Stochastic origin of Gompertzian growths

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This work faces the problem of the origin of the logarithmic character of the Gompertzian growth. We show that the macroscopic, deterministic Gompertz equation describes the evolution from the initial state to the final stationary value of the median of a log-normally distributed, stochastic process. Moreover, by exploiting a stochastic variational principle, we account for self-regulating feature of Gompertzian growths provided by self-consistent feedback of relative density variations. This well defined conceptual framework shows its usefulness by allowing a reliable control of the growth by external actions.

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I. INTRODUCTION

The Gompertz model, in its original conception, was born as phenomenological one namely describing the observed age tables of humans [12]. In fact, B. Gompertz concluded his empirical studies of tables introducing the distribution of human ages for a given community, the now well known function

$$P(\tau) = \alpha e^{-e^{c-\beta\tau}} \tag{1}$$

where $\alpha > 0$, $\beta < 0$ and c are constant.

It is interesting to note that Gompertz posed at the core of his deduction the properties of geometrical progression; "This law of geometrical progression pervades, in an approximate degree, large portions of different tables of mortality". The relevance of the geometrical progression in the framework of the natural phenomena in a variety of experimental environments was pointed out at the end of nineteenth century in the works of Galton [10] and McAlister [17]. They showed that the geometrical mean (median) describes the behavior of a large set of natural phenomena better than the arithmetic one. We note that Gompertz law according to the Gompertz observation emerges from the equilibrium between geometrical series associated to degradation and an arithmetical progression ruling indefinite (Malthusian) growth having the experimental observations to be made on suitable time intervals. The characteristics of simplicity of Gompertz law due to this general and profound mathematical framework, attract the attention of nascent biological disciplines, where the growth studies go back to the thirty years of last century. Since this distribution has had so remarkable success in a variety of very different situations that a lot of literature refers it simply as "law of growth".

The laws of growth of natural systems, and the deep origin of their characteristic scales of, e. g., length, mass, energy, or numerosity, are, now, intensively investigated in many branches of science, such as biomedicine [8, 16], economy [9], population dynamics [18], astrophysics and cosmology [7]. So, starting from 1930 the Gompertz equation has became one of the most used tool to account for mechanisms of growth in a variety of systems in many fields [1–4, 8, 18]. If we exclude, for example, from incomes distribution the little percentage of rich people (1%) Gompertz law is the fitting distribution. Obviously so general applicability has developed a very interesting debate regarding the origin of its logarithmic structure. The arguments called down to this aim look at the main aspects of the underlying systems i.e., biological social or/and economics.

General theory of dynamical systems, quiescence, cell kinetics theory, entropic and thermodynamical arguments have been advocated and illustrated by many authors in a variety of interesting papers along many years introducing also suitable generalizations and connections with other growth models as logistic one. A good synthetic description with a large bibliography can be considered that of Bajzer et al (1997)[2].

We remark three main aspects of the delineated problem that we consider relevant.

The first one; although, it can be significant to start attaching the problem from specificity of a discipline, in fact this can enlighten nodal points, the arguments bringing to logarithmic behavior must be so general as well as is the applicability of Gompertz law;

The second one; Gompertz curve cannot be other than a "suitable" description of a mean behavior of systems under studies that are all characterized by a basic stochasticity.

The third one; many of the considered systems reach the limiting size exploiting self-controlled evolutions. We take these considerations as starting points to recovering the features, in particular logarithmic behavior, of Gompertz equation. Before to go into the details of our deduction it is usefulness to make some preliminary consideration and as first step to give a description of deterministic Gompertz equation also to establish our notation.

II. GOMPERTZ EQUATION

The standard form of the deterministic Gompertz equation is:

$$z^{-1}\frac{dz}{dt} = \beta - \alpha \ln\left(\frac{z}{\tilde{z}}\right), \tag{2}$$

where z describes the "size" of some quantity characterizing the system, β and α denote two positive constants with the

dimensions of the inverse of time, and $\tilde{z}$ is a constant which the same dimensions of z.
Eq. (2) can be recast as:

$$\frac{d(\ln s)}{dt} = -\alpha \ln s, \tag{3}$$

where $s(t) \doteq z(t)/z_\infty$, and $z_\infty = \tilde{z} \exp{(\beta/\alpha)}$. The Gompertz equation is then associated to four parameters (all dependent on the specific system): α, β, $\tilde{z}$, and the initial condition ("scale") $z(0) = z_0$. Its solution is:

