

Fisher's theorems for multivariable, time- and space-dependent systems, with applications in population genetics and chemical kinetics

Marcel O. Vlad*[†], Stefan E. Szedlacsek[‡], Nader Pourmand[§], L. Luca Cavalli-Sforza[¶], Peter Oefner[§], and John Ross*^{||}

*Department of Chemistry, Stanford University, Stanford, CA 94305-5080; [†]Institute of Mathematical Statistics and Applied Mathematics, Casa Academiei Romane, Calea Septembrie 13, 76100 Bucharest, Romania; [‡]Department of Enzymology, Institute of Biochemistry of the Romanian Academy, Splaiul Independentei 296, 060031, Bucharest 17, Romania; [§]Stanford Genome Technology Center, Stanford University, Palo Alto, CA 94304; and [¶]Department of Genetics, School of Medicine, Stanford University, Stanford, CA 94305

Contributed by John Ross, May 17, 2005

We study different physical, chemical, or biological processes involving replication, transformation, and disappearance processes, as well as transport processes, and assume that the time and space dependence of the species densities are known. We derive two types of Fisher equations. The first type relates the average value of the time derivative of the relative time-specific rates of growth of the different species to the variance of the relative, time-specific rates of growth. A second type relates the average value of the gradient or the divergence of the relative, space-specific rates of growth to the space correlation matrix of the relative, space-specific rates of growth. These Fisher equations are exact results, which are independent of the detailed kinetics of the process: they are valid whether the evolution equations are linear or nonlinear, local or nonlocal in space and/or time and can be applied for the study of a large class of physical, chemical, and biological systems described in terms of time- and/or space-dependent density fields. We examine the implications of our generalized Fisher relations in population genetics, biochemistry, and chemical kinetics (reaction–diffusion systems). We show that there is a connection between the enhanced (hydrodynamic) transport of mutations induced by population growth and space-specific rate vectors: the velocity of enhanced transport is proportional to the product of the diffusion coefficient of the species and the space rate vector; this relation is similar to a fluctuation–dissipation relation in statistical mechanics.

Fisher's fundamental theorem of natural selection is one of the basic laws of population genetics. In 1930, Fisher showed that for single-locus genetic systems with pure selection and constant selection coefficients, the rate of variation of the average population fitness equals the genetic variance of the fitness (1). Because the variance is nonnegative, it follows that for systems with pure selection and constant rate coefficients, the average fitness always increases in time, a result that is compatible with general ideas of biological evolution. Fisher claimed that this law should hold the same position among biological sciences as the second law of thermodynamics in physical sciences (1). Many generalizations of Fisher's theorem have been suggested in the literature. A first generalization was introduced by Fisher himself, by taking into account the effects of overpopulation and the effect of deterioration of the environment (1). Further generalizations were introduced by Wright (2), Kimura (3), Price (4), Frank (5) and Ewens (6), Lessard (7), Crow (8), Nagylaki (9), and Edwards (10). A recent article in PNAS (11) reports on a general fluctuation–dissipation relation for biological systems, which is qualitatively similar to the Fisher equation. Fisher's theorem also was used for the analysis of economic competition (12).

Our research on Fisher's theorem was stimulated by a number of different problems in chemistry and biology. We noticed that several problems in chemical kinetics lead naturally to a chemical Fisher's theorem. For example, a recent research technique uses

certain chain reaction for amplifying chemical signals in gene expression and sequencing studies (13); the contribution of response signals of chains of different lengths may be expressed in terms of a Fisher's theorem. Similar approaches may be useful for the study of pattern formation in reaction–diffusion systems as well as geographical population genetics (14, 15). We eventually came up with two sets of generalized Fisher equations that can be applied to various physical, chemical, and biological problems, involving time- and/or space-dependent density fields.

In *Time-Dependent Generalized Fisher's Theorems* and *Space-Dependent Generalized Fisher's Theorems*, we discuss the time-dependent and space-dependent versions of our generalized Fisher's theorem, respectively. Finally, in *Implications in Genetics and Chemical Kinetics*, we discuss the general significance of our results as well as analyze the implications of our generalized Fisher's theorems in genetics and chemical kinetics.

Time-Dependent Generalized Fisher's Theorems

Although our approach can be presented in a general form, valid for any set of time- and/or space-dependent density fields, we prefer to use population genetics as a simple example. In the literature of population genetics, there are many versions of Fisher's theorem, depending on whether the time is considered discrete or continuous, the age structure of the population is ignored or taken into account, the population is haploid or diploid, etc. In the following, we give a short summary of a formulation suggested by Nagylaki (9), which can be easily compared with our own approach. He considers a single locus, with many alleles in a haploid population with age structure. Following Fisher, only selection is taken into account; that is, the individuals with different alleles have different natality and mortality coefficients, and the contributions of mutations and random drift are neglected. He shows that, for time-dependent rates of growth, the numbers $N_u(t)$, $u = 1, 2, \dots$ of individuals at time t carrying the alleles $u = 1, 2, \dots$ are given by

$$N_u(t) = N_u(0) \exp \left[\int_0^t r_u(t') dt' \right], \quad [1]$$

where $N_u(0)$ are initial population sizes and $r_u(t)$ are intrinsic rates of growth attached to individuals with different alleles; because only selection is taken into account, $r_u(t)$ is the (absolute) fitness of individuals carrying the allele u . Following Fisher, he introduces the gene frequencies

^{||}To whom correspondence should be addressed. E-mail: john.ross@stanford.edu.

