FBST FOR COVARIANCE STRUCTURES OF GENERALIZED GOMPERTZ MODELS

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Abstract.

The Gompertz distribution is commonly used in biology for modeling fatigue and mortality. This paper studies a class of models proposed by Adham and Walker, featuring a Gompertz type distribution where the dependence structure is modeled by a lognormal distribution, and develops a new multivariate formulation that facilitates several numerical and computational aspects. This paper also implements the FBST, the Full Bayesian Significance Test for pertinent sharp (precise) hypotheses on the lognormal covariance structure. The FBST's *e*-value, ev(H), gives the epistemic value of hypothesis, *H*, or the value of evidence in the observed in support of *H*.

Keywords: Full Bayesian Significance Test, Evidence, Multivariate Gompertz models

INTRODUCTION

This paper presents a framework for testing covariance structures in biological survival data. Gavrilov (1991,2001) and Stern (2008) motivate the use of Gompertz type distributions for survival data of biological organisms. Section 2 presents Adham and Walker (2001) characterization of the univariate Gompertz Distribution as a Gamma mixing stochastic process, and the Gompertz type distribution obtained by replacing the Gamma mixing distribution by a Log-Normal approximation. Section 3 presents the multivariate case. Section 4 presents the formulation of the FBST for sharp hypotheses about the covariance structure in these models. Section 5 presents some details concerning efficient numerical optimization and integration procedures. Section 6 and 7 present some experimental results and our final remarks.

THE UNIVARIATE LOG-NORMAL GOMPERTZ DISTRIBUTION

This section presents Adham and Walker (2001) characterization of the (reparameterized) univariate Gompertz Distribution as a Gamma mixing stochastic process. Furthermore, Adham and Walker (2001) suggest the use of a Log-Normal approximation for the Gamma mixing distribution that greatly simplifies both numerical computations and multivariate extensions of the univariate model. Section 7 of Pereira and Stern (2008) describe similar uses of Log-Normal approximations to the Gamma distribution, see also Aitchison and Shen (1980). In many examples of the authors consulting practice these approximations proved to be a powerful modeling tool, leading to efficient computational procedures.

A non-negative random variable t follows a Univariate Gompertz distribution with parameters a and c, if its distribution function is given by:

$$f(t|a,c) = f(t) = ac\exp(at)\exp(-c(\exp(at) - 1))$$

Adham and Walker (2001) show that we can rewrite the previous density with parameters a > 0 e c > 0 as a product of mixtures using the Gamma distribution, $\Gamma(2,c)$, as follow:

$$f(t|u) = au^{-1} \exp(at) \mathbf{I}[u > \exp(at) - 1]$$
 and $f(u) = \Gamma(2, c) = c^2 u \exp(-cu)$.

In their work, Adham and Walker (2001) introduce the GOLN distribution, an alternative to the Gompertz, which uses the representation of mixtures with a log-normal distribution $LN(\mu, \sigma^2)$ whose parameters are determined by the minimum Kullback-Leibler distance for the gamma distribution $\Gamma(2, c)$. The final formula has Gaussian core and is given by:

$$f(t|u) = a \exp(at) \exp(-u) \mathbf{I}[u > \log(\exp(at) - 1)] \text{ and}$$

$$u \sim N(\mu, \sigma^2), \ \mu = E(\log(x)), \ \sigma^2 = E\{(\log(x))^2\} - \mu^2, \ x \sim \Gamma(2, c).$$

Lemma We can write the GOLN distribution as follows:

$$f(t) = a \exp\left(at - \mu + \frac{\sigma^2}{2}\right) \left[1 - \Phi\left(\frac{\log(\exp(at) - 1) - \mu + \sigma^2}{\sigma}\right)\right],$$

where $\Phi(\cdot)$ is the cumulative probability function of standard normal distribution.

