Neutrality condition and response law for nonlinear reaction-diffusion equations, with application to population genetics

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We study a general class of nonlinear macroscopic evolution equations with ''transport'' and ''reaction'' terms which describe the dynamics of a species of moving individuals (atoms, molecules, quasiparticles, organisms, etc.). We consider that two types of individuals exist, ''not marked'' and ''marked,'' respectively. We assume that the concentrations of both types of individuals are measurable and that they obey a neutrality condition, that is, the kinetic and transport properties of the ''not marked'' and ''marked'' individuals are identical. We suggest a response experiment, which consists in varying the fraction of ''marked'' individuals with the preservation of total fluxes, and show that the response of the system can be represented by a linear superposition law even though the underlying dynamics of the system is in general highly nonlinear. The linear response law is valid even for large perturbations and is not the result of a linearization procedure but rather a necessary consequence of the neutrality condition. First, we apply the response theorem to chemical kinetics, where the ''marked species'' is a molecule labeled with a radioactive isotope and there is no kinetic isotope effect. The susceptibility function of the response law can be related to the reaction mechanism of the process. Secondly we study the geographical distribution of the nonrecurrent, nonreversible neutral mutations of the nonrecombining portion of the Y chromosome from human populations and show that the fraction of mutants at a given point in space and time obeys a linear response law of the type introduced in this paper. The theory may be used for evaluating the geographic position and the moment in time where and when a mutation originated.

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I. INTRODUCTION

A great deal of attention has been given to the study of nonlinear evolution equations including ''transport'' as well as ''reaction'' (that is, generation and disappearance) terms. These equations, which are generally referred to as ''reaction-diffusion'' equations describe a broad class of phenomena in physics, chemistry, and biology, including excitability, stable propagation fronts, solitary waves, solitons, stable nonuniform patterns and other nonlinear effects [1]. The investigation of these nonlinear effects is generally based on the use of numerical methods as well as approximate analytical approaches. Exact analytical results are relatively scarce and therefore valuable. Most exact results refer to special types of evolution equations for which analytical solutions are available, for example, the Burgrer equation [2].

The purpose of the present paper is to suggest a response experiment for exploring the dynamical behavior of a general type of reaction-diffusion equation. We show that, under suitable assumptions, it is possible to design an experiment for which the response of the system can be described by a linear superposition equation, even though the underlying dynamics of the process is highly nonlinear. Our research has been motivated by two different problems. First, in a series of papers three of us have studied the transit time distributions for complex chemical reaction networks in homogeneous systems [3]. We have shown that for such systems it is possible to design an experiment involving labeled compounds for which the response to an excitation can be described by a linear law, even if the kinetics of the process is nonlinear. In this case the linearity of the response is generated by a ''neutrality condition'' of the labeled and unlabeled compounds, that is, we assumed that the rate coefficients are identical for the labeled and unlabeled compounds. This neglect of the kinetic isotope effect is a reasonable approximation, frequently used in chemical kinetics [4]; it results in simplified evolution equations for the concentrations of labeled and unlabeled species. Linear response laws are highly desirable, especially in nonlinear kinetics, because they make it possible to carry out experiments for which the result can be easily interpreted. Secondly, the research of the other three of us is concerned with the geographical distribution of the nonrecurrent, nonreversible neutral mutations of the nonrecombining portion of the Y chromosome from human populations [5,6]. There is experimental evidence that most mutations of this type are neutral, which is consistent with Kimura's theory of neutral evolution [7]. Kimura's theory is based on a ''neutrality condition,'' that is, on the assumption that the natality and mortality functions as well as the transport coefficients are the same for the main population as well as for the mutants. For neutral mutations the nonlinear reaction-diffusion equations for the spreading of a mutation within a growing population which is expanding in space have a special structure, which make it possible to transform

them into linear evolution equations for the fractions of mutants (gene frequencies) at a given position and time, even though the global evolution equation for the total population density is nonlinear. The linearity of the evolution equations for the gene frequencies is due to Kimura's ''neutrality condition.'' The comparative analysis of these two apparently unrelated problems has shown that, by introducing a general ''neutrality condition'' it is possible to derive a linear response theorem for a general class of reaction-diffusion systems, which include the case of homogeneous, space-independent chemical systems discussed in Ref. [3] as a particular case. With minor adaptations this response theorem can be used for the description of the space and time propagation of neutral mutations. We believe that such a general response theorem may have implications in the study of various problems in physics, chemistry, biology, and genetic anthropology.

The structure of the paper is the following. In Sec. II we give a general formulation of the problem. In Sec. III we derive the response theorem and present a physical interpretation of the delay functions entering the response law. In Sec. IV we discuss the implications of the response theorem in chemical kinetics. In Sec. V we study a nonlinear model for the propagation of a neutral mutation in a growing population which is expanding in space and we derive a linear response law for this problem of population genetics. In Sec. VI we illustrate our approach by studying a simple, one-dimensional reaction-diffusion system. Finally in Sec. VII we discuss the utility of our results as well as the limitations and the possibilities of generalizing our approach.

II. FORMULATION OF THE PROBLEM

We consider a macroscopic system containing different types of individuals (species) which can be atoms, molecules, quasiparticles, biological organisms, etc. We assume that the different types of individuals interact with each other and at the same time are involved in random walk motions, which can be described by transport operators local in time. We denote by $\rho_u(\mathbf{r};t)$, $u=1,2,\ldots$, the concentrations of the different species at position $\mathbf{r}$ and time t, expressed in numbers of individuals per unit volume and assume that the rate of change of the species u, $R_u(t)$, can be expressed as a local, nonlinear, function of the composition vector $\rho(\mathbf{r};t)=[\rho_u(\mathbf{r};t)]_{u=1,2,\ldots}$ and of time t

$$R_u(t)=R_u(\rho(\mathbf{r};t))=R_u^+(\rho(\mathbf{r};t))-R_u^-(\rho(\mathbf{r};t)),$$

$$u=1,2,\ldots. \tag{1}$$

where $R_u^+(\rho(\mathbf{r};t))\geqslant 0$ and $R_u^-(\rho(\mathbf{r};t))\geqslant 0$ are formation and consumption rates, respectively. The transport of the different species can be described by transport operators, which are local in time and generally nonlocal in space:

$$\begin{aligned}\mathbb{L}_u\cdots &= \int_{\mathbf{r}'}[\cdots W_u(\rho(\mathbf{r}';t),\mathbf{r}'\rightarrow\mathbf{r})d\mathbf{r}' \\ &\quad -\cdots W_u(\rho(\mathbf{r};t),\mathbf{r}\rightarrow\mathbf{r}')d\mathbf{r}'] \\ &= \sum_{m=1}^{\infty}(-1)^m\sum_{\mu_1}\cdots\sum_{\mu_m}\frac{\partial^m}{\partial r_{\mu_1}\cdots\partial r_{\mu_m}} \\ &\quad \times\{D^{u(m)}_{\mu_1\cdots\mu_m}(\rho(\mathbf{r};t),\mathbf{r})\cdots\},\end{aligned} \tag{2}$$

where $W_u(\rho(\mathbf{r}';t),\mathbf{r}'\rightarrow\mathbf{r})d\mathbf{r}$, $u=1,2,\ldots$, are transport rates for the different species from a position between $\mathbf{r}'$ and $\mathbf{r}'+d\mathbf{r}'$ to a position between $\mathbf{r}$ and $\mathbf{r}+d\mathbf{r}$ and

$$\begin{aligned}D^{u(m)}_{\mu_1\cdots\mu_m}(\rho(\mathbf{r};t),\mathbf{r}) &= \frac{1}{m!}\int_{\mathbf{r}'}\prod_{u=1}^{m}(r_{\mu_u}-r'_{\mu_u}) \\ &\quad \times W_u(\rho(\mathbf{r};t),\mathbf{r}'\rightarrow\mathbf{r})d\mathbf{r}',\end{aligned} \tag{3}$$

are generalized diffusion coefficients of different orders. In most physical, chemical and biological applications the transport rates $W_u(\rho(\mathbf{r}';t),\mathbf{r}'\rightarrow\mathbf{r})d\mathbf{r}$ can be assumed to be independent of the composition vector $\rho(\mathbf{r}';t)$; however, in some cases such a dependence must be taken into account. For example, a dependence of the transport rates on the composition vector must be considered in order to describe the ''anticrowding'' effects in the diffusion of biological populations [8]. A similar dependence must be considered in order to describe bacterial chemotaxis [9].

For simplicity, in this article we limit ourselves to response experiments, which involve a single species, say species v. The evolution equations of the process are the following:

$$\partial\rho_u(\mathbf{r},t)/\partial t=R_u[\rho(\mathbf{r},t)]+\mathbb{L}_u\rho_u(\mathbf{r},t),\quad u\neq v, \tag{4}$$

$$\begin{aligned}\partial\rho_v(\mathbf{r},t)/\partial t &= J_v^+(\mathbf{r},t)-J_v^-[\rho(\mathbf{r},t)]+R_v[\rho(\mathbf{r},t)] \\ &\quad +\mathbb{L}_v\rho_v(\mathbf{r},t),\end{aligned} \tag{5}$$

where $J_v^+(\mathbf{r},t)$ is the input flux of species v, which is generally space and time dependent and can be controlled by the experimenter, and $J_v^-[\rho(\mathbf{r},t)]$ is the output flux of species v, which is assumed to depend on the composition vector; the composition dependence of the output flux can be expressed by a kinetic law. Our approach takes into account explicitly only the input and output fluxes of species v. The input and output fluxes for other species are not taken explicitly into consideration and can be embedded in the reaction rates.

We assume that each species $u=1,2,\ldots$, may exist in two different forms, ''marked'' and ''not marked'' and that both forms fulfill a ''neutrality condition,'' that is, their kinetic and transport properties are identical. In chemical kinetics a ''marked species'' can be a molecule containing a radioactive isotope and we neglect the kinetic isotope effect. In fluid mechanics a ''marked species'' can be a colored fluid for which the hydrodynamic properties (density, viscosity, diffusion coefficients) are the same as the ones of the main fluid. In population genetics a ''marked species'' can be an individual carrying a neutral mutation, and for which the

main functions describing the vital statistics (natality and mortality functions, diffusion coefficients) are the same as in the case of a nonmutant individual. In the following we denote by $\rho_u(\mathbf{r},t)$ and $\rho_u^*(\mathbf{r},t)$, $u=1,2,\ldots,$ the concentrations of the ''not marked'' and ''marked'' species, respectively, and by $\rho_u^\Sigma(\mathbf{r},t)=\rho_u(\mathbf{r},t)+\rho_u^*(\mathbf{r},t), u=1,2,\ldots,$ the total concentrations of the species.

We consider that at the beginning of the experiment the system contains only ''not marked'' species. The system need not be in a stationary state. The experiment consists in varying the ratio

$$\alpha_v(\mathbf{r},t)=J_v^{+*}(\mathbf{r},t)/J_v^{+\Sigma}(\mathbf{r},t), \tag{6}$$

between the input flux of $J_v^{+*}(\mathbf{r},t)$ the ''marked'' compound and the total input flux of species $v, J_v^{+\Sigma}(\mathbf{r},t)$, with the preservation of the total input flux $J_v^{+\Sigma}(\mathbf{r},t)$. We record the response to this variation, the fraction

$$\beta_v(\mathbf{r},t)=J_v^{-*}[\rho(\mathbf{r},t),\rho^*(\mathbf{r},t)]/J_v^{-\Sigma}[\rho(\mathbf{r},t),\rho^*(\mathbf{r},t)], \tag{7}$$

of the outflow flux of the marked species v, $J_v^{-*}[\rho(\mathbf{r},t),\rho^*(\mathbf{r},t)]$, to the total output flux $J_v^{-\Sigma}[\rho(\mathbf{r},t),\rho^*(\mathbf{r},t)]$ of species v. The purpose of our theoretical analysis is the derivation of a relation between the excitation of the system, expressed by the fraction $\alpha_v(\mathbf{r},t)$, and the response of the system, expressed by the fraction $\beta_v(\mathbf{r},t)$.