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$$\gamma_u(t) = N_u(t) \left/ \sum_u N_u(t), \right. \quad \text{with} \quad \sum_u \gamma_u(t) = 1. \quad [2]$$

In terms of these gene frequencies, he defines the average value $\overline{r(t)}$ and the variance $\overline{\Delta r^2(t)}$ of the intrinsic rate of growth as follows:

$$\overline{r(t)} = \sum_u r_u(t) \gamma_u(t), \quad [3]$$

$$\overline{\Delta r^2(t)} = \sum_u [r_u(t) - \overline{r(t)}]^2 \gamma_u(t), \quad [4]$$

and shows by direct computations that

$$d\overline{r(t)} = \overline{\Delta r^2(t)} + \overline{d_r r(t)}, \quad [5]$$

where

$$\overline{d_r r(t)} = \sum_u (d_r r_u(t)) \gamma_u(t) \quad [6]$$

is the average value of the rate of variation of the intrinsic rate of growth. Eq. 5 is a generalization of Fisher's theorem for the time-dependent intrinsic rates of growth $r_u(t)$. If the intrinsic rates of growth are constant, then the term 6 is equal to zero and Eq. 5 reduces to Fisher's theorem $d\overline{r(t)} = \overline{\Delta r^2(t)}$.

Nagylaki's approach is limited to homogeneous systems with pure selection; he derived Eq. 1 for the population numbers and the generalized Fisher's theorem, Eq. 5, from an age-dependent selection model. Our approach is different: instead of considering a particular genetic model, we focus on experimental data regarding the time variation of population number. In addition, we consider time- and space-dependent systems, and thus our variables are infinitesimal allele numbers $dN_u(\mathbf{x}, t) = n_u(\mathbf{x}, t) d\mathbf{x}$, $u = 1, 2, \dots$ at time t and at a position between \mathbf{x} and $\mathbf{x} + d\mathbf{x}$, where $n_u(\mathbf{x}, t)$ is the density of alleles u at time t and at a position between \mathbf{x} and $\mathbf{x} + d\mathbf{x}$. One advantage of such an approach is that we can develop a unified treatment for haploid and diploid populations, space-dependent or space-independent systems. We consider a single locus with many alleles and assume that the time dependences of the densities $n_u(\mathbf{x}, t)$, $u = 1, 2, \dots$ of different alleles in the population are known from experiments or observations; in particular for haploid populations $n_u(\mathbf{x}, t)$, $u = 1, 2, \dots$ are the same as the densities of individuals carrying different alleles. Because in nature selection rarely acts alone, the time variation of the densities $n_u(\mathbf{x}, t)$, $u = 1, 2, \dots$, is influenced by various genetic processes, such as selection, mutation, and random drift. To characterize the time variation of the allele numbers, we introduce the absolute, time-specific rates of growth of the different alleles,

$$\sigma_u^{(t)}(\mathbf{x}, t) = [n_u(\mathbf{x}, t)]^{-1} \partial_t n_u(\mathbf{x}, t) = \partial_t \ln n_u(\mathbf{x}, t). \quad [7]$$

In particular, for homogeneous (space-independent) haploid populations with only selection present, the specific rates of growth $\sigma_u^{(t)}(\mathbf{x}, t)$ reduce to the intrinsic rates of growth $\sigma_u^{(t)}(\mathbf{x}, t) = r_u(t)$ independent of \mathbf{x} ; otherwise, these two quantities are different. We also introduce the overall specific rate of growth $\sigma_\Sigma^{(t)}(\mathbf{x}, t)$ for the total density of genes $n(\mathbf{x}, t) = \sum_u n_u(\mathbf{x}, t)$

$$\sigma_\Sigma^{(t)}(\mathbf{x}, t) = \partial_t \ln n(\mathbf{x}, t), \quad [8]$$

the local gene frequencies

$$\gamma_u(\mathbf{x}, t) = n_u(\mathbf{x}, t) / n(\mathbf{x}, t), \quad \text{with} \quad \sum_u \gamma_u(\mathbf{x}, t) = 1, \quad [9]$$

and the relative, time-specific rates of variation $\chi_u^{(t)}(\mathbf{x}, t)$ attached to the various gene frequencies $\gamma_u(\mathbf{x}, t)$

$$\chi_u^{(t)}(\mathbf{x}, t) = \partial_t \ln \gamma_u(\mathbf{x}, t). \quad [10]$$

From Eqs. 9 it follows that $n_u(\mathbf{x}, t) = n(\mathbf{x}, t) \gamma_u(\mathbf{x}, t)$, and thus,

$$\sigma_u^{(t)}(\mathbf{x}, t) = \partial_t \ln [n(\mathbf{x}, t) \gamma_u(\mathbf{x}, t)] = \sigma_\Sigma^{(t)}(\mathbf{x}, t) + \chi_u^{(t)}(\mathbf{x}, t). \quad [11]$$

The average values of the absolute and relative specific rates of growth can be easily evaluated. We have

$$\overline{\chi^{(t)}(\mathbf{x}, t)} = \sum_u \overline{\chi_u^{(t)}(\mathbf{x}, t) \gamma_u(\mathbf{x}, t)} = \partial_t \sum_u \gamma_u(\mathbf{x}, t) = 0, \quad [12]$$

$$\begin{aligned} \overline{\sigma^{(t)}(\mathbf{x}, t)} &= \sum_u \sigma_u^{(t)}(\mathbf{x}, t) \gamma_u(\mathbf{x}, t) \\ &= \sum_u [\sigma_\Sigma^{(t)}(\mathbf{x}, t) + \chi_u^{(t)}(\mathbf{x}, t)] \gamma_u(\mathbf{x}, t) \\ &= \sigma_\Sigma^{(t)}(\mathbf{x}, t) + \overline{\chi^{(t)}(\mathbf{x}, t)} = \sigma_\Sigma^{(t)}(\mathbf{x}, t). \end{aligned} \quad [13]$$

