behaves like a size N_{var} single-peak (or opposite pole) partitions. All members of a particular class ($D_{(\text{var})\,j,1}$,$D_{(\text{fix}),j}$) shares exactly the same number of neighbors in class ($D_{(\text{var})\,j,1}$+1, $D_{(\text{fix}),j}$) etc.

In turn, it can be shown that the variable and fixed loci are determined by the Hamming distances of each genotype to the reference vertices and by D_{12}. Over the N_{var} loci, the respective Hamming distances from x_j to $N_{\text{var},1}$ and $N_{\text{var},2}$ are denoted as $D_{(\text{var})\,j,1}$ and $D_{(\text{var})\,j,2}$=N_{var}-$D_{(\text{var})\,j,1}$, i.e.

(4.1)

$$d_{j,1} = D_{(\text{fix}),j} + D_{(\text{var})\,j,1}$$
$$d_{j,2} = D_{(\text{fix}),j} + D_{(\text{var})\,j,2} = D_{(\text{fix}),j} + (N_{\text{var}} - D_{(\text{var})\,j,1}) \Longrightarrow$$
$$d_{j,1} + d_{j,2} = 2\,D_{(\text{fix}),j} + D_{(\text{var})\,j,1} = 2\,D_{(\text{fix}),j} + D_{12}$$
$$d_{j,1} - d_{j,2} = D_{(\text{var})\,j,1} - D_{(\text{var})\,j,2} = 2\,D_{(\text{var})\,j,1} - D_{12} \Longrightarrow$$
$$d_{j,1} = D_{(\text{fix}),j} + D_{(\text{var})\,j,1}$$
$$d_{j,2} = D_{(\text{fix}),j} + D_{(\text{var})\,j,2} = D_{(\text{fix}),j} + (N_{\text{var}} - D_{(\text{var})\,j,1}) \Longrightarrow$$
$$2\,d_{j,1} = 2\,(D_{(\text{fix}),j} + D_{(\text{var})\,j,1})$$
$$d_{j,1} + d_{j,2} - D_{12} = 2\,D_{(\text{fix}),j}$$

From the last set of derived relations, it can be seen that $d_{j,1}$,$d_{j,2}$, and D_{12} are in themselves sufficient to compute D_{fix} and D_{var}. In turn, the latter values define the mutational equivalence classes, because any genotypes which have a common $D_{(\text{var})\,j,1}$ $D_{(\text{var})\,j,2}$ and $D_{(\text{fix}),j}$ with respect to the two reference vertices share the same number of mutational neighbors in other equivalence classes (because D_{fix} and D_{var} fully determine the number of neighbors in hamming classes $D_{(\text{var})\,j,1}$+1, $D_{(\text{var})\,j,2}$-1 etc).

This implies that we can fully describe the mutation-selection dynamics on a fitness function of two variables in terms of pairwise Hamming distances. As there are n possible distances to either x_1 or x_2, there are (n-D_{12}+1)(D_{12}+1) Hamming partitions, each of which has cardinality

(4.2) $$|\,C_{D_{\text{fix}},D_{\text{var}}}\,| = \binom{n - D_{12}}{D_{\text{fix}}} \binom{D_{12}}{D_{\text{var}}}$$

Since D is of order n, the effective dimensionality of the aggregated system is of the order n^2, as one might expect for a system defined by two degrees of freedom. The dynamical sufficiency of pairwise distance classes is illustrated in Figure 3, in which the equilibrium distributions are again computed for a range of mutation rates. The fitness functions are in all cases chosen such that given two local optima

(at 00000 and 10101) with fitness values w_1, w_2, while the fitness of all other genotypes x are given by $w_1(1-s_1)^d + w_2(1-s_2)^d$.

In 3a, we compute distributions for a fitness function corresponding to Eigen et al's degenerate quasispecies, one where $w_1 = w_2 = 1$ over a range of mutation rates (the only difference being in the choices of s values, with $s_2 = .05 < s_1 = 0.1$ so that the fitness function is "sharper" near the first optimum). Unlike the Eigen et al model, the frequencies plotted are not individual genotype frequencies but rather (d_1, d_2) equivalence class frequencies (with (0,3) and (3,0) the frequencies of the local optima). Figure 3b repeats the same for a near-degenerate quasispecies, one where $w_1 = 1$ and $w_2 = .99$, giving error threshold results qualitatively similar to those of Eigen and colleagues.

Taking as an example a fitness function $F_w(d_1, d_2, d_3)$ defined by three variables, it can be shown with a counterexample that at least in the general case, Hamming distances to each of the three reference vertices do not define equivalence relations with respect to the number of neighbors in other Hamming distance classes. If in a four locus system our reference points are 1110,1101,1011, both 1000 and 0111 are in the equivalence class specified by the Hamming distances (2,2,2). However, while 1000 has a neighbor (0000) in the (3,3,3) class, there are no single-set neighbors in the (3,3,3) class for 0111. Consequently, not all genotypes in an equivalence class defined by pairwise Hamming distance (and in this model, fitness) are equivalent in their neighborhood relations. Therefore, from the standpoint of mutation-selection operators, which depend on invariance in both fitness values and number of neighbors across classes, these equivalence classes will not give a dynamically sufficient aggregation.

We can instead ask which equivalence relations do give satisfy the equitable partitioning properties with respect to mutation operators, and to what extent these partitions are concordant with equivalence classes defined by constant fitness. We propose the following method of defining equivalence classes which can be shown to define an equitable partitioning: let κ reference vertices be given. We pick a particular reference vertex (the first one, for instance) and divide the set of all n sites into the allelic state with respect to reference vertex 1.

