Functional, fractal nonlinear response with application to rate processes with memory, allometry, and population genetics

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We give a functional generalization of fractal scaling laws applied to response problems as well as to probability distributions. We consider excitations and responses, which are functions of a given state vector. Based on scaling arguments, we derive a general nonlinear response functional scaling law, which expresses the logarithm of a response at a given state as a superposition of the values of the logarithms of the excitations at different states. Such a functional response law may result from the balance of different growth processes, characterized by variable growth rates, and it is the first order approximation of a perturbation expansion similar to the phase expansion. Our response law is a generalization of the static fractal scaling law and can be applied to the study of various problems from physics, chemistry, and biology. We consider some applications to heterogeneous and disordered kinetics, organ growth (allometry), and population genetics. Kinetics on inhomogeneous reconstructing surfaces leads to rate equations described by our nonlinear scaling law. For systems with dynamic disorder with random energy barriers, the probability density functional of the rate coefficient is also given by our scaling law. The relative growth rates of different biological organs (allometry) can be described by a similar approach. Our scaling law also emerges by studying the variation of macroscopic phenotypic variables in terms of genotypic growth rates. We study the implications of the causality principle for our theory and derive a set of generalized Kramers–Kronig relationships for the fractal scaling exponents.

Response laws play important roles in physics, chemistry, and biology (1–3). In its simplest form a response law establishes a functional relationship $\mathbf{\Delta y} = \boldsymbol{\varphi}(\mathbf{\Delta x})$ between the variations $\Delta x_u = x_u - x_u^{(0)}$, $u = 1, 2, \ldots$ of a set of excitation variables, x_u and the variations $\Delta y_u = y_u - y_u^{(0)}$ of a set of response variables y_u. Here $x_u^{(0)}$ and $y_u^{(0)}$ are reference values and $\boldsymbol{\varphi}(\mathbf{\Delta x})$ is a generally nonlinear vectorial function of the variation of the excitation vector $\mathbf{\Delta x}$, which, by definition, fulfills the condition $\boldsymbol{\varphi}(\mathbf{0}) = \mathbf{0}$, and $\mathbf{x}^{(0)}$, $\mathbf{y}^{(0)}$ are reference values of the excitation and response vectors, respectively. For linear response $\varphi(\mathbf{\Delta x})$ is linear

$$\mathbf{\Delta y} = \mathbf{A}_1 \mathbf{\Delta x}, \qquad [1]$$

where $\mathbf{A}_1$ is a (response) susceptibility matrix. If the function $\varphi(\mathbf{\Delta x})$ is nonlinear and analytic near $\mathbf{\Delta x} = \mathbf{0}$, then the linear response law (Eq. **1**) is a first-order approximation derived from a Taylor series expansion of $\varphi(\mathbf{\Delta x})$. If the function $\varphi(\mathbf{\Delta x})$ is nonlinear and nonanalytic near $\mathbf{\Delta x} = \mathbf{0}$, then a Taylor series expansion does not exist and a linear response law of the type (Eq. **1**) does not hold even for very small values of the variations $\mathbf{\Delta x}$ and $\mathbf{\Delta y}$ of the excitation and response variables. The most common type of nonanalytic response law is the fractal response law (4)

$$\Delta y_u = B_u \prod_{u'} (\Delta x_{u'})^{\varepsilon_{uu'}}, \qquad [2]$$

where B_u are proportionality coefficients and $\varepsilon_{uu'}$ are nonintegral, dimensionless fractal exponents.

If the response and excitation variables $\mathbf{x}$ and $\mathbf{y}$ are replaced by functions depending on a state vector ρ such as a position vector, $\rho = (\mathbf{r})$ in real space, in time, $\rho = (t)$, in space-time continuum, $\rho = (\mathbf{r},t)$ or even in an abstract state space, then a linear response law analog to Eq. **1** has the form

$$\Delta y_u(\rho) = \sum_{u'} \int_{\rho'} \xi_{uu'}(\rho;\rho') \Delta x_{u'}(\rho') d\rho', \qquad [3]$$

where $\xi_{uu'}(\rho;\rho')$ are susceptibility functions which depend on the labels of the excitation and response variables and on the corresponding state vectors ρ,ρ'. Eq. **3** can be viewed as a fist order approximation of a functional Taylor expansion of the response functions in terms of the excitation functions.

If the relationships between the excitation and response functions are nonlinear and nonanalytic near $\mathbf{\Delta x}(\rho) = \mathbf{0}$, then linear response law of the type (Eq. **3**) does not hold even for very small variations $\mathbf{\Delta x}(\rho)$ and $\mathbf{\Delta y}(\rho)$ of the excitation and response vectors, and in this case Eq. **3** should be replaced by a functional analog of the fractal response law (Eq. **2**); as far as we know functional analogs of the fractal response law (Eq. **2**) have not been considered in the literature. The present article addresses this problem: We introduce functional analogs of the nonlinear fractal response law (Eq. **2**) and consider simple examples from disordered kinetics or transport and biology.