Proof:

Using the law of total probability for f(t) from its representation of mixtures, we have:

$$f(t) = \int_{\Omega} f(t|u) f(u) du = a \exp\left(at\right) \int_{\log(\exp(at) - 1)}^{\infty} \frac{1}{\sigma\sqrt{2\pi}} \exp\left(-u - \frac{(u - \mu)^2}{2\sigma^2}\right) du$$

Adding and subtracting μ of the integral's exponent, we have

$$f(t) = a \exp\left(at - \mu\right) \int_{\log(\exp(at) - 1)}^{\infty} \frac{1}{\sigma\sqrt{2\pi}} \exp\left(-(u - \mu) - \frac{(u - \mu)^2}{2\sigma^2}\right) du \,.$$

Using the change of variables $v = u - \mu$ and dv = du

$$f(t) = a \exp(at - \mu) \int_{\log(\exp(at) - 1) - \mu}^{\infty} \frac{1}{\sigma \sqrt{2\pi}} \exp\left(-v - \frac{v^2}{2\sigma^2}\right) dv .$$

Using the change of variables $y = v + \alpha$, it is possible to rewrite the integral's exponent as

$$-v - \frac{v^2}{2\sigma^2} = \frac{-y^2 - 2y(\sigma^2 + \alpha) - \alpha(2\sigma^2 + \alpha)}{2\sigma^2} .$$

Considering the last equality as a quadratic equation in y, we can eliminate the linear term by taking $\alpha = -\sigma^2$ and get

$$-v - \frac{v^2}{2\sigma^2} = \frac{-y^2}{2\sigma^2} + \frac{\sigma^2}{2}.$$

Using one more change of variables, $y = v + \sigma^2$ and dy = dv, we can re-write the integral as

$$f(t) = a \exp\left(at - \mu + \frac{\sigma^2}{2}\right) \int_{\log(\exp(at) - 1) - \mu + \sigma^2}^{\infty} \frac{1}{\sigma\sqrt{2\pi}} \exp\left(\frac{-y^2}{2\sigma^2}\right) dy.$$

After another change of variables, $w = \frac{y}{\sigma}$ and $dw = \frac{dy}{\sigma}$, we get

$$f(t) = a \exp\left(at - \mu + \frac{\sigma^2}{2}\right) \int_{\frac{\log(\exp(at) - 1) - \mu + \sigma^2}{\sigma}}^{\infty} \frac{1}{\sqrt{2\pi}} \exp\left(\frac{-w^2}{2}\right) dw .$$

Hence, we can see that the integrand is the probability density of the random variable w which follows standard normal distribution. In this case, it is worth noticing that $P(A \le w \le B) = \Phi(B) - \Phi(A)$. Hence, remembering that $\Phi(\infty) = 1$, we have

$$f(t) = a \exp\left(at - \mu + \frac{\sigma^2}{2}\right) \left[1 - \Phi\left(\frac{\log(\exp(at) - 1) - \mu + \sigma^2}{\sigma}\right)\right] Q.E.D.$$

Lemma In order to get a good GOLN approximation to the Gompertz distribution with parameters a > 0 and c > 0, we can choose the parameters of the normal distribution as follows:

$$\mu = 1 - \gamma - \log(c)$$
 and $\sigma^2 = \pi^2/6 - 1$,

where $\gamma \approx 0.5572156$ is the Euler-Mascheroni constant.

Proof:

$$\mu = E_{\Gamma(2,c)}[\log(x)] = \int_0^\infty c^2 x \exp(-cx) \log(x) dx = 1 - \gamma - \log(c) ;$$

$$\begin{split} \sigma^2 &= E_{\Gamma(2,c)}[\log(X)^2] - \mu^2 = \int_0^\infty c^2 x \exp(-cx) \log(x)^2 dx - (1 - \gamma - \log(c))^2 \\ &= [\gamma^2 - 2\gamma + \frac{\pi^2}{6} - 2\log(c) - 2\gamma \log(c) + \log(c)^2] - \\ &- [-1 + 2\gamma + 2\log(c) - \gamma^2 - 2\gamma \log(c) - \log(c)^2] \\ &= \frac{\pi^2}{6} - 1 \ Q.E.D. \end{split}$$

MULTIVARIATE GOMPERTZ LOG-NORMAL DISTRIBUTION

Adham and Walker (2001) present the *p*-dimensional GOLN distribution for a random variable $T = (t_1, \dots, t_p)$ with parameters $A = (a_1, \dots, a_p)$ and $C = (c_1, \dots, c_p)$. This is an extension of one-dimensional representation of mixtures, based on $U = (u_1, \dots, u_p)$, a multivariate normal distribution. The construction of the multivariate GOLN is as follows:

$$f(T|U) = \prod_{j=1}^{p} f(t_j|u_j) = \prod_{j=1}^{p} a_j \exp(a_j t_j - u_j) \mathbf{I}[u_j > \log(\exp(a_j t_j) - 1)]$$

