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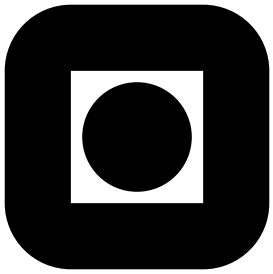

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Estimation methods for HIV dynamics models

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Abstract

We consider two statistical problems connected with the HIV dynamics: estimation of parameters characterizing the immune system of an individual patient and estimation of the distribution of the delay between initial infection of a cell and the release of new virions. Some estimators (for the second problem both parametric and nonparametric) are suggested and studied.

Keywords: HIV; AIDS; Dynamical systems with delay; Distribution of delay

1 Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus that infects and destroys a particular type of immune system cell, the CD4+ T Helper cell, and is the causative agent for Acquired Immune Deficiency Syndrome (AIDS). HIV and AIDS are among the world's most serious public health concerns. Despite of enormous exertions since the first identification of HIV-positive patients in 1981, there is no cure and the HIV/AIDS epidemic continues to grow.

Although HIV/AIDS is still incurable, an appropriate treatment can essentially slow down the progress of the disease. The optimal treatment of HIV infection is currently the subject of intense research activity. This requires deep understanding of interaction processes between the virus and the immune system of the patient. One of the useful tools here is mathematical modeling. There are several monographs and many articles concerning this topic, see for example Nowak and May (2000), Adams et al. (2005).

There are several directions in modeling of HIV dynamics, including modeling of interactions between the virus and the immune system of an infected patient or modeling of effects of drugs. An important stage of construction of the mathematical models is determination of parameters and other characteristics of the equations that describe the dynamical system under consideration. These quantities have to be estimated from the available observations. In this work, we develop methods of statistical estimation in two problems connected with the HIV dynamics. Estimation of parameters characterizing the immune system of an individual patient is considered in Section 2. The problem of estimation of the distribution of the delay between initial infection of a cell and the release of new virions is studied in Section 3.

Although we use two specific models, the methods of estimation, developed in the work, are quite general and can be easily adapted to other dynamical models in biology and medicine.

2 Estimation of parameters characterizing the immune system of an individual patient

Interaction between HIV and the immune system of an infected patient is a dynamical system of a "predator-prey" type which can be described by several nonlinear differential equations. There are a number of such models, some simpler, other more detailed, see Adams et al. (2005), Nowak and May (2000), Mittler et al. (1998), Vergu et al. (2005), Wodarz (2005). In this section we use the following model suggested by Wodarz (2005), which, on the one hand, is detailed enough to describe the process adequately in many situations and, on the other hand, is sufficiently simple to allow one to solve the problem of parameter estimation more or less accurately on the basis of data available up to the present. The model has form

$$\dot{x}(t) = \lambda - dx(t) - \beta x(t)v(t)$$

$$\dot{y}(t) = \beta x(t)v(t) - ay(t) - py(t)z(t)$$

$$\dot{v}(t) = ky(t) - uv(t) - qv(t)w(t)$$

$$\dot{w}(t) = gv(t)w(t) - hw(t)$$

$$\dot{z}(t) = cy(t)z(t) - bz(t)$$

where $x(t)$ and $y(t)$ are population sizes of target cells, non-infected and infected respectively, $v(t)$ is the number of free virus particles, $z(t)$ and $w(t)$ are cells of the immune system responsible for the elimination of infected target cells and free viruses, respectively.

The parameters of this system of equations are λ, d, β, a, p, k, u, q, g, h, c, b, with the following meaning. Target cells x are newly created at a rate λ, die at a rate dx and become infected by virus at a rate βxv. Infected cells die at a rate ay and are killed by the CTL response at a rate pyz. Free virus is produced by infected cells at a rate ky, decays at a rate uv, and is neutralized by antibodies at a rate qvw and decay at a rate hw. Immune cells responsible for the elimination of infected cells expand at a rate cyz and decay at a rate bz. Immune cells responsible for the elimination of virus particles expand at a rate gvw and decay at a rate hw.