III. GENERAL RESPONSE LAW

In order to derive a response law we need a convenient mathematical representation of the ''neutrality condition,'' in the form of a scaling law, which connects the kinetic and transport laws for the whole system to the corresponding laws for the ''marked'' and ''not marked'' species, respectively. This problem has been already dealt with in chemistry, in the context of kinetic isotope method [4,10]. It has been shown that if the kinetic isotope effect is neglected, the formation and disappearance rates of the ''marked'' species $R_u^{\pm *}$, to the total rates of formation and disappearance $R_u^{\pm}(\rho^*(\mathbf{r};t)+\rho(\mathbf{r};t))$ are

$$R_u^{\pm *}(\rho^*(\mathbf{r};t),\rho(\mathbf{r};t))=\frac{\rho_u^*(\mathbf{r};t)}{\rho_u^*(\mathbf{r};t)+\rho_u(\mathbf{r};t)}R_u^{\pm}(\rho^*(\mathbf{r};t)+\rho(\mathbf{r};t)), \quad u=1,2,\ldots. \tag{8}$$

Equations (8) express the fact that the ''marked'' and ''not marked'' species contribute equally to the transport process. In Appendix A we present a simple derivation of Eqs. (8) for rate processes obeying the mass-action law. The main point of our approach is the assumption that these scaling conditions hold not only in chemistry, but for any other type of generation-consumption process of discrete particles obeying a neutrality condition. Equations (8) do not hold for variables which are not related directly to the formation or disappearance of particles, such as the temperature of the system.

Since we assume that the output flux $J_v^{-\Sigma}[\rho(\mathbf{r},t)]$ is expressed by a kinetic law, we introduce an additional scaling condition

$$J_v^{-*}(\rho^*(\mathbf{r};t),\rho(\mathbf{r};t))=\frac{\rho_v^*(\mathbf{r};t)}{\rho_v^*(\mathbf{r};t)+\rho_v(\mathbf{r};t)}J_u^{-\Sigma}(\rho^*(\mathbf{r};t)+\rho(\mathbf{r};t)). \tag{9}$$

We also introduce similar scaling conditions for the transport rates $W_u(\rho(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r})d\mathbf{r}$, $u=1,2,\ldots.$

$$W_u^*(\rho^*(\mathbf{r};t),\rho(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r})d\mathbf{r} = \frac{\rho_u^*(\mathbf{r}';t)}{\rho_u^*(\mathbf{r}';t)+\rho_u(\mathbf{r}';t)}W_u^*(\rho^*(\mathbf{r}';t)+\rho(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r})d\mathbf{r}, \quad u=1,2,\ldots. \tag{10}$$

Considering the response experiment suggested in the preceding section, we introduce two sets of transport equations (a) for the total species, ''marked'' and ''not marked''

$$\frac{\partial}{\partial t}\rho_u^\Sigma(\mathbf{r},t)=R_u[\rho^\Sigma(\mathbf{r},t)]+\int_{\mathbf{r}'}[\rho_u^\Sigma(\mathbf{r}',t)W_u(\rho^\Sigma(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r}) - \rho_u^\Sigma(\mathbf{r},t)W_u(\rho^\Sigma(\mathbf{r};t),\mathbf{r}\to\mathbf{r}')]d\mathbf{r}', \quad u\neq v, \tag{11}$$

$$\frac{\partial}{\partial t}\rho_v^\Sigma(\mathbf{r},t)=R_v[\rho^\Sigma(\mathbf{r},t)]+J_v^+(\mathbf{r},t)-J_v^-[\rho^\Sigma(\mathbf{r},t)] + \int_{\mathbf{r}'}[\rho_v^\Sigma(\mathbf{r}',t)W_v(\rho^\Sigma(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r}) - \rho_v^\Sigma(\mathbf{r},t)W_v(\rho^\Sigma(\mathbf{r};t),\mathbf{r}\to\mathbf{r}')]d\mathbf{r}' \tag{12}$$

and (b) for the ''marked'' species

$$\frac{\partial}{\partial t}\rho_u^*(\mathbf{r},t)=\frac{\rho_u^*(\mathbf{r},t)}{\rho_u^\Sigma(\mathbf{r},t)}R_u[\rho^\Sigma(\mathbf{r},t)] + \int_{\mathbf{r}'}[\rho_u^*(\mathbf{r}',t)W_u(\rho^\Sigma(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r}) - \rho_u^*(\mathbf{r},t)W_u(\rho^\Sigma(\mathbf{r};t),\mathbf{r}\to\mathbf{r}')]d\mathbf{r}', \quad u\neq v, \tag{13}$$

$$\frac{\partial}{\partial t}\rho_v^*(\mathbf{r},t)=\frac{\rho_v^*(\mathbf{r},t)}{\rho_v^\Sigma(\mathbf{r},t)}R_v[\rho^\Sigma(\mathbf{r},t)]+J_v^{*+}(\mathbf{r},t) - \frac{\rho_v^*(\mathbf{r},t)}{\rho_v^\Sigma(\mathbf{r},t)}J_v^-[\rho^\Sigma(\mathbf{r},t)] + \int_{\mathbf{r}'}[\rho_v^*(\mathbf{r}',t)W_v(\rho^\Sigma(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r}) - \rho_v^*(\mathbf{r},t)W_v(\rho^\Sigma(\mathbf{r};t),\mathbf{r}\to\mathbf{r}')]d\mathbf{r}'. \tag{14}$$

Together with suitable initial and boundary conditions, Eqs. (11)–(14) determine the time and space dependence of the total concentrations of the different species, as well as the concentrations of the marked species. Equations (11)–(14) are nonlinear; however, despite their nonlinearity, they lead to a linear response law, which relates the excitation function $\alpha_v(\mathbf{r},t)$ to the response function $\beta_v(\mathbf{r},t)$. From Eqs. (7) and (9) it follows that

$$\rho_v^*(\mathbf{r},t)=\beta_v(\mathbf{r},t)\rho_v^{\Sigma-}(\mathbf{r},t). \tag{15}$$

We insert Eq. (15) into Eq. (14) and make use of Eq. (12). After some algebraic manipulations we come to a linear integrodifferential equation for the response function $\beta_v(\mathbf{r},t)$

$$\frac{\partial}{\partial t}\beta_v(\mathbf{r},t)=(\alpha_v(\mathbf{r},t)-\beta_v(\mathbf{r},t))\Omega_v^+(\mathbf{r},t) + \int_{\mathbf{r}'}\beta_v(\mathbf{r}',t)\tilde{W}_v(\mathbf{r}'\to\mathbf{r};t)d\mathbf{r}' - \beta_v(\mathbf{r},t)\int_{\mathbf{r}'}\tilde{W}_v(\mathbf{r}'\to\mathbf{r};t)d\mathbf{r}', \tag{16}$$

where

$$\Omega_v^+(\mathbf{r},t)=J_v^{+\Sigma}(\mathbf{r},t)/\rho_v^{\Sigma}(\mathbf{r},t), \tag{17}$$

is a specific input rate and

$$\tilde{W}_v(\mathbf{r}'\to\mathbf{r};t)=\frac{\rho_v^{\Sigma}(\mathbf{r}',t)}{\rho_v^{\Sigma}(\mathbf{r},t)}W_v(\rho^{\Sigma}(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r}), \tag{18}$$

is an adjoint transport rate. Since Eq. (16) is linear, its solution corresponding to the initial condition

$$\beta_v(\mathbf{r},t=t_0)=\beta_v^0(\mathbf{r}) \tag{19}$$

can be expressed as

$$\beta_v(\mathbf{r},t)=\int_{\mathbf{r}'}\beta_v^0(\mathbf{r}')\Omega_v^+(\mathbf{r}',t_0)G(\mathbf{r}',t_0\to\mathbf{r},t)d\mathbf{r}' + \int_{t_0}^{t}\int_{\mathbf{r}'}\alpha_\nu(\mathbf{r}',t')\Omega_v^+(\mathbf{r}',t') \times G_v(\mathbf{r}',t'\to\mathbf{r},t)d\mathbf{r}'dt', \tag{20}$$

where $G_v(\mathbf{r}',t'\to\mathbf{r},t)$ is the Green function attached to Eq. (16), that is, it is the solution of

$$\left[\Omega_v^+(\mathbf{r},t)+\frac{\partial}{\partial t}\right]G_v(\mathbf{r}',t'\to\mathbf{r},t) - \int_{\mathbf{r}''}G_v(\mathbf{r}',t'\to\mathbf{r}'',t)\tilde{W}_v(\mathbf{r}''\to\mathbf{r};t)d\mathbf{r}'' + G_v(\mathbf{r}',t'\to\mathbf{r},t)\int_{\mathbf{r}''}\tilde{W}_v(\mathbf{r}''\to\mathbf{r};t)d\mathbf{r}'' = \delta(\mathbf{r}-\mathbf{r}')\delta(t-t'). \tag{21}$$

It is mathematically convenient to embed the initial condition of the response function, $\beta_v^0(\mathbf{r})$ into the excitation function. If we define the modified excitation function

$$\tilde{\alpha}_v(\mathbf{r},t)=\beta_v^0(\mathbf{r})\delta(t-t_0)+\alpha_v(\mathbf{r},t), \tag{22}$$

then we can embed the first integral term in Eq. (20) into the second integral term in the same equation and extend the time integration limit to minus infinity. We come to

$$\beta_v(\mathbf{r},t)=\int_{-\infty}^{t}\int_{\mathbf{r}'}\tilde{\alpha}_v(\mathbf{r}',t')\chi_v(\mathbf{r}',t'\to\mathbf{r},t)d\mathbf{r}'dt', \tag{23}$$

where

$$\chi_v(\mathbf{r}',t'\to\mathbf{r},t)=\Omega_v^+(\mathbf{r}',t')G_v(\mathbf{r}',t'\to\mathbf{r},t), \tag{24}$$

is a space and time dependent susceptibility function. Equation (23) is the main result of this section; Eq. (23) is the space-dependent generalization of the linear response theorem derived for tracer experiments in space-independent, homogeneous chemical systems [3].

In order to obtain a physical interpretation of the susceptibility function $\chi_v(\mathbf{r}',t'\to\mathbf{r},t)$ we introduce the transit time τ of an individual from the species v, that is, the time necessary for that individual to cross the system, from its entrance in the input flux $J_v^+(\mathbf{r},t)$ to its departure in the output flux $J_v^-[\rho(\mathbf{r},t)]$. We introduce the notation

$$\eta_v(\tau,\mathbf{r}',\mathbf{r},t)d\tau d\mathbf{r}'d\mathbf{r} \quad \text{with}$$

$$\int_0^{\infty}\int_{\mathbf{r}'}\eta_v(\tau,\mathbf{r}',\mathbf{r},t)d\tau d\mathbf{r}'=\rho_v(\mathbf{r},t), \tag{25}$$

for the number of individuals from the species v which at time t are placed position between $\mathbf{r}$ and $\mathbf{r}+d\mathbf{r}$, have a residence time in the system between τ and $\tau+d\tau$, and entered the system at a position between $\mathbf{r}'$ and $\mathbf{r}'+d\mathbf{r}'$. Since our evolution equations in the absence of the ''marked'' species, Eqs. (4) and (5), depend only on total concentrations, it follows that the individuals with different transit times and entry positions obey a ''neutrality condition,'' in the sense that they are characterized by the same kinetic and transport coefficients. The scaling conditions (8)–(10) can be easily extended for a continuous distribution of residence times and entry positions, resulting in

$$\mathcal{R}_v^{\pm}(\eta_v(\tau,\mathbf{r}',\mathbf{r},t),\rho(\mathbf{r};t))d\tau d\mathbf{r}' = \frac{\eta_v(\tau,\mathbf{r}',\mathbf{r},t)d\tau d\mathbf{r}'}{\rho_v(\mathbf{r};t)}R_v^{\pm}(\rho(\mathbf{r};t)), \tag{26}$$

$$\mathcal{I}_v^{-}(\eta_v(\tau,\mathbf{r}',\mathbf{r},t),\rho(\mathbf{r};t))d\tau d\mathbf{r}' = \frac{\eta_v(\tau,\mathbf{r}',\mathbf{r},t)d\tau d\mathbf{r}'}{\rho_v(\mathbf{r};t)}J_v^{-}(\rho(\mathbf{r};t)), \tag{27}$$

$$\mathcal{W}_v(\eta_v(\tau,\mathbf{r}',\mathbf{r}'',t),\rho(\mathbf{r}';t),\mathbf{r}''\to\mathbf{r})d\tau d\mathbf{r}' = \frac{\eta_v(\tau,\mathbf{r}',\mathbf{r}'',t)d\tau d\mathbf{r}'}{\rho_v(\mathbf{r}'';t)} W_v(\rho(\mathbf{r}'';t),\mathbf{r}''\to\mathbf{r}), \tag{28}$$

where $\mathcal{R}_v^{\pm}((\eta_v(\tau,\mathbf{r}',\mathbf{r},t),\rho(\mathbf{r};t))$, $\mathcal{I}_v^{-}(\eta_v(\tau,\mathbf{r}',\mathbf{r},t),\rho(\mathbf{r};t))$, and $\mathcal{W}_v(\eta_v(\tau,\mathbf{r}',\mathbf{r}'',t),\rho(\mathbf{r}';t),\mathbf{r}''\to\mathbf{r})\mathbf{d}\tau d\mathbf{r}'$ are rate and flux densities which obey the integral conditions

$$\int_0^\infty \int_{\mathbf{r}'} \mathcal{R}_v^{\pm}(\eta_v(\tau,\mathbf{r}',\mathbf{r},t),\rho(\mathbf{r};t))d\tau d\mathbf{r}' = R_v^{\pm}(\rho(\mathbf{r};t)), \tag{29}$$

$$\int_0^\infty \int_{\mathbf{r}'} \mathcal{I}_v^{-}(\eta_v(\tau,\mathbf{r}',\mathbf{r},t),\rho(\mathbf{r};t))d\tau d\mathbf{r}' = J_v^{-}(\rho(\mathbf{r};t)), \tag{30}$$

$$\int_0^\infty \int_{\mathbf{r}'} \mathcal{W}_v(\eta_v(\tau,\mathbf{r}',\mathbf{r}'',t),\rho(\mathbf{r}';t),\mathbf{r}''\to\mathbf{r})d\tau d\mathbf{r}' = W_v(\rho(\mathbf{r}'';t),\mathbf{r}''\to\mathbf{r}). \tag{31}$$