The biological significance of Eqs. 12 and 13 is clear. As expected the average, time-specific rate of growth $\overline{\sigma^{(t)}(\mathbf{x}, t)}$ is the same as the time-specific rate of growth for the whole population, $\sigma_\Sigma^{(t)}(\mathbf{x}, t)$, (Eq. 13). From Eqs. 11 and 13, we obtain: $\chi_u^{(t)}(\mathbf{x}, t) = \sigma_u^{(t)}(\mathbf{x}, t) - \sigma_\Sigma^{(t)}(\mathbf{x}, t)$; that is, the relative, time-specific rate of growth of the allele u , $\chi_u^{(t)}(\mathbf{x}, t)$, is the difference between the absolute specific rate of growth of the allele u , $\sigma_u^{(t)}(\mathbf{x}, t)$, and the average rate of growth of the whole population, $\sigma_\Sigma^{(t)}(\mathbf{x}, t)$; it follows that $\chi_u^{(t)}(\mathbf{x}, t)$ is a measure for the relative evolutionary advantage of the allele u compared with the average population. Because the reference state is the average population, the average value of the relative rate of growth is equal to zero, $\overline{\chi^{(t)}(\mathbf{x}, t)} = 0$ (Eq. 12).

In terms of $\sigma_u^{(t)}(\mathbf{x}, t)$ and $\chi_u^{(t)}(\mathbf{x}, t)$ we can introduce the absolute and relative, time-specific rate of evolution for the allele u , $\psi_u^{(t)}(\mathbf{x}, t)$ and $\varphi_u^{(t)}(\mathbf{x}, t)$, respectively,

$$\begin{aligned} \psi_u^{(t)}(\mathbf{x}, t) &= \partial_t \sigma_u^{(t)}(\mathbf{x}, t) = \partial_{t^2}^2 \ln [n(\mathbf{x}, t) \gamma_u(\mathbf{x}, t)] \\ &= \partial_{t^2}^2 \ln n(\mathbf{x}, t) + (\gamma_u(\mathbf{x}, t))^{-1} \partial_{t^2}^2 \gamma_u(\mathbf{x}, t) \\ &\quad - (\partial_t \ln \gamma_u(\mathbf{x}, t))^2, \end{aligned} \quad [14]$$

$$\begin{aligned} \varphi_u^{(t)}(\mathbf{x}, t) &= \partial_t \chi_u^{(t)}(\mathbf{x}, t) = \partial_{t^2}^2 \ln \gamma_u(\mathbf{x}, t) \\ &= (\gamma_u(\mathbf{x}, t))^{-1} \partial_{t^2}^2 \gamma_u(\mathbf{x}, t) - (\partial_t \ln \gamma_u(\mathbf{x}, t))^2, \end{aligned} \quad [15]$$

and the average time-specific rate of evolution $\Psi^{(t)}(\mathbf{x}, t)$ for the total population

$$\Psi^{(t)}(\mathbf{x}, t) = \partial_t \sigma_\Sigma^{(t)}(\mathbf{x}, t) = \partial_t \overline{\sigma^{(t)}(\mathbf{x}, t)} = \partial_{t^2}^2 \ln n(\mathbf{x}, t). \quad [16]$$

From Eqs. 14–16 it follows that

$$\psi_u^{(t)}(\mathbf{x}, t) = \Psi^{(t)}(\mathbf{x}, t) + \varphi_u^{(t)}(\mathbf{x}, t), \quad [17]$$

that is, the absolute rate of evolution $\psi_u^{(t)}(\mathbf{x}, t)$ for the allele u is the sum of the absolute rate of evolution for the total population,

$\Psi^{(t)}(\mathbf{x}, t)$ and that of the relative rate of evolution $\varphi_u^{(t)}(\mathbf{x}, t)$ for the allele u .

In our approach, a Fisher's theorem of type 5 can be viewed as a statement about the average rate of evolution. The average relative rate of evolution $\overline{\varphi^{(t)}(\mathbf{x}, t)}$ can be easily evaluated by using Eq. 15

$$\begin{aligned} \overline{\varphi^{(t)}(\mathbf{x}, t)} &= \sum_u \varphi_u^{(t)}(\mathbf{x}, t) \gamma_u(\mathbf{x}, t) \\ &= \sum_u \gamma_u(\mathbf{x}, t) [(\gamma_u(\mathbf{x}, t))^{-1} \partial_{t^2}^2 \gamma_u(\mathbf{x}, t) \\ &\quad - (\partial_t \ln \gamma_u(\mathbf{x}, t))^2] \\ &= \sum_u \partial_{t^2}^2 \gamma_u(\mathbf{x}, t) - \sum_u \gamma_u(\mathbf{x}, t) (\chi_u^{(t)}(\mathbf{x}, t))^2, \end{aligned} \quad [18]$$

from which we come to

$$\overline{\varphi^{(t)}(\mathbf{x}, t)} = -\overline{(\chi^{(t)}(\mathbf{x}, t))^2} \leq 0, \quad [19]$$

that is, the average value of the relative rate of evolution is nonpositive and equal to the variance $\overline{(\chi^{(t)}(\mathbf{x}, t))^2} = \sum_u \gamma_u(\mathbf{x}, t) (\chi_u^{(t)}(\mathbf{x}, t))^2$ of the relative rate of growth with changed sign.

