(Genetic) Epidemiology of Inflammation, Age-related Pathology and Longevity

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Chapter 6

Gompertz' hazard law as a network principle of aging

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Abstract

Life-spanning population survivorship curves (the number of survivors versus age) is conventionally regarded as a demographic issue. Most often, the term hazard, the relative mortality per age-interval, is used as a typical survivorship parameter. Population survivorship curves are construed from cross-sectional data (single event per individual; here mortality) and -obviously- not from longitudinal data (multiple measurements per individual). In a previous article we have tested the hypothesis that Gompertz' survivorship law describes human population mortality.
Here, we tested quantitatively the idea that Gompertz' law describes the mortality pattern of a wide variety of organisms, some of them fed with lifespan affecting diets. We show the wide applicability of Gompertz' law and concluded that this law reflects a general biological principle of aging-associated mortality.

Because of this, we have searched for a mathematical model to interpret Gompertz' law. We tested semiquantatively whether Gompertz' law reflects the pattern of gradual disintegration of well-organized (biological) networks.

The first test shows that the Gompertz law, does not only describe the life-spanning mortality patterns well of both the Dutch population, but also those of of a wide variety of organisms. The data of all organisms were compatible with old-age deceleration of mortality. The current approach allows to distinguish whether the incidence of a pathology is associated with general aging or with incidental (i.e. patient specific) causes.

The second, semiquantitative, test, supports the finding that Gompertz' pattern of mortality closely follows the increasing randomization of network connections. We suggest that aging has to be understood as a lifetime increase of excitatory, or a decrease of inhibitory connections so that consequently pathogenic mechanisms might develop.

Keywords: acceleration of mortality, aging, ergodicity, Gompertz' hazard law, modeling, small world network

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INTRODUCTION

Population survivorship curves are used to assess quantitative parameters associated with aging or interventions affecting longevity of human and animal populations [1-4]. These curves, showing all-cause mortality, do not necessarily disclose a specific pathology. Instead they may emphasize general aging processes and causing a multiplicity of molecular and other processes causing or associated with mortality [1-4]. Survivorship patterns have been explained by assuming individual (often Gaussian) variability in, among others, frailty, genes or defective proteins [5, 6]. In his classical report, Gompertz [7] suggested that "death may be the consequence of two generally coexisting causes; the one, chance, without previous disposition to death or deterioration; the other, an unspecified force that destroyed the material of organization necessary for life" [quoted in 1]. The present report describes an approach that might clarify a biological principle underlying population survivorship curves.

In a protective environment, i.e. with little external causes of death such as severe infections, starvation and accidents, a survivorship curve may be considered a population-specific characteristic. Western human and many laboratory animal survival curves show relatively little mortality during the first period of life, whereas the number of survivors shows an approximately exponential decline thereafter. The human survivorship curves show exceptionally long periods (almost 60 years in the Netherlands) with relatively low mortality. At advanced age, mortality might attenuate [discussed in 1, 2, 4, 8, 9]. Such deceleration has often remained unnoticed or was questioned [10, 4, 9]. Apparently, additional aging-dependent mechanisms have to be considered. Previously, we reported that the Gompertz approach distinguishes well general aging as a risk to develop pathology, as compared to aging-independent pathology, such as some forms of cancer and genetic disorders [4].

THE MODEL

Our approach is based on the application of the ergodicity principle to population survivorship data. According to (simplified) statistical thermodynamics, ergodicity implies that the distribution of a large number of (identical) particles (or functions) over sub-compartments (or space) equates the probability of a single particle to be found in a particular sub-compartment. In conventional terminology: in an ideal system, cross-sectional observations (here spatial dimensions) equate longitudinal observations (here, time courses). Ergodicity of a system is guaranteed if the final state is irreversible, i.e. all constituting elements (i.e. particles) sooner or later end in that final state (here, death) [4]. The principle of ergodicity, i.e. the equivalence of cross-sectional and longitudinal data, can be illustrated with an intuitively easily understandable example of human growth curves: weight versus age. In a population of (young) subjects these curves can be composed following one of two strategies. First, the longitudinal approach: recruit a representative group of babies, weigh them frequently (approximately every 4 months) and follow them until adulthood (e.g. 18 years); for every individual compose (compute or simulate) the growth curve and calculate the average (and deviation). The alternative, the cross-sectional approach, is to recruit a large group of youngsters of various ages (babies and children up to 18 years), weigh them, register their age, and calculate the best fitting curve. In the ideal experiment (and in principle), the two computed growth curves are identical and at least one person of the investigated populations approximates this "ideal" growth curve. Only the second strategy is useful here, because survivorship data and curves are composed of cross-sectional data, as individual measurements can – obviously- be done only once.