By using the rate and flux densities (27)–(29) we can derive the following balance equations for the population density:

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial \tau}\right)\eta_v(\tau,\mathbf{r}',\mathbf{r},t) = \frac{\eta_v(\tau,\mathbf{r}',\mathbf{r},t)}{\rho_v(\mathbf{r};t)} R_v(\rho(\mathbf{r};t)) - \frac{\eta_v(\tau,\mathbf{r}',\mathbf{r},t)}{\rho_v(\mathbf{r};t)} J_v^{-}(\rho(\mathbf{r};t)) + \int_{\mathbf{r}''}[\eta_v(\tau,\mathbf{r}',\mathbf{r}'',t) W_v(\rho^{\Sigma}(\mathbf{r}'';t),\mathbf{r}''\to\mathbf{r}) - \eta_v(\tau,\mathbf{r}',\mathbf{r},t) W_v(\rho^{\Sigma}(\mathbf{r};t),\mathbf{r}\to\mathbf{r}'')]d\mathbf{r}'', \tag{32}$$

and

$$\eta_v(\tau=0,\mathbf{r}',\mathbf{r},t) = J_v^{+}(\mathbf{r};t)\,\delta(\mathbf{r}-\mathbf{r}'). \tag{33}$$

We introduce the probability density of the initial position $\mathbf{r}'$ and transit time τ for an individual from species v which at time t is at the position $\mathbf{r}$:

$$\varphi_v(\tau,\mathbf{r}'|\mathbf{r},t) = \eta_v(\tau,\mathbf{r}',\mathbf{r},t) \Big/ \int_0^\infty \int_{\mathbf{r}'} \eta_v(\tau,\mathbf{r}',\mathbf{r},t)d\tau d\mathbf{r}' = \eta_v(\tau,\mathbf{r}',\mathbf{r},t)/\rho_v(\mathbf{r},t) \tag{34}$$

which obeys the normalization condition

$$\int_0^\infty \int_{\mathbf{r}'} \varphi_v(\tau,\mathbf{r}'|\mathbf{r},t)d\tau d\mathbf{r}' = 1. \tag{35}$$

In order to derive an evolution equation for the conditional probability density $\varphi_v(\boldsymbol{\tau},\mathbf{r}'|\mathbf{r},t)$ we insert Eq. (34) into Eqs. (32) and (33) and make use of Eq. (5) for the total population density of species v. After some calculations we obtain

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial \tau}\right)\varphi_v(\tau,\mathbf{r}'|\mathbf{r},t) = -\varphi_v(\tau,\mathbf{r}'|\mathbf{r},t)\Omega_v^{+}(\mathbf{r},t) + \int_{\mathbf{r}''} \varphi_v(\tau,\mathbf{r}''|\mathbf{r},t)\widetilde{W}_v(\mathbf{r}''\to\mathbf{r};t)d\mathbf{r}'' - \varphi_v(\tau,\mathbf{r}'|\mathbf{r},t)\int_{\mathbf{r}'} \widetilde{W}_v(\mathbf{r}'\to\mathbf{r};t)d\mathbf{r}', \tag{36}$$

with the boundary condition

$$\varphi_v(\tau=0,\mathbf{r}'|\mathbf{r},t) = \Omega_v^{+}(\mathbf{r};t)\,\delta(\mathbf{r}-\mathbf{r}'). \tag{37}$$

By comparing Eq. (36) with the evolution equation (21) for the Green function $G_v(\mathbf{r}',t'\to\mathbf{r},t)$ we notice that these two equations have a similar structure and thus the probability density $\varphi_v(\tau,\mathbf{r}'|\mathbf{r},t)$ can be expressed in terms of $G_v(\mathbf{r}',t'\to\mathbf{r},t)$. By integrating Eq. (36) along the characteristics we come to

$$\varphi_v(\tau,\mathbf{r}'|\mathbf{r},t) = h(t-\tau-t_0)\Omega_v^{+}(\mathbf{r}',t-\tau)G_v(\mathbf{r}',t-\tau\to\mathbf{r},t) + h(\tau-t+t_0)\int_{\mathbf{r}''}\varphi_v(\tau,\mathbf{r}'|\mathbf{r}'',t_0) \times G_v(\mathbf{r}'',t_0\to\mathbf{r},t)d\mathbf{r}'', \tag{38}$$

where $h(x)$ is the Heaviside step function. If in Eq. (38) we push the initial time to $t_0\to-\infty$, we notice that the conditional probability density $\varphi_v(\tau,\mathbf{r}'|\mathbf{r},t)$ is related to the delay function $\chi_v(\mathbf{r}',t'\to\mathbf{r},t)$, defined by Eq. (24) We have

$$\varphi_v(\tau,\mathbf{r}'|\mathbf{r},t) = \chi_v(\mathbf{r}',t-\tau\to\mathbf{r},t) \quad \text{and}$$
$$\chi_v(\mathbf{r}',t'\to\mathbf{r},t) = \varphi_v(t-t',\mathbf{r}'|\mathbf{r},t). \tag{39}$$

The susceptibility function $\chi_v(\mathbf{r}',t'\to\mathbf{r},t)$ can be viewed as a conditional probability density of the initial time $t'=t-\tau$ and of the initial position $\mathbf{r}'$, which fulfills the normalization condition

$$\int_{-\infty}^{t}\int_{\mathbf{r}'}\chi_v(\mathbf{r}',t'\to\mathbf{r},t)d\mathbf{r}'dt' = 1. \tag{40}$$

The linear response law (23) can be rewritten as

$$\beta_v(\mathbf{r},t) = \int_{-\infty}^{t}\int_{\mathbf{r}'}\widetilde{\alpha}_v(\mathbf{r}',t')\chi_v(\mathbf{r}',t'\to\mathbf{r},t)d\mathbf{r}'dt' = \int_0^\infty\int_{\mathbf{r}'}\widetilde{\alpha}_v(\mathbf{r}',t-\tau)\varphi_v(\boldsymbol{\tau},\mathbf{r}'|\mathbf{r},t)d\mathbf{r}'d\tau. \tag{41}$$

Now the physical significance of the linear response law is straightforward: it expresses the contribution to the output fraction of marked particles entering the system at different initial positions $\mathbf{r}'$ and different initial times, $t'=t-\tau$. The

weight function (susceptibility function) attached to various initial positions and times is the conditional probability density of these two random variables.

In conclusion, in this section we have shown that for neutral systems obeying the scaling laws (8)–(10) the response to the excitation experiment suggested in Sec. II can described by a linear superposition law where the susceptibility function is the conditional probability of the initial position and time of a marked individual entering the system.

IV. IMPLICATIONS OF THE THEORY IN CHEMISTRY, BIOCHEMISTRY, CHEMICAL ENGINEERING, AND HYDRODYNAMICS

The implications of our theory in chemical and biochemical kinetics, chemical engineering and hydrodynamics can be discussed by using the same approach. In these fields it is easy to design response experiments which make it possible to evaluate the susceptibility function, which enters the response law (23). The problem of population genetics, which motivated the present research in the first place, is more complicated and necessitates a special approach. This special approach is presented in Sec. V.

In the particular case of reaction-diffusion systems in chemistry or biochemistry the response law (23) is a direct generalization of the response theorem introduced by three of us for homogeneous chemical systems, without a concentration gradient [3].

Similar response laws have been derived in chemical engineering and physicochemical hydrodynamics [11]. Based on these response laws, tracer experiments have been designed which can be used for measuring various hydrodynamic properties of flowing mixtures in open vessels, for example, in chemical reactors or separation columns. These tracer experiments are somewhat similar, although not identical, with the tracer experiments based on our response law (23). Unlike our suggested experiments, the input and output variables are concentrations, not fractions of fluxes. Moreover, no neutrality condition is used in the derivation of the response laws, and thus the response laws and the tracer experiments only hold for systems obeying linear conservation laws, such as the continuity equation of hydrodynamics in absence of chemical reaction. Our approach allows the introduction of a new type of response experiment, which also holds for systems with underlying nonlinear dynamics, provided that a set neutrality conditions holds for the transport and reaction processes occurring in the system.

In pharmacokinetics similar response experiments are used, based on the assumption of a linear response law, which connects the input concentration of a drug introduced in the human body and the output concentrations in urine, liver, perspiration, etc. [12]. The main assumptions on which such an approach is based are the following. (1) The human body can be described as a set of interconnecting compartments, which correspond to different biological organs. (2) The drug is assumed to be uniformly distributed in each compartment. (3) The transport of the drug among the different compartments is described by linear transport laws. (4) If the drug is transformed (metabolized) in the organism then this transformation can be described by a linear kinetic law of first order. This approach is limited to the particular case of relatively low concentrations for which the nonlinearity of the transport among different compartments can be neglected and the nonlinear kinetic laws can be linearized. Once again, our approach makes it possible to extend the response laws and response experiments to the nonlinear regime, provided that a set of neutrality conditions for labeled compounds is a reasonable approximation. However, in this paper we do not discuss pharamakokinetic systems because they do not involve reaction-diffusion models.

For the abovementioned systems from chemistry, biochemistry, chemical engineering, and hydrodynamics we can imagine two different types of response experiments. (1) Transient experiments, which consist in varying the fraction of a labeled compound at different times and positions in space and in recording the fraction of the labeled compound at different times and positions. (2) Frequency response experiments, for which we assume that the fraction of labeled compound in the input flux can be varied as a wave in space and time.

The simplest type of transient experiment is based on the assumption that the input fraction $\tilde{\alpha}_v(\mathbf{r}',t')$ has the form of a delta function

$$\tilde{\alpha}_v(\mathbf{r}',t')=A_v^0\delta(\mathbf{r}'-\mathbf{r}_0)\,\delta(t'-t_0). \tag{42}$$

By inserting Eq. (42) into Eq. (41) we obtain

$$\beta_v(\mathbf{r},t)=A_v^0\chi_v(\mathbf{r}_0,t_0\rightarrow\mathbf{r},t)=A_v^0\varphi_v(t-t_0,\mathbf{r}_0|\mathbf{r},t), \tag{43}$$

from which we can evaluate the susceptibility function $\chi_v(\mathbf{r}',t'\rightarrow\mathbf{r},t)$ and the probability density $\varphi_v(\tau,\mathbf{r}'|\mathbf{r},t)$ of the transit time and initial position. In order to evaluate these functions, we need to repeat the transport experiment many times, for different initial positions and initial times, which can be very difficult task. The problem simplifies considerably for time and space invariant systems, for which we have

$$\begin{aligned}\varphi_v(\tau,\mathbf{r}'|\mathbf{r},t)d\tau d\mathbf{r}'&=\varphi_v(\tau,\mathbf{r}'-\mathbf{r}|\mathbf{0},0)d\tau d\mathbf{r}'\\&=\psi_v(\tau,\Delta\mathbf{r})d\tau d\Delta\mathbf{r},\end{aligned} \tag{44}$$

where $\psi_v(\tau,\Delta\mathbf{r})d\tau d\Delta\mathbf{r}$ is the probability that the transition time is between τ and $\tau+d\tau$ and the displacement vector $\Delta\mathbf{r}=\mathbf{r}-\mathbf{r}'$ is between $\Delta\mathbf{r}$ and $\Delta\mathbf{r}+d\Delta\mathbf{r}$. If Eq. (44) is valid then the response law (41) reduces to a convolution equation in space and time

$$\beta_v(\mathbf{r},t)=\int_0^\infty\int_{\Delta\mathbf{r}}\tilde{\alpha}_v(\mathbf{r}-\Delta\mathbf{r},t-\tau)\,\psi_v(\tau,\Delta\mathbf{r})d\tau d\Delta\mathbf{r}, \tag{45}$$

The convolution equation (45) can be solved for an arbitrary excitation $\tilde{\alpha}_v(\mathbf{r}',t')$ by performing an inverse numerical Fourier and Laplace transformation. In this case, in order to

evaluate the probability $\psi_v(\tau,\Delta\mathbf{r})d\tau d\Delta\mathbf{r}$ and the susceptibility function $\chi_v(\mathbf{r}',t'\to\mathbf{r},t)$ it is enough to carry out a single response experiment.