In the next section, we introduce functional analogs of the fractal response law (Eq. **2**) by using a simple scaling argument. We show that our nonlinear functional fractal response law is a first-order approximation of a double phase expansion. In subsequent sections, we discuss some applications of our scaling law in disordered kinetics, allometry, and population genetics, and the implications of the causality principle for time-dependent response laws.

Functional Generalization of the Fractal Response Law

We consider a differential scaling property of the fractal response law (Eq. **2**). We take the logarithm of both sides of Eq. **2** and differentiate, resulting in

$$d(\Delta y_u)/\Delta y_u = \sum_{u'} \varepsilon_{uu'} d(\Delta x_{u'})/\Delta x_{u'}, \qquad [4]$$

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that is, the relative variation of Δy_u, $d(\Delta y_u)/\Delta y_u$, is proportional to the sum of the additive contributions of the relative variations of $\Delta x_{u'}$, $d(\Delta x_{u'})/\Delta x_{u'}$; Eq. **4** can be easily extended to the functional case. We start out with a discrete representation of the problem. We consider a large but finite number of state vectors $\rho_1, \rho_2, \ldots$ and denote by $\mathbf{x}(\rho)$ and $\mathbf{y}(\rho)$ the excitation and the response vectors at state ρ. We also consider a reference state vector $\rho^{(0)}$ and introduce the differences $\Delta\mathbf{x}(\rho) = \mathbf{x}(\rho) - \mathbf{x}(\rho^{(0)})$ and $\Delta\mathbf{y}(\rho) = \mathbf{y}(\rho) - \mathbf{y}(\rho^{(0)})$. A suitable generalization of the differential fractal scaling laws (Eq. **4**) is

$$d(\Delta y_u(\rho))/\Delta y_u(\rho) = \sum_{u'} \sum_{w'} \lambda^{(1)}_{uu'}(\rho;\rho_{w'}) d(\Delta x_{u'}(\rho_{w'}))/\Delta x_{u'}(\rho_{w'}), \quad [5]$$

where $\lambda^{(1)}_{uu'}(\rho;\rho_{w'})$ are fractal exponents that are at the same time susceptibility functions. The right sides of Eq. **5** are Pfaff forms that are at the same time are total differentials; thus, Eq. **5** can be easily integrated, resulting in

$$\frac{\Delta y_u(\rho)}{\Delta y_u(\rho^{(0)})} = \exp\left\{ \sum_{u',w'} \lambda^{(1)}_{uu'}(\rho;\rho_{w'}) \ln\left[\frac{\Delta x_{u'}(\rho_{w'})}{\Delta x_{u'}(\rho^{(0)})} \right] \right\}$$

$$= \exp\left\{ \sum_{u'} \int_{\rho'} \eta^{(1)}_{uu'}(\rho;\rho') \ln\left[\frac{\Delta x_{u'}(\rho')}{\Delta x_{u'}(\rho^{(0)})} \right] d\rho' \right\}, \quad [6]$$

with $\eta^{(1)}_{uu'}(\rho;\rho') = \Sigma_{w'} \lambda^{(1)}_{uu'}(\rho;\rho_{w'})\delta(\rho' - \rho_{w'})$. Eq. **6** is the functional analog of the fractal response law (Eq. **2**). For systems without functional dependence, we have $\eta^{(1)}_{uu'}(\rho;\rho') = \varepsilon_{uu'}\delta(\rho - \rho')$ and Eq. **6** reduces to Eq. **2**, where $B_u = \Delta y^{(0)}_u/\Pi_{u'}(\Delta x^{(0)}_{u'})^{\varepsilon_{uu'}}$. If the susceptibility functions $\eta^{(1)}_{uu'}(\rho;\rho')$ are real, then Eq. **6** makes sense only if both $\Delta x_u(\rho)/\Delta x_u(\rho^{(0)})$ and $\Delta y_u(\rho)/\Delta y_u(\rho^{(0)})$ are positive. In some applications, for example, for wave propagation, both the susceptibility functions and the excitations and responses may be complex, and the restrictions of positivity are not necessary.

An alternative way of deriving Eq. **6** is based on considering a double logarithmic transformation of the dependences between the relative values of excitation and response variables, expressed by the differences $\Delta\mathbf{x}(\rho) = \mathbf{x}(\rho) - \mathbf{x}(\rho^{(0)})$ and $\Delta\mathbf{y}(\rho) - \mathbf{x}(\rho^{(0)})$ and $\Delta\mathbf{y}(\rho) = \mathbf{y}(\rho) - \mathbf{y}(\rho^{(0)})$. We express the dependence between $\Delta\mathbf{x}(\rho)$ and $\Delta\mathbf{y}(\rho)$ as $\Delta\mathbf{y}(\rho) = \Phi[\Delta\mathbf{x}(\rho_1), \Delta\mathbf{x}(\rho_2), \ldots; \rho]$, where Φ is a nonlinear function which is nonanalytic for $\Delta\mathbf{x}(\rho) = \mathbf{0}$. We use the functional transformations

$$\mathfrak{X}_u(\rho) = \ln[\Delta x_u(\rho)/\Delta x_u(\rho^{(0)})], \quad \mathfrak{Y}_u(\rho) = \ln[\Delta y_u(\rho)/\Delta y_u(\rho^{(0)})], \quad [7]$$