We applied the idea of ergodicity to Gompertz' law, which is among the best models to describe population survivorship. In contrast to various other models, it describes a wide variety of data sets fairly accurately with two parameters [e.g. 1, 2, 4, 7]. Most population survivorship studies use Gompertz' law to assess the aging related hazard (the fraction of a population of a defined age interval that dies in that interval), which is modeled as a single exponential age-function. In Kirkwood's words [2]: "In essence, the (Gompertz) equation represents a force of mortality that increases exponentially with age in such manner that a hazard parameter (defined below) grows linearly." As an alternative to the hazard function, we apply Gompertz' law to model the mortality pattern of the whole population from birth onwards and use the real number of survivors of a population versus age. Therefore, the hazard function has to be integrated and this integrated function is used for modeling. As far as we know, this procedure has only been explored in a human population [4]; here, we examined also data of a variety of organisms, some exposed to life-time extending interventions. In a protective environment with little external causes of death, human and laboratory animal survival curves may be considered as an aging characteristic of the population in question. Applying the idea of ergodicity and assuming that all individuals are (nearly) biologically identical at birth, a survival curve not only reflects the time course of aging of a population, but also an aging process (or principle) active in every subject of that population. Unexpectedly, our approach provides an explanation of the shift from increasing mortality at younger ages to its deceleration at old-age in all species examined: the various ages of inflection are calculated.

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GOMPERTZ and NETWORK MODELLING

It has been speculated that they may relate to random damage or to characteristics already present at birth. It should be emphasized that such assumptions are well compatible with the exponentially increasing mortality during the first period of life, but not necessarily with late-life deceleration. The explanatory power of a direct connection between cellular aging processes and the actual mortality seems rather speculative to us. Therefore, we searched for a bridging concept. A well-fitting model was found in reports on small-world networks. The idea is the following: consider the living system or a part of it (organism, organ or cell) as a well-organized and communicating network of entities and consider that the process of aging gradually impairs that organization. Most current network models focus on the opposite direction of temporarity: the realization of an organized system starting with randomly active entities: as for instance how clocks (oscillators) may synchronize through weak interactions [11]. Synchronization depends on the strength of coupling: above a certain threshold the entities synchronize, otherwise they remain uncoupled. Aging might then be considered as the reverse process: well-synchronized (or coupled) systems disintegrate gradually [11].

Research method

General Approach

We tested firstly the idea that Gompertz' law explains lifetime mortality patterns well, including old old-age deceleration of mortality, not only in human population [as described in 4], but in several animal species as well. Because of this generality, we tested whether Gompertz curves are compatible with some other models. We show that the pattern of all-cause mortality clearly deviates from a Gaussian distribution (it is skewed). Hence, Gompertz' law seems incompatible with a Gaussian pattern of individual properties present at birth or early in life. Because of this result, we tested the hypothesis whether a Gompertz pattern of mortality is compatible with the dissolution of a small world network [11]. This idea was tested semi-quantitatively with an overlay method.