In the case of a frequency response experiment we assume that the input fraction $\tilde{\alpha}_v(\mathbf{r}',t')$ has the form of a wave

$$\tilde{\alpha}_v(\mathbf{r}',t')=A_v^0+\Delta A_v\exp(i\omega t'-i\mathbf{k}\cdot\mathbf{r}'), \tag{46}$$

where ω and $\mathbf{k}$ are the frequency and the wave vector of the wave, and A_v^0 and ΔA_v are the temporal average and the amplitude of the excitation function, respectively. By combining Eqs. (41) and (46) we come to

$$\beta_v(\mathbf{r},t)=A_v^0+\Delta A_v\exp(i\omega t-i\mathbf{k}\cdot\mathbf{r})\Xi_v(\omega,\mathbf{k}|\mathbf{r},t), \tag{47}$$

where

$$\Xi_v(\omega,\mathbf{k}|\mathbf{r},t)=\int_0^{\infty}\int_{\Delta\mathbf{r}=-\infty}^{+\infty}\exp(-i\omega t'+i\mathbf{k}\cdot\Delta\mathbf{r})\times\psi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t)d\Delta\mathbf{r}d\tau, \tag{48}$$

is a complex susceptibility function and

$$\psi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t)=\varphi_v(\tau,\mathbf{r}-\Delta\mathbf{r}|\mathbf{r},t), \quad \text{where}$$

$$\int_0^{\infty}\int_{\Delta\mathbf{r}=-\infty}^{+\infty}\psi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t)d\Delta\mathbf{r}d\tau=1 \tag{49}$$

is the probability density of the transit time τ and of the displacement vector $\Delta\mathbf{r}=\mathbf{r}-\mathbf{r}'$. By repeating the response experiment for different values of the frequency ω and the wave vector $\mathbf{k}$ it is possible to evaluate the complex susceptibility $\Xi_v(\omega,\mathbf{k}|\mathbf{r},t)$, from which, by means of an inverse Fourier transformation, we can evaluate the conditional probability density $\psi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t)$ of the transit time τ and of the displacement vector $\Delta\mathbf{r}=\mathbf{r}-\mathbf{r}'$. If the numerical data are not very accurate the numerical evaluation of the inverse Fourier transforms may be impossible. In this case, however, we can evaluate the moments and the cumulants of τ and $\Delta\mathbf{r}=\mathbf{r}-\mathbf{r}'$. We notice that, according to the definition (48), the complex susceptibility function $\Xi_v(\omega,\mathbf{k}|\mathbf{r},t)$ is the characteristic function of the probability density $\psi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t)$. It follows that the moments $\langle\tau^m(\Delta r_{u_1})^{n_{u_1}}\cdots(\Delta r_{u_\rho})^{n_{u_\rho}}\rangle$ and the cumulants $\langle\langle\tau^m(\Delta r_{u_1})^{n_{u_1}}\cdots(\Delta r_{u_\rho})^{n_{u_\rho}}\rangle\rangle$ can be evaluated from the derivatives of the complex susceptibility $\Xi_v(\omega,\mathbf{k}|\mathbf{r},t)$

$$\langle\tau^m(\Delta r_{u_1})^{n_{u_1}}\cdots(\Delta r_{u_\rho})^{n_{u_\rho}}\rangle=j^{m-\Sigma n_{u_\alpha}}\frac{\partial^{m+\Sigma n_{u_\alpha}}}{\partial\omega^m\partial(k_{u_1})^{n_{u_1}}\cdots\partial(k_{u_1})^{n_{u_1}}}\Xi_v(\omega,\mathbf{k}|\mathbf{r},t)\Bigg|_{\omega=0,\mathbf{k}=\mathbf{0}}, \tag{50}$$

$$\langle\langle\tau^m(\Delta r_{u_1})^{n_{u_1}}\cdots(\Delta r_{u_\rho})^{n_{u_\rho}}\rangle\rangle=j^{m-\Sigma n_{u_\alpha}}\frac{\partial^{m+\Sigma n_{u_\alpha}}}{\partial\omega^m\partial(k_{u_1})^{n_{u_1}}\cdots\partial(k_{u_1})^{n_{u_1}}}\ln\Xi_v(\omega,\mathbf{k}|\mathbf{r},t)\Bigg|_{\omega=0,\mathbf{k}=\mathbf{0}}, \tag{51}$$

We notice a formal analogy between the description of the tracer experiments suggested in this article and the linear response theory of Kubo for nonequilibrium systems with memory [13]. From this point of view Eq. (41) and its particular case (47) corresponding to a frequency response experiment, are the analogs of the force-flux relationships for systems with memory. This analogy is only superficial because Kubo's theory is limited to linear systems whereas the underlying dynamics of the chemical processes studied in this article are nonlinear. The linear structure of Eqs. (41) and (47) is generated by the particular experiment suggested in this article. For our problem the underlying nonlinear dynamics of the process generates some features which are missing from the linear systems described by the Kubo's theory. The complex susceptibility function $\Xi_v(\omega,\mathbf{k}|\mathbf{r},t)$ is given by a Fourier transform with respect to the transit time and the displacement vector and not with respect to the time variable and the absolute position. For this reason, unlike in the case of Kubo's theory, in our approach the complex susceptibility function $\Xi_v(\omega,\mathbf{k}|\mathbf{r},t)$ depends both on frequency, wave vector, time, and absolute position.

Despite these differences some general features of Kubo's theory are preserved in the case of our approach. An important consequence is generated by the causality principle which leads to a general relationship of the Kramers-Kronig type between the real and imaginary parts of the susceptibility function. We express $\Xi_v(\omega,\mathbf{k}|\mathbf{r},t)$ in the form

$$\Xi_v(\omega,\mathbf{k}|\mathbf{r},t)=\int_{\Delta\mathbf{r}=-\infty}^{+\infty}\exp(i\mathbf{k}\cdot\Delta\mathbf{r})\Theta_v(\omega,\Delta\mathbf{r}|\mathbf{r},t)d\Delta\mathbf{r}, \tag{52}$$

where

$$\Theta_v(\omega,\Delta\mathbf{r}|\mathbf{r},t)=\int_0^{\infty}\exp(-i\omega t')\psi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t)d\tau, \tag{53}$$

is a displacement-dependent complex susceptibility. $\Theta_v(\omega,\Delta\mathbf{r}|\mathbf{r},t)$ is generally complex and thus we have

$$\Theta_v(\omega,\Delta\mathbf{r}|\mathbf{r},t)=\varepsilon_v'(\omega,\Delta\mathbf{r}|\mathbf{r},t)-i\varepsilon_v''(\omega,\Delta\mathbf{r}|\mathbf{r},t), \tag{54}$$

where

$$\varepsilon_v'(\omega,\Delta\mathbf{r}|\mathbf{r},t)=\mathrm{Re}\,\Theta_v(\omega,\Delta\mathbf{r}|\mathbf{r},t),$$

$$\varepsilon_v''(\omega,\Delta\mathbf{r}|\mathbf{r},t)=-\mathrm{Im}\,\Theta_v(\omega,\Delta\mathbf{r}|\mathbf{r},t), \tag{55}$$

are the real and imaginary contributions to $\Theta_v(\omega,\Delta\mathbf{r}|\mathbf{r},t)$, respectively. The relationships between $\varepsilon_v'(\omega,\Delta\mathbf{r}|\mathbf{r},t)$ and $\varepsilon_v''(\omega,\Delta\mathbf{r}|\mathbf{r},t)$ have the form

$$\varepsilon_v'(\omega,\Delta\mathbf{r}|\mathbf{r},t)=-\frac{1}{\pi}\int_{-\infty}^{+\infty}d\omega'\frac{\mathrm{P}}{\omega'-\omega}\varepsilon_v''(\omega',\Delta\mathbf{r}|\mathbf{r},t), \tag{56}$$

$$\varepsilon_v''(\omega,\Delta\mathbf{r}|\mathbf{r},t)=\frac{1}{\pi}\int_{-\infty}^{+\infty}d\omega'\frac{\mathrm{P}}{\omega'-\omega}\varepsilon_v'(\omega',\Delta\mathbf{r}|\mathbf{r},t), \tag{57}$$

where the notation P indicates the Cauchy principal value. These relationships can be derived in the same way as the classical Kramers-Kronig relationships for time-independent complex susceptibility functions. To save space the detailed derivation is not given here. The main idea is to introduce the complex function

$$\Sigma_v(z,\Delta\mathbf{r}|\mathbf{r},t)=\int_0^{\infty}\exp(iz\tau)\psi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t)d\tau, \tag{58}$$

where z is a complex frequency variable and to investigate the influence of the causality on the analytic properties of this function. The function is related to the susceptibility by means of the relation

$$\begin{aligned}\Theta_v(\omega,\Delta\mathbf{r}|\mathbf{r},t)&=\lim_{v\to+0}\Sigma_v(z=-\omega+iv,\Delta\mathbf{r}|\mathbf{r},t)\\&=\lim_{v\to+0}\int_0^{\infty}\exp[-(i\omega+v)\tau]\psi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t)d\tau.\end{aligned} \tag{59}$$

Since in Eq. (56) the integral is taken from zero to infinity the function $\Sigma_v(z,\Delta\mathbf{r}|\mathbf{r},t)$ is analytic in the upper z plane. This analyticity property is a consequence of the causality principle which requires that the transit time is never negative. The analytic behavior of the function $\Sigma_v(z,\Delta\mathbf{r}|\mathbf{r},t)$ in the upper z plane makes it possible to express it by a closed path integral of the Cauchy type. By separating the real and imaginary parts in this Cauchy integral and using Eqs. (54) and (58) we obtain the generalized Kramers-Kronig relationships (56) and (57).

In conclusion, in this section we have suggested that the linear response law and the response experiments can be applied to various reaction-diffusion systems from chemistry, biochemistry, chemical engineering, and physicochemical thermodynamics, provided that they obey a neutrality condition. We have shown that the response experiments make it possible to evaluate the susceptibility functions from transient as well as frequency response experiments. Further, the complex susceptibility functions which result from frequency response experiments obey a system of integral equations of the Kramers-Kronig type, which express the condition of causality.

V. EVOLUTION EQUATIONS FOR THE PROPAGATION OF A NEUTRAL MUTATION IN EXPANDING POPULATIONS

In this section we derive a simple model for the space and time propagation of neutral mutations in an expanding population. The model is motivated by the study of the geographical distribution of the nonrecurrent, nonreversible, neutral mutations of the nonrecombining portion of the Y chromosome from human populations [5,6]. The ultimate goal of the model is to evaluate the geographic position and the moment in time where and when a mutation observed in a current population originated. Simulation studies have shown that the saturation effects in the total population play an important role in the dynamics of the process and thus a linear population model is not satisfactory. For the description of the saturation effects we use a nonlinear generalization [14] of Lotka's theory of stable population [15]. We consider that the maternity (natality) function of the population λ depends only on the age a, $\lambda=\lambda(a)$, and that the mortality function μ is made up of two components, an age-dependent component $\mu_0(a)$ and a density-dependent component $\delta\mu(\rho)$ which is a function of the population density $\rho(\mathbf{r},t)$. Under these circumstances, after a transient regime of a few centuries, the population reaches a stable regime for which the fraction of individuals with a given age $c(a)da$ becomes stationary [14]:

$$c(a)da=c_{st}(a)da=l(a)e^{-\nu a}da\Big/\int_0^{\infty}l(a)e^{-\nu a}da, \tag{60}$$

where ν, the intrinsic rate of growth, is the unique real root of the transcendental equation

$$\int_0^{\infty}\lambda(a)l(a)e^{-\nu a}da=1, \tag{61}$$

and where

$$l(a)=\exp\left(-\int_0^a\mu_0(a')da'\right) \tag{62}$$

is the survival function (the life table) evaluated from the density-independent component of the mortality function $\mu_0(a)$.