For κ reference vertices, there are $2^{\kappa-1}$ possible overlap classes $\omega_1, \omega_{12}, \omega_{13} \ldots \omega_{123}, \ldots \omega_{123\ldots\kappa}$ defined in this way, the sizes of which are denoted as

$$n_1,\ n_{12},\ n_{13},\ \ldots n_{123},\ \ldots n_{123\ldots\kappa}$$

with

$$\sum_{\nu\text{-tuples}} n_{1..ij\ldots} = n; \quad \sum_{\nu=1}^{\kappa-1} \binom{\kappa-1}{\nu} = 2^{\kappa-1}$$

where n_1 are the loci with allelic states unique to the first reference vertex, n_{12} is the number of loci shared between reference vertices 1 and 2 but different for all other vertices etc. By simple symmetry arguments, the overlap classes $n_1 = n_{23\ldots\kappa} \ldots n_{123..\kappa} = n_0$ etc, because by definition allelic states that are shared on some set of reference vertices are also shared (in the opposite configuration) by the comple-

menting subset of reference vertices. For example, if an allelic identity of "1" at some locus is unique to a particular reference vertices, then the remaining reference vertices must have the allelic state "0" at that site.

The neighborhood equivalence classes are defined by Hamming distances on the subsets $d_1, d_{12} ... d_{123} ... d_{123...\kappa}$. These represent the (partial) Hamming distances from any genotype to the subsets of loci shared between various ν-tuples of reference vertices, i.e. d_{123} is the Hamming distance of the subset of loci on some genotype to the shared subset configuration defining references vertices 1,2,3.

For the reasons discussed above in the two-dimensional case, the Hamming distances across overlap subsets define equivalence classes with respect to mutational neighborhoods. This can be seen by noting that each overlap set acts as an effective single reference genotype with respect to the appropriate subset of loci, and therefore the partial Hamming distances within any subset of loci defined as shared over a ν-tuple behave in the same way as Hamming distances on a single peak landscape. To see that a partition of loci into overlap classes corresponds to equivalence classes under the action of point mutation, we offer the following proof:

Result: Given a partitioning of loci into ν-tuples, each corresponding to a class of loci with identical allelic states over reference vertices in the ν-tuple, the partial Hamming distances from any genotype to the ν-tuple reference vertices specifies an equitable partitioning.

Proof: We define the Hamming distance from any genotype to the ith reference vertex as D_i and the partial distances to the ν-tuple overlap classes as d_ν. Consider two genotypes x_1 and x_2.

First, equal partial distances to the ν-tuple classes imply equal Hamming distances, because each D is a function of the d, namely

$$D_i = \sum_{\nu\text{-tuples}} \delta_{\nu,i} \left(\frac{n_\nu}{2} + \delta_{\nu,i} \left[d_{\nu,i} - \frac{n_\nu}{2} \right] \right)$$

where $\delta_{\nu,i}$=1 if i∈ν-tuple, -1 otherwise. In other words, if i is a member of the ν-tuple, we add d, otherwise (n-d). Similarly, equal overlap classes imply equal Hamming distance neighborhood classes for any number of point mutations in a ν-tuple set of loci. Assuming that x_1 and x_2 are in the same overlap classes, then for any mutation in x_1, one can pick a mutation in x_2 such that the mutant sequences are in the same overlap (ν-tuple) equivalence class. In turn, equal overlap classes imply equal Hamming distance classes, therefore corresponding mutations in the same ν-tuples of x_1 and x_2 will result in genotypes in the same Hamming classes ($D_1 ... D_\kappa$).

We note that while these results were derived for a 2-allele system, they can in principle be generalized to scenarios with an arbitrary number of allels provided that certain constraints on the fitness effects of each mutation are met (see Appendix). Because the equivalence classes defined by overlap classes in the k-reference vertex case reduce to equivalence classes defined by Hamming dis-

tances in the k=1 and k=2 cases, Hamming distance-based classes can be made to define equitable partitions for l-allele models.

To illustrate an equitable partitioning for a three variable fitness function, consider again the four locus system with the reference vertices 1110,1101,1011. The ν-tuplet subsets of loci (g_ν) defined by overlaps are g_{123}=1***, g_{12}=*1**, g_{13}=**1*, g_{23}= ***1, each with corresponding size n_ν=1. By symmetry, n_{12} is the mirror-image of n_3 (defining the same loci) and so forth for other doubles and singletons. For any genotype (we will use 0000,0101,1010,1111 as examples), the partial Hamming distances of these four genotypes on the four subsets are, respectively (d_{123}, d_{12}, d_{13},d_{23})=1111,1010,0101,0000.

In this case there are four overlap classes with sixteen possible partial Hamming distance configurations. The example suggests a generalized expression for the number of configuration classes and by extension the size of the aggregated state space.

A neighborhood equitable partitioning into subsets defined by overlap class distances gives us a state space of size:

$$(4.3) \qquad \prod_{\nu\text{-tuples}} (n_{ijk\ldots}+1) \le \left(\frac{n}{2^{k-1}}+1\right)^{2^{k-1}}$$

the upper bound is for the "worst case scenario" of reference vertices spaced equidistantly from another (with an expected distance of $\frac{n}{2^{k-1}}$ between each vertex). The number of aggregate variables is of the order $n^{2^{k-1}}<2^n$, which is a substantial reduction of system dimensionality when k<<n.

In turn, the number of genotypes in each equivalence class defined by ($d_{1\,j}$,$d_{12\,j}$,...$d_{123\,j}$,...$d_{123\ldots\kappa\,j}$) is

$$(4.4) \qquad \left| C_{d_1, d_{12\,j}, \ldots d_{123\,j}, \ldots d_{123\ldots\kappa\,j}} \right| = \prod_{\nu\text{-tuples}} \binom{n_{12..\nu}}{d_{12..\nu}}$$

In the case of two reference vertices, (4.3) and (4.4) reduce to (4.2), as expected. Furthermore, if the reference vertices are chosen "sequentially" with respect to one another such that every reference vertex contains a subset or mirror image of every other one (e.g. 0000,1100,1111), the state space is reduced due to the number of degrees of freedom being less than the number of reference vertices (i.e. the distance to 0000 is simply n minus the distance to 1111).