TESTING THE HYPOTHESES

Gompertz' function and applications

The model. Equation 1 shows Gompertz' expression of the proportional hazard rate μ(t) as a function of age (t); α and β are population specific constants:

$$\mu(t) = \alpha e^{\beta t} \quad (1)$$

Reformulation and integration of equation 1 by taking the size of the original population S0 at birth (= 1 after normalization) and S(t) as the relative size of the population at age t gives:

$$S(t) = e^{c(1-e^{kt})} \quad (2)$$

The parameters c and k are population-specific constants. They were used instead of α and β to distinguish them from equation 1. The derivative of equation 2, m(t), gives the mortality rate at age t:

$$m(t) = -kcS(t)e^{kt} \quad (3)$$

Formula (3) is negative because of the decreasing number of survivors during aging. One implication of Gompertz' law is that, after an initial increase, the relative mortality decreases at old age. We calculated the age of inflection tad when an accelerated rate of mortality transits into decelerating mortality from the derivative of equation 3, or dm/dt = 0 at tad:

$$t_{ad} = k^{-1} \ln c^{-1} \quad (4)$$

Notice that tad is independent of the population size.

Data sets. We fitted data for a wide variety of cohorts chosen rather arbitrarily from literature or acquired through personal contacts. The following data sets were used: 1) males and females (Dutch population *[www.cbs.nl; 4 acknowledged]*); 2) mice under caloric restriction[12, 13]; 3) houseflies (Musca domestica) fed a variety of diets [14]; 4) West-Indian fruit flies (Anastrepha obliqua) males and females; 5) wasps *(Diachasmimorpha longicaudata)*, males and females (data provided by Dr. James Carey); and 6) honeybees *(Apis mellifera)*.

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Quantitative and semi quantitative fits

Gompertz' fittings were done using Graph pad Prism 5 (non-linear regression analysis), resulting in two free parameters, c (no dimension) and k (k in days-1). The confidence intervals and tad were also calculated. As indicated, we examined the mortality pattern of the entire populations (from birth to death), not the hazard function. The applied overlay procedure [4] is based on a visual inspection procedure without quantitative or theoretic computations.

Fittings and *results*. Figures 1 and 2 show the fitted survivorship curves; table 1 the quantitative data. The quantitative fits and parameters illustrate that Gompertz' equation provides good fits with survival data of the Dutch population and nearly all animal species. The derivative of the Gompertz curve illustrates life-time the asymmetry, suggesting that a Gaussian distribution is either inadequate or is lost as the consequence of aging. Minor deviations were noticed with the data of honeybees and ad libidum fed mice, but not with those of the calorie-restricted fed mice. Notice that although the hazard increases exponentially during aging, the relative mortality at old age decreases. We estimated tad of each population as shown in the table. Semi-quantitative (overlay) analyses [described in 4] were done on published survivorship curves of nematodes *(Caenorhabditis elegans)* [15, 16] and fruit flies *(Drosophila melanogaster)* [17, 18]. These overlay results support the quantitative analyses, showing the accuracy of the fits in a wide variety of organisms and additionally the advanced-age deceleration of mortality of all populations.

Network modeling

What could be the nature of a general process underlying aging? The result of the overlay approach [as described in 4] was applied to the study of Watts and Strogatz [19] and shown here in figure 3. The latter model suggests that a change of connectivity increases with a factor of 10 every 25 years. These network models suggest that a gradual increasing connectivity between entities ends in a randomized state of the system. In the present context, aging-dependent connectivity might either point to increasing activating connections (excitatory mechanisms) or to a gradual decrease of inhibiting connections. We suggest that the loss of connectivity in a network causes individual entities of that network to become less controlled by the organism (the system) and that it might increase the risk of developing fatal pathogenic processes. Alternatively, the proposed increasing randomness of connectivity might point towards an increasing number of freedom parameters of the connected entities. The proposed network model does not necessarily apply to the whole organism, but may also apply to cell aggregates or organs that are critically involved in vital functions of the organism.