and assume that this transformation leads to analytic dependences of $\mathfrak{Y}_u(\rho)$ in terms of $\mathfrak{X}_u(\rho)$, which can be expressed in expansions of the Taylor type. After the expansion, we come back to the original variables $\Delta x_u(\rho)$ and $\Delta y_u(\rho)$. We obtain

$$\frac{\Delta y_u(\rho)}{\Delta y_u(\rho^{(0)})} = \exp\left\{ \sum_{m=1}^{\infty} \sum_{u'_1,\ldots,u'_m} \int_{\rho'_1} \cdots \int_{\rho'_m} \eta^{(m)}_{uu'_1,\ldots,u'_m}(\rho;\rho'_1,\ldots,\rho'_m) \right.$$

$$\left. \prod_{v=1}^{m} \ln\left[\frac{\Delta x_{u'_v}(\rho'_v)}{\Delta x_{u'_v}(\rho^{(0)})} \right] d\rho'_1, \ldots d\rho'_m \right\}, \quad [8]$$

where

$$\eta^{(m)}_{uu'_1\ldots u'_m}(\rho;\rho'_1,\ldots,\rho'_m) = \sum_{w_1,\ldots,w_m} \prod_{u=1}^{m} \delta(\rho'_u - \rho_{w_u}) \lambda^{(m)}_{uu'_1\ldots u'_m}(\rho;\rho'_1,\ldots,\rho'_m), \quad [9]$$

$$\lambda^{(m)}_{uu'_1\ldots u'_m}(\rho;\rho_1,\ldots,\rho_m) = \frac{1}{m!} \frac{\partial^m}{\partial \ln[x_{u'_1}(\rho_1)/x_{u'_1}(\rho^{(0)})] \ldots \partial \ln[x_{u'_m}(\rho_m)/x_{u'_m}(\rho^{(0)})]}$$

$$\ln\left[\frac{\Phi_u[\Delta\mathbf{x}(\rho_1), \Delta\mathbf{x}(\rho_2), \ldots; \rho]}{\Delta y_u(\rho^{(0)})} \right]. \quad [10]$$

If we keep the first-order terms in the exponent in Eq. **8**, we come to Eq. **6**.

In some cases, it is possible to consider a continuous limit of the response laws (Eqs. **7** and **8**). Formally, by increasing the number of state vectors, $\Phi[\Delta\mathbf{x}(\rho_1), \Delta\mathbf{x}(\rho_2), \ldots; \rho]$ becomes a functional $\Phi[\Delta\mathbf{x}(\rho');\rho]$. In the continuous limit, if it exists, the scaling law Eq. **8** remains valid but the continuous susceptibility functions $\lambda^{(m)}_{uu'_1}\ldots u'_m(\rho;\rho'_1,\ldots,\rho'_m)$ can be expressed as functional derivatives

$$\lambda^{(m)}_{uu'_1\ldots u'_m}(\rho;\rho'_1,\ldots,\rho'_m) = \frac{1}{m!} \frac{\delta}{\delta \ln\left[\frac{\Delta x_{u'_1}(\rho'_1)}{\Delta x_{u'_1}(\rho^{(0)})} \right] \ldots \delta \ln\left[\frac{\Delta x_{u'_m}(\rho'_m)}{\Delta x_{u'_m}(\rho^{(0)})} \right]} \ln\left\{ \frac{\Phi_u[\Delta\mathbf{x}(\rho');\rho]}{\Delta y_u(\rho_0)} \right\}. \quad [11]$$

The continuous limit leads to the same generalized response law (Eq. **8**), with the difference that the susceptibility functions $\lambda^{(m)}_{uu'_1\ldots u'_m}(\rho;\rho'_1,\ldots,\rho'_m)$ are no longer superpositions of delta functions but are given by Eq. **11**. The continuous limit may lead to serious mathematical difficulties, singularities may exist, and the above equations become meaningless. A careful analysis should be carried out for each particular application; in some cases, regularization methods can be used, but their applicability is not always warranted. In some applications, it makes sense to consider only discrete models and not pass to the continuous limit; such an example is presented below.

The approach which leads to the Eq. **8** is actually a type of phase expansion (5, 6), based on the introduction of two sets of phase factors, $\mathfrak{X}_u(\rho)$ and $\mathfrak{Y}_u(\rho)$. The use of the two phase factors, $\mathfrak{X}_u(\rho)$ and $\mathfrak{Y}_u(\rho)$, produces a structure for the response law (Eq. **8**), which is similar to a cumulant expansion in statistical physics. This transformation of variables is a "mathematical microscope," similar, for example, to a wavelet transformation (7), which reveals the details of $\Phi_u[\Delta\mathbf{x}(\rho_1), \Delta\mathbf{x}(\rho_2), \ldots;\rho]$ or of $\Phi_u[\Delta\mathbf{x}(\rho');\rho]$. We emphasize that the logarithmic transformations of the excitations and the responses do not always lead to analytic transformed dependences. In some cases other types of functional transformations are needed, for example based on iterated logarithms, in order to obtain a transformed functional which is analytic. Such transformations, based on iterated logarithms, are of interest in connection with some physical and chemical applications (8).