The difference between the two dimensional and k-dimensional fitness functions, of course, is that in the general k-vertex model there is no one to one correspondence between mutational neighborhood equivalence classes (defined by Hamming distances on overlap class subsets) and equivalence classes defined by common Hamming distances with respect to all vertices (and by extension, fitness classes when fitness is determined by these Hamming distances).

Result: Unequal overlap classes imply unequal Hamming distance neighborhood classes under point mutation, even for genotypes with identical Hamming distance classes.

Proof: Let x_1 and x_2 have the same Hamming distance classes $(D_1 ... D_\kappa)$, but with different overlap classes in some subset of ν-tuples. Chose some arbitrary ν-tuple such that $d_{\nu,2} > d_{\nu,1}$ (without loss of generality). Select some ν tuple distance $d_\nu' = d_{\nu,1} + 1$. For sake of argument (and again without loss of generality), assume that locus 1 is a member of the ν-tuple. Then under the action of a d_ν'-step mutation in the ν-tuple class of loci in x_2, the progeny are in the Hamming class $(D_1 - d_\nu', ..., D_i - \delta_{i,\nu} d_\nu', ... D_\kappa - \delta_{\kappa,\nu} d_\nu')$ with $\delta_{i,\nu}$ defined as in the previous result. From this it can be seen that x_2 is in the d_ν' partial distance class of the ν-tuple and in the d_ν' Hamming distance class with respect to the reference vertices.

The construction of a Hamming distance d' neighborhood set for x_2 requires d' point mutations on the ν-tuple in question. The same cannot be done for x_1, for even though it is in the same Hamming distance class, by assumption we have $d_\nu' > d_{\nu,1}$.

To demonstrate that equivalence classes defined by distances to reference vertices do not generally give equitable partitions, consider the graph in Figure 4a versus those in Figure 4b. In 4a, the transition matrices **A** and their aggregate approximation $\hat{\boldsymbol{A}}$ were computed by using a fitness function $W(x) = \sum_i w_i (1 - s_i)^{d_i}$, with three reference vertices 11101,11010,10110 and $w_1 = w_2 = w_2 = 1$, $s_1 = 0.1$,$s_2 = 0.05$, $s_3 = 0.01$.The distribution x(t) was computed over 10 time steps, and in the figure shown **Q**x(10) is plotted against X(10) to show their divergence. A square error of $\sim 10^{-2}$ is obtained. For this particular choice of fitness functions, the aggregate approximation to the stationary distribution is quite accurate, simply because the macrovariable dominating the aggregate distribution X(t) happens to contain the optimal genotypes in the original system x(t).

In contrast, for the distributions shown in 4b, mutsel matrices were computed using a fitness function $W(x) = \sum_i w (1 - s_i)^{\omega_i}$ with fitness components determined by overlap class identity o_i rather than κ-tuple Hamming distances (by coincidence, there are 3 overlap classes in this case, so the same w and s parameters are used for convenience). Not surprisingly, the distributions **Q**x(t) and X(t) are practically superimposed for any choice of t, with square errors of $\sim 10^{-16}$ corresponding to the limits of *Mathematica*'s numerical accuracy.

It is fairly obvious that constructing fitness functions defined by overlap classes is highly unnatural and contrived, in that it is difficult to invision how such a fitness function would occur in nature. The example was chosen simply to illustrate the limits of aggregation of variables in systems with multidimensional fitness functions. It should also be noted that in this particular case aggregation of variables offered no great reduction in the size of the state space even in the case where it was exact, though this caveat becomes less significant for very large genotype spaces.

The non-congruence between mutational neighborhoods and Hamming distance classes (in this case corresponding to phenotype or fitness classes) illustrates a fairly ubiquitous phenomenon in evolutionary biology, in which genotypes with identical (or at least functionally equivalent) phenotypes have different evolutionary histories by virtue of having different phenotypes in their immediate mutational neighborhoods. For example, one can have a fitness landscape with κ peaks, some subset of which have

identical fitness values. However, some peaks will be surrounded by relatively high fitness single-point mutation neighbors while others will have low fitness mutation neighbors (corresponding to high versus low mutational robustness, e.g. Wagner et al 1997), and the equilibrium densities about each peak will ultimately reflect the fitness values of their mutational neighbors (Schuster and Swetina 1989, Wilke 2001).

■ Discussion

Aggregation methods have two major implications for the analysis of mutation-selection models, one practical, the other conceptual. At a practical level, the identification of equivalence classes and dynamically sufficient aggregate variables reduces the dimensionality necessary for predicting system dynamics and deriving equilibrium distributions. For mutation-selection models where Hamming graphs are the underlying configuration space (a standard model for point mutation) and the fitness functions are determined by Hamming distances to a small subset of local optima, the computational reduction is quite substantial, one from an exponential number of variables (α^n for a size α alphabet) to a relatively small polynomial of the order $\frac{n^{\alpha^{\kappa-1}}}{2^{\kappa-1}}$ for κ local optima as reference points.

More significant perhaps are the conceptual implications of the equivalence classes themselves. By identifying equivalence classes of genotypes that are identical to one another in both their fitness values and in their mutational neighborhoods (i.e. the number of mutational neighbors in other classes defined by their mutational neighborhoods), one partitions genotypes into subsets that act identically under the action of both the transmission (mutation) and selection operators. Numerous discussions on the units of evolution (Lewontin 1970) have used dynamical sufficiency as a criterion for identifying evolutionary units above or below the level of the individual. Implicit in this definition is the identification of equivalence classes that can be described by aggregate variables under the action of higher-order selection and transmission processes.