$$z(t) = z_\infty \exp{[(\ln \gamma) \cdot e^{-\alpha t}]}, \tag{4}$$

where $\gamma \doteq z_0/z_\infty$. It is immediately verified that this solution always approaches monotonically in time z_∞: depending on the conditions $z_0 < z_\infty \equiv \tilde{z} \exp \beta/\alpha \quad (\gamma < 1)$, or $z_0 > z_\infty \equiv \tilde{z} \exp \beta/\alpha \quad (\gamma > 1)$, the system monotonically grows or monotonically decreases, respectively, from the dimension z_0 to the dimension z_∞, approaching the asymptotic value z_∞ with the characteristic time α^{-1}. It is worth noticing that the solutions of the eq. (3) satisfy some, somewhat simple and self evident properties, deriving by peculiar features of logarithmic function. These properties justify why the Gompertz equation plays a major role among all the equations describing growth phenomena.

If we characterize a solution $s(t)$ by the pair of values of its parameters (γ, α), the properties are the following:

1. the product $s_1(t) \cdot s_2(t)$ of two solutions with parameters (γ_1, α) and (γ_2, α), respectively, is again a solution with parameters $(\gamma_1 \cdot \gamma_2, \alpha)$,

2. if $s(t)$ is a solution with parameters (γ, α), then $s^a(t)$, with $a \in \mathbf{R}$ is a solution as well, with parameters (γ^a, α).

3. the constant function $s(t) = 1$ is a (trivial) solution.

Note that, for $a = -1$ we obtain that the inverse of $s(t)$, $s^{-1}(t)$ is a solution associated to (γ^{-1}, α). Then it is straightforward to verify that if for example the original solution is obtained with $z_0 > z_\infty$ (aggregation process) $s^{-1}(t)$ describes the time-reversed (fragmentation) process from z_∞ to z_0. Note also that this property, together with properties 1), 3) makes the set of solutions of the Gompertz equation an Abelian group. Note finally that the property 3) implies that any other quantity $M(t)$ linked to $z(t)$ by an allometric relation $(M(t) = b \cdot z^a(t))$ satisfies the same Gompertz equation with modified parameter γ^a

III. GOMPERTZ EQUATION AS EVOLUTION EQUATION FOR THE MEDIAN OF GEOMETRICAL BROWNIAN MOTION.

A. Lognormality as basic in a variety of natural systems

In 1947 H.R. Jones linked the problem of mortality to life expectancy and ageing processes [14]. His germinal point of view was that diseases and disfunctions accumulate slowly along the time damaging *multiplicatively* the human bodies. The extensive analysis of Jones showed that Gompertz equation applies exactly to people that have not eliminated the first cause of diseases, i.e. hygienic condition. A good mean improvement of these last one, namely slight, modifies the general behavior. Then, following Jones, at the basis of the analysis of life expectancy, there is a stochastic process built with independent random variables (diseases and/or social and economic condition) that add multiplicatively. Moreover at the end of sixties years of the last century a detailed statistical analysis performed by Sachs showed that physiological parameters like blood pressure, tolerability of medicaments, body size survival rate are lognormally distributed [21]. Finally it is worthwhile to note that the lognormal i.e. geometric Brownian motion appears to be asymptotic to a variety of branching processes introduced to describe cell systems growth [4, 5].

On the other hand it is well known that lognormal distribution arises in a variety of classification procedures and in physical and biological systems when natural genesis involves repeated breakages or aggregations. Very relevant, in 1941, Kolmogorov [15] has shown that when the frequency of aggregation-disaggregation in a growth process is independent of the size of the constituents, the asymptotic size distribution of the aggregate should tend to be lognormal. This so general multiplicative behavior of basic randomness of underlying processes has been indicated as a "Multiplicative Gestaltungs-Principle of Nature". It is also assumed as its possible accounting a general property of "coherence" of natural systems [22]. The simple considerations outlined above, at the light of the two first points of our introductory section namely basic stochasticity of systems and large applicability of the Gompertz model, bring us to postulate that the Gompertz equation is the deterministic one emerging from geometric Brownian motion, that is the general stochastic structure associated with a variety of systems. The necessary step at this point is to give a simple mathematical procedure connecting stochastic structure with deterministic one.