A feature of fractal response laws (Eq. **2**) is that the response functions are homogeneous functions of the excitation variables, which thus obey Euler's theorem of homogeneous functions, which is an important mathematical tool used for studying the properties of the fractal scaling laws. Here we derive a functional analog of Euler's theorem of homogeneous function, valid for Eq. **6**. We introduce a scaling factor μ, real and different from zero and consider the transformation $\Delta\mathbf{x}(\rho') \to \mu\Delta\mathbf{x}(\rho')$. Eq. **6** leads to $\Delta y_u[\mu\Delta\mathbf{x}(\rho');\rho] = \mu^{\sigma_u(\rho)} \Delta y_u[\Delta\mathbf{x}(\rho');\rho]$, where $\sigma_u(\rho) =$

$\Sigma_{u'} \int \eta^{(1)}_{uu'}(\rho;\rho')d\rho' = \Sigma_{u',w'} \lambda^{(1)}_{uu'}(\rho;\rho_{w'})$ are global fractal exponents. We differentiate both terms of this equation with respect to μ and then make $\mu = 1$. We obtain a functional generalization of Euler's theorem

$$\sum_w \int_{\rho''} \Delta x_w(\rho'') \frac{\delta}{\delta \Delta x_w(\rho'')} \{\Delta y_u[\Delta \mathbf{x}(\rho');\rho]\} d\rho'' = \sigma_u(\rho)\Delta y_u[\Delta \mathbf{x}(\rho');\rho]. \quad [12]$$

The fractal scaling law can (Eq. **6**) be applied to problems which are not described in terms of response to an excitation, such as systems described by fractal stochastic processes; such an example is presented below.

In conclusion, in this section we have derived a functional analog of the fractal response laws, for the case where both the excitation and response variables are functions of known state vectors. We have shown that our results are a first-order approximation of a modified phase expansion based on a logarithmic transformation of both the excitation and the response.

Functional Fractal Response Laws for Rate Processes with Aging

In this section, we show that some kinetic processes with aging are described by rate equations given by Eq. **6**. We consider the low concentration limit of a catalytic reaction on a heterogeneous, aging surface (9–13) (possibly due to surface reconstruction, ref. 14). Our approach might be applied to other rate processes from biochemistry (enzyme aging, ref. 15) or biology (processes described by a "virtual" mass-action law, ref. 16).

We begin with a rate process characterized by a single state variable. We make the following assumptions. (*i*) There is an upper limit r_* for the rate r of transformation. (*ii*) The rate processes are aging, and because of this their efficiency is decreasing in time. The aging process is "adiabatic" that is, although it occurs in a time scale of the order of magnitude of the chemical process, the diminution of the rate follows without inertia the concentration c of the species considered. For each small time interval between t_v and $t_v + \Delta t_v$, there is a diminution factor of the rate $r(t_v + \Delta t_v)/r(t_v) = \varphi(t;t_v)$, which depends on the concentration at time t_v,$c(t_v)$ and the current time t. (*iii*) In the limit of small concentrations the diminution factor at time t_v obeys a fractal scaling law $\varphi(t_v) = [c(t_v)/c_*]^{\alpha(t;t_v)}$, where c_* is a reference concentration and $\alpha(t;t_v)$ is a fractal exponent. (*iv*) For very small time intervals, $\Delta t_v \to 0$ the fractal exponent $\alpha(t;t_v)$ scales linearly with the time difference Δt_v: $\alpha(t;t_v) \approx \eta(t;t_v)\Delta t_v$ as $\Delta t_v \to 0$. These assumptions may seem arbitrary; however, we shall show later, that, at least in the case of a heterogeneous catalytic reaction with aging operated at low concentrations, they are a consequence of the homottatic patch approximation (9–13).

For a process without memory, the rate process at time t is simply given by: $r = r_*\varphi = r_*[c/c_*]^\alpha$ an expression that contains a single diminution factor. For systems with aging, the diminution of the rate due to aging takes place at all times between the initial moment t_0 and the current time t. The rate at time t depends on the whole previous evolution of the concentration c from the initial time t_0 to the current time t. We have

$$r = r_* \prod\nolimits_v \varphi(t_v) = r_* \prod\nolimits_v [c(t_v)/c_*]^{\alpha(t;t_v)} = r_* \exp\left\{ \sum\nolimits_v \alpha(t;t_v) \ln[c(t_v)/c_*] \right\}, \quad [13]$$

from which, by passing to the continuous limit we obtain

$$r[c(t');t] = r_* \exp\left\{ \int_{t_0}^{t} \eta(t;t') \ln[c(t')/c_*] dt' \right\}. \quad [14]$$

