GOMPERTZ – A PROGRAM FOR EVALUATION AND COMPARISON OF SURVIVAL CURVES

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ABSTRACT

Principles, properties and use of a program for evaluation of survival curves are described. Parameters of Gompertzian mortality curves are computed from survival data of two populations by help of nonlinear regression. The differences in parameters of both curves are evaluated statistically. This method evaluates effectively even survival data of very small populations. The results are presented in numeric, verbal and graphic forms. Finally, reading of the results is offered to distinguish changes corresponding to altered aging rate from changes caused by influences not affecting the basic mechanism of aging. Program GOMPERTZ in the form of Microsoft Excel workbook equipped with Visual Basic procedures is offered free through e-mail (klemra@faf.cuni.cz).

INTRODUCTION

Gompertz law (1) of exponential growth of mortality

$$R(t) = R_0 \exp(k(t - t_0))$$

holds, at least approximately, for human populations in industrial countries (2) as well as for the majority of laboratory mammals and even for many other species of laboratory animals for substantial part of adult period of their life (3,4). Significant deviations from Gompertz course of mortality appear in the first period of life before adulthood (5) and in very advanced age, too (6,7,8).

Provided that the population is numerous enough, values of mortality $R(t)$ can be computed from the survival data precisely enough, e.g. by formula

$$R(t) \cong \frac{N(t - \Delta t) - N(t + \Delta t)}{2\Delta t} \times \frac{1}{N(t_0)}$$

where $N(t)$ is the number of subjects surviving at age t (8). In this case, the two Gompertz parameters R_0, k are easily computed by help of linear regression for logarithm of mortality:

$$\ln R(t) = \ln R_0 + k(t - t_0)$$

In case that the number of individuals in survival experiments is limited, direct computing of the values of mortality may be extremely inexact. Nevertheless, there is another possibility - to extract the requisite information from the survival curve as whole. Gompertzian survival curve is given by expression

$$S(t) = \exp \left[-\frac{R_0}{k} \exp(k(t - t_0)) - 1 \right] \text{ where } S(t) = \frac{N(t)}{N(t_0)}$$

Since linearization of survival function $S(t)$ is impossible, the use of nonlinear regression is necessary if its parameters R_0, k are to be found. Acceptable results even for small experimental groups can be obtained by means of this method.

The basic step of evaluation of survival experiments is to compare survival curves of two populations. A proper statistical evaluation of significance of differences in corresponding parameters is necessary for the validity of conclusions.

The last step of the evaluation should be interpretation of the results. In this respect, the essential problem is to distinguish between changes corresponding to altered aging rate and changes caused by influences not affecting the basic mechanism of aging. Criteria for such decision should be based on a proper theoretic model of aging.

METHODS

Nonlinear parameters R_0, k of Gompertzian survival curves corresponding to minimum residual dispersion of the experimental data are computed for both populations. The crucial point in the computing process proved to be a proper choice of the initial values of these parameters. Our method based on estimation of the inflection point of the survival curve was tested as effective and reliable for guaranteeing the convergence of the computing process. The principle of the method is as follows: The inflection point t_i of survival function $S(t)$ is given by equation

$$t_i - t_0 = -\frac{\ln(R_0/k)}{k}$$

and the first derivative in the inflection point is

$$S'(t_i) = -k \times \exp(R_0/k - 1)$$

As far as the inflection point t_i as well as the value of derivative $S'(t_i)$ can be roughly but easily estimated from the data points, the two unknowns R_0, k can be numerically computed from the system of two (nonlinear) equations. Using these as initial values, a modified version of method of Hooke and Jeeves (9) is used for estimating the values of the parameters corresponding to the minimum residual dispersion.

The differences in both curves are evaluated by the help of statistical estimation of differences in corresponding parameters. The formulae used are based on

the fact that the model is locally linearizable in parameters. The dispersions $D(R_0)$, $D(k)$ are computed as diagonal elements of variance matrix

$$V = D (J^T J)^{-1}$$

where J is the Jacobian and D the residual dispersion (10). The dispersions are then used for interval estimations of unknown true values of differences of parameters (11) as the computed values of pairs of corresponding parameters are expected to be independent random variables with approximately normal distribution.

A special statistical method – test of successive differences (12) – is used to verify whether the data do not contradict the supposed Gompertzian property. The summary results are presented in numeric, verbal and graphic forms. Finally, interpretation of the results of comparison of both survival curves based on a simple pacemaker model of aging is offered.

The model describes aging in “Gompertz population” where the logarithm of mortality $y(t) = \ln R(t)$ is a linear function of time:

$$y(t) = y(t_0) + k(t - t_0) .$$

Homogeneity of the population is supposed, so that each individual represents a stochastic system with equal probability $P(t)$ of living till the age t . The time course of $P(t)$ is then identical with the survival curve of the population, which is in one to one correspondence with the course of mortality of the population.

Since the analysis of the model is described in detail in our papers (13,14), only the main results are outlined here:

1. Changes exclusively in the slope of the Gompertz line can be caused entirely by changes of “speed” of the pacemaker, i.e. by affecting the aging rate.
2. Vertical displacements of the initial point $y(t_0)$ of Gompertz line are not caused by affecting the speed of the pacemaker.
3. The point of intersection in case of convergent Gompertz lines does not depend on changes of environmental parameters but strongly depends on the parameters of the pacemaker. Hence, influences expressed in convergent Gompertz lines with common intersection point do not affect the aging rate.