Most of the discussions of evolution of entities above the individual (genotype) level (such as group selection, species selection etc) focuses on the identification of equivalence classes from the standpoint of selection only. As was shown above in the case of a κ>2 reference vertex fitness function, it is not sufficient for genotypes to be equivalent under selection for any subset be an evolutionary equivalence class. If the equivalence classes defined with respect to mutation and with respect to selection are not identical, neither a partition into fitness classes nor a partition into mutational neighborhood classes gives a dynamically sufficient description for the mutation-selection process.

Our results presented here suggest that the actual range of fitness functions which allow exact equitable partitioning may be quite limited. An obvious direction to take future inquiries into aggregation and decomposability would be to look for mutation-selection systems where the operator is nearly equitably partitionable, and ask over which time scales approximation by equitable partitions gives a good approximation of system dynamics.

The decomposability and aggregation properties of one particular class of dynamical systems have actually been studied in some detail, namely the "nearly decomposable" fast-slow linear systems treated in Simon and Ando's (1961) work. Their approach focuses on the fact that some dynamical systems can be partitioned into subsets such that within-partition interactions are much stronger than cross-partition interactions. Such near-decoupling leads to short-term near-decomposability for each subset and longer-term aggregation of variables as each subset tends to quasi-equilibrium. This class of models may prove to be more generally applicable to evolutionary systems (Shpak et al, in preparation) than the exact aggregation of equitable partitions.

However, decomposition of fast-slow dynamical systems is still a special class of (weighted) equitable partitions, at least as an approximation. As our analysis in the first section showed, any aggregation of variables in a linear system will be some form of equitable partition. Yet we know of many example of dynamical decomposability and aggregability in biological systems that do not correspond to equitable partitions. The reason, we believe, lies in the fact that other forms of decomposability and aggregability are always associated with nonlinear systems and their properties.

A well-known example of decomposability in population genetics is the concept of selection acting on genes (or specific characters) as opposed to genotypes. For instance, given an n-locus, multi-allelic genetic system under linkage equilibrium and additive (or multiplicative) fitness functions, the state dynamics can be sufficiently described in terms of allele frequencies at individual loci (Lewontin and Kojima, 1960), in fact, the dynamics of alleles at each individual locus is dynamically sufficient. For example, for a genotype space on the frequencies of {AB,Ab,aB,ab}, the frequencies {p(-A*),p(a*),p(*b),p(*B)} (with A* denoting any genotype associated with allele A at the first locus) are dynamically sufficient descriptors if W(AB)=w(A)w(B) and so on for the other genotypes, and if p(AB)=p(A*)p(B*) etc.

The ability to predict genotype frequencies from allele frequencies under linkage equilibria and to derive fitness functions with reference to lower (single locus) units has suggested generalized models of character decomposition analyzed by Wagner and Laubichler (2000), Laubichler and Wagner (2000), and in a somewhat different formulation by Kim and Kim (2000). We propose that this form of dynamical decomposability (i.e. through identification of equivalence classes with respect to "characters" such as allelic states at a particular locus) is one which is independent and ultimately incompatible with equitable partitioning.

Following Wagner and Laubichler but using a notation specific to genotype spaces consistent with the fitness landscape analyses in this paper, define a set of genotypes $\{x_1....x_N\}$ with an associated frequency vector $p_i=\{p_1...p_N\}$. The equivalence classes $C^1=\{C_1....C_k\}$ and their associated frequencies $\pi_I=\{\pi_1...\pi_m\}$ are defined such that (for example) every genotype $x\epsilon C_I$ has an identical allelic state at a particular locus. More generally, the equivalence classes can be defined as a set of genotypes identical over some subset of sites, or a "schema" (sensu Holland 1975, Goldberg 1988, Altenberg 1995). For example, one such equivalence class for a 4-locus genotype would be the set of all genotypes C_1 of the form 0***, C_2 of those of the form 1***, defining partition C. In turn, another class of

partitions C^2 will be defined by the allelic identity at the second locus, and so on.

Wagner and Laubichler define the Cartesian product $C^1 \text{x} C^2$ to be an oc (orthogonal compliment) partitioning if $C=C^1 \text{x} C^2$, or more generally, $C=C^1 \text{x} C^2 ... \text{x} C^v$. They construct oc-partition by choosing a set of invertible functions $F=\{ f_{ij} | f: C_i \rightarrow C_j \}$ which maps every element in one equivalence class to the corresponding genotype in another class. For example, f could map 101 to 001, with *01 defining an equivalence class with respect to all loci except the first. In the case where F is a transitive map, i.e. $s=f_{IJ}(x)$ and $t=f_{JL}(u)$ implies $t=f_{IL}(x)$, F defines a complementary (orthogonal) partitioning $\overline{C}=\{\overline{C_1} ... \overline{C_k}\}$, with every class in the complementary partition is $\overline{C}=\{s \simeq x$ if there is $f_{IJ} \epsilon F | s=f_{IJ}(x)\}$. This map defines an equivalence class because the functions in f are transitive and invertible (Rosen 1984, Bogart 1990), and defines each genotype x as $x=C_I \bigcap \overline{C_J}$.

Given an oc-partitioning, Wagner and Laubichler have shown that for fitness functions satisfying the additivity condition and for "character" frequencies satisfying a generalized linkage equilibrium, the equivalence class frequencies π_I are a dynamically sufficient descriptor of evolution under a selection operator. Specifically, they require that all fitness functions satisfy what they refer to as "pi-additivity," with m the Malthusian fitness parameter:

$$m(f_{IJ}(x)) = m(x) + c_{IJ}. \qquad (5.1)$$

In other words, the fitness differences between members of the same equivalence class (i.e. allelic state at a particular locus) are some constant c_{IJ} determined by the rest of the genotype or character state configuration. This effectively excludes any type of nonlinearity due to epistasis in fitness functions. The other condition, of course, is generalized ("Pi") linkage equilibrium,

$$p_I(f_{IJ}(x)) = p_J(x), \text{ where } p_J(x) = \frac{p(x)}{\pi_J} \qquad (5.2)$$

with p(x) denoting the frequency of x while $p_J(x)$ refers to the marginal frequency in the Jth partition. This definition is equivalent to the conventional linkage equilibrium condition $p(x \in \pi_I \bigcap \overline{\pi}_J) = \pi_I \overline{\pi}_J$.