We consider a neutral gene with different alleles $u=1,2,\ldots,$ and denote by $\varepsilon_{uu'}$ the probability per generation that the allele u mutates into the allele u'. In the final application the mutations are irreversible and nonrecurrent and thus it is enough to consider a single mutation, say $1\to2$, occurring with the probability $\varepsilon_{12}=\varepsilon$. In the development of the general theory, however, in order to preserve the symmetry of the equations, we consider an arbitrary mutation matrix $\varepsilon=[\varepsilon_{uu'}]$. We use the notation $\xi_u(a;\mathbf{r};t)dad\mathbf{r}$ for the

number of individuals with a gene u which at time t are at a position between $\mathbf{r}$ and $\mathbf{r}+d\mathbf{r}$ and have an age between a and $a+da$. In terms of this function we can compute the partial population densities $\vartheta_u(\mathbf{r},t)$ of the carriers of different genes as well as the total population density

$$\vartheta_u(\mathbf{r},t)=\int_0^\infty \xi_u(a,\mathbf{r},t)da,\quad \rho(\mathbf{r};t)=\sum_u \int_0^\infty \xi_u(a,\mathbf{r},t)da. \tag{63}$$

We assume that the population migration can be described by a transport operator $\mathbb{L}\cdots$ of the type (2):

$$\mathbb{L}\cdots=\int_{\mathbf{r}'}[\cdots W(\rho(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r})-\cdots W(\rho(\mathbf{r};t),\mathbf{r}\to\mathbf{r}'))]d\mathbf{r}'. \tag{64}$$

By taking into account that the mutations are neutral, so that all individuals are characterized by the same natality and mortality functions and transport rate coefficients we can derive the following evolution equations for the density functions $\xi_u(a;\mathbf{r};t)$, $u=1,2,\ldots$:

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)\xi_u(a;\mathbf{r};t)=-\rho_u(a;\mathbf{r};t)\{\mu^0(a)+\delta\mu[\rho(\mathbf{r};t)]\}+\int_{\mathbf{r}'}[\xi_u(a;\mathbf{r}';t)W(\rho(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r})-\xi_u(a;\mathbf{r};t)W(\rho(\mathbf{r};t),\mathbf{r}\to\mathbf{r}')]d\mathbf{r}' \tag{65}$$

and

$$\xi_u(a=0;\mathbf{r};t)=\sum_{u'}\varepsilon_{u'u}\int_0^\infty \lambda(a')\xi_{u'}(a',\mathbf{r};t)da'. \tag{66}$$

Since the process of gene propagation takes place in a time scale of $\sim 10^5$ yr whereas the stable age profile is reached in a few centuries, we may eliminate the age structure from Eqs. (65) and (66). In Appendix B we derive a system of evolution equations for the partial population densities

$$\frac{\partial}{\partial t}\vartheta_u(\mathbf{r},t)=\vartheta_u(\mathbf{r},t)[\nu-\delta\mu[\rho(\mathbf{r};t)]]+\sum_{u'}\sigma_{u'u}\vartheta_{u'}(\mathbf{r},t)-\sum_{u'}\sigma_{uu'}\vartheta_u(\mathbf{r},t)+\int_{\mathbf{r}'}\vartheta_u(\mathbf{r}',t)\times W[\rho(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r}]d\mathbf{r}'-\vartheta_u(\mathbf{r},t)\times\int_{r'}W[\rho(\mathbf{r};t),\mathbf{r}\to\mathbf{r}']d\mathbf{r}'. \tag{67}$$

Here

$$\sigma_{uu'}=\varepsilon n_{uu'}/Z(\nu) \tag{68}$$

are mutation rates, ν is the intrinsic rate of growth, and

$$Z(\nu)=\int_0^\infty l(a)e^{-\nu a}da \tag{69}$$

is the partition function attached to the Lotka age profile given by Eq. (60)

Due to the neutrality condition we can derive from Eqs. (67) a closed evolution equation for the total population density. By summing Eqs. (67) over the label u we come to

$$\frac{\partial}{\partial t}\rho(\mathbf{r};t)=\rho(\mathbf{r};t)[\nu-\delta\mu[\rho(\mathbf{r};t)]]+\int_{\mathbf{r}'}\rho(\mathbf{r}';t)W[\rho(\mathbf{r};t);\mathbf{r}-\mathbf{r}']d\mathbf{r}'-\rho(\mathbf{r};t)\times\int_{\mathbf{r}'}W[\rho(\mathbf{r};t);\mathbf{r}'-\mathbf{r}]d\mathbf{r}'. \tag{70}$$

We introduce the frequencies of the different alleles at a position between $\mathbf{r}$ and $\mathbf{r}+d\mathbf{r}$ and time t

$$\gamma_u(\mathbf{r},t)=\vartheta_u(\mathbf{r},t)/\rho(\mathbf{r},t)\ \text{ with }\ \sum_u\gamma_u(\mathbf{r},t)=1. \tag{71}$$

By combining Eqs. (67), (70), and (71) we can derive a system of evolution equations for the allele frequencies $\gamma_u(\mathbf{r},t)$. After some algebraic manipulations we come to

$$\frac{\partial}{\partial t}\gamma_u(\mathbf{r},t)=\sum_{u'}\sigma_{u'u}\gamma_{u'}(\mathbf{r},t)-\sum_{u'}\sigma_{uu'}\gamma_u(\mathbf{r},t)+\int_{\mathbf{r}'}\gamma_u(\mathbf{r}',t)\frac{\rho(\mathbf{r}';t)}{\rho(\mathbf{r};t)}W[\rho(\mathbf{r}';t);\mathbf{r}-\mathbf{r}']d\mathbf{r}'-\gamma_u(\mathbf{r},t)\int_{\mathbf{r}'}\frac{\rho(\mathbf{r}';t)}{\rho(\mathbf{r};t)}W[\rho(\mathbf{r}';t);\mathbf{r}-\mathbf{r}']d\mathbf{r}'. \tag{72}$$

In particular, if the population diffusion can be described by Fick's law from physics, then the evolution equations (67) for partial population densities turn into a simple form

$$\frac{\partial}{\partial t}\vartheta_u(\mathbf{r},t)=\sum_{u'}\sigma_{u'u}\vartheta_{u'}(\mathbf{r},t)-\sum_{u'}\sigma_{uu'}\vartheta_u(\mathbf{r},t)+\vartheta_u(\mathbf{r},t)\times[\nu-\delta\mu[\rho(\mathbf{r};t)]]+D\nabla^2\vartheta_u(\mathbf{r},t), \tag{73}$$

where D is a population diffusion coefficient and the evolution equations (70) and (72) for the total population density and allele frequencies, become

$$\frac{\partial}{\partial t}\rho(\mathbf{r};t)=\rho(\mathbf{r};t)[\nu-\delta\mu[\rho;(\mathbf{r};t)]]+D\nabla^2\rho(\mathbf{r};t) \tag{74}$$

and

$$\frac{\partial}{\partial t}\gamma_u(\mathbf{r},t)=\sum_{u'}\sigma_{u'u}\gamma_{u'}(\mathbf{r},t)-\sum_{u'}\sigma_{uu'}\gamma_u(\mathbf{r},t)+D\nabla^2\gamma_u(\mathbf{r},t)+(\mathrm{grad}\,\gamma_u(\mathbf{r},t))\cdot\varphi(\mathbf{r},t), \quad (75)$$

where

$$\varphi(\mathbf{r},t)=2D\,\mathrm{grad}\ln[\rho(\mathbf{r},t)]=2D\frac{\nabla\rho(\mathbf{r},t)}{\rho(\mathbf{r},t)} \quad (76)$$

is a velocity vector which expresses the ''hydrodynamic'' flow of different allele frequencies generated by the gradient of the total population density. We notice that the hydrodynamic velocity vector $\varphi(\mathbf{r},t)$ is proportional to the ratio between the gradient of the total population density and the total population density.

Equations (74) and (75) describe the time and space evolution of the total population density as well as of the various allele frequencies in the case of Fickian diffusion. In population genetics Eq. (74) is referred to as a Fisher equation [16]. Equation (74) has been extensively studied in the literature [16] and it has been shown that for $\not>0$ its solutions are solitary waves which correspond to a constant velocity of propagation of the population front. In the large time limit a constant population density ρ_{st} emerges, which is the solution of the equation $\not=\delta\mu[\rho_{st}]$. The constant population density ρ_{st} expresses the capacity of the environment to support the survival of the population and is referred to as ''carrying capacity.'' We notice that, unlike Eq. (74), Eqs. (75) for the different gene frequencies are linear; this is a consequence of the neutrality hypothesis, according to which the natality and mortality functions of different mutants are the same. We distinguish two different regimes for the propagation of the different mutations.

(a) If the total population density is space and time dependent then the space propagation of a mutation is made up of two different components: (1) A slow, diffusive motion, expressed by the Fick terms $D\nabla^2\gamma_u(\mathbf{r},t)$ in Eqs. (75), corresponding to different types of individuals and (2) a fast, hydrodynamic motion expressed by the convective terms $(\mathrm{grad}\,\gamma_u(\mathbf{r},t))\cdot\varphi(\mathbf{r},t)$ in Eqs. (75). The convective terms in Eqs. (75) can be expressed as

$$J_u=(\mathrm{grad}\,\gamma_u(\mathbf{r},t))\cdot\varphi(\mathbf{r},t)=|\mathrm{grad}\,\gamma_u(\mathbf{r},t)||\varphi(\mathbf{r},t)|\cos\Theta_u, \quad (77)$$

where Θ_u is the angle between the vector γ_u and the hydrodynamic velocity vector φ. It follows that the contribution of the hydrodynamic motion is large if the angle Θ_u is small and the absolute values $|\,\mathrm{grad}\,\gamma_u\,|$ and $|\varphi|$ of the gradient of the gene frequencies and of the hydrodynamic velocity vector are large. Typically the convective fluxes J_u are large for a population far away from saturation, which corresponds to a mutation generated at an initial position $(\mathbf{r}_0,t_0)$ for which the population density is much smaller than the carrying capacity of the environment, that is, $\rho(\mathbf{r}_0,t_0)\ll\rho_{st}$. Under these circumstances a mutation has the opportunity to spread fast; the mutation is carried by the solitary wave of the total population.

(b) If the total population density is constant, $\rho(\mathbf{r},t)=\rho_{st}$ then, according to Eq. (76) the hydrodynamic velocity is equal to zero, $\varphi(\mathbf{r},t)=0$ and the hydrodynamic motion does not exist anymore. The space propagation of a mutation is given by a slow, diffusive motion, expressed by the Fick terms $D\nabla^2\gamma_u(\mathbf{r},t)$. A typical situation corresponding to this case is a mutation generated late in time at a position $(\mathbf{r}_0,t_0)$ for which the population density has reached the stationary value given by the carrying capacity of the environment $\rho(\mathbf{r}_0,t_0)=\rho_{st}$. Under these circumstances a mutation is moving slowly and does not have the opportunity to spread away from its point of origin quickly.