B. Mathematical procedure

The main feature of lognormal can be so summarized: a random variable X is said to have a lognormal distribution with suitable parameters associated to mean and variance if $\ln\{(X(t))\}$ is normally distributed. Consider then the diffusion process $X(t)$ taking non negative values, and satisfying the Ito differential equation:

$$dX(t) = \{\lfloor \frac{\nu}{2} X(t) - \alpha X(t) \ln{[\frac{X(t)}{K}]}\}dt + \sqrt{\nu} X(t) dW(t), \tag{5}$$

where α and ν are positive constants, K has the same dimensions of $X(t)$, and $dW(t)$ denotes a Gaussian stochastic process (Wiener process) with zero mean and variance dt. Here $X(t)$ can describe any quantity. X(t) is a multiplicativy diffusive process (geometrical brownian motion) and its Ito equation can be recast as:

$$dX(t) = -\alpha X(t) \ln\big[\frac{X(t)}{K}\big] dt + \sqrt{\nu} X(t) dW(t), \qquad (6)$$

where

$$K = \tilde{K} e^{\frac{\nu}{2\alpha}}$$

.

We now prove that this process generates the deterministic Gompertz equation. Let us in fact associate to $X(t)$ a new process $Y(t)$ defined by the relation

$$\frac{X(t)}{K} \equiv e^{Y(t)}, \qquad (7)$$

where $Y(t)$ is adimentional and takes values ranging on $(-\infty, +\infty)$ when X(t) takes values on $[0, \infty$). By exploiting Eq. (6) and definition 7, we can compute $d(\exp Y(t))$: by Ito's lemma obtaining:

$$dY(t) = -\alpha Y(t) dt + \sqrt{\nu} dW(t), \qquad (8)$$

We see that $Y(t)$ is an *Ornstein-Uhlenbeck process*. Its probability density $p(y, t; y_0, 0) \equiv p(y, t)$, satisfies the Fokker-Plank equation

$$\partial_t p(y,t) = \alpha \partial_y [y p(y,t)] + \frac{1}{2} \nu_r \partial_y^2 p(y,t), \qquad (9)$$

and can be exactly computed for any initial condition [11]:

$$\int_{-\infty}^{-\infty} du e^{-iuy} \chi_0(u e^{-\alpha t}) e^{\left[-\frac{\nu_r u^2}{4\alpha}(1-e^{-\alpha} t)\right]}, \qquad (10)$$

where $\chi_0(u)$ is the characteristic function of the initial probability. The moments $< Y^n(t) >$ of the process $Y(t)$:

$$< Y^n(t) > \doteq \int_{-\infty}^{-\infty} dy \; y^n \; p(y,t), \qquad (11)$$

satisfy the set of *branching equations*

$$\frac{d}{dt} < Y^n(t) >= -n\alpha < Y^n(t) > + \frac{1}{2} \sigma_r n(n-1) \alpha < Y^{n-2}(t) > \qquad (12)$$

which can be solved, iteratively at any finite order. We now focus on the case $n = 1$:

$$\frac{d}{dt} < Y(t) >= -\alpha < Y(t) >, \qquad (13)$$

exploit the relation (7), and obtain

$$\frac{d}{dt} < ln\big[\frac{X(t)}{K}\big] >= -\alpha < ln\big[\frac{X(t)}{K}\big] > . \qquad (14)$$

If we define the time-dependent quantity $z(t)$ by the relation

$$\frac{z(t)}{K} = \exp^{< ln\left[\frac{X(t)}{K}\right]>}, \qquad (15)$$

we see that $z(t)$, which has the same dimensions of $X(t)$, satisfies the Gompertz equation, where the constant K is identified with z_∞, i. e. with the asymptotic value of $z(t)$. But *what about the meaning of* $z(t)$*?*. We nown provide a precise meaning to $z(t)$. Let us suppose that the initial probability of the process $Y(t)$ is Gaussian (for example, the solution is the fundamental one with an initial delta function condition). By Eq. (10), the solution at any time is Gaussian:

$$p(y,t)dy = \frac{1}{\sqrt{2\pi\sigma(t)}} e^{-\frac{1}{2\sigma(t)}(y-\mu(t))^2} dy, \qquad (16)$$

where $\sigma(t) \doteq< [Y(t) - \mu(t)]^2 >$, and $\mu(t) \doteq< Y(t) >$. By exploiting the relation (7), we can recast Eq. (17), obtaining the probability of the process $X(t)$ as

$$p(x,t)dx = \frac{1}{\sqrt{2\pi\sigma(t)}} e^{\left[-\frac{1}{2\sigma(t)}\left(\ln\left(\frac{x}{K}\right)-\mu(t)\right)^2\right]} \frac{dx}{x}. \qquad (17)$$

where, by solving the first two branching equation (12)), mean $\mu(t)$ and variance $\sigma(t)$ are given by:

$$\mu(t) = \mu_0 e^{-\alpha t}, \qquad (18)$$

$$\sigma(t) = \sigma_0 e^{-2\alpha t} + \frac{\nu}{2\alpha}(1 - e^{-2\alpha t}). \qquad (19)$$