BIOLOGICAL IMPLICATIONS

Our conceptualizations of Gompertz' law and network models imply that deterioration of functions is a continuous process starting at birth, and not after reproductive success (as suggested in [1]). The apparent rate of disintegration of human female and male survivorship curves are almost similar, which is not well compatible with the notion that the female reproductive period (being determined by the exponential loss of fertilizable ova) ends earlier than the male's reproductive capacity, which remains largely intact at older age. Age-related. diseases have to be viewed from two perspectives: many of them (e.g. cancer, cardiovascular disorders) closely follow Gompertz' aging law, suggesting that the expression of pathology not only depends on a particular pathogenic process, but to a substantial extent also on the actual state (or network connections) of the organism or of its organs [4]. One challenge could be how to identify the biological basis of the network connections and to understand their role in senescence.
Old-age mortality deceleration has often remained unnoticed or has even been rejected by some demographic investigators. For instance, Gavrilova and Gavrilov [10, and their previous reports] were unable to observe a decline of the mortality rate in humans of advanced age and rodents. The difference in their conventional approach is that their hazard functions are based on the mortality of sub-cohorts of the entire population taken over a fixed period, one year or so. Gavrilova and Gavrilov [10] noticed correctly "that the famous Gompertz law was suggested to fit hazard rate (mortality force), rather than the probability of death." But they have erroneously suggested[10], that the deceleration of mortality implies "near non-aging" at advanced age [also discussed in 1, 2, 4, 9]. In contrast: the present analysis indeed points to a continuously increasing hazard function, but it implies that the evolving pattern of mortality depends on additional aspects of organisms, possibly related to their complexity.

In a previous study we examined the incidence of several cancers using a semi-quantitative method [4]. The incidence of a variety of cancers (new diagnoses per year per 100,000 persons) shows an almost exponential increase during aging [20, 21, 22], but at higher ages the incidence rate is less than predicted by the exponential function [23]. It appeared that the incidence of prostate and colon cancer was nearly identical with the survivorship curves for the entire population, including a tendency of old-age deceleration, whereas the incidence data on cervix carcinoma clearly deviates from Gompertz' law. Indeed, the latter cancer is caused by an infection of the papilloma virus at a young age and our approach illustrates its potential to distinguish between predominantly intrinsically aging-associated versus extrinsically caused mortality. Moreover, the mortality and morbidity during aging might be the combined consequences of general aging and specific pathology. Attempts to identify specific pathogenic mechanisms or the involvement of particular genes should take both processes into account. The process of general

aging might stimulate the expression of some pathogenic mechanisms in an age-dependent way. Old-age deceleration of mortality might serve as an example of such possibility.

Gompertz' mortality function is bi-exponential. This suggests at least two active biological principles during life. First, the exponent; this function is characterized by a continuous mono-exponential decrease and does not take into account a linear aging dependence. The latter has to be incorporated in case of aging-independent risk of mortality. Indeed, this is known as the Makeham correction and has to be applied when a substantial proportion of a population dies because of accidents or fatal infections. At time zero (t=0), the exponential function is zero, as if there is not yet an age-related lesion present in the organism; whereas at old age this function becomes highly negative, something that has no real biological meaning. But, considering the complete Gompertz function, the impact of high values of the exponent "causes" a slowing down of mortality at advanced age. If the exponential function has some direct relationship with accumulating damage, the complete function suggests that the impact of such damage is continuously attenuated during aging. It is as if the expression of damage and/or the consequences of damage for mortality become impaired during aging. We have suggested that the expression of fatal damage (e.g. cancer or arteriosclerosis) requires a vital organism, similar to parasites needing a functioning organism to induce a fatal disease [4]. The Gompertz function might then describe the combined consequences of both the risk of damage increasing during lifetime (hazard) and the capacity of the organism to compensate or combat the expression of (at least some) pathological processes.

CONCLUSIONS

The hypothesis presented here -that Gompertz' hazard population law disclosing an aging principle of every individual of that population- has been tested only indirectly. Our principal argument is based on the assumption of equivalence of longitudinal and cross-sectional population data (the ergodicity theorem). Gompertz' law accurately describes lifetime patterns of acceleration and deceleration of mortality of a wide variety of organisms, including humans. This conclusion applies to untreated organisms, to life-span extending interventions and to the incidence of aging-associated pathologies [4].