Wodarz (2005) had shown that, under stability conditions, the system converges to an equilibrium.

Knowledge of the parameters is important both for prediction of the disease dynamics and for the choice of the optimal treatment. Estimation of parameters is usually based on observations which are made during a dynamical (non stationary) period namely either soon after infection, just after a treatment is started or just after a treatment interruption. Usually the Least Squares method is used for the estimation (see for example Adams et al., 2005) or Bayes estimators. Accuracy however is not sufficiently high because the number of parameters to be estimated (from 12 in the considered model up to 27 in Adams et al. (2005)) is comparable with the number of observations (about 50 during a dynamical interval) and errors of measurements are quite large.

But note that the parameters under consideration have different nature. The parameters λ, g and c are determined by the generation abilities of the immune system and therefore are completely individual for each patient. The parameters d, h and b are mainly determined by properties of the corresponding cell, and the parameters β, a, p, k, u, q characterize virus-cell interactions. These

parameters weakly depend on individual characteristics of the immune system and can be estimated from other patients. Therefore, in this work we consider only λ, g, c as unknown parameters. The other parameters (d, h, b, β, a, p, k, u, q) are considered as known constants. This essentially simplifies the estimation problem and makes it possible to obtain confidence bounds and test hypotheses.

Under the assumptions made above, we do not need to have observations from a dynamical interval; estimation is possible even only from measurements close to equilibrium. This is both a theoretical and a practical advantage, because, on the one hand, it allows one to obtain more accurate estimators and, on the other hand, interruptions of a treatment are not needed. Let x^*, y^*, v^*, w^*, z^* be equilibrium values of x, y, v, w, z respectively, i.e.

$$x^* = \lim_{t\to\infty} x(t),\ y^* = \lim_{t\to\infty} y(t),\ v^* = \lim_{t\to\infty} v(t),\ w^* = \lim_{t\to\infty} w(t),\ z^* = \lim_{t\to\infty} z(t).$$

Then

$$\lambda - dx^* - \beta x^* v^* = 0 \tag{1}$$

$$\beta x^* v^* - ay^* - py^* z^* = 0 \tag{2}$$

$$ky^* - uv^* - qv^* w^* = 0 \tag{3}$$

$$gv^* - h = 0 \tag{4}$$

$$cy^* - b = 0. \tag{5}$$

Suppose that there are n independent measurements $V_1, ..., V_n$ of the quantity v^* with the same distribution, with expectation equal to the equilibrium value and finite variance,

$$\mathrm{E}V_i = v^*, \quad \mathrm{Var}V_i = \sigma_v^2 < \infty.$$

Then, on the basis of equation (4), g is estimated by the estimator

$$\hat{g} = \frac{h}{\bar{V}},$$

where

$$\bar{V} = \frac{1}{n}\sum_{i=1}^{n} V_i.$$

Denote, as usual, convergence almost surely and in distribution by $\xrightarrow{a.s.}$ and $\xrightarrow{D}$, respectively. A normal distribution with expectation μ and variance σ^2 is denoted by $\mathcal{N}(\mu, \sigma^2)$.

Theorem 1. *As $n \to \infty$,*

(a) $\hat{g} \xrightarrow{a.s.} g$,

(b) $\sqrt{n}(\hat{g} - g) \xrightarrow{D} \mathcal{N}(0, \sigma_v^2 h^2/(v^*)^4)$.

If, in addition, the distribution of V_i belongs to an exponential family, and $\bar{V}$ is a natural sufficient statistic of this family, then $\hat{g}$ is the maximum likelihood estimator (MLE) of g.

Proof. Due to the Strong Law of Large Numbers, $\bar{V} \xrightarrow{a.s.} v^*$ as $n \to \infty$. But since $g = h/v^*$ (equation (4)), this immediately implies (a).