It was shown by Wagner and Laubichler that if these criteria are met, the Crow and Kimura (1970) selection equation on genotypes (in continuous time)

$$p_i = p_i (m_i - m) \qquad (5.3a)$$

can be aggregated into a dynamically sufficient description as

$$\pi_I = \pi_I (m_I - m) \qquad (5.3b)$$

with $\overline{m}_I$ being the mean fitness of all genotypes in equivalence class I. The aggregation of $p_1 ... p_N$ into state variables $\pi_1 ... \pi_v$ requires that the action of selection of genotypes within partition not changing the fitness differences between partitions, so that ultimately the only "relevant" dynamics are due to competition between partitions.

Aggregation into equivalence classes defined by allelic states at a given locus are shown to be

dynamically sufficient if each equivalence class has an equal variance in fitness, a condition which if fulfilled under pi-additivity and generalized linkage equilibrium. Their results have been extended to discrete-time selection systems (Wagner and Carter, unpublished) and to mutation-selection scenarios (Altenberg, unpublished) where the mutation operators fulfill the factorizability conditions of (3.1).

What is interesting about the Wagner and Laubichler results is that their equivalence classes do not constitute an equitable partition. In fact, for the simplest case of a "Fujijama" landscape (e.g. 0000 the optimal genotype, with fitness $m^{d(x,x_0)}$ for Hamming distance d neighbors), the equivalence classes are actually orthogonal to one another. Under equitable partitioning, {1000,0100,0010,0001} constitute an equivalence class, while a partition into per-locus allelic identity classes gives the eight genotypes {1000,1100,1010,...1111} for the partition determined by 1***.

The question arises as to how a partitioning which is non-equitable but nevertheless gives a dynamically sufficient aggregation of variables occurs in apparent violation of Result (1.3). The answer seems to lie in the fact that the general result of aggregations corresponding toe equitable partitions is restricted to linear dynamical systems. In order for mutation-selection dynamics to be linearized, it is necessary to use absolute frequencies and fitness values rather than relative frequencies and fitness values (as in 3.2). This linearization is what allows for equitable partitioning into Hamming distance (or overlap classes) given a congruence between fitness values and mutational distance.

In contrast, the partitioning and aggregation into equivalence classes based on shared character/allelic states is only possible in a system with relative frequencies as state variables and relative fitness values as the selection parameters. The reason is that the aggregation (5.3b) uses the invariance property of the Crow-Kimura equation, which is invariant under he addition of a constant to all fitness values (Wagner and Laubichler, 2000). The linearized dynamical system analyzed in the first section of this paper does not have this property and hence does not allow this form of aggregation.

In other words, there exist decompositions and aggregations of variables in nonlinear systems which do not apply to their linear counterparts. The transformation from absolute to relative frequencies involves a projection of an N dimensional space onto a N-1 dimensional manifold (because of the constraint that $\sum_i p_i = 1$ and $\sum_I \pi_I = 1$). Consequently, an aggregation which holds in the lower dimensional space need not apply to the higher dimensional representation.

However, the fact that the transformation of a linear representation of mutation-selection dynamics to a nonlinear representation (using relative frequencies) involves a projection onto a lower-dimensional substance implies that aggregability in the linear representation is probably a necessary (but not sufficient) criterion for aggregability in the nonlinear representation. This suggests that there probably exist entire families of aggregable and decomposable nonlinear dynamical systems. Given the fact that the conditions under which linear systems can be decomposed is rather restrictive, and that most biological systems involve some kind on nonlinear interactions, the majority of modular structures and emergent "aggregate" characters in biological systems probably involve different aggregation and decomposition rules than can be described by equitable partitioning.

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■ Appendix: Equitable Partitions for Multiple Alleles

In general, the equitable partitions defined over Hamming classes for 1 and 2 reference vertex fitness landscapes or by overlap classes for larger numbers of reference vertices do not apply for genetic systems with more than two alleles per locus. This is simply because for multiple alleles with arbitrary fitness effects for any allele at a given locus do not define equivalence classes with respect to distance, i.e. for any genotype no two Hamming distance d neighbors need have the same fitness value, and thus the correspondence between mutational distance classes and fitness classes generally breaks down (of course, the same is true if one allows for different effects of substitution at different loci). For instance, if we allow 3 alleles per locus with different fitness effects, the genotypes 200 and 100 will not have the same fitness distance to (Hamming distance one) sequence 000.

However, if one orders the L allelic states at each locus as $\alpha=\{\alpha_1,\alpha_2...\alpha_L\}$ and posits L-1 mutation parameters $\mu_1,\mu_2,...\mu_{L-1}$ (ordered such that μ is the symmetric mutation rate between appropriately chosen subsets of α) , if the fitness differences δw_i correspond in proportion to each μ_i, then mutational distance will be congruent with fitness differences. As an example, consider the familiar Kimura 3-parameter model for nucleotides A,C,G,T with mutation rates

$$\begin{array}{ccc} A & \overset{\mu_2}{\longleftrightarrow} & G \\ \mu_1 \updownarrow & & \updownarrow \mu_1 \\ C & \underset{\mu_2}{\longleftrightarrow} & T \end{array} \quad ; \quad \begin{array}{ccc} A & \overset{\mu_3}{\longleftrightarrow} & T \\ & & \\ C & \underset{\mu_3}{\longleftrightarrow} & G \end{array}$$

and a fitness effect of δw_i fixed for each mutation event μ_i at all loci.