The rate of transformation is given by an equation similar to Eq. **6**. The function $\eta(t;t')$ is a time density of an apparent reaction order. The total apparent reaction order is given by

$$\alpha_{\text{apparent}}(t) = \int_{t_0}^{t} \eta(t;t')dt'. \quad [15]$$

We can also introduce an effective reaction order

$$\alpha_{\text{effective}}[c(t');t] = \frac{1}{\ln[c(t)/c_*]} \int_{t_0}^{t} \eta(t;t') \ln[c(t')/c_*] dt', \quad [16]$$

which is a functional of the previous evolution of concentration as a function of time. In terms of this effective reaction order, the rate equation (Eq. **14**) can be formally written in a simplified form

$$r[c(t');t] = r_*[c(t)/c_*]^{\alpha_{\text{effective}}[c(t');t]}. \quad [17]$$

There are two important extreme cases of Eq. **14**. For systems with no aging and thus no memory, the density of reaction order has the shape of a delta function, $\eta(t;t') = \alpha\delta(t - t')$ and, as expected, Eqs. **14** and **17** reduce to $r = r_*[c/c_*]^\alpha$ valid for systems without aging and $\alpha_{\text{apparent}}(t) = \alpha_{\text{effective}}[c(t');t] = \alpha$. The other extreme case corresponds to infinite memory (no memory decay) for which $\eta(t;t') = \eta$ = constant, independent of t,t'. The intermediate cases correspond to some degree of memory decay, for example short memory, for which the tail of the reaction order density decays exponentially, $\eta(t;t') \sim \exp[-\text{const}(t - t')]$, for $t \gg t'$, or long memory, for which the tail of the reaction order density obeys a negative power law $\eta(t;t') \sim (t - t')^{-\varepsilon}$.

In the case of an irreversible chemical reaction involving S chemical species $\Sigma_{w=1}^{S} \nu_w^+ A_w \to \Sigma_{w=1}^{S} \nu_w^- A_w$, we have

$$r[\mathbf{c}(t');t] = r_* \exp\left\{ \sum\nolimits_{w=1}^{S} \int_{t_0}^{t} \eta_w(t;t') \ln[c_w(t')/c_{w^*}] dt' \right\} = r_* \prod\nolimits_{w=1}^{S} [c_w(t)/c_{w^*}]^{\alpha_w^{\text{effective}}[\mathbf{c}(t');t]}, \quad [18]$$

where the apparent and effective reaction orders are given by

$$\alpha_w^{\text{apparent}}(t) = \int_{t_0}^{t} \eta_w(t;t')dt'. \quad [19]$$

$$\alpha_w^{\text{effective}}[\mathbf{c}(t');t] = \frac{1}{\ln[c_w(t)/c_*]} \int_{t_0}^{t} \eta_w(t;t') \ln[c_w(t')/c_{w^*}] dt'. \quad [20]$$

A simple system for which this type of rate equations may be applied is a heterogeneous catalytic reaction A → Products (9–13), which takes place on a surface that is undergoing transformation (reconstruction, ref. 14) during the reaction and is energetically inhomogeneous; thus, the adsorption energy has a random component ΔU, which is selected from a known probability law, usually a "frozen" Maxwell–Boltzmann distribution. The adsorption–desorption process is much faster than

the chemical reaction itself, and in the limit of low concentrations, this averaging leads to a power law for the surface coverage θ of the species as a function of the bulk concentration $\theta \approx c^{\alpha}$ (Freundlich isotherm). In its original (9) form, this type of approach leads to a fractal exponent α, which is proportional to the current temperature of the system, which was observed experimentally for many systems. In order to explain experimental data that do not display a linear dependence of α on temperature, the theory was modified by including α as an additional parameter (10–12) in the probability density of ΔU, which establishes a connection between the current state of the system and a previous state of the system. If there is no surface reconstruction, then the previous state of the system is assumed constant and expressed by a frozen distribution, which describes the fluctuations of ΔU; α is constant and we get $\theta = \varphi$ and $r \approx \theta \approx c^{\alpha}$. For surface reconstruction, α establishes a connection between a slowly changing previous state of the system and depends both on the previous and current times t' and t, respectively; then, as explained before, we have to take into account many diminution factors, resulting in Eqs. **13** and **14**.

The kinetic law (Eq. **14**) might be also applied to enzymatic reactions with aging. Fractal kinetic laws are commonly used for describing the effects of molecular crowding in "*in vivo*" kinetics; however, aging phenomena are described by different molecular mechanisms; to check the possible applicability of approaches leading to the rate equation (Eq. **14**), further investigations are necessary.

There are various mechanisms, which lead to aging and memory effects in chemical kinetics, which, unlike our model, do not lead to nonanalytic rate laws. A typical example is that of fast chemical reactions for which the chemical transformation destroys the local equilibrium distribution. At a mesoscopic level, such processes are described by a generalized master equation (GME, refs. 17 and 18) of the type $\partial_t p(\mathbf{x},t) = \int d\mathbf{x}' p(\mathbf{x},t) \otimes w(\mathbf{x}' \rightarrow \mathbf{x},t) - \int d\mathbf{x}' p(\mathbf{x},t) \otimes w(\mathbf{x} \rightarrow \mathbf{x}',t)$, where $p(\mathbf{x},t)$ is a state probability density, $w(\mathbf{x}' \rightarrow \mathbf{x},t)$ are time densities of transition rates, and $\otimes$ denotes the temporal convolution product. In the macroscopic (thermodynamic) limit, the GME approach leads to kinetic laws of the type $r_u = \int_0^t \chi_u(\tau)\, \Pi_w(x_u(t-\tau))^{\alpha_u} d\tau$, which are different from our rate equations (Eqs. **13**, **14**, and **18**).