The average value $\overline{\psi^{(t)}(\mathbf{x}, t)}$ of the absolute rate of evolution can be evaluated from Eqs. 14–16. We have

$$\begin{aligned} \overline{\psi^{(t)}(\mathbf{x}, t)} &= \sum_u \psi_u^{(t)}(\mathbf{x}, t) \gamma_u(\mathbf{x}, t) = \Psi^{(t)}(\mathbf{x}, t) + \overline{\varphi^{(t)}(\mathbf{x}, t)} \\ &= \Psi^{(t)}(\mathbf{x}, t) - \overline{(\Delta \sigma^{(t)}(\mathbf{x}, t))^2}, \end{aligned} \quad [20]$$

where

$$\begin{aligned} \overline{(\Delta \sigma^{(t)}(\mathbf{x}, t))^2} &= \sum_u \gamma_u(t) [\sigma_u^{(t)}(\mathbf{x}, t) - \overline{\sigma^{(t)}(\mathbf{x}, t)}]^2 \\ &= \sum_u \gamma_u(\mathbf{x}, t) (\chi_u^{(t)}(\mathbf{x}, t))^2 = \overline{(\chi^{(t)}(\mathbf{x}, t))^2} \end{aligned} \quad [21]$$

is the variance of the absolute rate of evolution. From Eq. 20 we have

$$\Psi^{(t)}(\mathbf{x}, t) = \overline{\psi_u^{(t)}(\mathbf{x}, t)} + \overline{(\Delta \sigma^{(t)}(\mathbf{x}, t))^2} \geq \overline{\psi_u^{(t)}(\mathbf{x}, t)}, \quad [22]$$

that is, the rate of evolution of the whole population is equal to the sum of the average value $\overline{\psi(t)}$ of the absolute rate of evolution and the variance of the specific (absolute or relative) growth rate. Eqs. 19 and 22 are equivalent to each other; they can be derived from one another by passing from relative to absolute evolutionary variables and vice versa. They are both equivalent formulations of a generalized Fisher theorem.

To outline the analogies between our approach and Nagylaki's derivation of Fisher's theorem, we rewrite Eq. 22 in terms of the absolute rates of growth attached to the different alleles

$$\overline{\partial_t \sigma^{(t)}(\mathbf{x}, t)} = \overline{(\Delta \sigma^{(t)}(\mathbf{x}, t))^2} + \overline{\partial_t \sigma^{(t)}(\mathbf{x}, t)}. \quad [23]$$

Eq. 23 has the same structure as the generalized Fisher equation (5). In particular, for homogeneous (space-independent), haploid populations with pure selection, we have $\sigma_u^{(t)}(\mathbf{x}, t) = r_u(t)$, and Eq. 23 reduces to Eq. 5.

A convenient way of expressing the generalized Fisher equations 19 and 22 is in terms of a commutator operator,

$$\begin{aligned} \mathbb{C}^{(t)} \dots &= \overline{\partial_t(\dots)} - \overline{(\partial_t \dots)} \\ &= \partial_t \left(\sum_u \gamma_u(\mathbf{x}, t) \dots \right) - \sum_u \gamma_u(\mathbf{x}, t) \partial_t(\dots), \end{aligned} \quad [24]$$

between the time differentiation and the averaging with respect to the gene frequencies. In terms of $\mathbb{C}^{(t)}$ Eqs. 19 and 22 can be expressed in the same form,

$$\mathbb{C}^{(t)} \sigma^{(t)}(\mathbf{x}, t) = \overline{\Delta \sigma^{(t)}(\mathbf{x}, t)^2}, \quad [25]$$

$$\mathbb{C}^{(t)} \chi^{(t)}(\mathbf{x}, t) = \overline{\Delta \chi^{(t)}(\mathbf{x}, t)^2}. \quad [26]$$

In conclusion, in this section we have shown that generalized Fisher theorems can be derived without use of any genetic models. By assuming that the genetic structure of the population is known from observation or experiment, we introduced absolute and relative functions, which describe the evolutionary process and derived generalized Fisher theorems depending on these functions. Our results apply to one locus with multiple alleles in populations subject to selection, mutation, random drift, and other genetic processes.

Space-Dependent Generalized Fisher's Theorems

Our generalized Fisher equations derived in the preceding section express the process of evolution as a function of time. In this section, we attempt to derive a new type of Fisher equations, which express the evolution in space. The main idea is to define space-specific rates of growth and to study the space variation of their statistical properties. For each allele u , we introduce space-specific rates of growth

$$\sigma_u^{(x)}(\mathbf{x}, t) = [n_u(\mathbf{x}, t)]^{-1} \nabla_{\mathbf{x}} n_u(\mathbf{x}, t) = \nabla_{\mathbf{x}} \ln n_u(\mathbf{x}, t). \quad [27]$$