For a k-reference vertex system, we again use the first reference vertex as the sequence used to derive all subsequent overlap classes. For any sequence, the alleles at each locus are labeled according to their position in the mutation order scheme relative to the first reference vertex, i.e. for A: A=1,G=2,-C=3,T=4, for C: C=1, T=2,A=3,G=4.

The overlap classes themselves are defined as follows: let n_{C_I} denote the number of loci at which all vertices in the set $\{i_1\}$ are identical to the first vertex at the ith site, all vertices in the set $\{i_2\}$ carrying label 2, and so forth through L. There are a total of $L^{\kappa-1}$ classes of the form:

$$n_{C_I} = n_{\{1_1\, 2_1 \ldots i_1 \ldots \kappa_1\},\{1_2 \ldots i_2 \ldots \kappa_2\},\ldots,\{1_L \ldots i_L \ldots \kappa_L\}}, \qquad \sum_I n_{C_I} = n$$

Having defined subsets of loci as overlap classes, the partial Hamming distances ($\vec{d}_{C_1}\,\vec{d}_{C_2},...\vec{d}_{C_I},...\vec{d}_{C_L}$) define equivalence classes (as for the diallelic case, for k>2 reference vertices the fitness values of genotypes must be determined by partial Hamming distances in order to be equitable). Each vector $\vec{d}_{C_I}=(d^1_{C_1}...d^L_{C_L})$ such that each $d^1_{C_I}\in\{0...n_{C_I}\}$ and $\sum_r d^r_{C_I}$=n. In turn, every overlap class n_{C_I} has subspace size:

$$\sum_{k_1=0}^{n_{C_I}}\sum_{k_2=0}^{k_1}\cdots\sum_{k_{L-1}=0}^{k_{L-2}}1=\binom{n+L-1}{n}<L^{n_{C_I}}$$

for n_{C_I} greater than some critical value, while over the entire space of possible overlap relations the number of equivalence classes is

$$\prod_{C_I}\binom{n_{C_I}+L-1}{n_{C_I}}=\prod_{C_I}\frac{(n+L-1)!}{n!\,(L-1)!}<L^n$$

which again, for large numbers of loci, gives an effective reduction in the dimensionality. For the k=1 and k=2 vertex systems, overlap class partitions reduce to Hamming distance equivalence classes as they did in the L=2 diallelic case.

The same reasoning used to show that partial Hamming distances define equitable partitions in the diallelic case apply here, the only difference being that multiple mutational steps must be taken into account for each type.

■ Figures

Figure 0:
An equitable partition of a 12-vertex graph and its reduced 6-vertex graph (from Stadler and Tinhofer, 2000), showing the four equivalence classes defined by equal numbers of neighboring vertices the other classes.

Figure 1:
a) The spectrum of a mutation-selection matrix **A** for a 5-locus, 2-allele system with an optimum fitness value W_0=1.0 at 00000 and a fitness function W(x)=W_0(.9)$^{d(x,x_0)}$ (corresponding to a single-peak fitness landscape) and a per-locus mutation rate μ=0.1. Note the $\binom{n}{d}$-fold multiplicity of eigenvalues in the dth class.
b) The spectrum of the aggregate representation $\hat{\boldsymbol{A}}$ where the aggregation matrix sums members of the same d-value equivalence classes into single variables. The eigenvalues are identical to those in part a, but in the aggregate representation there is no eigenvalue degeneracy, each one has a multiplicity of one.

Figure 2:
For the same single-peak fitness function as shown in Figure 1, the frequencies of the d-class entries are shown for the stationary (quasispecies) distribution of the aggregate mutsel matrix $\hat{\boldsymbol{A}}$. The frequencies of the optima and the class 1...5 Hamming distance neighbors are shown for a range of point mutation rates 0<μ<1.0. The figure illustrates the error threshold phenomenon at $\mu\approx$.25, as shown by the fact that Hamming error 1...5 classes become as frequent as the optimum.

Figure 3:
a) Equilibrium distributions for "degenerate" quasispecies, i.e. a two-peak fitness landscape where 00000 and 10101 both have fitness equal to unity, while other genotypes have a fitness value determined by their minimum distance to one of the peaks $(1 - s_i)^{\min(d_i)}$, with s_i=0.1 for the first peak and 0.05 for the second (corresponding to a "steeper" slope about the first optimum). Of the twelve equivalence classes, only the frequencies of each peak sequence and its Hamming distance one neighbor classes are shown for clarity. Each frequency value corresponds to the aggregate pairwise Hamming distance classes, with (0,3) and (3.0) corresponding to the respective local optima.
b) Shows the same scenari as in 3a, but with almost degenerate quasispecies, the fitness values of the local optima are 1.0 and .99, respectively.

Figure 4:
a) Plot of **Q**x(10) versus X(10) for Hamming distance class aggregation after 10 time steps (with an

initial distribution such that the frequency at 00000 is set to unity) and a per-locus mutation rate of 0.1. The fitness function is chosen to be $W(x)=(.99)^{d_1}+(.95)^{d_2}+(.9)^{d_3}$, giving the aggregate equivalence classes (22 total) defined by equal entries (d_1,d_2,d_3). The figure clearly shows that the frequencies (across all equivalnce classes) derived from the aggregate dynamical operator $\hat{\boldsymbol{A}}$ are not equivalent to the aggregation of the frequencies derived from **A**.
b) Plot of **Q**x versus x for overlap class aggregation for a fitness function defined on the overlap classes $W(x)=(.99)^{o_1}+(.95)^{o_2}+(.9)^{o_3}$,where each o_i represents the partial overlap distance. For this partitioning there are 12 equivalence classes. The essentially perfect superposition of **Q**x(10) and X(10) demonstrate that a fitness function defined on overlap classes gives an exact equitable partition.