We see that the process $X(t)/K$ is lognormally distributed. But it is well known that in a lognormally distributed process the mean of the logarithm of the process is the logarithm of the *median* of the process. Then, we can conclude that if the process $Y(t)$ is initially Gaussian, i.e. if the process $x(t)/K$ is initially lognormally distributed, this last process remains lognormally distributed at any time, and the variable $z(t)/K$ (which we denoted $z(t)/z_\infty$) *is the median of this process.*

In conclusion we have proved that: *the deterministic Gompertz equation is the macroscopic consequence of a lognormally distributed, diffusion process X(t); the macroscopical size z(t) whose evolution is ruled by the Gompertz equation is the median of process* $X(t)$.

It follows that the multiplicative stochastic process (a standard geometric brownian motion) that many times is introduced as "Gompertz stochastic tumor growth model" is not due to an extra noise disturbing the Gompertz growth, but it is itself the origin of the deterministic growth.

To further support this conclusion we remark that deterministic Gompertz model was extracted by B. Gompertz, just looking to the properties of a geometric progression that emerges from the mortality tables; i.e. the Gompertz function has its natural interpretation as median of a multiplicative process.

C. Short remark on the observability of microscopic parameters

The underlying process $X(t)$ is characterized by three parameters: α, ν, K. Their determination completely define the process. As a first observation, we note that the Malthusian parameter β in the standard form (2) of the Gompertz equation is provided, in a consistent way, by the diffusion parameter: $\beta = \nu/2$. We remark also that the drift parameter α is clearly macroscopically observable by fitting the macroscopic size growth of the selected systems. Therefore, if one is able to provide a method to extract by observational data the diffusion parameter ν, the whole process $X(t)$ can be reconstructed. To this end, we consider that the observed size (i. e., the median of the process) must displace a range of variability; in fact

$$\ln z(t)/z_\infty \equiv \ln z(t)/K \equiv < \ln X(t)/K > \equiv < Y(t) > \tag{20}$$

is the mean of a Gaussian process with variance (width) $\sigma(t)$. And, in particular, when the last stage $K \equiv z_\infty$ is reached, the width (i.e variability of the size) becomes that of the stationary distribution (see Eq. (19)). If one performs a statistics of the observed sizes, one could find that the sizes of a system at the last stage range from a minimum one z_{min} to a maximum one z_{max}, with the following relations:

$$z_\infty = \sqrt{z_{min} \cdot z_{max}}, \tag{21}$$

(just geometric mean),

$$z_{min} = \frac{z_\infty}{r}, \;\; z_{max} = z_\infty \cdot r, \; r = e^{\frac{\nu}{2\alpha}}, \tag{22}$$

and

$$\nu = \alpha \ln \frac{z_{max}}{z_{min}}. \tag{23}$$

Summing up: α, z_{max}, z_{min} can be extracted by observational data, and, in principle, their values provide an estimate of all the other parameters of the underlying process; in particular, of the order of magnitude of the diffusion parameter ν.

IV. CHARACTERIZING THE GOMPERTZIAN GROWTH PROCESS

The conclusions reached in the previous section ascribe the Gompertz equation within the framework of “Multiplicative Gestaltung-Principle of Nature”, i.e. to the ubiquitous nature of lognormal distribution, which characterizes a variety of natural system, i.e. those in which emerge characteristic scales of “coherence”. The “actual” Gompertz equation is then the stochastic one. The stochastic description however does not exhaust all the aspects of Gompertzian model, namely stochasticity allows spontaneous growth until a final size if and when systems undergo to a stationary state. The Gompertzian growth is characterized, on the contrary, as remarked in the third point of introductory section, by a self-controlled evolution ruled by variation of density. Now we incorporate in our description this relevant behavior of growing systems.

A. Dynamical updating of geometrical Brownian motion

In standard treatment the drift terms in a Fokker-Planck equation is a function given a priori; backward and forward evolutions are described with two different equations. The systems spontaneously approach a stationary state when balancing is reached between the stochastic term (Wiener process) and deterministic (drift); consequently there is not, for example, time reversal invariance. In order to have self-control (feedback) we must to add to Fokker-Planck equation a dynamical equation updating the drift and allowing time reversal behavior. The equation is the stochastic equivalent of $\mathbf{F} = m\mathbf{a}$, and it can be written also as the equation describing a suitable interface [20].