The Definitions 27 have a similar structure with Eqs. 8 for the time-specific rates of growth $\sigma_u^{(t)}(\mathbf{x}, t)$; the main difference is that the time derivative ∂_t is replaced by the real space gradient $\text{grad}_{\mathbf{x}} \dots = \nabla_{\mathbf{x}} \dots$. We notice that the space-specific rates of growth are vectors $\sigma_u^{(x)}(\mathbf{x}, t)$. The overall space-specific rate of growth, $\sigma_{\Sigma}^{(x)}(\mathbf{x}, t)$, and the space-specific rates of variation $\chi_u^{(x)}(\mathbf{x}, t)$ attached to the various gene frequencies, $\gamma_u(\mathbf{x}, t)$ are also vectors

$$\sigma_{\Sigma}^{(x)}(\mathbf{x}, t) = \nabla_{\mathbf{x}} \ln n(\mathbf{x}, t), \quad [28]$$

$$\chi_u^{(x)}(\mathbf{x}, t) = \nabla_{\mathbf{x}} \ln \gamma_u(\mathbf{x}, t). \quad [29]$$

These space-specific rates are related to each other through a set of relations similar to Eqs. 11,

$$\sigma_u^{(x)}(\mathbf{x}, t) = \sigma_{\Sigma}^{(x)}(\mathbf{x}, t) + \chi_u^{(x)}(\mathbf{x}, t). \quad [30]$$

The average values of the absolute and relative space-specific growth rates are given by a set of equations similar to Eqs. 12 and 13. We have

$$\overline{\chi_u^{(x)}(\mathbf{x}, t)} = 0, \quad [31]$$

$$\overline{\sigma^{(x)}(\mathbf{x}, t)} = \sigma_{\Sigma}^{(x)}(\mathbf{x}, t). \quad [32]$$

In terms of $\sigma_u^{(x)}(\mathbf{x}, t)$ and $\chi_u^{(x)}(\mathbf{x}, t)$, we can introduce the absolute and relative, space-specific rates of evolution for the allele u , $\psi_u^{(x)}(\mathbf{x}, t)$ and $\varphi_u^{(x)}(\mathbf{x}, t)$, respectively,

$$\begin{aligned}
\psi_u^{(x)}(\mathbf{x}, t) &= \nabla_{\mathbf{x}} \otimes \sigma_u^{(x)}(\mathbf{x}, t) \\
&= \nabla_{\mathbf{x}} \otimes \nabla_{\mathbf{x}} \ln[n(\mathbf{x}, t) \gamma_u(\mathbf{x}, t)] \\
&= \nabla_{\mathbf{x}} \otimes \nabla_{\mathbf{x}} \ln n(\mathbf{x}, t) + (\gamma_u(\mathbf{x}, t))^{-1} \nabla_{\mathbf{x}} \otimes \nabla_{\mathbf{x}} \gamma_u(\mathbf{x}, t) \\
&\quad - (\nabla_{\mathbf{x}} \ln \gamma_u(\mathbf{x}, t)) \otimes (\nabla_{\mathbf{x}} \ln \gamma_u(\mathbf{x}, t)) \quad [33]
\end{aligned}$$

$$\begin{aligned}
\varphi_u^{(x)}(\mathbf{x}, t) &= \nabla_{\mathbf{x}} \otimes \chi_u^{(x)}(\mathbf{x}, t) \\
&= \nabla_{\mathbf{x}} \otimes \nabla_{\mathbf{x}} \ln \gamma_u(\mathbf{x}, t) \\
&= (\gamma_u(\mathbf{x}, t))^{-1} \nabla_{\mathbf{x}} \otimes \nabla_{\mathbf{x}} \gamma_u(\mathbf{x}, t) \\
&\quad - (\nabla_{\mathbf{x}} \ln \gamma_u(\mathbf{x}, t)) \otimes (\nabla_{\mathbf{x}} \ln \gamma_u(\mathbf{x}, t)), \quad [34]
\end{aligned}$$

and the space-specific rate of evolution $\Psi^{(x)}(\mathbf{x}, t)$ for the total population

$$\begin{aligned}
\Psi^{(x)}(\mathbf{x}, t) &= \nabla_{\mathbf{x}} \otimes \sigma_{\Sigma}^{(x)}(\mathbf{x}, t) \\
&= \nabla_{\mathbf{x}} \otimes \overline{\sigma^{(x)}(\mathbf{x}, t)} \\
&= \nabla_{\mathbf{x}} \otimes \nabla_{\mathbf{x}} \ln n(\mathbf{x}, t). \quad [35]
\end{aligned}$$

From Eqs. 33 and 35 we have:

$$\psi_u^{(x)}(\mathbf{x}, t) = \Psi^{(x)}(\mathbf{x}, t) + \varphi_u^{(x)}(\mathbf{x}, t). \quad [36]$$

We notice that $\psi_u^{(x)}(\mathbf{x}, t)$, $\varphi_u^{(x)}(\mathbf{x}, t)$, and $\Psi^{(x)}(\mathbf{x}, t)$ are two-label tensors.

The average space-specific, relative rate of evolution, $\overline{\varphi^{(x)}(\mathbf{x}, t)}$, can be easily evaluated

$$\begin{aligned}
\overline{\varphi^{(x)}(\mathbf{x}, t)} &= \sum_u \varphi_u^{(x)}(\mathbf{x}, t) \gamma_u(\mathbf{x}, t) \\
&= \sum_u \gamma_u(\mathbf{x}, t) [(\gamma_u(\mathbf{x}, t))^{-1} \nabla_{\mathbf{x}} \otimes \nabla_{\mathbf{x}} \gamma_u(\mathbf{x}, t) \\
&\quad - (\nabla_{\mathbf{x}} \ln \gamma_u(\mathbf{x}, t)) \otimes (\nabla_{\mathbf{x}} \ln \gamma_u(\mathbf{x}, t))] \\
&= \sum_u \gamma_u(\mathbf{x}, t) [(\gamma_u(\mathbf{x}, t))^{-1} \nabla_{\mathbf{x}} \otimes \nabla_{\mathbf{x}} \gamma_u(\mathbf{x}, t) \\
&\quad - \chi_u^{(x)}(\mathbf{x}, t) \otimes \chi_u^{(x)}(\mathbf{x}, t)], \quad [37]
\end{aligned}$$