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Figure 0

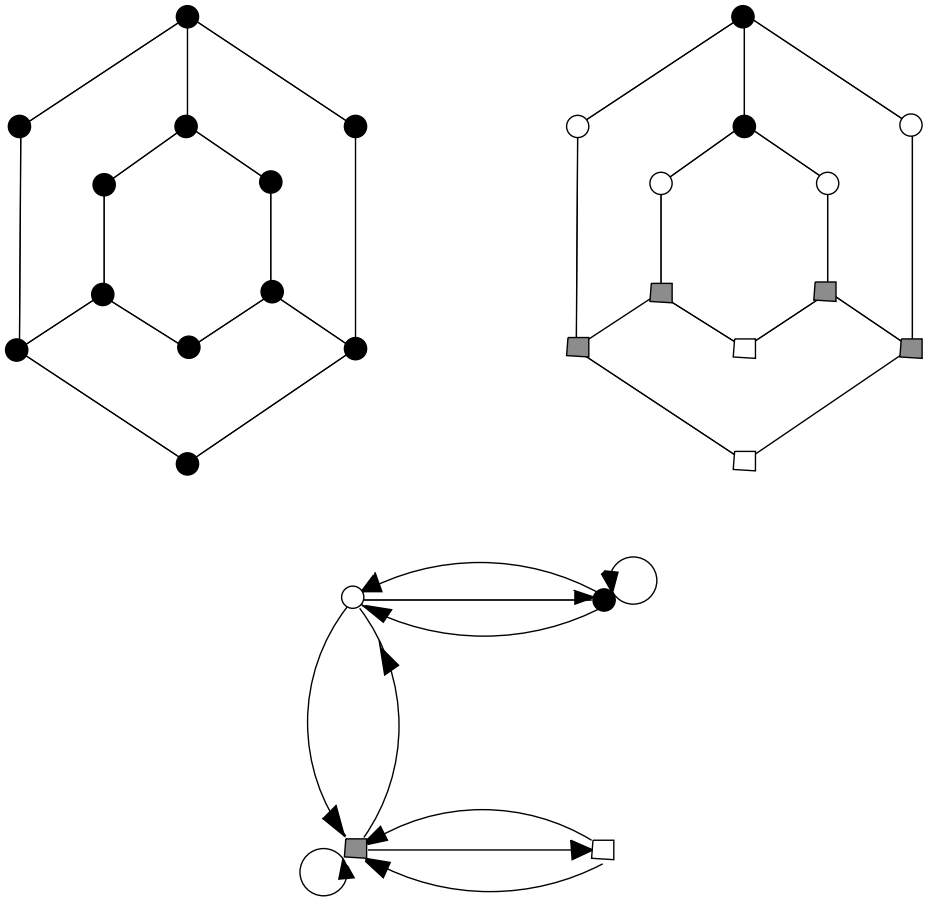
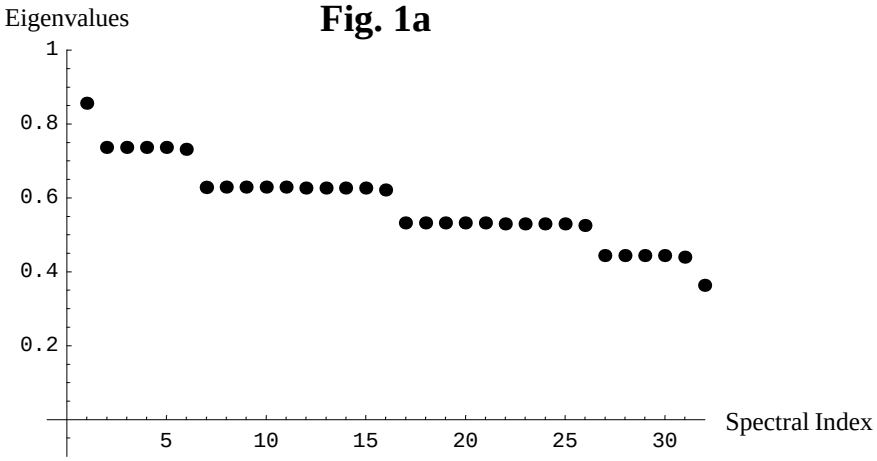


Fig. 1a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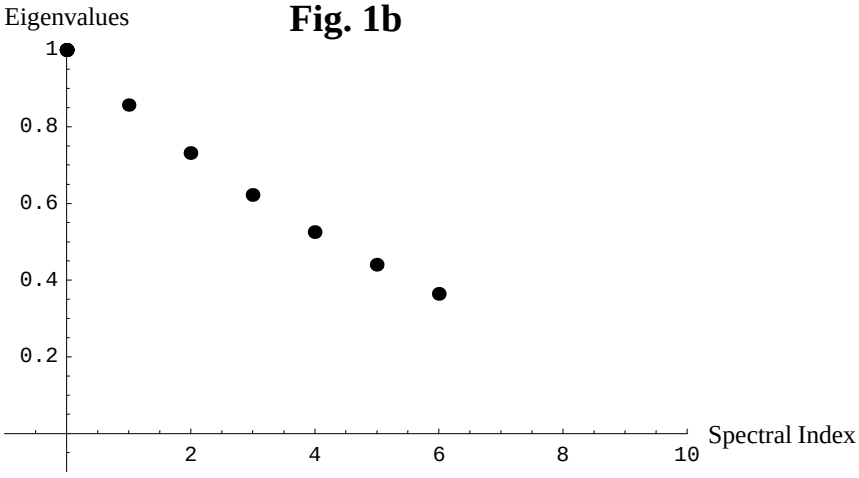
0.2
5
10
15
20
25
30
Spectral Index