= $K \exp(A'T - \mathbf{1}'U) \mathbf{I}[B]$,

where

$$K = \prod_{j=1}^{p} a_j, \ \mathbf{1} = \{ x \in \mathbb{R}^p | x_j = 1 \},\$$

$$B = \{ u \in \mathbb{R}^p | u_j > \log(\exp(a_j t_j) - 1) \}, \text{ and }$$

$$U \sim MVN(M, \Sigma), \ M = (\mu_1, \cdots, \mu_p)', \ \Sigma = [\sigma_{ij}]_{p \times p}, \ \sigma_{ii} = var(u_i), \ \sigma_{ij} = cov(u_i, u_j).$$

Lemma We can write the *p*-dimensional GOLN distribution with parameters *A*, *M* and Σ , $a_i, \mu_i > 0, i = 1 \cdots, p$ of a random variable *T* as follows:

$$f(T) = \exp\left(\mathbf{1}'\log(A) + A'T - \mathbf{1}'M + \frac{1}{2}\mathbf{1}'\Sigma\mathbf{1} + \log\left(\Phi(B'')\right)\right) \quad \text{where}$$
$$B'' = \left\{u \in \mathbb{R}^p | u_j > \log(\exp\left(a_j t_j\right) - 1) - \mu_j + \sum_{k=1}^p \sigma_{jk}\right\},$$

 $\Phi(X)$ is the "cumulative probability function" of a p-variate normal distribution, $MVN(0,\Sigma)$, in the range $[X,\infty]$. As it is usual for scalar functions taking vector arguments, the $\log(X)$ operator is applied element by element on vector X.

Proof: The demonstration is similar to the one-dimensional case. We start from f(T) represented as a mixture and use the law of total probability

$$f(T) = \int_{\Omega} f(t|u) f(u) du = \int_{B} K \frac{\exp(A'T - \mathbf{1}'U)}{\sqrt{|2\pi\Sigma|}} \exp\left(-\frac{1}{2}(U - M)'\Sigma^{-1}(U - M)\right) dU.$$

Adding and subtracting 1'M to the integral's exponent and taking the change of variables V = U - M and dV = dU, we have

$$f(T) = \prod_{A} \exp\left(A'T - \mathbf{1}'M\right) \int_{B'} \frac{\exp\left(-\mathbf{1}'V - \frac{1}{2}V'\Sigma^{-1}V\right)}{\sqrt{|2\pi\Sigma|}} dV \quad \text{with}$$
$$B' = \left\{u \in \mathbb{R}^{p} | u > \log(\exp\left(a_{j}t_{j}\right) - 1) - \mu_{j}\right\}.$$

Using the change of variables $V = Y + \Lambda$, and remembering that matrix Σ^{-1} is symmetric, it is possible to rewrite the integral's exponent as

$$-\frac{1}{2}V'\Sigma^{-1}V = -\frac{1}{2}Y'\Sigma^{-1}Y - (\Sigma^{-1}\Lambda + \mathbf{1})'Y + (-\frac{1}{2}\Lambda - \mathbf{1})'\Lambda$$

Considering the last equality as a quadratic equation in *Y*, we can eliminate the linear term by taking $\Lambda = -\Sigma^2$ and get

$$-\frac{1}{2}V'\Sigma^{-1}V = -\frac{1}{2}Y'\Sigma^{-1}Y + \frac{1}{2}\mathbf{1}'\Sigma\mathbf{1} .$$

Using one more change of variables, $Y = V + \Sigma 1$ and dY = dV, we can re-write the integral as

$$f(T) = K \exp\left(A'T - \mathbf{1}'M + \frac{1}{2}\mathbf{1}'\Sigma\mathbf{1}\right) \int_{B''} \frac{\exp\left(-\frac{1}{2}Y'\Sigma^{-1}Y\right)}{\sqrt{|2\pi\Sigma|}} dY \quad \text{with}$$
$$B'' = \left\{ u \in \mathbb{R}^p | u_j > \log(\exp\left(a_jt_j\right) - 1) - \mu_j + \sum_{k=1}^p \sigma_{jk} \right\},$$

where the integrand is the centered multivariate Normal distribution, $N(0, \Sigma)$. Hence, we have

$$f(T) = K \exp\left(A'T - \mathbf{1}'M + \frac{1}{2}\mathbf{1}'\Sigma\mathbf{1}\right)\Phi(B'') \ .$$