from which we come to

$$\overline{\varphi^{(x)}(\mathbf{x}, t)} = -\overline{\chi^{(x)}(\mathbf{x}, t) \otimes \chi^{(x)}(\mathbf{x}, t)}, \quad [38]$$

that is, the average value of the tensor of the space-specific relative rate of evolution is equal to the average value of the tensorial product of the vector of the space-specific relative rate of growth by itself, with changed sign. Eq. 38 is a space-dependent generalization of our generalized Fisher equation, Eq. 19. Eq. 38 is a statement about tensors, and thus, it does not lead to an inequality. Its scalar transcription is the following:

$$\begin{aligned}
\overline{[\varphi^{(x)}(\mathbf{x}, t)]_{\alpha\beta}} &= -\overline{[\chi^{(x)}(\mathbf{x}, t)]_{\alpha} [\chi^{(x)}(\mathbf{x}, t)]_{\beta}} \\
&= \text{cov}\{[\chi^{(x)}(\mathbf{x}, t)]_{\alpha}, [\chi^{(x)}(\mathbf{x}, t)]_{\beta}\}, \quad [39]
\end{aligned}$$

where

$$\begin{aligned}
\text{cov}\{[\chi^{(x)}(\mathbf{x}, t)]_{\alpha}, [\chi^{(x)}(\mathbf{x}, t)]_{\beta}\} \\
= \sum_u \gamma_u^{(x)}(\mathbf{x}, t) [\chi_u^{(x)}(\mathbf{x}, t)]_{\alpha} [\chi_u^{(x)}(\mathbf{x}, t)]_{\beta} \quad [40]
\end{aligned}$$

is the covariance matrix of the components of the vector $\chi_u^{(x)}(\mathbf{x}, t)$. From Eqs. 30–39, we note that, if we take the trace of the

tensors in Eq. 39, we can derive an inequality similar to Eq. 19. We have

$$\text{Tr}[\overline{\varphi^{(x)}(\mathbf{x}, t)}] = \sum_{\alpha} \overline{\partial_{x_{\alpha}} [\chi^{(x)}(\mathbf{x}, t)]_{\alpha}} = -\sum_{\alpha} \overline{\{[\chi^{(x)}(\mathbf{x}, t)]_{\alpha}\}^2} \leq 0. \quad [41]$$

The average of the tensor of space-specific, absolute rate of evolution $\psi_u^{(x)}(\mathbf{x}, t)$ can be easily evaluated by following the method of derivation for Eqs. 20 presented in the preceding section. We obtain

$$\begin{aligned}
\overline{\psi^{(x)}(\mathbf{x}, t)} &= \sum_u \overline{\psi_u^{(x)}(\mathbf{x}, t) \gamma_u(\mathbf{x}, t)} \\
&= \Psi^{(x)}(\mathbf{x}, t) + \overline{\varphi_u^{(x)}(\mathbf{x}, t)} \\
&= \Psi^{(x)}(\mathbf{x}, t) - \overline{\Delta \sigma^{(x)}(\mathbf{x}, t) \otimes \Delta \sigma^{(x)}(\mathbf{x}, t)}, \quad [42]
\end{aligned}$$

where

$$\begin{aligned}
\overline{\Delta \sigma^{(x)}(\mathbf{x}, t) \otimes \Delta \sigma^{(x)}(\mathbf{x}, t)} \\
= \sum_u \gamma_u(t) [\overline{\sigma_u^{(x)}(\mathbf{x}, t)} - \overline{\sigma^{(x)}(\mathbf{x}, t)}] \\
\otimes [\overline{\sigma_u^{(x)}(\mathbf{x}, t)} - \overline{\sigma^{(x)}(\mathbf{x}, t)}] = \overline{\chi^{(x)}(\mathbf{x}, t) \otimes \chi^{(x)}(\mathbf{x}, t)}. \quad [43]
\end{aligned}$$

From Eq. 42 we have

$$\begin{aligned}
\Psi^{(x)}(\mathbf{x}, t) &= \overline{\psi^{(x)}(\mathbf{x}, t)} + \overline{\Delta \sigma^{(x)}(\mathbf{x}, t) \otimes \Delta \sigma^{(x)}(\mathbf{x}, t)}, \quad [44] \\
[\Psi^{(x)}(\mathbf{x}, t)]_{\alpha\beta} &= \overline{[\psi^{(x)}(\mathbf{x}, t)]_{\alpha\beta}} \\
&\quad + \text{cov}\{[\overline{\sigma^{(x)}(\mathbf{x}, t)}]_{\alpha}, [\overline{\sigma^{(x)}(\mathbf{x}, t)}]_{\beta}\}, \quad [45]
\end{aligned}$$

and

$$\begin{aligned}
\text{Tr}[\Psi^{(x)}(\mathbf{x}, t)]_{\alpha\beta} &= \sum_{\alpha} \partial_{x_{\alpha}} [\overline{\sigma_{\Sigma}^{(x)}(\mathbf{x}, t)}]_{\alpha} \\
&= \sum_{\alpha} \partial_{x_{\alpha}} [\overline{\sigma_u^{(x)}(\mathbf{x}, t)}]_{\alpha} + \sum_{\alpha} \overline{\{[\Delta \sigma^{(x)}(\mathbf{x}, t)]_{\alpha}\}^2} \\
&\geq \sum_{\alpha} \partial_{x_{\alpha}} [\overline{\sigma_u^{(x)}(\mathbf{x}, t)}]_{\alpha}, \quad [46]
\end{aligned}$$