We remark, that, being our systems self-controlled the dynamical update must contain self coupling non linearity. We use a stochastic variational principle theory. We recall this theory briefly: deterministic dynamic evolutions are characterized by two independent principles, the first kinematic the second dynamic. The kinematic principle is provided by standard differential rules, and the dynamic one by a variational principle, i.e. the Lagrangian principle. The theory of stochastic variational principle assumes Ito’s equation as a kinematic rule and the Lagrangian variational principle as dynamic rule. The variation is made by considering conditional expectation. As a consequence: the configuration of our systems is described, in general, by a vectorial Markov process $\xi(t)$ taking values in $\Re^3$. This process is characterized by a probability density $\rho(\mathbf{r}, t)$ and a transition probability density $p(\mathbf{r}, t|\, \mathbf{r}', t')$, and its components satisfy an Itô stochastic differential equation of the form

$$d\xi_j(t) = v_{(+)j}\big(\xi(t), t\big)dt + d\eta_j(t), \tag{24}$$

where $v_{(+)j}$ are the components of the forward velocity field. As already observed here the fields $v_{(+)j}$ must not be given a priori, but play the role of dynamical variables and are consequently determined by imposing a specific dynamics. The noise $\eta(t)$ is a standard Wiener process, D is the diffusion coefficient. We indicate by E_t the conditional expectations with respect to $\xi(t)$. In what follows, for sake of notational simplicity, we will limit ourselves to the case of one dimensional trajectories, but the results that will be obtained can be immediately generalized to any number of dimensions. We will suppose for the time being that the forces will be defined by means of purely configurational, possibly time-dependent $V(x, t)$, potentials, this includes also a non linear potential functional of the density of the process. A suitable definition of the Lagrangian and of the stochastic action functional for the system described by the dynamical variables ρ and $v_{(+)}$ allows to select, the processes which reproduce the correct dynamics [6, 13, 19]. In fact, while the probability density $\rho(x, t)$ satisfies, as usual, the forward Fokker-Planck equation associated to the stochastic differential equation

$$\partial_t \rho = D\partial_x^2 \rho - \partial_x(v_{(+)}\rho) = \partial_x(D\partial_x \rho - v_{(+)}\rho) \tag{25}$$

the following choice for the Lagrangian field

$$L(x,t) = \frac{m}{2} v^2_{(+)}(x,t) + mD\partial_x v_{(+)}(x,t) - V(x,t) \quad (26)$$

enables to define a stochastic action functional

$$\mathcal{A} = \int_{t_0}^{t_1} E_t[L(\xi(t),t)]dt \quad (27)$$

which leads, through the stationarity condition $\delta\mathcal{A} = 0$, to the equation

$$\partial_t S + \frac{(\partial_x S)^2}{2m} + V \; - 2mD^2 \, \frac{\partial_x^2 \sqrt{\rho}}{\sqrt{\rho}} = 0 \, . \quad (28)$$

The field $S(x,t)$ is defined as

$$S(x,t) = -\int_t^{t_1} E\left[L\big(\xi(s),s\big) \,\big|\, \xi(t) = x\right] ds + \\ + E\left[S_1\big(\xi(t_1)\big) \,\big|\, \xi(t) = x\right] \quad (29)$$

where $S_1(\,\cdot\,) = S(\,\cdot\,, t_1)$ is an arbitrary final condition. This equation is the well know equation of interfaces theory where the term depending on density ρ represents the contribute due to surface tension.

By introducing the function $R(x,t) \equiv \sqrt{\rho(x,t)}$ and the de Broglie ansatz

$$\psi(x,t) = R(x,t)\, \mathrm{e}^{iS(x,t)/2mD} \quad (30)$$

equation (28) takes the form

$$\partial_t S + \frac{(\partial_x S)^2}{2m} + V \; - \; 2mD^2 \, \frac{\partial_x^2 R}{R} = 0 \quad (31)$$

and the pair of real equations (25) and (31) are equivalent to the single linear equation for ψ

$$i(2mD)\partial_t \psi = -\, 2mD^2 \, \partial_x^2 \psi + V\psi, \quad (32)$$

This connects our dynamic equations with an ordinary eigenvalue problem on Hilbert space.