To prove (b), let us use the Delta Method (see for example Casella and Berger, 2002, p.243): if $T_1, T_2, ...$ is a sequence of random variables that satisfies

$$\sqrt{n}(T_n - \theta) \xrightarrow{D} \mathcal{N}(0, \sigma^2),$$

and $\psi(\cdot)$ is such a function that $\psi'(\theta)$ exists and is not 0, then

$$\sqrt{n}(\psi(T_n) - \psi(\theta)) \xrightarrow{D} \mathcal{N}(0, \sigma^2[\psi'(\theta)]^2).$$

Put

$$\psi(t) = \frac{h}{t}, \quad \theta = \frac{h}{g}, \quad T_n = \bar{V}.$$

Then

$$\psi'(\theta) = -\frac{g^2}{h},$$

and due to the Central Limit Theorem

$$\sqrt{n}\left(\bar{V} - \frac{h}{g}\right) \xrightarrow{D} \mathcal{N}(0, \sigma_v^2).$$

Thus

$$\sqrt{n}(\hat{g} - g) = \sqrt{n}\left(\frac{h}{\bar{V}} - \frac{h}{h/g}\right) \xrightarrow{D} \mathcal{N}(0, \sigma_v^2[\psi'(\theta)]^2) =$$
$$= \mathcal{N}(0, \sigma_v^2 g^4/h^2) = \mathcal{N}(0, \sigma_v^2 h^2/(v^*)^4).$$

To prove the last statement of the theorem, note that under conditions of the theorem, $\bar{V}$ is the maximum likelihood estimator of the expectation, i.e. of h/g. So, the statement follows from the invariance property of MLE.

Thus, if, in particular, errors in the measurement of v^* have a normal distribution then $\hat{g}$ is the MLE of g. Note, by the way, that $\hat{g}$ is always (without any assumptions about the distribution of V_i) the method of moments estimator of g.

Theoretically, the parameter c is estimated from equation (5) in the same way as the parameter g is estimated from equation (4). Practically, however, there is an essential difference. The quantity $v(t)$ is observable and therefore so is v^*. The quantities $x(t)$ and $y(t)$, and therefore x^* and y^*, are not observable. It is only possible to observe the total number of target cells, infected and non-infected, i.e. $x(t) + y(t)$ (and respectively $x^* + y^*$). The same difficulty is in estimation of λ. To overcome this difficulty we eliminate x^* and y^* from the equations containing the parameters c and λ. It follows from (2) and (3) that

$$x^* = (a + pz^*)\frac{y^*}{v^*} \tag{6}$$

and

$$y^* = \frac{u}{k}v^* + \frac{q}{k}v^*w^*. \tag{7}$$

Substitute y^* from (7) to (5). Then equation (5) becomes

$$c = \frac{bk}{uv^* + qv^*w^*}.$$

Substitute y^* from (7) to (6) and then replace x^* in (1) by the corresponding expression. Equation (1) becomes

$$\lambda = \frac{1}{\beta k}(au + aqw^* + puz^* + pqw^*z^*)(d - \beta v^*).$$

Suppose now that in addition to $V_1, \dots, V_n$ there are samples $W_1, \dots, W_n$ and $Z_1, \dots, Z_n$ which are independent measurements of w^* and z^*, identically distributed in each sample and such that

$$\mathrm{E}W_i = w^*, \quad \mathrm{E}Z_i = z^*, \quad i = 1, \dots, n.$$

We allow correlation between V_i, W_i and Z_i and define

$$\rho_{vw} = \mathrm{Cov}(V_i, W_i), \ \rho_{vz} = \mathrm{Cov}(V_i, Z_i), \ \rho_{wz} = \mathrm{Cov}(W_i, Z_i)$$

(if $i \neq j$ then in each pair (V_i, W_j), (V_i, Z_j), (W_i, Z_j), the random variables are supposed to be independent).

We estimate c and λ by the following plug-in estimators

$$\hat{c} = \frac{bk}{\bar{V}(u + q\bar{W})}$$

and

$$\hat{\lambda} = \frac{1}{\beta k}(au + aq\bar{W} + pu\bar{Z} + pq\bar{W}\bar{Z})(d - \beta\bar{V}),$$

where

$$\bar{W} = \frac{1}{n}\sum_{i=1}^{n} W_i, \quad \bar{Z} = \frac{1}{n}\sum_{i=1}^{n} Z_i.$$

Like the estimator $\hat{g}$, the estimators $\hat{c}$ and $\hat{\lambda}$ are consistent and asymptotically normal.