The following procedures are offered in GOMPERTZ program:

Edit and evaluate data

Survival data of two populations can be put in as values of age and corresponding counts of surviving individuals. The data points are shown in graphs promptly (see Figure 1). Restrictions: the initial values of age must be the same for both populations and minimum four points for each population are needed.

Compute

Values of Gompertz coefficients R_0 , k , their standard deviations and interval estimates of differences between coefficients of both populations are computed.

Figure 1: Screen with an example of survival data and graphically represented data points.

Conclusions of corresponding significance tests are formulated explicitly and an interpretation of the results is offered. Nevertheless, except this interpretation, no other results depend on accepting the theory postulated in papers (13,14) and are valid for any approximately Gompertzian survival data.

In case of non-Gompertzian data, identified by the test of successive differences, inspection of corresponding graph(s) and eventual removing first and/or last points from the data is recommended.

Numeric values

The table of numeric results contains coefficients R_0 , k , their standard deviations and interval estimates of differences between coefficients of both populations (see Figure 2).

Figure 2: Screen with numeric results of the evaluation of experimental data.

Graphs 1

Graphs of data points together with theoretical survival curves apart for populations A, B are shown.

Graphs 2

Two graphs comparing the properties of populations A , B are shown: (a) both survival curves in the same graph;

Figure 3: Screen with graphs comparing survival curves (left) and Gompertz lines (right) of both populations.

(b) corresponding Gompertz lines for the natural logarithm of mortality and their symbolic upper and lower limit lines determined by adding or subtracting values of corresponding standard deviations to parameters R_0 , k (see Figure 3).

Examples

Four types of example data can be chosen, illustrating some typical situations: (a) significant change in aging rate (i.e. affecting pacemaker); (b) significant change in environmental conditions not affecting the pacemaker; (c): no significant change in survival curves; (d): non-Gompertzian data.

Comment

Short explanation of the theory and detailed instruction for the user are presented.

DISCUSSION

Proper choice of starting values for iterative algorithms of nonlinear regression is the crucial point in case of "double-exponential" function of the type of Gompertzian survival curve $S(t)$. The method of determining these starting values developed and used in GOMPERTZ program guarantees the convergence of the process for any feasible data.

Another important property of the program is a self-acting procedure testing Gompertzian character of the data as an important criterion of validity of the results. The advantage of the method of successive differences used for the testing resides in its versatility. The program itself is able to indicate only the fact of non-Gompertzian character of a survival curve. The analysis of the cause of this character might be of interest, but the survival data alone do not allow to decide whether the cause of it is (say) heterogeneity of the population or other possible reasons.

Interval estimates of differences in Gompertzian parameters of both populations yield the most important, quantitative evaluation of prospective impact of experimental conditions on the process of aging. In case of proved significant difference(s), an interpretation of the result is offered in accordance to the theoretical model of aging presented in (13,14). Nevertheless, no other results of the program are dependent on the acceptance of the model.

The benefit of the program consist among others in the simplicity of its use. It is supported also by verbal presentation of the results and by ready-made graphs. Self-contained comment offers short explanation of the theory as well as complete direction.

Program GOMPERTZ in the form of Microsoft Excel workbook **gompertz.xls** equipped with special Visual Basic procedures runs under Microsoft Excel 5 or higher versions. Survival data of two populations are the only inputs of the program. The program is offered free by the authors through e-mail (klemmera@faf.cuni.cz). There are no limitations of free using and copying the program provided that the user, when publishing results of GOMPERTZ program, quotes two relevant papers: the present paper and the most related former paper (14) explaining the theoretical background of the interpretation of results.

REFERENCES

1. Gompertz, B: On the nature of the function expressive the law of human mortality. Philos. Trans. R. Soc. London 115: 513-585, 1825.
2. Riggs, JE: Longitudinal Gompertzian analysis of adult mortality in the US 1900-1986. Mech. Ageing Dev. 54: 235-247, 1990.
3. Strehler, BL: Time, cells and aging. NewYork, Academic Press, 1977.
4. Doubal, S: Theory of reliability, biological systems and ageing. Mech. Ageing Dev. 18: 339-353, 1982.
5. Dolejs, J: The extension of Gompertz law's validity. Mech. Ageing Dev. 99: 233-244, 1997.
6. Carey, JR: Slowing of mortality rates at older ages in large medfly cohorts. Science 255-258, 1992.
7. Smith, DWE: The tails of survival curves. BioEssays 16: 907-911, 1994.
8. Klemmera, P , Doubal, S: Human mortality at very advanced age might be constant. Mech. Ageing Dev. 98: 167-176, 1997.
9. Bazaraa, S, Shetty, CM: Nonlinear programming. Theory and algorithms. New York, John Wiley and Sons, 1979, sec.8.4.
10. Nash, JC, Walker-Smith, M: Nonlinear parameter estimation. An integrated system in BASIC. New York, Marcel Dekker, Inc., 1987, p. 259.

11. Dowdy, S, Wearden, S: Statistics for research. New York, John Wiley and Sons, 1983, p.188.
12. Hart, BI: Significance levels for the ratio of the mean square successive difference to the variance. *Annals Math. Statistics* 13: 445-447, 1942.
13. Doubal, S , Klemra, P: Influence of aging rate on mortality curves. *Mech. Ageing Dev.* 54: 75-58, 1990.
14. Doubal, S , Klemra, P: Practical methodology of evaluation of mortality curves and detection of aging-related interventions. *Age* 20: 229-233, 1997.