We acknowledge that the present network analyses are based on semi-quantitative analyses. Nevertheless, our interpretation of Gompertz' law might help to develop biologically relevant aging laws, as was attempted here with network models. Accordingly, Gompertz' law might be understood as a gradual dissolution of networks. Direct testing of our proposal requires dedicated studies of age-related functions of individual organisms, their cells or organs. Our approach might also be seen as an invitation to develop quantitative (mathematical) models to prove the compatibility of Gompertz' law with network models.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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Table 1. Gompertz' parameters and t_{ad} age

Population	Parameter *c* (95% CI)	Parameter *k* (days $^{-1}$) (95% CI)	Absolute sum of squares	t_{ad}
Dutch population 2003 Male + Female (n ≈15,000,000)	$1.74 * 10^{-4}$ ($1.54 * 10^{-4} – 1.94 * 10^{-4}$)	$2.87* 10^{-4}$ ($2.74*10^{-4} – 2.85*10^{-4}$)	0.007149	86.5 years
Dutch population 1994 Male (n ≈ 7,585,000)	$3.52 * 10^{-4}$ ($3.20 * 10^{-4} – 3.85 * 10^{-4}$)	$2.76\ 10^{-4}$ ($2.66*10^{-4} – 2.73* 10^{-4}$)	0.005600	80.0 years
Female (n ≈ 7,755,000)	$1.12 * 10^{-4}$ ($9.41 * 10^{-5} – 1.30 * 10^{-4}$)	$2.95*10^{-4}$ ($2.82*10^{-1} – 2.93* 10^{-4}$)	0.01212	86.6 years
Mouse Fed normally (n = 60)	$1.28 * 10^{-3}$ ($5.14 * 10^{-4} – 2.04 * 10^{-3}$)	$6.87* 10^{-3}$ ($6.23*10^{-3} –7.50*10^{-3}$)	0.07075	32.3 months
Caloric restriction (n = 60)	$9.63 * 10^{-4}$ ($5.88 * 10^{-4} – 1.33 * 10^{-3}$)	$6.13 *10^{-3}$ ($5.80* 10^{-3} – 6.50*10^{-3}$)	0.03123	37.7 months
House fly Diet I (n = 200)	$3.28 * 10^{-2}$ ($2.70 * 10^{-2} – 3.89 * 10^{-2}$)	$1.58 *10^{-1}$ ($1.49*10^{-1} –.66 * 10^{-1}$)	0.02111	21.6 days
Diet V (n = 200)	$1.80 * 10^{-2}$ ($1.45 * 10^{-2} – 2.16 * 10^{-2}$)	$1.36 * 10^{-1}$ ($1.29*10^{-1} –1.43*10^{-1}$)	0.02785	29.5 days
Diet VI (n = 200)	$3.26 * 10^{-3}$ ($2.72 * 10^{-3} – 3.80 * 10^{-3}$)	$1.61 * 10^{-1}$ ($1.56 *10^{-1}–1.66*10^{-1}$)	0.01091	35.6 days
Fruit fly Male (n = 162,280)	$6.44 * 10^{-1}$ ($5.62 * 10^{-1} – 7.25 * 10^{-1}$)	$5.26 * 10^{-2}$ $4.85*10^{-2}$-$5.68*10^{-2}$)	0.02145	44.1 days
Female (n = 134,807)	$8.85 * 10^{-1}$ ($8.26 * 10^{-1} – 9.45 * 10^{-1}$)	$3.63 * 10^{-2}$ ($3.47*10^{-2}–3.80*10^{-2}$)	0.00630	31.1 days
Honey Bee Male (n = 200)	$3.96 * 10^{-2}$ ($3.11*10^{-2} – 4.82*10^{-2}$)	$9.42 * 10^{-2}$ ($8.81*10^{-2} –1.00 * 10^{-1}$)	0.05360	34.3 days
Wasp Male (n = 13,358)	$5.50 * 10^{-1}$ ($4.56 * 10^{-1} – 6.45 * 10^{-1}$)	$1.15 * 10^{-2}$ ($1.03*10^{-1} –1.27*10^{-1}$)	0.01712	52.2 days
Female (n = 14,184)	$7.78 * 10^{-1}$ ($6.47*10^{-1} – 9.09 *10^{-1}$)	$8.56 *10^{-2}$ ($7.62*10^{-2} –9.50*10^{-2}$)	0.01610	2.92 days