Nonequilibrium Ensemble Approach to Rate Processes with Dynamic Disorder

Here, we present another example of our scaling law (Eq. **6**): the distribution of rate or transport coefficients for a process involving the passage over a fluctuating random energy barrier (19–21). Consider a rate or transport parameter χ, such as a rate or diffusion coefficient, which obeys the Arrhenius equation: $\chi = \nu \exp(-E/k_BT) = \chi_* \exp(-\Delta E/k_BT)$, where E is an activation energy which is made up of a constant component E_* as well as a random component ΔE ($E = E_* + \Delta E$); ν is a pre-exponential factor, and $\chi_* = \nu \exp(-E_*/k_BT)$ is maximum value of the parameter χ corresponding to a process without fluctuations ($\Delta E = 0$), k_B is Boltzmann's constant, and T is the temperature of the system. We assume that the fluctuating component ΔE of the energy barriers may take any value between zero and plus infinity. The simplest version of the random activation energy model assumes that the fluctuations of the random component ΔE of the energy barrier are static; that is, once they occur, they last forever and are selected from an "adjusted" Maxwell–Boltzmann energy distribution $p_{\eta}(\Delta E) = (\eta/k_BT)\exp(-\eta\Delta E/k_BT)$, where η is a fractal scaling exponent similar to the one introduced above. The exponent η is related to the average value $\langle \Delta E \rangle$ of the random energy barrier through the relationship $\eta = k_BT/\langle \Delta E \rangle$. This model of static disorder can be easily extended to systems with dynamic disorder by assuming an approximation of the quasi-static type. We consider an isothermal process and assume that the time dependence of the average value $\langle \Delta E \rangle = \langle \Delta E(t) \rangle$ of the height of the known random component of the energy barrier is known. We apply a generalization of the method of nonequilibrium ensemble of Zubarev and McLennan (22), suggested in refs. 23 and 24. We introduce the probability functional $\mathcal{P}[\chi(t');t]\mathcal{D}[\chi(t');t]$ of a random trajectory, $\chi(t')$, which obeys the normalization condition $\overline{\int\int} \mathcal{P}[\chi(t');t]\mathcal{D}[\chi(t');t] = 1$, and introduce the entropy functional

$$\mathcal{S}[\mathcal{P}[\chi(t');t]] = \overline{\int\int}\mathcal{P}[\chi(t');t]\ln\{\mathcal{P}[\chi(t');t]\}\mathcal{D}[\chi(t');t]. \qquad [21]$$

The optimization of this entropy functional, with suitable constraints, leads to an expression for the probability density functional $\mathcal{P}[\chi(t');t]$ of the rate parameter $\chi(t')$. One constraint results by expressing the average value $\langle \Delta E(t) \rangle$ in terms of $\mathcal{P}[\chi(t');t]$. As $\Delta E = k_BT\ln(\chi_*/\chi)$ it follows that

$$\langle \Delta E(t'') \rangle = k_BT/\alpha(t'') = k_BT\overline{\int\int}\ln(\chi_*/\chi(t''))\mathcal{P}[\chi(t');t]\mathcal{D}[\chi(t');t]. \qquad [22]$$

The other constraint is that $\mathcal{P}[\chi(t');t]$ is normalized to unity. To avoid the difficulties related to the definition of a non-Gaussian path integral in our computations we consider a large, but finite number m of time variables t_u, $u = 1, 2, \ldots, m$ between the initial time t_0 and the current time $t = t_{m+1}$ and never pass to the continuous limit $m \rightarrow \infty$ (such a limit cannot be properly defined mathematically). Under these circumstances, the path integral over $\chi(t')$ is actually an $m + 2$ dimensional integral over the rate parameters $\chi(t_0), \ldots, \chi(t_m), \chi(t)$. Carrying out the optimization of the entropy functional (Eq. **21**) we obtain

$$\mathcal{P}[\chi(t');t]\mathcal{D}[\chi(t');t] = \exp\left[-\int_{t_0}^{t} \alpha(t')\ln[\chi(t')/\chi_*]dt'\right]\mathcal{D}[\chi(t');t], \qquad [23]$$

where the susceptibility function $\alpha(t')$ and the integration measure $\mathcal{D}[\chi(t');t]$ are given by

$$\alpha(t') = \sum_{u=0}^{m+1} \eta(t_u)\delta(t' - t_u), \qquad [24]$$

$$\mathcal{D}[\chi(t');t] = (\chi_*)^{-(m+2)}\prod_{u=0}^{m+1}\{[\vartheta(\chi(t_u)) - \vartheta(\chi(t_u) - \chi_*)]d\chi(t_u)\}, \qquad [25]$$

and $\vartheta(x)$ is Heaviside's step function. It is easy to check that the marginal probability density of the rate parameter corresponding to a given time t_u, $\chi(t_u) = \chi$, is a fractal scaling law $p(\chi) = \eta(\chi_*)^{-\eta}(\chi)^{\eta-1}$ of the Debye type $p(\chi) = \eta(\chi_*)^{-\eta}(\chi)^{\eta-1}$ for $\chi_* > \chi > 0$ and $p(\chi) = 0$ for $\chi > \chi_*$. This Debye fracton spectrum (25) corresponds to adjusted Maxwell–Boltzmann distributions: for each time t_u we have: $p(\Delta E) = \eta(k_BT)^{-1}\exp(-\eta\Delta E/k_BT)$, where $\Delta E = \Delta E(t_u)$ and $\eta = \eta(t_u)$.