Note that the observables are the density ρ, which here represents just the (mass) density of the system, and the drift mean velocity of the system v; where the connection with the pair ψ, v is provided, at every point and at every time, by $\rho = |\psi|^2$, and $v = \partial_x S/m$. Note also that

$$mv_{(+)} = \partial_x S + mD \, \frac{\partial_x R}{R}. \quad (33)$$

If we choose the potential in the form of $V(x) = f(\rho)$, where $f(\rho)$) is a nonlinear functional of density (e.g. $ln(\rho)$), we obtain a dynamic system that provides self-regulation by the self consistent feedback action of relative density variations typically associated to osmotic phenomena across interfaces. So well this very general model contains the third of relevant aspects considered to describe growing systems, in particular cells proliferation in solid tumor. Lognormal stochastic background, self-control and interface theory are the constitutive elements of this model, which leads to the deterministic Gompertz equation as equation for the median. This approach, being conceptually well-founded, allows to face, in principle, the growth problems as a controlled one namely it is possible to intervene with outdoor control. For example our method poses the reduction of tumoral mass from a new and interesting point of view as we describe in the next section.

B. Controlled growth

In this section we move on to implement the controlled evolution. In fact we exploit the transition probabilities of the Gompertz self-controlled evolution to model controlled evolutions from a given initial state to arbitrarily assigned final states. We start by observing that to every solution $\psi(x,t)$ of the Fokker-Planck equation (25), with a given $v_(+)(x,t)$ and constant diffusion coefficient D, we can always associate a ”wavefunction” descriptions of eq.(32), of a dynamical system. To this aim, it is sufficient to introduce a suitable time-dependent potential $V_c(x,t)$, by exploiting the wave equation (32) as a control equation[6].

Here we quickly recall those elements of the controlling procedure which are needed for our aim, referring to Cufaro et al. 1999 [6] for further details. Let us consider a solution $\rho(x,t)$ of the Fokker–Planck equation, with a given $v_{(+)}(x,t)$ and a constant diffusion coefficient D; let us introduce the functions $R(x,t)$ and $W(x,t)$ defined by

$$\rho(x,t) = R^2(x,t)\, , \qquad v_{(+)}(x,t) = \partial_x W(x,t), \quad (34)$$

and remind that the relation

$$mv_{(+)} = \partial_x S + mD \, \frac{\partial_x R}{R} \\ \equiv \partial_x S + mD/2 \, \frac{\partial_x \rho}{\rho} = \partial_x \left(S + mD/2 \ln \tilde{\rho}\right) \quad (35)$$

must hold, where $\tilde{\rho}$ is an adimensional function (argument of a logarithm) obtained from the probability density ρ by means of a suitable and arbitrary dimensional multiplicative constant. If we now impose that the function $S(x,t)$ must be the phase of a wave function, we immediately obtain from the Eqs. (34) and (35).

$$S(x,t) = mW(x,t) - \frac{mD}{2} \ln \tilde{-}\theta(t), \quad (36)$$

which allows to determine S from ρ and $v_{(+)}$ (namely W) up to an additive arbitrary function of time $\theta(t)$. However, we must ensure that the wave function (34) with R and S given above, is a solution of the wave equation (32). Since S and R are now fixed, equation (32) must be considered as a relation (constraint) defining the controlling potential V_c, which, after straightforward calculations, yields

$$V_c(x,t) = mD^2 \, \partial_x^2 \ln \tilde{\rho} + mD(\partial_t \ln \tilde{\rho} \\ + v_{(+)} \partial_x \ln \tilde{\rho}) - \frac{mv^2_{(+)}}{2} - m\partial_t W + \dot{\theta}. \quad (37)$$

Of course, if we start with a wave function $\psi(x,t)$ associated to a given time–independent potential $V(x)$, the self-consistency is ensured, and this formula always yields back the given potential, as it should.

We now leave the general way, and focus on the very interesting case, useful for our goal, of simple controlling potentials able to produce a evolution which can vary, and in particular reverse, the growth trend. We start by observing that, to our purposes, it is expedient to handle the Gaussian Ornstein-Uhlenbeck process $Y(t)$, Eq. (8), because this is a simple task, and it is equivalent to modify the underlying non Gaussian process $X(t)$. In fact, being $< Y(t) >= \mu(t) =< \ln(X(t)/K) >= lnz(t)$, where $z(t)$ is the median describing the macroscopic size, the monotonicity of the logarithmic function ensures that a reduction of $\mu(t)$ leads to a corresponding (multiplicative) reduction of the size. The probability distribution for $Y(t)$ is the Gaussian (17), characterized by the two time-dependent parameters ($\mu(t), \sigma(t)$). Let us suppose now that the time evolution at some instant $\bar{t}$ has led to the pair of values $\mu(\bar{t}) \equiv \mu_0, \sigma(\bar{t}) \equiv \sigma_0$, and that we aim to reduce this values in such a way that, after some characteristic time τ, they becomes $\mu_1 < \mu_0,\ \ \sigma_1 < \sigma_0$. As proved in Cufaro et al.[6], in this Gaussian instance the controlling potential to be applied is harmonic, and has the form:

$$V_c(x,t) = \frac{m}{2}\,\left[\omega^2(t)x^2 - 2a(t)x + c(t)\right]. \qquad (38)$$

This harmonic potential is completely determined by the choice of mean and variance, $\mu_c(t), \sigma_c(t)$, of the Gaussian process self consistently generated by the controlling harmonic potential (38). In fact, the time-dependent coefficients $\omega^2(t), a(t), c(t)$ are all functions of $\mu_c(t), \sigma_c(t)$ and of their time derivatives, but a further free function of time that can be exploited to simplify the expression of the potential or of the phase. Being we here merely interested to outline the general conceptual frame allowing control, we avoid burdening this subsection with the explicit expressions of the time-dependent coefficients, which can be found in Cufaro et al. [6]. We only sum up again the procedure. One chooses the form of the controlling mean and variance $\mu_c(t), \sigma_c(t)$, which in the characteristic time τ go to the final reduced values μ_1, σ_1; then one inserts their expressions, and a suitably chosen form of the further free function of time, in the time dependent parameters $\omega^2(t), a(t), c(t)$, so obtaining an harmonic controlling potential that, applied to the system, drives it towards the reduced mean and variance. We comment here on an important aspect: one can choose many functions $\mu_c(t), \sigma_c(t)$ leading to the reduced mean and variance. If we set $\mu_c(t) = \mu_0 f(t)$, and $\sigma_c(t) = \sigma_0 g(t)$, the functions $f(t), g(t)$ must satisfy the constraints:

$$f(0) = 1,\ f(\infty) = \mu_0/\mu_1\ \ ;\ \ g(0) = 1,\ g(\infty) = \sigma_0/\sigma_1.$$

A possible form for $g(t)$, for example, could be:

$$\frac{1 + b\exp(t/\tau)}{c + d\exp(t/\tau)},$$

with $c + d = 1 + b;\ \ d = b\cdot(\sigma_0/\sigma_1)$. Another possible choice can be found in [6]. The important point is that the choice of this functions, together with that of the further free function of time, must be made in such a way to define a controlling potential $V_c(x,t)$ which can be effectively engineered and applied to the system. It is also evident that, from the point of view of practical implementations, one can resort to suitable approximations which can anyhow realize the goal within a permissible error.

V. CONCLUSION

The ubiquity of the Gompertz equation, raises a very interesting question in the framework of growth phenomena, namely the key presence of the logarithmic function ruling the nonlinear growth. In this work, we have shown that the ubiquity of this equation and its logarithmic regulation are the macroscopic expression of the ubiquity of the log-normal distribution. In fact, we have proved that Gompertzian growths are generated by a log-normally distributed stochastic process, being the macroscopic Gompertz equation the evolution in time of the median of the process. The median then describes the macroscopic size of the growing system. We remark, therefore, that the growth is not, as often supposed, *disturbed* by a stochastic noise, but that the stochastic process is its *origin*, and its *guidance* at any time. This scheme agrees with the claim of Galton [10] and McAlister [17] who at the end of the nineteenth century have shown that many natural systems are well described by log-normality; their actual behavior is then described by the median rather than the mean, thus implying that the basic geometric series plays a key role in describing relevant natural phenomena as already inferred by Gompertz [12]. In other words, the root causes do not add but multiply among them in many systems, including economic and social ones. Our analysis accounts for the stochastic origin of ubiquity of Gompertzian growths, suggesting also a method to determine the order of magnitude of the microscopic stochastic parameters, and in particular of the diffusion parameter, by the statistical observation of macroscopic sizes.