The genetic problem presented in this section is different from the examples discussed in the previous section. The difference is due to the fact that the design of a response experiment is generally not possible in human population genetics, due to the fact that the evolution of the human species has taken place over many millennia and the geneticists can only observe the present effects of different evolutionary events which tool place a long time ago. However, it is possible that our theory leads to a response theorem, which is similar to the general law (23). We express the initial conditions of Eqs. (67) and (70) in the following form:

$$\vartheta_u(\mathbf{r}=\mathbf{r}_0,t=t_0)=\theta_u(\mathbf{r}_0,t_0),\quad \rho(\mathbf{r}=\mathbf{r}_0,t=t_0)=\not\rho(\mathbf{r}_0,t_0). \quad (78)$$

Now we embed the initial conditions (78) into the evolution equations (67) and (70) by introducing the input fluxes

$$J^{+\Sigma}(\mathbf{r},t)=\not\rho(\mathbf{r},t_0)\,\delta(t-t_0),\quad J_u^{+}{}^{*}(\mathbf{r},t)=\theta_u(\mathbf{r},t_0)\,\delta(t-t_0) \quad (79)$$

and the specific input rate

$$\Omega^{+}(\mathbf{r},t)=J^{+\Sigma}(\mathbf{r},t)/\rho(\mathbf{r},t). \quad (80)$$

Equations (67) and (70) become

$$\frac{\partial}{\partial t}\rho(\mathbf{r};t)=\rho(\mathbf{r};t)[\Omega^{+}(\mathbf{r},t)+\not-\delta\mu[\rho(\mathbf{r};t)]]+\int_{\mathbf{r}'}\rho(\mathbf{r}';t)W[\rho(\mathbf{r};t);\mathbf{r}-\mathbf{r}']d\mathbf{r}'-\rho(\mathbf{r};t)\int_{\mathbf{r}'}W[\rho(\mathbf{r};t);\mathbf{r}'-\mathbf{r}]d\mathbf{r}' \quad (81)$$

and

$$\frac{\partial}{\partial t}\vartheta_u(\mathbf{r},t)=J_u^{+}{}^{*}(\mathbf{r},t)+\vartheta_u(\mathbf{r},t)[\nu-\delta\mu[\rho(\mathbf{r};t)]]$$
$$+\sum_{u'}\sigma_{u'u}\vartheta_{u'}(\mathbf{r},t)-\sum_{u'}\sigma_{uu'}\vartheta_u(\mathbf{r},t)$$
$$+\int_{\mathbf{r}'}\vartheta_u(\mathbf{r}',t)W[\rho(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r}]d\mathbf{r}'$$
$$-\vartheta_u(\mathbf{r},t)\int_{\mathbf{r}'}W[\rho(\mathbf{r};t)\mathbf{r}\to\mathbf{r}']d\mathbf{r}' \tag{82}$$

with the initial conditions

$$\rho(\mathbf{r}=\mathbf{r}_0,t=t_0)=0,\quad \vartheta_u(\mathbf{r}=\mathbf{r}_0,t=t_0)=0. \tag{83}$$

The interesting variables, which are experimentally accessible, are the gene frequencies, that is, the fractions of different mutations in the gene pool at position $\mathbf{r}$ and time t

$$\gamma_u(\mathbf{r},t)=\vartheta_u(\mathbf{r},t)/\rho(\mathbf{r},t). \tag{84}$$

Sequence analysis makes it possible to measure the geographical distribution of different mutations at the current (present) time t and at different positions on Earth, from which it is possible to evaluate the gene frequencies $\gamma_u(\mathbf{r},t)$. The functions $\gamma_u(\mathbf{r},t)$ can be considered to be the response to an excitation vector

$$\alpha_v(\mathbf{r},t)=[\alpha_v(\mathbf{r},t)], \tag{85}$$

where the different excitation functions

$$\alpha_v(\mathbf{r},t)=\frac{J_v^{+}{}^{*}(\mathbf{r},t)}{J^{+\Sigma}(\mathbf{r},t)}=\frac{\theta_v(\mathbf{r},t_0)}{\mathscr{J}(\mathbf{r},t_0)} \tag{86}$$

are the ratios between the initial population densities of the different types of individuals $\theta_v(\mathbf{r},t_0)$ of the newly generated mutations of type v at an initial time $t=t_0$ and the total population concentration $\mathscr{J}(\mathbf{r},t_0)$ at that initial time $t=t_0$ [see Eq. (79)]. By combining Eqs. (80)–(86) we can derive a set of integrodifferential equations, which relate the response functions $\gamma_u(\mathbf{r},t)$ to the excitation function $\alpha_v(\mathbf{r},t)$:

$$\frac{\partial}{\partial t}\gamma_u(\mathbf{r},t)=(\alpha_v(\mathbf{r},t)-\gamma_u(\mathbf{r},t))\Omega^{+}(\mathbf{r},t)+\sum_{u'}\sigma_{u'u}\gamma_{u'}(\mathbf{r},t)$$
$$-\sum_{u'}\sigma_{uu'}\gamma_u(\mathbf{r},t)+\int_{\mathbf{r}'}\gamma_u(\mathbf{r}',t)\tilde{W}(\mathbf{r}'\to\mathbf{r};t)d\mathbf{r}'$$
$$-\gamma_u(\mathbf{r},t)\int_{\mathbf{r}'}\tilde{W}(\mathbf{r}'\to\mathbf{r};t)d\mathbf{r}', \tag{87}$$

where

$$\tilde{W}(\mathbf{r}'\to\mathbf{r};t)=\frac{\rho(\mathbf{r}',t)}{\rho(\mathbf{r},t)}W(\rho(\mathbf{r}';t),\mathbf{r}'\to\mathbf{r}), \tag{88}$$

is an adjoint transport rate similar to the ones defined by Eqs. (18).

The solution of the integrodifferential equations (87) can be expressed in a form similar to the integral response law (23)

$$\gamma_u(\mathbf{r},t)=\sum_{u''}\int_{t''=-\infty}^{t}\int_{\mathbf{r}''}\alpha_{u''}(\mathbf{r}'',t'')\chi_{u''u}(\mathbf{r}'',t''\to\mathbf{r},t)d\mathbf{r}''dt'', \tag{89}$$

where the susceptibility function

$$\chi_{u''u}(\mathbf{r}'',t''\to\mathbf{r},t)=\Omega^{+}(\mathbf{r}'',t'')\mathfrak{G}_{u''u}(\mathbf{r}'',t''\to\mathbf{r},t) \tag{90}$$

is proportional to a Green function which is the solution of the equation

$$\frac{\partial}{\partial t}\mathfrak{G}_{u''u}(\mathbf{r}'',t''\to\mathbf{r},t)$$
$$=\sum_{u'}\mathfrak{G}_{u''u'}(\mathbf{r}'',t''\to\mathbf{r},t)\sigma_{u'u}$$
$$-\mathfrak{G}_{u''u}(\mathbf{r}'',t''\to\mathbf{r},t)\left(\Omega^{+}(\mathbf{r},t)+\sum_{u'}\sigma_{uu'}\right)$$
$$+\int_{\mathbf{r}'}\mathfrak{G}_{u''u}(\mathbf{r}'',t''\to\mathbf{r}',t)\tilde{W}(\mathbf{r}'\to\mathbf{r};t)d\mathbf{r}'$$
$$-\mathfrak{G}_{u''u}(\mathbf{r}'',t''\to\mathbf{r},t)\int_{\mathbf{r}'}\tilde{W}(\mathbf{r}'\to\mathbf{r};t)d\mathbf{r}'$$
$$+\delta_{uu''}\delta(\mathbf{r}-\mathbf{r}'')\delta(t-t''). \tag{91}$$

We notice that for the genetic problem the evolution equations are more complicated than the evolution equations of the general theory developed in Sec. III. Despite this difference it is still possible to show that the susceptibility function has a simple probabilistic interpretation. By analogy with the general theory we introduce the age τ of the first mutation event in the system. The age τ is the time interval that elapsed from the initial appearance of a first mutation many generations ago, in an ancestor of the current population and the current time. We have

$$\tau=t-t_0, \tag{92}$$

where t is the current time and t_0 is the time when the first mutation event initially occurred in the population. The age of a mutation should not be confounded with the age a of an individual. These two quantities have different orders of magnitude ($a\sim 0-10^2$ yr and $\tau\sim 10^2-10^5$ yr). We also introduce the displacement vector of the mutation

$$\Delta\mathbf{r}=\mathbf{r}-\mathbf{r}_0, \tag{93}$$

which is the difference between the current position vector $\mathbf{r}$ and the position vector $\mathbf{r}_0$ attached to the place where the first mutation event occurred.

We denote by

$$\eta_{vu}(\tau,\Delta\mathbf{r},\mathbf{r},t)d\tau d\Delta\mathbf{r}d\mathbf{r}, \tag{94}$$

with

$$\sum_v \int_0^\infty \int_{\Delta r} \eta_{vu}(\tau,\Delta\mathbf{r},\mathbf{r},t)d\tau d\Delta\mathbf{r}$$
$$= \vartheta_u(\mathbf{r},t), \sum_u \sum_v \int_0^\infty \int_{\Delta r} \eta_{vn}(\tau,\Delta\mathbf{r},\mathbf{r},t)d\tau d\Delta\mathbf{r}$$
$$= \rho(\mathbf{r},t) \tag{95}$$

the number of individuals which at time t carry the gene u, are placed at a position between $\mathbf{r}$ and $\mathbf{r}+d\mathbf{r}$, have a mutation age between τ and $\tau+d\tau$, and a displacement vector between $\Delta\mathbf{r}$ and $\Delta\mathbf{r}+d\Delta\mathbf{r}$ provided that the initial mutation event generated a gene of type v.

By using the neutrality condition we can derive the following system of evolution equation for $\eta_{vu}(\tau,\Delta\mathbf{r},\mathbf{r},t)$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial\tau}\right)\eta_{vu}(\tau,\Delta\mathbf{r},\mathbf{r},t)$$
$$= \eta_{vu}(\tau,\Delta\mathbf{r},\mathbf{r},t)[\nu-\delta\mu[\rho(\mathbf{r};t)]]$$
$$+\sum_{u'}\eta_{vu'}(\tau,\Delta\mathbf{r},\mathbf{r},t)\sigma_{u'u}-\eta_{vu}(\tau,\Delta\mathbf{r},\mathbf{r},t)\sum_{u'}\sigma_{vu'}$$
$$+\int_{r''}[\eta_{uv}(\tau,\mathbf{r}-\mathbf{r}'',\mathbf{r},t)W(\rho(\mathbf{r}'';t),\mathbf{r}''\to\mathbf{r})$$
$$-\eta_{uv}(\tau,\mathbf{r}-\mathbf{r}'',\mathbf{r},t)W(\rho(\mathbf{r};t),\mathbf{r}\to\mathbf{r}'')]d\mathbf{r}'', \tag{96}$$

with the boundary conditions

$$\eta_{vu}(\tau=0,\Delta\mathbf{r},\mathbf{r},t)=J^+(\mathbf{r};t)\delta_{uv}\delta(\Delta\mathbf{r}). \tag{97}$$

We introduce the fraction of individuals which at time t carry the gene u, are placed at a position between $\mathbf{r}$ and $\mathbf{r}+d\mathbf{r}$, have a mutation age between τ and $\tau+d\tau$, and a displacement vector between $\Delta\mathbf{r}$ and $\Delta\mathbf{r}+d\Delta\mathbf{r}$, provided that the initial mutation event generated a gene of type v:

$$\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u)=\frac{\eta_{vu}(\tau,\Delta\mathbf{r},\mathbf{r},t)}{\sum_v\int_0^\infty\int_{\Delta r}\eta_{vu}(\tau,\Delta\mathbf{r},\mathbf{r},t)d\tau d\Delta\mathbf{r}}$$
$$=\frac{\eta_{vu}(\tau,\Delta\mathbf{r},\mathbf{r},t)}{\vartheta_u(\mathbf{r},t)}, \tag{98}$$

which obeys the normalization condition

$$\sum_v\int_0^\infty\int_{\Delta r}\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u)=1. \tag{99}$$

The function $\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u)d\tau d\Delta\mathbf{r}$ can be interpreted as the probability that at time t and position $\mathbf{r}$, an individual which carries a gene of type u is characterized by a mutation age between τ and $\tau+d\tau$, and a displacement vector between $\Delta\mathbf{r}$ and $\Delta\mathbf{r}+d\Delta\mathbf{r}$, and the first mutation present in its ancestors was of type v.