Moving everything to the exponential, we finally obtain

$$f(T) = \exp\left(\mathbf{1}' \log(A) + A'T - \mathbf{1}'M + \frac{1}{2}\mathbf{1}'\Sigma\mathbf{1} + \log\left(\Phi(B'')\right)\right), \ Q.E.D.$$

FBST FOR GOLN COVARINCE STRUCTURES

The FBST and its significance measure, the *e*-value - ev(H), were specially designed to handle sharp or precise hypotheses. Further details, demonstration of theoretical properties, comparison with other statistical tests for sharp hypotheses, and an extensive list of references, see Borges and Stern (2007) and Pereira et al. (2008).

Likelihood and Posteriori distribution

The likelihood function of multivariate GOLN, with sample size *n* where the *i*-th observation is denoted $T^{(i)}$, is given by:

$$\begin{split} L(A,M,\Sigma|T) &= \prod_{i=1}^n \exp\left(\mathbf{1}'\log(A) + A'T^{(i)} - \mathbf{1}'M + \frac{1}{2}\mathbf{1}'\Sigma\mathbf{1} + \log(\Phi(B''^{(i)}))\right) \\ &= \exp\left(\sum_{i=1}^n \left(\mathbf{1}'\log(A) + A'T^{(i)} - \mathbf{1}'M + \frac{1}{2}\mathbf{1}'\Sigma\mathbf{1} + \log(\Phi(B''^{(i)}))\right)\right) \ . \end{split}$$

Assuming the following independent priors for the parameters,

$$\pi(a_j) \propto 1/a_j$$

$$\pi(C) \sim MVLN(0,\Omega) \quad \text{with}$$

$$\pi(\Sigma^{-1}) \sim Wishart(p,(pR)^{-1})$$

$$\Omega = \text{diag}(\tau_{jj}^2), \quad \tau_{jj}^2 = E = 100; \quad j = 1, \dots, p$$

$$R = \text{diag}(r_{jj}), \quad r_{jj} = \varepsilon = 0.1; \quad j = 1, \dots, p$$

and the previously established relationship on μ and c for the multivariate case,

,

$$M = 1 - \gamma - \log(C)$$
, $\gamma \approx 0.5572156$,

we can write the GOLN's model posterior as follows:

$$f(A, M, \Sigma | T) \propto \pi(A, M, \Sigma) l(A, M, \Sigma | T)$$

with

$$\pi(A, M, \Sigma) = \left(\prod_{j=1}^p \pi(a_j)\right) \pi(M) \pi(\Sigma^{-1}) .$$

Hence, the log-posterior is:

$$lp(A,M,\Sigma|t) = l\pi(A) + l\pi(M) + l\pi(\Sigma^{-1}) + lL,$$

with

$$\begin{split} l\pi(A) &= \ l\pi(A, |T) \ = \ -\sum_{j=1}^{p} \log(a_{j}) \ ; \\ l\pi(M) &= \ l\pi(C|\Omega, T) \ \propto \ -\frac{1}{2} \sum_{j=1}^{p} \left(\frac{\log(\mu_{j})^{2}}{E} + \log(\mu_{j}) \right) \ ; \\ l\pi(\Sigma^{-1}) &= \ l\pi(\Sigma^{-1}|T) \ \propto \ -\frac{1}{2} (\log(|\Sigma^{-1}|) + p \varepsilon tr(\Sigma^{-1})) \ ; \\ lL &= \ lL(A, M, \Sigma|T) \ = \\ &= \ n \left[\mathbf{1}' \left(\log(A) - M + \frac{1}{2} \Sigma \mathbf{1} \right) \right] + A' \left(\sum_{i=1}^{n} T^{(i)} \right) + \sum_{i=1}^{n} \log \left(\Phi(B''^{(i)}) \right) \ . \end{split}$$

Null Hypothesis

We will consider hypotheses on the structure of the covariance matrix Σ of GOLN models, using exactly the same notation defined in Lauretto et al. (2003). Hence, $\Sigma =$

 $\Sigma(\gamma) = \sum_{h=1}^{m} \gamma_h G^h$, m = (1/2)p(p+1) where the matrices G^h form a basis for the space of $p \times p$ symmetric matrices. Including the calibration or proportionality parameter δ into the parameter space, we have:

$$\begin{array}{lll} \Theta &=& \{\theta = [A', M', \gamma', \delta]' \in \mathbb{R}^{4+4+10+1}, \Sigma(\gamma) > 0\} ; \\ \Theta_0 &=& \{\theta \in \Theta | h(\theta) = 0\} . \end{array}$$

where $h(\theta)$ is a structural hypothesis with parameters γ and δ .