In conclusion, we showed that, for dynamic disorder, the random activation energy model leads to a probability density functional for the rate parameters (rate or transport coefficients), which obeys the functional scaling law derived in this article. The scaling law (Eq. **23**) is a functional generalization of the Debye fracton spectrum. This scaling law can be used for computing experimental observables for processes with dynamic disorder.

Application to Allometric Growth and Population Genetics

"Allometry" (26, 27) is a term used in biology for describing the relative proportions of two or more biological organs from the

same organism. There is a large amount of experimental data showing that, for many organisms, the y size of an organ scales with the size x of another organ according to a fractal response law of the type (Eq. **2**): $y \sim x^{\eta}$. This type of law has been extended for correlating various anatomic or metabolic parameters (surface, metabolic rate, etc.) of an organism to its size (28); however, in this paper we consider only the relative proportions of two organs of an organism. A simple explanation for the allometric laws is to assume that both organs grow according to an autocatalytic mechanism, for example according to the Malthus equations $dx/dt = k_x x$, $dy/dt = k_y y$, where in general $k_x \neq k_y$; these two equations lead to an allometric scaling law with: $\eta = k_y/k_x$. A limitation of this explanation is that such an equation leads to unlimited growth of the organs whereas for a real organism the growth stops at maturity. The model can be easily improved by adding a universal growth factor F in both equations: $dx/dt = k_x xF$, $dy/dt = k_y yF$, which is the same for both organs. The factor F can be an arbitrary functional of the whole previous history of the organism, from the moment of birth up to the current time, it can even be a random function. The factor F has the role of coordinating the absolute rates of growth of the various organs; in particular as the organism is approaching maturity, the factor F varies around zero, which leads to a limitation of growth and to approximately constant organ sizes; nevertheless, because F is assumed to be the same for all organs, the allometric law still holds.

The above explanation of allometric scaling illustrates, once again, a general mechanism for the emergence of the fractal scaling law: the balance between two exponential processes characterized by different rates. However, it is somewhat simplistic, because it does not allow us to describe memory effects, except those taken into account by the growth factor F. This limitation can be easily corrected by considering memory effects directly, which lead to a functional dependence and considering infinitesimal relative rates of growth and including the factor F in their definitions. For a system without memory, the relative rates are simply given by: $k_x dt = dx/Fx$, $k_y dt = dy/Fy$, and the allometric law results from the balance condition $k_y dt = \eta k_x dt$. For systems with memory, the infinitesimal relative rates are given by $K_y(t'')dt'' = \delta y(t'')/Fy(t'')$, $K_x(t')dt' = \delta x(t')/Fx(t')$ and the balance condition is $K_y(t'')dt'' = \vartheta(t'';t')K_x(t')dt'$; by assuming that F is a universal factor, this equation can be written in a form similar to Eq. **5**, resulting in the functional scaling law of type (Eq. **6**), where the state vector is the real time, $\rho = (t)$ and there is only one excitation and one response function, respectively.

Regarding the possible applications of Eq. **6** for improving the allometric law, we note that most experimental data on relative organ growth contain a large degree of variability; in general, it is not clear whether this variability is due to experimental error or to random variations characteristic for biological growth. Attempts of fitting data to more general scaling laws of the type (Eq. **6**) might clarify these issues. A serious limitation of Eq. **6** is that our approach does not specify an explicit form for the time-dependence of the susceptibility function $\vartheta(t'';t')$; the susceptibility function should be extracted from experimental data.

Another biological application is related to the study of correlations between phenotypic and genotypic variables in population genetics (29, 30). We consider a population characterized by different genotypes identified by a discrete label w, $w = 1, 2, \ldots, m$. We denote the population sizes of the different genotypes at time t by $N_1, \ldots, N_m$ and by $\sigma = (\sigma_w)$, with $\sigma_w = \partial \ln N_w/\partial t$ the vector of their relative rates of growth. We consider an extensive phenotypic variable M such as the total mass of the population, or the total milk or egg production, and denote by $r = \partial \ln M/\partial t$ its relative rate of growth. A common approach in quantitative genetics is to consider linear correlation equations that are obtained by assuming analytic dependence expressed in terms of Taylor series. In particular, by assuming an analytic dependence without memory, $r = r(\sigma)$, and considering that for a stationary population ($\sigma = 0$) the phenotypic variable is also stationary ($r = 0$) for small deviations of the growth rates, we get $r = \Sigma_w(\partial r/\partial \sigma_w)_{\sigma=0}\ \sigma_w + \mathbb{O}((\sigma_w)^2)$. In the more general case, where memory effects exist, we have

$$r(t) = \sum_{w=1}^{m} \int_{t_0}^{t} \lambda_w(t;t')\sigma_w(t')dt' + \mathbb{O}((\sigma_w)^2), \qquad [26]$$

with $\lambda_w(t;t'') = \delta r[\sigma(t');t]/\delta\sigma_w(t'')$. In Eq. **26** we express $r(t)$ and $\sigma_w(t')$ in terms of N_w and M, respectively, and integrate the resulting equation term by term over t from t_0 to t. By neglecting $\mathbb{O}((\sigma_w)^2)$, we come to a scaling law which is a particular case of Eq. **6**

$$M(t) = M(t_0)\exp\left\{\sum_{w=1}^{m} \int_{t_0}^{t} \lambda_w(t;t')\ln\left[\frac{N_w(t')}{N_w(t_0)}\right]dt'\right\}. \qquad [27]$$