Theorem 2. *As $n \to \infty$,*

(a) $\hat{c} \xrightarrow{a.s.} c$,

(b) $\sqrt{n}(\hat{c} - c) \xrightarrow{D} \mathcal{N}(0, \tau_c^2)$, where

$$\tau_c^2 = \sigma_v^2 \left(\frac{bk}{(v^*)^2(u + qw^*)}\right)^2 + 2\rho_{vw}\frac{(bk)^2 q}{(v^*)^3(u + qw^*)^3} + \sigma_w^2 \left(\frac{bkq}{v^*(u + qw^*)^2}\right)^2$$

Proof. Part (a) follows from the Strong Law of Large Numbers. To prove (b) let us use the following form of the multivariate Delta Method (Casella and Berger, 2002, p. 245). Suppose that $\mathbf{T}_1, \dots, \mathbf{T}_n$ are independent and identically distributed m-dimensional random vectors, $\mathbf{T}_k = (T_{1k}, \dots, T_{mk})$, $k = 1, \dots, n$. Define

$$\bar{T}_i = \frac{1}{n}\sum_{k=1}^{n} T_{ik}, \ \mu_i = \mathrm{E}T_{ik}, \ i = 1, \dots, m;$$

$$\mu = (\mu_1, \dots, \mu_m), \quad \sigma_{ij} = \mathrm{Cov}(T_{ik}, T_{jk}).$$

Then for a given function ψ of m real variables with continuous first partial derivatives,

$$\sqrt{n}(\psi(\bar{T}_1, \dots, \bar{T}_m) - \psi(\mu_1, \dots, \mu_m)) \xrightarrow{D} \mathcal{N}(0, \tau^2)$$

where

$$\tau^2 = \sum_{i=1}^{m}\sum_{j=1}^{m} \sigma_{ij}\frac{\partial\psi(\mu)}{\partial\mu_i}\frac{\partial\psi(\mu)}{\partial\mu_j}.$$

Let us define, for $m = 2$,

$$\psi(v^*, w^*) = \frac{bk}{v^*(u + qw^*)}.$$

Then

$$\mu = (v^*, w^*),\ \sigma_{11} = \sigma_v^2,\ \sigma_{12} = \sigma_{21} = \rho_{vw},\ \sigma_{22} = \sigma_w^2$$

and therefore

$$\sqrt{n}(\hat{c} - c) = \sqrt{n}\left(\frac{bk}{\hat{V}(u + q\hat{W})} - \frac{bk}{v^*(u + qw^*)}\right) \xrightarrow{D} \mathcal{N}(0, \tau_c^2).$$

Theorem 3. *As $n \to \infty$,*

(a) $\hat{\lambda} \xrightarrow{a.s.} \lambda$,

(b) $\sqrt{n}(\hat{\lambda} - \lambda) \xrightarrow{D} \mathcal{N}(0, \tau_\lambda^2)$, where

$$\mu_1 = v^*,\ \mu_2 = w^*,\ \mu_3 = z^*,$$

$$\psi(v^*, w^*, z^*) = \frac{1}{\beta k}(au + aqw^* + puz^* + pqw^*z^*)(d - \beta v^*),$$

$$\sigma_{11} = \sigma_v^2,\ \sigma_{22} = \sigma_w^2,\ \sigma_{33} = \sigma_z^2,$$

$$\sigma_{12} = \sigma_{21} = \rho_{vw},\ \sigma_{13} = \sigma_{31} = \rho_{vz},\ \sigma_{23} = \sigma_{32} = \rho_{wz},$$

and

$$\tau_\lambda^2 = \sum_{i=1}^{3}\sum_{j=1}^{3} \sigma_{ij} \frac{\partial \psi(\mu)}{\partial \mu_i} \frac{\partial \psi(\mu)}{\partial \mu_j}.$$

Proof of the theorem is analogous to the proof of Theorem 2.