By combining Eqs. (101)–(103) we can derive a system of evolution equations for the fraction $\varphi(\tau,\Delta\mathbf{r}|\mathbf{r},t)$. We come to

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial\tau}\right)\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u)$$
$$=-\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u)\Omega^+(\mathbf{r},t)$$
$$+\sum_{u'}\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u')\sigma_{u'u}-\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u)\sum_{u'}\sigma_{uu'}$$
$$+\int_{\mathbf{r}''}\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r}'',t,u)\tilde{W}_v(\mathbf{r}''\to\mathbf{r};t)d\mathbf{r}''$$
$$-\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t)\int_{\mathbf{r}''}\tilde{W}_v(\mathbf{r}''\to\mathbf{r};t)d\mathbf{r}'', \tag{100}$$

with the boundary condition

$$\varphi_v(\tau=0,\Delta\mathbf{r}|\mathbf{r},t,u)=\Omega^+(\mathbf{r};t)\delta_{uv}\delta(\Delta\mathbf{r}). \tag{101}$$

By integrating Eq. (100) along the characteristics we can express the probability density $\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u)$ in terms of the Green function $\mathfrak{G}_{u''u}(\mathbf{r}'',t''\to\mathbf{r},t)$. We have

$$\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u)+h(t-\tau-t_0)\Omega^+(\mathbf{r}-\Delta\mathbf{r},t-\tau)\mathfrak{G}_{vu}(\mathbf{r}-\Delta\mathbf{r},t$$
$$-\tau\to\mathbf{r},t)+h(\tau-t+t_0)\sum_{u''}\int_{\mathbf{r}''}\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r}'',t_0,u'')$$
$$\times\mathfrak{G}_{u''u}(\mathbf{r}'',t_0\to\mathbf{r},t)d\mathbf{r}'', \tag{102}$$

If in Eq. (102) we push the initial time to $t_0\to-\infty$, we notice that the conditional probability density $\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u)$ is related to the susceptibility function $\chi_{u''u}(\mathbf{r}'',t''\to\mathbf{r},t)$, defined by Eq. (24). We have

$$\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u)=\chi_{vu}(\mathbf{r}-\Delta\mathbf{r},t-\tau\to\mathbf{r},t) \quad \text{and}$$
$$\chi_{vu}(\mathbf{r}',t'\to\mathbf{r},t)=\varphi_v(t-t',\mathbf{r}-\mathbf{r}'|\mathbf{r},t,u). \tag{103}$$

By using Eq. (103) we can rewrite the linear response law (89) in an alternative form

$$\gamma_u(\mathbf{r},t)=\sum_v\int_0^\infty\int_{\Delta r}\alpha_v(\mathbf{r}-\Delta\mathbf{r},t-\tau)$$
$$\times\varphi_v(\tau,\Delta\mathbf{r}|\mathbf{r},t,u)d\Delta\mathbf{r}d\tau. \tag{104}$$

The biological meaning of the linear response law (104) is clear: it expresses the contribution to the current values of the gene frequencies of the various possible initial mutations which may have occurred in the past, at different initial times and different initial positions and which may have generated various initial mutations. The weight function (susceptibility function) attached to various initial positions, times and mutations is the probability density of these three random variables.

In conclusion, in this section we have developed a simple mathematical model for the space and time propagation of neutral mutations in expanding human populations. The model considers a single haploid locus with different neutral alleles and the evolution equations of the population are assumed to be age dependent and nonlinear. Since the characteristic time scale describing the mutation events is much

larger than the time scale describing the variations in the age profiles, we have performed an adiabatic elimination of the age variable. The resulting overall evolution equations for the populations are a generalization of the classical Fisher model for the wave of advance of an advantageous gene. We have discussed some qualitative features of the solutions of these equations. We have shown that solitary waves in total population density may exist. Concerning the time and space propagation of the mutations, we have shown that two different propagation regimes exist, for low and large population densities, respectively. We have shown that the geographic distribution of the current values of the gene frequencies can be expressed by a linear superposition law. We have shown that the susceptibility function from the response law has a probabilistic interpretation which is similar to the interpretation of the response law derived in Sec. III.

VI. APPLICATION TO ONE-DIMENSIONAL REACTION-DIFFUSION SYSTEMS

In this section we illustrate our theory by considering a one species, one-dimensional reaction diffusion system of length L. We assume that in the absence of a tracer the dynamics of the system is described by the reaction diffusion equation

$$\frac{\partial}{\partial t}\rho = D\frac{\partial^2}{\partial x^2}\rho + R(\rho), \tag{105}$$

with the boundary condition

$$J^+ = -D\frac{\partial}{\partial x}\rho\bigg|_{x=0} = \text{const}, \tag{106}$$

where t is the time, x is the position, ρ is the number density of the species, D is its diffusion coefficient, $R(\rho)$ is its rate of transformation, which is a local function assumed to depend only on the population density. At position $x=0$ system receives a constant flux of individuals J^+. The system releases individuals at position $x=L$; the corresponding output flux can be evaluated by using a relation similar to Eq. (106):

$$J^- = -D\frac{\partial}{\partial x}\rho\bigg|_{x=L}. \tag{107}$$

Models of this type are commonly used in various branches of physics, chemistry and biology. For example they can describe the population dynamics in a linear habitat, or a catalytic process in chemical engineering occurring in a linear pore.

Usually for large times the models described by Eqs. (105) and (106) lead to a unique stationary concentration profile and to a constant output flux. Although for special forms of the reaction rate $R(\rho)$, more complicated types of large time behavior may emerge, in this paper we limit ourselves to the case of stationary concentration profiles. Moreover, we assume that the reaction rate $R(\rho)$ is non-negative, $R(\rho)\geqslant 0$ and thus the number of individuals of the species considered is generally growing. For example, we can consider an autocatalytic chemical reaction or the logistic growth of a single biological species in population dynamics A stationary concentration profile is the solution of the equation

$$D\frac{\partial^2}{\partial x^2}\rho(x) + R(\rho(x)) = 0 \quad \text{with} \quad J^+ = -D\frac{\partial}{\partial x}\rho(0). \tag{108}$$

By using the identity

$$\frac{\partial}{\partial x}\left[\frac{\partial}{\partial x}\rho(x)\right]^2 = 2\left[\frac{\partial}{\partial x}\rho(x)\right]\left[\frac{\partial^2}{\partial x^2}\rho(x)\right], \tag{109}$$

from Eq. (108) we can evaluate the output flux J^- in terms of the input flux J^+. We have

$$\frac{\partial}{\partial x}\left[D\frac{\partial}{\partial x}\rho(x)\right]^2 = -2DR(\rho)\frac{\partial}{\partial x}\rho(x), \tag{110}$$

and then

$$J^- = \sqrt{(J^+)^2 - 2D\int_{\rho(0)}^{\rho(L)} R(\rho)d\rho}. \tag{111}$$

We notice that a stationary regime is generally possible only if the input flux J^+ is larger than a minimum threshold value $J^+_{\min}$

$$J^+ > J^+_{\min}, \quad \text{with} \quad J^+_{\min} = \sqrt{2D\int_{\rho(0)}^{\rho(L)} R(\rho)d\rho}. \tag{112}$$

The physical interpretation of Eq. (112) is straightforward. A stationary density profile is the result of balancing between the population growth, which tends to increase the population concentration and the diffusion process, which reduces the concentration by dispersion, this balancing is only possible if the diffusion process is efficient enough. The inequality (112) can be rewritten as

$$D\left(\frac{\partial\rho}{\partial x}\right)^2\bigg|_{x=0} > 2\int_{\rho(0)}^{\rho(L)} R(\rho)d\rho. \tag{113}$$

Equation (113) clearly shows that a stationary profile may exist only if the contribution of the diffusion process, expressed by the factor $D(\partial\rho/\partial x)^2|_{x=0}$ outweighs the contribution of the population growth, expressed by the factor $2\int R(\rho)d\rho$.

Now we can suggest a tracer experiment. We assume that the species can exist in two forms, unlabeled and labeled and denote their concentrations by ρ and ρ^*, respectively, and by

$$\rho^\Sigma = \rho + \rho^*, \tag{114}$$

the total concentration of the species. We assume the existence of a neutrality condition, that is, the diffusion coefficient D is the same for the unlabeled and labeled species and the rate of transformation of the labeled species is given by

$$R^*=\frac{\rho^*}{\rho^{\Sigma}(x)}R[\rho^{\Sigma}(x)]. \tag{115}$$

We assume the existence of a constant input flux $J^{+\Sigma}$ for which there is a stationary concentration profile $\rho^{\Sigma}(x)$ and a constant output flux $J^{-\Sigma}$ which obey the equations

$$D\frac{\partial^2}{\partial x^2}\rho^{\Sigma}(x)+R[\rho^{\Sigma}(x)]=0, \text{ with } J^{+\Sigma}=-D\frac{\partial}{\partial x}\rho^{\Sigma}(0) \tag{116}$$

and

$$J^{-\Sigma}=\sqrt{(J^{+\Sigma})^2-2D\int_{\rho^{\Sigma}(0)}^{\rho^{\Sigma}(L)}R(\rho)d\rho}. \tag{117}$$

The total input and output fluxes, $J^{+\Sigma}$, $J^{-\Sigma}$ are made up of additive contributions corresponding to the labeled and unlabeled species, respectively,

$$J^{+\Sigma}=J^{+}+J^{+}*, \quad J^{-\Sigma}=J^{-}+J^{-}*, \tag{118}$$

Although the total fluxes $J^{+\Sigma},J^{-\Sigma}$ are maintained constant, their components $J^{+},J^{+}*,J^{-},J^{-}*$, can be arbitrary functions of time. We suggest a tracer experiment, which consists in the variation of the labeled input fraction

$$\alpha(t)=J^{+}*(t)/J^{+\Sigma}, \tag{119}$$

in a controlled way and in the recording of the labeled output fraction

$$\beta(t)=J^{-}*(t)/J^{-\Sigma}. \tag{120}$$

The concentration of labeled individuals $\rho^*(x,t)$ obeys the evolution equation

$$\frac{\partial}{\partial t}\rho^*(x,t)=D\frac{\partial^2}{\partial x^2}\rho^*(x,t)+w(x)\rho^*(x,t) \tag{121}$$

with the initial and boundary conditions

$$\rho^*(x>0,t=t_0)=0, \quad -D\frac{\partial}{\partial x}\rho^*(x=0,t)=J^{+}*(t), \tag{122}$$

where

$$w(x)=\frac{1}{\rho^{\Sigma}(x)}R[\rho^{\Sigma}(x)] \tag{123}$$

is a position-dependent effective rate coefficient. Equation (121) is a reaction-diffusion balance equation which can be derived from the rate equation (113). Since the evolution equation (121) is linear and space inhomogeneous its solution can be expressed in terms of an inhomogeneous Green function $G(x'\to x;t-t')$, which obeys the equation

$$\frac{\partial}{\partial t}G(x'\to x;t-t')=D\frac{\partial^2}{\partial x^2}G(x'\to x;t-t')+w(x)\times G(x'\to x;t-t')+\delta(x-x')\delta(t-t'). \tag{124}$$

We have

$$\rho^*(x,t)=\frac{1}{D}\int_{t_0}^{t}G(0\to x;t-t')J^{+}*(t')dt'. \tag{125}$$

In Eq. (125) we take the derivative with respect to x and put $x=L$. After some calculations we get a linear response theorem of the type considered in the general theory developed in the preceding sections

$$\beta(t)=\int_{t_0}^{t}\chi(t-t')\alpha(t')dt'=\int_{0}^{t-t_0}\varphi(\tau)\alpha(t-\tau)d\tau, \tag{126}$$

where the susceptibility functions $\chi(t-t')$ and $\varphi(\tau)$ are given by

$$\chi(t-t')=-\frac{J^{+\Sigma}}{J^{-\Sigma}}\frac{\partial}{\partial L}G(0\to L;t-t'), \tag{127}$$

$$\varphi(\tau)=-\frac{J^{+\Sigma}}{J^{-\Sigma}}\frac{\partial}{\partial L}G(0\to L;\tau), \tag{128}$$

and $\tau=t-t'$ is the transit time of the labeled species.