Fig. 1b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2
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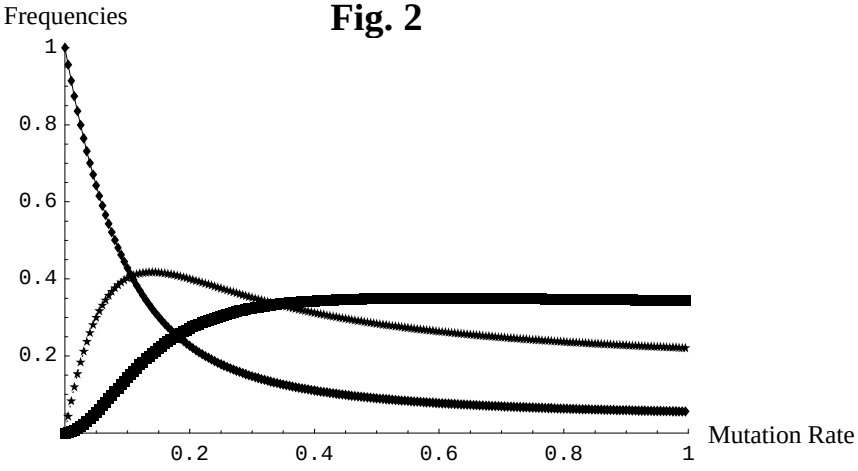
Spectral Index

Fig. 2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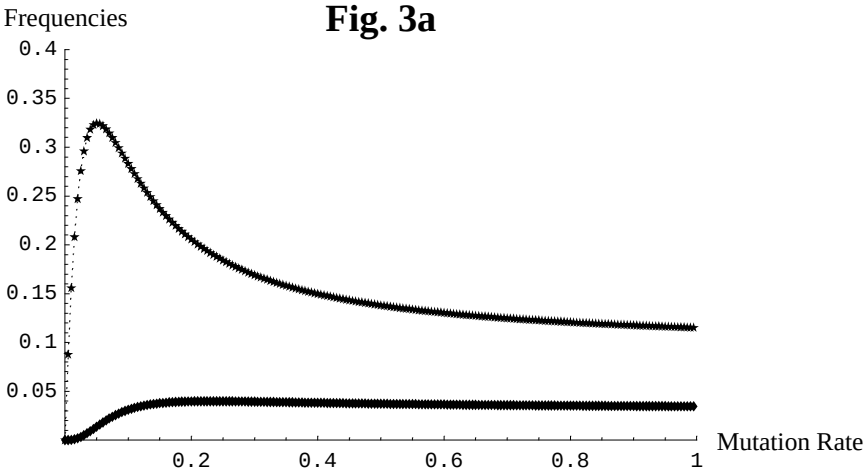
Mutation Rate

Fig. 3a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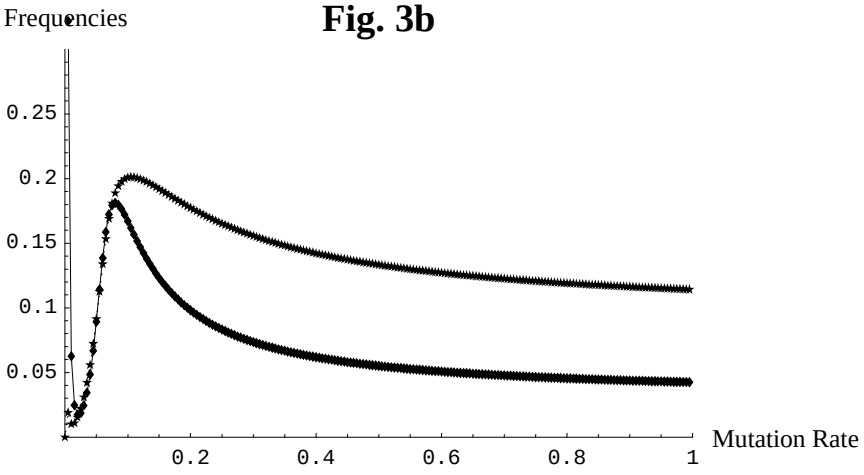
Mutation Rate

Fig. 3b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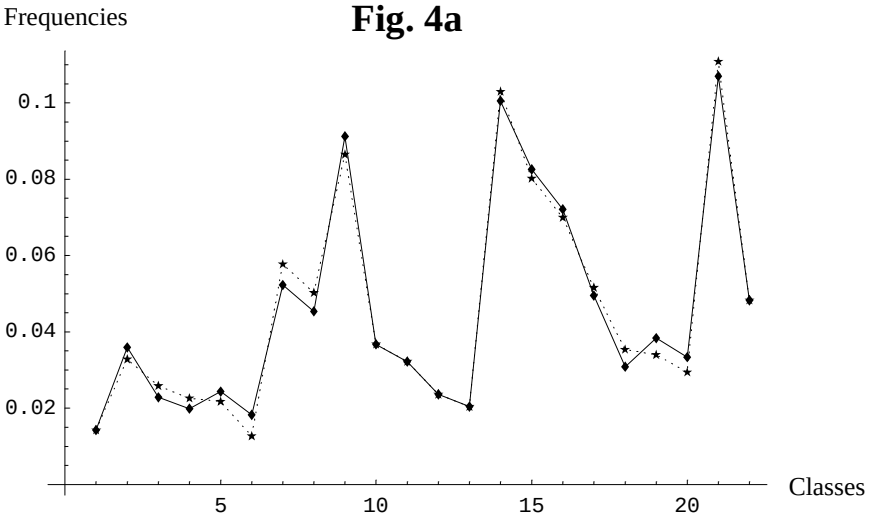
Mutation Rate

Fig. 4a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Classes

Fig. 4b