If we keep all terms in the functional Taylor expansion (Eq. **26**), we get a scaling equation that is a particular case of Eq. **8**.

Both biological examples considered in this section show that the balance of two or more growth processes leads to the functional fractal scaling laws (Eqs. **6** or **8**); this is true for both the functional allometry and for the phenotypic response of a population to its genotypic structure. The application of the nonlinear functional response laws to biological problems requires complicated computations.

Time-Dependent Systems: Implications of Causality

Systems with a time-dependent response, like the ones considered in above, must obey the principle of causality; that is, the cause cannot precede the effect; this leads to $\eta^{(1)}_{uu'}(t;t') = 0$ for $t' > t$. This condition leads to a generalization of the Kramers–Kronig relationships (31). We introduce the time delay $\tau = t - t'$ and express the susceptibility functions as $\eta^{(1)}_{uu'}(t;t') = \psi_{uu'}(\tau;t)$. By following a standard procedure in response theory, we introduce complex susceptibilities as Fourier transforms $\Xi_{uu'}(\omega;t) = \int_0^{\infty} \exp(-i\omega\tau)\psi_{uu'}(\tau;t)d\tau = \xi'_{uu'}(\omega;t) - i\xi''_{uu'}(\omega;t)$, where $\xi'_{uu'}(\omega;t)$ and $\xi''_{uu'}(\omega;t)$ are the real and imaginary parts of the complex susceptibility functions $\Xi_{uu'}(\omega;t)$. The Kramers–Kronig relationships establish connections between $\xi'_{uu'}(\omega;t)$ and $\xi''_{uu'}(\omega;t)$

$$\xi''_{uu'}(\omega;t) = -\frac{1}{\pi}\int_{-\infty}^{+\infty} d\omega' \frac{P}{\omega' - \omega}\xi'_{uu'}(\omega';t),$$

$$\xi''_{uu'}(\omega;t) = \frac{1}{\pi}\int_{-\infty}^{+\infty} d\omega' \frac{P}{\omega' - \omega}\xi'_{uu'}(\omega';t), \qquad [28]$$

where the notation P indicates the Cauchy principal value. These equations can be derived by generalizing the classical derivation of the Kramers–Kronig relationships (31), which refers to the particular case where the complex susceptibilities depend only on frequency and not on time. The main idea is to introduce the complex function: $\Xi^*_{uu'}(z;t) = \int \psi_{uu'}(\tau;t)\exp(iz\tau)d\tau$, 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 $\Xi_{uu'}(\omega;t) = lim_{\varepsilon\to+0}\ \Xi^*_{uu'}(z = -\omega + i\varepsilon;t)$. Due to causality, the integral in the definition of $\Xi^*_{uu'}(z;t)$ is taken from zero to infinity and thus $\Xi^*_{uu'}(z;t)$ is analytic in the upper z plane, which makes it possible to express it as an integral of the Cauchy type.

By separating the real and imaginary parts in this Cauchy integral, we obtain the generalized Kramers–Kronig relationships (Eq. **28**).

Conclusions

In this article, we gave a functional generalization of fractal (power function) response laws for the case where both the excitation and response variables are functions of time and/or space, and examined briefly a few applications from physics, chemistry, and biology. Because the fractal scaling laws are ubiquitous in nature, we expect that our nonlinear response law may be applied to many other scientific problems. A problem of great interest in chemistry and biology is that of the analysis of the response behavior of a relatively small part of a large chemical or biochemical network. In this case, scaling laws of type (Eq. **6**) occur due to long pathways, which go out of a small subnetwork far away into the big network and eventually come back. Corrections due to the interaction with the large networks can be described by using a renormalization group approach (32). Based on the theory, we intend to design response experiments for extracting mechanistic and kinetic information about the subnetwork.

To clarify the physical and mathematical significance of our scaling laws, we intend to use the same method of the renormalization group approach (32).

Another ongoing project is the application of the functional scaling law (Eq. **6**) to interconvertible metabolite cascades (33). By using modeling techniques from metabolic control theory (34), it is possible to describe the interaction of metabolites by a functional relationship similar to Eq. **6**. Upon testing the capability of Eq. **6** to represent the observed data, we intend to develop methods for extracting kinetic and mechanistic information from response experiments.

Our scaling law opens the possibility of extending the method of intermediate asymptotics (35) to integro-differential equations with possible applications in geographic population genetics (36) and geophysical magneto-hydrodynamics (37).

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