3 Estimation of the distribution of intracellular delay under HAART

In the previous section we considered a dynamical system describing the interaction between the immune system and the virus. Antiretroviral therapy and its influence on the system were not considered. In contrast, in the rest of the paper, we concentrate on treatment with a special drug, protease inhibitor, that causes newly produced virus particles to be non-infections. Under the simplifying assumption that $x(t) = x = \text{const}$, the following mathematical model is assumed to describe this dynamical system:

$$\dot{y}(t) = \xi x v_I(t) - \delta y(t) \tag{8}$$

$$\dot{v}_I(t) = (1 - \eta)\zeta y(t) - \alpha v_I(t) \tag{9}$$

$$\dot{v}_{NI}(t) = \eta\zeta y(t) - \alpha v_{NI}(t) \tag{10}$$

where ξ is the infection rate constant, ζ is the rate at which a productively infected cell releases new virions. Virus is classified as either infectious, $v_I(t)$, or as non-infectious, $v_{NI}(t)$, η is the drug efficacy (if $\eta = 1$, the drug is assumed to be absolutely effective so that all virions produced after drug takes effect, are noninfectious). Productively infected cells die at a rate per cell δ and plasma virions are

cleared at a rate α per virion. Perelson at al. (1996) used this model to analyze the response to a protease inhibitor.

In this model, however, it is not taken into account that there is some time between initial infection of the cell and the production of new virions — an intracellular delay. A more realistic model, in which the delay is taken into account and is supposed to be a random variable, was suggested by Mittler at al. (1998) and Nelson at al. (2002). In this model, equation (8) is replaced by the following integro-differential equation

$$\dot{y}(t) = \xi x \int_0^\infty v_I(t-s) f(s) ds - \delta y(t) \tag{11}$$

where $f(s)$ is the probability density function of the delay. This density has to be estimated from the data.

It was assumed in the aforementioned papers, that prior to treatment the system was at a steady-state, in which the values of free virus and infected cells did not change, and, in addition, the density of non-infectious virus was equal to zero. At time $t = 0^+$ the system was perturbed by the initiation of drug therapy and eventually converged to a new steady-state (see Mittler at al. (1998) and Nelson at al. (2002) for the details). Although the model under consideration is quite specific, the only essential requirement is the transition from one steady-state to another steady-state. In other respects the choice of the model is arbitrary, if it just can be described by a set of integro-differential equations with the integral part being a convolution, and this freedom of choice confers the possibility of application of the method to the wide range of dynamical models.

When the parameters ξ, x and δ are supposed to be known (for example, estimated), and functions $v_I(t)$ and $y(t)$ are observed, i.e. can also be considered as known, equation (11) can be considered as a special case of the convolution equation of the first kind

$$\int_0^\infty K(t-s) f(s) ds = u(t), \tag{12}$$

where $K(t)$ and $u(t)$ are known (more exactly are given at discrete points and with random errors) and $f(t)$ is the unknown function to be estimated.

First, note that in our case the functions $K(t)$ and $u(t)$ are, generally speaking (and usually), non-integrable. This is a problem, especially when a parametric approach is used. We overcome this problem as follows. $K(t) = K_0 = \text{const}$ for $t < 0$ (because of stationarity) and therefore, since $\int_0^\infty f(s) ds = 1$, $u(t) = K_0$ for $t < 0$. We replace equation (12) by the equivalent one

$$\int_0^\infty K_1(t-s) f(s) ds = u_1(t), \tag{13}$$

where $K_1(t) = K(t) - K_0$ and $u_1(t) = u(t) - K_0$. Now $K_1(t) = u_1(t) = 0$ for $t < 0$ but the functions $K_1(t)$ and $u_1(t)$ are still non-integrable (in general) because $\lim_{t\to\infty} K_1(t) \neq 0$. Therefore, rewrite (13) in the following equivalent form

$$\int_0^\infty K_2(t-s) f_2(s) ds = u_2(t), \tag{14}$$

where

$$K_2(t) = K_1(t)e^{-t}, \quad f_2(t) = f(t)e^{-t}, \quad u_2(t) = u_1(t)e^{-t}.$$