Table 1 Legend

This table shows the parameters of the best quantitative fits, 95% confidence intervals (CI), the sum of squares of the best fitting Gompertz' models and tad ages.The data sets used were: humans (total Dutch population); mice under caloric restriction (B6-mice fed ad libidum followed by a non-purified diet); houseflies *(Musca domestica)* fed with a variety of diets (Diet I, ad libidum sucrose fed; Diet V, 6:6:1 mixture of sucrose, powdered skim milk and powdered egg; Diet VI, 13:6 mixture of diet V plus powdered whey protein); West-Indian fruit flies (*Anastrepha oblique*, males and females); wasp (*Diachasmimorpha longicaudata,* males and females); and honeybees (*Apis mellifera*).

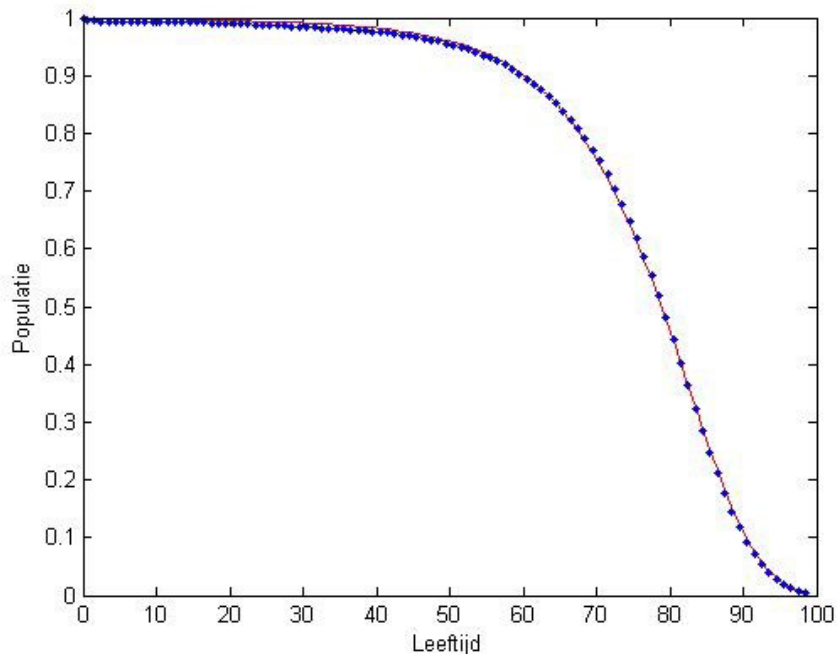

Figure 1. Example of a quantitative Gompertz fit of the survivorship curve of the Dutch population. Blue dots are observational data (yearly survival data); the red line is the best fitting Gompertz curve. The bold interrupted line is the population probability curve, which is the derivative of the Gompertz curve, being timeasymmetric, deviates from a Gaussian function. This example shows deceleration of mortality and subsequently the mortality rate at advanced age. Such deceleration is not explained by assuming the decrease of the size of the popuation at old age.