By following the general balance approach developed in Sec. III we can show that the susceptibility function $\varphi(\tau)$ expressed in terms of the transit time $\tau=t-t'$ can be interpreted as the probability density of the transit time $\tau=t-t'$. We are not going to repeat here the formal derivation presented in Sec. III. However, we show that the response law (126) derived in this section is compatible with the probabilistic interpretation of $\varphi(\tau)$. We notice that the Green function $G(0\to x;t-t')$ can be interpreted as a concentration field of the labeled species corresponding to a unitary excitation and thus it can never be negative, $G(0\to x;t-t')\geqslant 0$. Since at the exit of the system, $x=L$, there must a non-negative output of individuals, we must have $-D[\partial G(0\to x;t-t')/\partial L]\geqslant 0$. Because by definition the fluxes $J^{+\Sigma},J^{-\Sigma}$ are non-negative, $J^{+\Sigma},J^{-\Sigma}\geqslant 0$, from Eq. (128) it follows that

$$\varphi(\tau)\geqslant 0\,. \tag{129}$$

Moreover, in the limit, $t_0 \to -\infty$, the susceptibility function $\varphi(\tau)$ obeys the normalization condition

$$\int_0^\infty \varphi(\tau) d\tau = 1. \tag{130}$$

In order to obtain Eq. (130) we consider an excitation having the shape of a displaced step function

$$\alpha(t) = h(t - t_0), \tag{131}$$

where $h(x)$ is the Heaviside function. For the input (131) the total input flux $J^{+\Sigma}$ contains only labeled individuals, and thus for large time, $t_0 \to -\infty$, we must have

$$\beta(t) \to 1 \quad \text{as} \quad t_0 \to -\infty. \tag{132}$$

By combining Eqs. (126) and Eqs. (131) and (132) we come to the normalization condition (130)

In conclusion in this section we have illustrated our response theory by considering the particular case of a one-variable, one-dimensional nonlinear reaction diffusion system, which describes a growth process. We have shown that a stationary concentration profile may exist if the contribution of the diffusion process, which tends to reduce the concentration of individuals, outweighs the contribution of the growth process. We have shown that for such a system it is possible to design a linear response experiment of the type introduced in this paper.

VII. CONCLUSIONS

In this article we have studied space and time-dependent nonlinear systems from physics, chemistry, and biology which share a common feature: some of the types of individuals (atoms, molecules, quasiparticles, organisms, etc.) present in the system can exist in a ''marked'' and ''not marked'' state and obey a neutrality condition, that is, the kinetic and transport properties of the ''marked'' and ''not marked'' individuals are identical. We have shown that the neutrality condition has an important consequence: it opens the possibility of designing a response experiment characterized by a linear response law, even though the underlying dynamics of the system may be highly nonlinear. The linear response law is not the result of a linearization procedure, but a necessary consequence of the neutrality condition. Even though the response law is linear, the underlying nonlinearity of the process may influence its structure: in general nonlinear evolution equations lead to response laws, which are time and space variant.

We have shown that our theory can be applied to at least two different classes of systems. For certain problems of chemistry, biochemistry, and physicochemical hydrodynamics, for which the scientists have control on the processes studied, it is possible to use transient or frequency response experiments for the evaluation of the susceptibility functions from the linear response law. We have derived the basic equations necessary for the interpretation of these two types of experiments. We have shown that the causality principle leads to a set of generalized Kramers-Kronig relations. These Kramers-Kronig relations differ from the similar relations, from quantum optics, nonequilibrium thermodynamics, or particle physics: this difference is due to the fact that the nonlinear dynamics lead to space- and time-dependent susceptibility functions.

In human population genetics, scientists study a unique phenomenon, the evolution of human species during the last 10^5 yr and this phenomenon cannot be reproduced in a laboratory. Because of this, designing a direct response experiment is not possible in this case. However, we have shown that the current geographical distribution of mutations can be expressed by a linear response law similar to the ones derived for the other chemical and biological problems for which a response experiment can be carried out. This linear law makes it possible to estimate the original time and position of the occurrence of a mutation from the current geographical distribution of gene frequencies in human populations.

Further research will focus on the application of the approach developed here to various problems of physics, chemistry, and biology. In chemical kinetics preliminary studies have shown that the susceptibility functions contain important information about the reaction kinetics and mechanisms. In this field it is possible to evaluate the rate and transport coefficients from linear response experiments. In human population genetics the approach presented here can be used for evaluating the initial time and position at which a given mutation appeared for the first time in the human genome. Work on these two problems is in progress.

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APPENDIX A

We consider a simple chemical process involving the chemical species A as well as other species $B,C,\ldots$. We consider that the species A is involved in an elementary reaction of the type

$$\nu A + \cdots \rightleftarrows \text{products}, \tag{A1}$$

where ν is the molecularity of the process with respect to the species A. We assume that the rate of the process (A1) obeys the mass-action law, that is,

$$R = k[\rho_A(\mathbf{r})]^\nu \cdots, \tag{A2}$$

where $\rho_A(\mathbf{r})$ is the concentration of species A and the ellipsis in Eq. (A2) represent multiplicative terms depending on the concentrations of the other species $B,C,\ldots$, present in the system. We assume that the species A exists in two forms, unlabeled (A) and labeled (A^*) and that the kinetic isotope effect is missing, that is, the rate coefficient in Eq. (A2) is the same for both species, A and A^*. Since Eq. (A2) is generally

nonlinear, involving the νth power of the concentration $\rho_A(\mathbf{r})$, a naive approach would suggest that if both species A and A^* are present, then the rate of transformation corresponding to the labeled species is

$$R^* = [x_{A^*}(\mathbf{r})]^\nu R[\rho_{A^*}(\mathbf{r}) + \rho_A(\mathbf{r})] = \left\{ \frac{\rho_{A^*}(\mathbf{r})}{\rho_{A^*}(\mathbf{r}) + \rho_A(\mathbf{r})} \right\}^\nu R[\rho_{A^*}(\mathbf{r}) + \rho_A(\mathbf{r})], \quad \text{(A3)}$$

where $x_{A^*}(\mathbf{r}) = \rho_{A^*}(\mathbf{r})/[\rho_{A^*}(\mathbf{r}) + \rho_A(\mathbf{r})]$ is the fraction of labeled compound at position $\mathbf{r}$. However, a careful analysis of the problem shows that Eq. (A3) is incorrect and that the rate of transformation R^* corresponding to the labeled species is a linear function of the fraction $x_{A^*}(\mathbf{r})$ of the labeled compound at position $\mathbf{r}$, that is,

$$R^* = x_{A^*}(\mathbf{r}) R[\rho_{A^*}(\mathbf{r}) + \rho_A(\mathbf{r})] = \frac{\rho_{A^*}(\mathbf{r})}{\rho_{A^*}(\mathbf{r}) + \rho_A(\mathbf{r})} R[\rho_{A^*}(\mathbf{r}) + \rho_A(\mathbf{r})]. \quad \text{(A4)}$$

In order to prove Eq. (A4) we note that, if, both A and A^*, are present then there are actually ν reactions (A1) involving m labeled species, mA^*, and $(\nu - m)$ unlabeled species, $(\nu - m)A$ with $m = 1, \ldots, \nu$. These reactions can be represented as

$$mA^* + (\nu - m)A \cdots \rightleftarrows \text{products}, \quad m = 1, \ldots, \nu, \quad \text{(A5)}$$

Since we have assumed that the kinetic isotope effect is missing, all reactions (A5) are characterized by the same rate coefficient k. It follows that the rate of transformation of the labeled species R^* is given by

$$\begin{aligned} R^* &= \sum_{m=1}^{\nu} m \frac{(\nu-1)!}{m!(\nu-m)!} k[\rho_{A^*}(\mathbf{r})]^m [\rho_A(\mathbf{r})]^{\nu-m} \times \cdots \\ &= k\rho_{A^*}(\mathbf{r})[\rho_{A^*}(\mathbf{r}) + \rho_A(\mathbf{r})]^{\nu-1} \times \cdots \\ &= \frac{\rho_{A^*}(\mathbf{r})}{\rho_{A^*}(\mathbf{r}) + \rho_A(\mathbf{r})} A[\rho_{A^*}(\mathbf{r}) + \rho_A(\mathbf{r})] \\ &= x_{A^*}(\mathbf{r}) R[\rho_{A^*}(\mathbf{r}) + \rho_A(\mathbf{r})]. \end{aligned} \quad \text{(A6)}$$

APPENDIX B

In order to eliminate the age structure from the evolution equations (65) and (66) we introduce the conditional age profile

$$c(a|u;\mathbf{r},t) = \frac{\xi_u(a,\mathbf{r},t)}{\int da\, \xi_u(a,\mathbf{r},t)} = \frac{\xi_u(a,\mathbf{r},t)}{\vartheta_u(\mathbf{r},t)}. \quad \text{(B1)}$$

We insert Eq. (B1) into Eqs. (65) and (66), resulting in

$$\begin{aligned} c(a|u;\mathbf{r},t) \frac{\partial}{\partial t} \vartheta_u(\mathbf{r},t) + \rho_u(a;\mathbf{r};t) \left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a} \right) c(a|u;\mathbf{r},t) \\ = -\vartheta_u(\mathbf{r},t) c(a|u;\mathbf{r},t) \{\mu^0(a) + \delta\mu[\rho(\mathbf{r};t)]\} \\ + \int_{\mathbf{r}'} [\vartheta_u(\mathbf{r}',t) c(a|u;\mathbf{r}',t) W[\rho(\mathbf{r}';t);\mathbf{r}' \to \mathbf{r}] \\ - \vartheta_u(\mathbf{r},t) c(a|u;\mathbf{r},t) W[\rho(\mathbf{r};t);\mathbf{r} \to \mathbf{r}']] d\mathbf{r}' \end{aligned} \quad \text{(B2)}$$

and

$$\vartheta_u(\mathbf{r},t) c(a=0|u;\mathbf{r},t) = \sum_{u'} \varepsilon_{u'u} \int_0^\infty \lambda(a') \vartheta_u(\mathbf{r},t) c(a'|u';\mathbf{r},t) da'. \quad \text{(B3)}$$

By integrating Eqs. (B2) over age from $a = 0$ to $a = \infty$ and using Eqs. (B3) we get the following evolution equations for the partial population densities:

$$\begin{aligned} \frac{\partial}{\partial t} \vartheta_u(\mathbf{r},t) = \sum_{u'} \varepsilon_{u'u} \vartheta_{u'}(\mathbf{r},t) \int_0^\infty \lambda(a') c(a'|u';\mathbf{r},t) da' \\ - \vartheta_u(\mathbf{r},t) \left\{ \int_0^\infty c(a|u;\mathbf{r},t) [\mu^0(a) \right. \\ \left. + \delta\mu[\zeta(\mathbf{r};t)]] da \right\} + \int_{\mathbf{r}'} [\vartheta_u(\mathbf{r}',t) \\ \times W[\rho(\mathbf{r}';t);\mathbf{r}' \to \mathbf{r}] \\ - \vartheta_u(\mathbf{r},t) W[\rho(\mathbf{r};t);\mathbf{r} \to \mathbf{r}']] d\mathbf{r}'. \end{aligned} \quad \text{(B4)}$$

Now we take into account that, after a transient regime of a few centuries, the age profile tends towards the stable Lotka form (60) and thus

$$\rho_u(a;\mathbf{r};t) \sim c_{st}(a) \vartheta_u(\mathbf{r};t), \quad c(a|u;\mathbf{r},t) \sim c_{st}(a). \quad \text{(B5)}$$

We insert Eqs. (B5) into Eq. (B4) and we evaluate the average vital functions which enter these equations. We get the following expression for the average natality function:

$$\begin{aligned} \langle \lambda(a') \rangle &= \int_0^\infty \lambda(a') c(a'|u';\mathbf{r},t) da' \\ &\sim \int_0^\infty \lambda(a') c_{st}(a') da' \\ &= 1/Z(\curvearrowright). \end{aligned} \quad \text{(B6)}$$

The evaluation of the average mortality function is a bit more complicated. We obtain

$$\begin{aligned}\langle \mu(a) \rangle &= \int_0^\infty c(a|u;\mathbf{r},t)[\mu^0(a)+\delta\mu[\rho(\mathbf{r};t)]]da \\ &\sim \int_0^\infty c_{st}(a)[\mu^0(a)+\delta\mu[\rho(\mathbf{r};t)]]da \\ &= \int_0^\infty c_{st}(a)\mu^0(a)da+\delta\mu[\rho(\mathbf{r};t)]. \end{aligned} \tag{B7}$$

The last integral in Eq. (B7) can be evaluated in a number of steps. We get

$$\begin{aligned}\int_0^\infty c_{st}(a)\mu^0(a)da &= \frac{1}{Z(\nu)}\int_0^\infty \exp[-\nu a]\frac{\partial}{\partial a} \\ &\quad \times\left\{-\exp\left[-\int_0^a \mu^0(a')da'\right]\right\}da \\ &= \frac{1}{Z(\nu)}\left[1-\int_0^\infty\left\{\frac{\partial}{\partial a}\exp[-\nu a]\right\}\right. \\ &\quad \left.\times[-l(a)]da\right] \\ &= \frac{1}{Z(\nu)}-\nu. \end{aligned} \tag{B8}$$

By collecting these results and inserting them into Eqs. (B4) we come to Eqs. (67) and (68).

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