where

$$\begin{aligned}
\text{cov}\{[\overline{\sigma^{(x)}(\mathbf{x}, t)}]_{\alpha}, [\overline{\sigma^{(x)}(\mathbf{x}, t)}]_{\beta}\} \\
= \sum_u \gamma_u^{(x)}(\mathbf{x}, t) [\overline{\sigma_u^{(x)}(\mathbf{x}, t)} - \overline{\sigma^{(x)}(\mathbf{x}, t)}]_{\alpha} \\
\cdot [\overline{\sigma_u^{(x)}(\mathbf{x}, t)} - \overline{\sigma^{(x)}(\mathbf{x}, t)}]_{\beta}. \quad [47]
\end{aligned}$$

Eqs. 38, 39, and 41 are equivalent to Eqs. 44–47, respectively; they can be derived from one another by passing from relative to absolute evolutionary variables and vice versa. They are both equivalent space-dependent formulations of a generalized Fisher's theorem.

By analogy with the time-dependent case, we can also introduce a space-dependent commutator operator

$$\begin{aligned} \mathbb{C}^{(x)} \dots &= \nabla_x \overline{(\dots)} - \overline{(\nabla_x \dots)} \\ &= \nabla_x \left(\sum_u \gamma_u(\mathbf{x}, t) \dots \right) - \sum_u \gamma_u(\mathbf{x}, t) \nabla_x (\dots), \end{aligned} \quad [48]$$

between the gradient and the averaging with respect to the gene frequencies. In terms of $\mathbb{C}^{(x)}$ Eqs. 38 and 44 can be expressed in the same form,

$$\mathbb{C}^{(x)} \sigma^{(x)}(\mathbf{x}, t) = \overline{\Delta \sigma^{(x)}(\mathbf{x}, t) \otimes \Delta \sigma^{(x)}(\mathbf{x}, t)}, \quad [49]$$

$$\mathbb{C}^{(x)} \chi^{(x)}(\mathbf{x}, t) = \overline{\Delta \chi^{(x)}(\mathbf{x}, t) \otimes \Delta \chi^{(x)}(\mathbf{x}, t)}. \quad [50]$$

In conclusion, in this section we have developed a space-dependent version of our generalized Fisher's theorem, which can be used for analyzing the evolution of space patterns in physics, chemistry, and biology. Below, we illustrate its use for the study of enhanced transport due to population growth.

Implications in Genetics and Chemical Kinetics

Although our time- and space-dependent generalized Fisher theorems were introduced by considering a simple system in population genetics, involving a single locus with many alleles, our results are more general: they apply to any physical, chemical, or biological systems that can be described in terms of multiple time- and/or space-dependent density fields. In our derivations we did not make any assumptions that are specific only to population genetics. With an adequate change of vocabulary (wording), our equations can be applied to physical or chemical kinetics. For example, in chemical kinetics the allele densities are replaced by the concentrations of different chemical species present in the system.

In general terms, our approach is the following. We study a system made up of many individual components (alleles, individuals, atoms, molecules, etc.). For each component, we introduce a time- and space-dependent density function (allele density, concentration, etc.) and a local fraction (gene frequency, molar fraction, etc.). We define absolute time- and space-specific rates of growth, which are given by the time and space variation of the natural logarithms of the density functions, respectively. We also define relative time- and space-specific rates of growth that are given by the time and space variation of the natural logarithm of the local fractions, respectively. The time or space variations of the specific rates of growth are rates of evolution. We define statistical properties for the system (averages, correlation functions, etc.) by taking statistical expectations with respect to the abundance of the different species in the system. We derive generalized Fisher's theorems that state that the average values of the relative rates of evolution can be expressed in terms of the moments of the second order of the relative rates of growth. In particular, the average value of the time-specific relative rates of evolution is a scalar, which is equal to the variance of the time-specific relative rates of growth with changed sign. The average value of the space-specific relative rates of evolution is a tensor with two labels, which is equal to the covariance matrix of the space-specific relative rates of growth with changed sign. These laws can be used to evaluate the capability of a given component to prevail for long times or to fill out the available space, which may lead to interesting applications in physics, chemistry, and biology. Some of these applications are briefly discussed here.

An application that is of interest both in chemical kinetics and genetics is the enhanced transport in reaction-diffusion systems induced by population growth (14, 15). Although this type of enhanced transport may occur both in chemistry and genetics,

here we discuss it in connection with the genetic applications. Both simulations and theoretical analysis have shown that if a mutation occurs in an expanding population, two different transport patterns emerge. If a mutation occurs in an area where the total population is saturated, then the motion of the mutation is slow and diffusive. However, if the mutation occurs at a position close to the propagation front of the total population, then the transport of the mutation is enhanced and has a diffusive (slow) component as well as a hydrodynamic (fast) component. Considering a single locus with many alleles and isotropic diffusion, the hydrodynamic speed \mathbf{v}_u of the subpopulation carrying the allele u is given by $\mathbf{v}_u = 2D_u \nabla_x \ln n(\mathbf{x}, t)$, where D_u is the diffusion coefficient of the subpopulation u and $n(\mathbf{x}, t)$ is the total population density (15). For anisotropic diffusion characterized by a diffusion tensor \mathbb{D}_u the hydrodynamic speed is given by the more general relation

$$\mathbf{v}_u = 2\mathbb{D}_u \cdot \nabla_x \ln n(\mathbf{x}, t), \quad [51]$$

$$(\mathbf{v}_u)_\alpha = 2 \sum_\beta (\mathbb{D}_u)_{\alpha\beta} \partial_\beta \ln n(\mathbf{x}, t). \quad [52]$$

Eq. 51 is valid whether the mutations in the population are neutral or not; it is a straightforward consequence of modeling the genetic process by a system of reaction diffusion equations.