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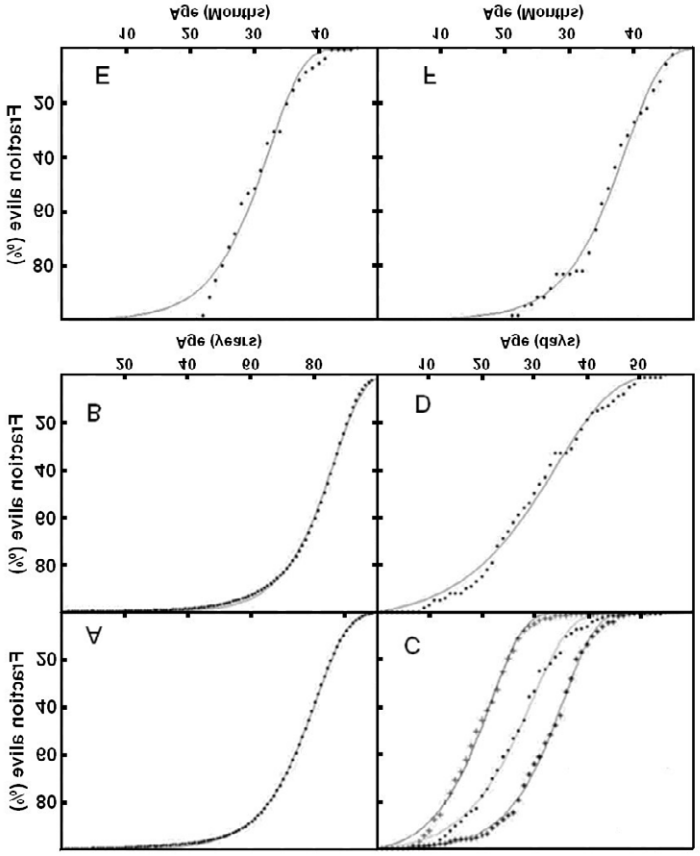

Figure 2. *Examples of quantitative Gompertz fits of survivorship curves.* **A:** *Dutch male population,* **B:** *Dutch female population:* **C:** *Houseflies on various diets: Diet I: Ad Libidum sucrose fed; Diet V: 6:6:1 mixture of sucrose, powdered skim milk and powdered egg; Diet VI: 13:6 mixture of diet V plus powdered whey protein.* **D:** *Honeybees under normal conditions;* **E:** *B6-mice fed ad libidum;* **F:** *B6-mice calory restricted diet. Black dots are observational data (yearly survival data of the human population; weekly or daily survival in the animal studies); lines are the best fitting curves. All examples show deceleration of mortality at advanced age.*

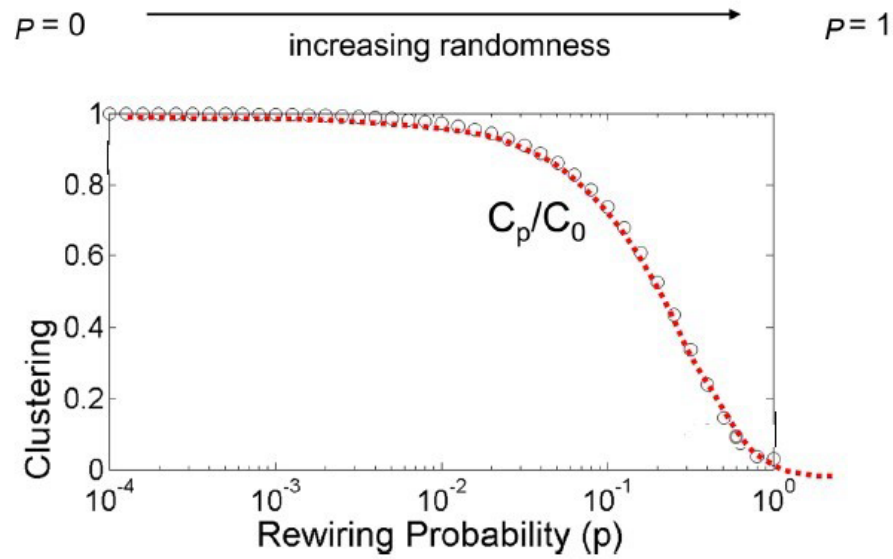

Figure 3. *Example of the similarity network model and Gompertz' law. Overlay procedure (described in 4). The semi-quantitative approach shows that an increasing number of connections (clustering) finally leads to some random structure. In the original model of the authors, clustering indicates the increasing number of connections between entities. The present concept of clustering (aging, leading to a decrease of survivors; 11, 19) is considered a parameter of increasing loss of connections between entities (clustering), so that the coordination of the organization of a living system is gradually lost. In the present case, we assume that the apparently increasing clustering between entities might be understood as the loss of inhibitory or regulatory connections, thereby leading to uncontrolled and possibly pathogenic activities of the thus affected entities.*