Some systems, as for example cell aggregates, develop by a ”birth-death” process, i. e. more general by the competition between aggregation and disaggregation. For this system, the basic process is then a branching process leading in a suitable limit to a log-normal behavior. Some of these aggregates are characterized by self-regulation: an example is that of tumor cells forced to grow in three dimensions, which cannot go beyond a critical diameter regardless of how often new medium is provided or how much open space is made available. These growths cannot thus be described by a stochastic background where the parameters are a priori defined and one must resort to a dynamical setting. In the last section of this work we then propose a dynamical conceptual framework that include self regulation mechanisms. We exploit a stochastic variational principle, whose canonical structure generates a control equation ruling the dynamical update of the forward velocity. Self regulation is then implemented by choosing the potential function as a (nonlinear) functional of the density of the system, so introducing a self consistent feedback of the relative density variations. This conceptual framework opens the way to a reliable control of the growing system by external actions which, for example, suitably modify, on some characteristic time scales, the density profile of the system. One can thus effectively develop practical methods to reverse the growing trend, reducing, for example, a cancer size. The general scheme here outlined will be applied and tested in forthcoming papers, focusing on the behavior of specific systems.

[1] Z. BaJzer S. Vuk-Pavlovic and M Huzak, *Mathematical modeling of tumor growth kinetics*, in: J. A. Adams and M. Bellomo eds. A survey of models for tumor-immune systems dynamics, Boston. Birkhauser 1997, 89–132.

[2] Z. Bajzer and S. Vuk-Pavlovic, *New dimensions in Gompertzian growth*, J. Theor. Med. 2, 307-315,(2000).

[3] Brunton G. F. and Wheldon T.E., *The Gompertz equation and the construction of tumor growth curves*, Cell Tissue Kinet, 13, 455–460, (1980).

[4] Cowan, R., *Branching process results in terms of moments of the generation time distribution*, Biometrics 41 681-689 (1985).

[5] T. S. Deisboeck, C. Guiot, P. P. Delsanto, N. Pugno, *Does cancer growth depend on surface extension?*, Med. Hypotheses, 67: 1338-1341, (2006).

[6] N. Cufaro Petroni, S. De Martino, S. De Siena, F. Illuminati, *Controlled quantum evolutions and transitions*, J. Phys. A 32, 7489-7508 (1999).

[7] S. De Martino and S. De Siena, Hierarchical gompertzian growth maps with application to astrophysics submitted to PRL (2010).

[8] de Vladar H.P., *Density-dependence as a size-independent regulatory mechanism*, J. Theor. Biol., 238(2), 245-56 (2006).

[9] F. C. Figueira, N.J. Moura Jr, M. B. Ribeiro, *The Gompertz-Pareto Income Distribution*, Physica A: Statistical Mechanics and its Applications Article in Press, Corrected Proof (2010).

[10] Galton, F. , *Is the geometrical mean in vital and social statistic*, Proc. Roy. Soc., 29, 365–367, (1879).

[11] C. W. Gardiner, Handbook of Stochastic Methods, Vol. 13 of Springer Series in Synergetics (Springer, Berlin, 1985).

[12] Gompertz, B., *On the nature of the function expressive of the law of human mortality and on a new method of determining the value of life contingencies,* Philos. Trans. R. Soc., 36, 513–585, (1825).

[13] Guerra F and Morato L M 1983 Phys. Rev. D, 27 (1774).

[14] H.B. Jones , A special consideration of the aging process, disease, and life expectancy. In: J.H. Lawrence and C.A. Tobias, Editors, Advances in Biological and Medical Physics vol. IV, Academic Press Inc, New York, 281–337, (1956).

[15] Kolmogorov N.A., *Uber das logarithmisch normale Verteilungsgesetz der Teilchen bei Zerstuckelung*, Dokl. Akad. Nauk SSSR, 31 99–101, (1941).

[16] Kozusko F, Bajzer Z.,*Combining gompertzian growth and cell population dynamics*. Math. Biosci. 185, 153-167, (2003).

[17] McAlister, D., *The law of the geometric mean*, Proc. Roy. Soc., v. 29, 367–376, (1879).

[18] L.D. Muller, T.J. Nurbaum and M.R. Rose, The Gompertz equation as a predictive tool in demography. Experimental Gerontology 30 6, 553-569,(1995).

[19] Nelson E., Quantum Fluctuations (Princeton: Princeton U.P.), (1985).

[20] J. S. Rowlinson and B. Widom: Molecular Theory of Capillarity, Clarendon Press, Oxford (1982).

[21] L. Sachs : Statistishe Auswertungsmethoden Springer, Berlin (1969)

[22] C.L. Zhang, F.A. Popp Medical Hypothesis 43 1-16 (1994) Longman group Ltd (1994)