Our approach leads to a simple physical (or biological) interpretation of Eq. 51. By using Eq. 27 we can rewrite Eq. 51 in the following form:

$$\mathbf{v}_u = 2\mathbb{D}_u \cdot \sigma_\Sigma^{(x)}(\mathbf{x}, t), \quad [53]$$

that is, the hydrodynamic speed of the subpopulation u is twice the contraction of the diffusion tensor \mathbb{D}_u and the vector of the space-specific rate of growth of the total population $\sigma_\Sigma^{(x)}(\mathbf{x}, t)$. Thus, the hydrodynamic speed of the subpopulation u is proportional to the diffusion tensor \mathbb{D}_u , which expresses the intrinsic mobility of the subpopulation u , and to the vector of space-specific rate of growth of the total population $\sigma_\Sigma^{(x)}(\mathbf{x}, t)$; this result in turn expresses the capability of the total population to fill out the available space. We notice that we can also derive a generalized Fisher relation that connects the average of the rate of space variation of the hydrodynamic speed to the covariance matrix of the space-specific rates of growth. We differentiate Eq. 52 with respect to x_α and take an average with respect to the different subpopulations. We have

$$\begin{aligned} \overline{\partial_\alpha (\mathbf{v}_u)_\beta} &= 2 \sum_\gamma (\mathbb{D}_u)_{\beta\gamma} \overline{[\psi^{(x)}(\mathbf{x}, t)]_{\gamma\alpha}} \\ &+ \text{cov}\{[\sigma^{(x)}(\mathbf{x}, t)]_\gamma, [\sigma^{(x)}(\mathbf{x}, t)]_\alpha\}. \end{aligned} \quad [54]$$

Genetic maps are commonly used to display the geographical distributions of various mutations. These maps display the space variation of local gene frequencies or of allele densities. Our approach suggests the elaboration of alternate genetic maps displaying the variation of absolute or relative space-specific rate of growth; because these variables are vectors such genetic maps would look similar to the "stream maps" used in fluid mechanics. The analysis of the spatial distribution of the space-specific rates of growth would provide useful information about the preferential direction of motion of the population, that is, the relative capabilities of different subpopulations to spread in different regions. All information necessary for constructing stream maps is contained in the regular genetic maps. Such stream maps may also be useful for analyzing chemical patterns in reaction kinetics.

Similar applications can be developed starting from the time-dependent version of our approach. In the case of complex

chemical or biochemical networks, the time-specific rates can be used for evaluating the relative contribution of various reaction pathways to a useful process and building simplified kinetics models that take into account the contributions of the most important pathways. For example, in the case of chain reactions used for amplifying signals in biochemical systems, the analysis of experimental data can be simplified by identifying the chains of optimal length that have the greatest contribution to the output signal (13).

In our derivations, we have assumed that the time and space variation of the density functions is known from experiments or theory. This assumption has important implications in population genetics: for example, it makes it possible to describe not only the effects of selection but also of other genetic processes, such as mutations, migration, or random drift; moreover, our approach makes it possible to study multi-locus systems and even problems of quantitative genetics, described in terms of continuous phenotypic variables. Regarding the effects of random drift, the approach presented in this work describes a single realization of a random process. To quantify the effects of random drift, we need to develop methods of dynamic averaging with respect to the sampling fluctuations. Such a task can be accomplished by using the method of curtailed characteristic functionals (16).

The space-dependent version of our approach can be easily extended to more complicated problems. For relativistic transport problems, it is convenient to replace real space by the space–time continuum. For problems of quantitative genetics, it

is useful to replace the real space by the space of a set of phenotypic variables. Other generalization of our approach for transport processes is based on the use of a Lagrangian description of the motion. The Lagrangian description of motion leads to Fisher equations similar to the ones derived in *Time-Dependent Generalized Fisher Theorems*, where the partial time derivative ∂_t is replaced by a transport (substantial) derivative D_t .

Our generalized Fisher's theorems also lead to interesting problems from the point of view of statistical physics. As pointed out by Fisher and many others, there is an analogy between Fisher's theorem and the second law of thermodynamics. This analogy raises many questions that have not been studied yet; in particular, it is not clear whether the Fisher's theorem is connected in some way to an extremum entropy principle. Our formulation makes it possible to further investigate this question. Our preliminary research has shown that there is an unexpected relation between our generalized Fisher's theorems and the theory of likelihood and Fisher information. In particular, our relative, time- and space-specific rates of growth can be interpreted as statistical scores. Another interesting problem is investigating the possible connections between our approach and the variational formulation of physical laws based on the use of Fisher information, suggested by Roy Frieden (17).

We thank David Hochberg, Federico Moran, and Stefan C. Müller for useful discussions. We also thank Lányi Szabolcs for useful discussions regarding kinetic and genetic maps. This work was supported in part by the National Science Foundation and by National Institute of General Medical Sciences Grants 28428, 063883, and NIH-HG 000205.

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