NUMERICAL OPTIMIZATION AND INTEGRATION

As in Lauretto et al. (2003), we adopt the following objective function to be maximized:

$$f(A, \mu, \Sigma|T) = lp - \rho p \operatorname{frob2}(\Sigma - S)$$
, where $\operatorname{frob2}(M) = \sum_{i=1}^{p} \sum_{j=1}^{p} (M_{ij})^2$

 ρ is a regularization factor that tends to zero as the optimization proceeds, and S is the empirical covariance, for details, see Lauretto et al. (2003).

The gradients of the objective function are:

$$\begin{split} \frac{\partial f(A,M,\Sigma|T)}{\partial a_{j}} &= \frac{n-1}{a_{j}} + \sum_{i=1}^{n} \left[t_{j}^{(i)} \right] + \sum_{i=1}^{n} \frac{-t_{j}^{(i)} \exp\left(a_{j}t_{j}^{(i)}\right)}{\exp\left(a_{j}t_{j}^{(i)}\right) - 1} \frac{\Phi_{j}(B'''^{(i)},B''_{j}^{(i)})}{\Phi(B''^{(i)})} ; \\ \frac{\partial f(A,M,\Sigma|T)}{\partial \mu_{j}} &= \left(-\frac{\log(\mu_{j})}{E\mu_{j}} \right) - (n+1) + \sum_{i=1}^{n} \frac{\Phi_{j}(B'''^{(i)},B''_{j}^{(i)})}{\Phi(B''^{(i)})} ; \\ \frac{\partial f(A,M,\Sigma|T)}{\partial \gamma_{j}} &= -\frac{1}{2} (tr(\Sigma^{-1}G^{j}) + p\varepsilon(2-\mathbf{1}'G^{j}\mathbf{1}) - n\gamma_{j}) + \\ &+ \sum_{i=1}^{n} \frac{\frac{\phi(B'')}{2} \left[T^{(i)'}\Sigma^{-1}G^{j}\Sigma^{-1}T^{(i)} - \frac{Ad_{j}(\Sigma)_{j}\mathbf{1}'G^{j}\mathbf{1}}{|\Sigma|} \right] \Phi_{j}(B'''^{(i)},B''^{(i)}_{j})}{\Phi(B''^{(i)}_{j})} ; \end{split}$$

where j = 1, ..., p, $B''' = \{v \in \mathbb{R}^{p-1} | v_k = B''_{k,k=1,...,p,k\neq j}\}$, $\phi(x)$ is the value of the density function of p-variate normal $MVN(0,\Sigma)$ in x, and $\Phi_j(\cdot, y)$ is the "cumulative probability function" of a p-variate normal distribution, $MVN(0,\Sigma)$, in the range $[X,\infty]$, setting $x_j = y$.

The initial parameter values for the optimization may be obtained by fitting a univariate Gompertz distribution for each random variable t_1, t_2, \ldots, t_p and by computing the sample covariance matrix. In this work, the numerical integration is performed by Metropolis-Hastings Markov Chain Monte Carlo, using a multivariate normal kernel as proposal distribution for parameters A, M and γ . The kernel covariance matrix is adjusted dynamically using the *MCMCpack* R package (Martin, 2011). All numerical routines were developed in R environment (R Development Core Team, 2011).

Procedures for the Cumulative Normal

Genz (1993) presents guidelines for the numerical implementations of the cumulative multivariate Normal distribution in a form that is amenable to ranges as used in this section, in particular for the implementation of Φ_j . Making the necessary adaptations for our specific needs, we can use the following algorithm to implement Φ_j .

Using previous notation and $l = {B''}_{i}^{(i)}$:

- 1. Input Σ , l, j, ε , α , N_{max} .
- 2. Swap j-th and last rows in Σ and l and j-th and last columns in Σ .
- 3. Compute lower triangular Cholesky factor C for Σ .
- 4. Initialize Intsum = 0, N = 0, Varsum = 0, $d_1 = \Phi(l_1/C_{1,1})$ and $f_1 = 1 d_1$
- 5. Repeat
 - (a) Generate uniform random $w_1, w_2, \ldots, w_{k-1} \in [0, 1]$
 - (b) For i = 2, 3, ..., p set $y_{i-1} = \Phi^{-1}(d_{i-1} + w_{i-1}(1 d_{i-1}))$, **IF** $i==p \ d_i = \phi((l_i - \sum_{k=1}^{i-1} C[i,k]y_k)/C[i,i])//C[i,i]) + 1$ **ELSE** $d_i = 1 - \Phi((l_i - \sum_{k=1}^{i-1} C[i,k]y_k)/C[i,i])/C[i,i]$ $f_i = (1 - d_i)f_{i-1}$.
 - (c) Set N = N + 1, $\delta = (f_k Intsum)/N$, $Intsum = Intsum + \delta$, $Varsum = (N - 2)Varsum/N + \delta^2$ and $Error = \alpha \sqrt{Varsum}$. **Until** $Error < \varepsilon$ or $N = N_{max}$.
- 6. **Output** F = Intsum, Error and N.

EXPERIMENTAL RESULTS

This section presents some numerical experiments motivated by the *Iris Flower Data Set*, of the species Iris Virginica available in Anderson (2003, pp.110,111). The dataset, gives four features measured from each sample, they are the length and the width of sepal and petal, in centimeters.

We considered two hypotheses in this case study:

• H1: The features are uncorrelated, that is, the Pearson's correlation coefficient between these variables, ρ , is zero. The null hypothesis $H1: \rho = 0$, against $\rho \neq 0$, corresponds to the structural hypothesis

$$h(\boldsymbol{ heta}) = [\gamma_5 \quad \gamma_6 \quad \gamma_7 \quad \gamma_8 \quad \gamma_9 \quad \gamma_{10}]' = 0$$
.

• H2: The features have the following covariance structure:

$$h(\boldsymbol{\theta}) = \begin{bmatrix} \delta^2 \gamma_1 - \gamma_3 & \delta^2 \gamma_2 - \gamma_4 & \delta^2 \gamma_5 - \gamma_6 \end{bmatrix}' = 0.$$

The estimated covariance matrix of the variables in the original data is

-	Sepal.Length	Sepal.Width	Petal.Length	[Petal.Width
Sepal.Length	0.40434286	0.09376327	0.30328980	0.04909388
Sepal.Width	0.09376327	0.10400408	0.07137959	0.04762857
Petal.Length	0.30328980	0.07137959	0.30458776	0.04882449
Petal.Width	0.04909388	0.04762857	0.04882449	0.07543265

The computed evidence value for the hypotheses H1 was 0 and for H2 was 0.96 on the original dataset. As expected, the results show a very strong evidence in favor of the hypothesis H2 and no evidence supporting the hypothesis H1.

Additionally, we performed a simulated experiment which consisted in drawing 100 samples with replacement from the original data, with the original sample size (n = 50). For each sample, we computed the evidences if favor of previous hypotheses. The goal was to estimate the empirical cumulative distributions for the evidences in favor of both hypotheses.

Figure 1 presents the numerical results. Each curve represents the cumulative distribution for the evidences in favor of H1 (dashed line) and H2 (dash-dotted line), respectively. Notice that most of the evidences for H1 and H2 are close to those obtained on the original data, which suggests that FBST is consistent even in the presence of a moderate sample size. Future works shall evaluate the evidence convergence for increasing sample sizes.

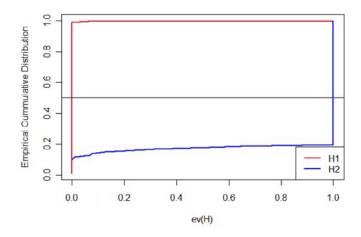


FIGURE 1. Empirical cumulative distributions for the evidence in favor of hypotheses H1 (dashed) and H2 (dash-dotted) computed from resamples of the original data

CONCLUSION

This paper presents several mathematical and computational details that are necessary to implement the Full Bayesian Significance Test for particular covariance structures in Gompertz type multivariate models. In studies already in progress, we hope to apply this framework for modeling medical and biological aging data. We are particularly interested in modeling the aging process acceleration of cancer cells by target specific chemotherapic drugs.

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