All the functions involved in (14) are integrable. Normalize them by putting

$$a = \int_0^\infty K_2(t)dt, \quad b = \int_0^\infty f_2(t)dt$$

and

$$K_3(t) = \frac{1}{a}K_2(t),\ f_3(t) = \frac{1}{b}f_2(t),\ u_3(t) = \frac{1}{ab}u_2(t).$$

Then an equivalent form of (14) is

$$\int_0^\infty K_3(t-s)f_3(s)ds = u_3(t). \tag{15}$$

Here $f_3(t)$ is a probability density function, $K_3(t)$ and $u_3(t)$ are integrable and both integrate to one, but they can take negative values. Since the initial equation (12) is equivalent to (15), and there is a one-to-one correspondence between the functions $K(t)$, $f(t)$, $u(t)$ and $K_3(t)$, $f_3(t)$, $u_3(t)$ (in particular, $f(t)$ is uniquely determined from $f_3(t)$), we will assume that the initial functions $K(t)$ and $u(t)$ are integrable and integrate to one.

3.1 Parametric estimation

In this subsection we assume that a functional form of $f(t)$ is known. For biological objects, a gamma distribution is often a good approximation for the delay distribution (that was discussed in MacDonald (1989)), so we assume that $f(t)$ has the form

$$f(t) = \frac{\beta^\alpha}{\Gamma(\alpha)}t^{\alpha-1}e^{-\beta t}, \quad t > 0; \quad \alpha > 0, \beta > 0,$$

where the parameters α and β are unknown and have to be estimated. Mittler et al. (1998) suggested to use the Least Squares method. This, however, leads to minimization (with respect to α and β) of the expression

$$S(\alpha,\beta) = \sum_{j=1}^{n}\left(\frac{\beta^\alpha}{\Gamma(\alpha)}\int_0^\infty K(t_j-s)s^{\alpha-1}e^{-\beta t}ds - u(t_j)\right)^2,$$

and therefore one needs to solve strongly nonlinear equations, very sensitive to measurement errors and to the replacement of the continuous model by the discrete one. Here we present a method which is simple and quite stable with respect to measurement errors.

The method is based on the following

Lemma. *Let $\varphi_1(x)$ and $\varphi_2(x)$ be two integrable functions such that*

$$\int_{-\infty}^\infty \varphi_1(x)dx = \int_{-\infty}^\infty \varphi_2(x)dx = 1,$$

and let $\varphi_3(x)$ be their convolution,

$$\varphi_3(x) = \int_{-\infty}^\infty \varphi_1(x-y)\varphi_2(y)dy.$$

Define

$$\mu_i = \int_{-\infty}^\infty x\varphi_i(x)dx, \quad i = 1,2,3;$$

$$\sigma_i^2 = \int_{-\infty}^{\infty} (x-\mu_i)^2 \varphi_i(x)dx, \quad i = 1,2,3.$$

Then

$$\mu_3 = \mu_1 + \mu_2, \tag{16}$$

and

$$\sigma_3^2 = \sigma_1^2 + \sigma_2^2. \tag{17}$$

Remark. If $\varphi_1(x)$ and $\varphi_2(x)$ are nonnegative, then (16) and (17) are very well known formulas for expectation and variance of the sum of independent random variables. Possibly (16) and (17) are known in the general case as well. However, since we cannot find a corresponding reference, we give a proof.

Proof. Prove (16). We have

$$\mu_3 = \int_{-\infty}^{\infty} x \left(\int_{-\infty}^{\infty} \varphi_1(x-y)\varphi_2(y)dy \right) dx = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} (x-y)\varphi_1(x-y)\varphi_2(y)dxdy +$$

$$+ \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} y\varphi_1(x-y)\varphi_2(y)dxdy = \int_{-\infty}^{\infty} \varphi_2(y) \left(\int_{-\infty}^{\infty} (x-y)\varphi_1(x-y)dx \right) dy +$$

$$+ \int_{-\infty}^{\infty} y\varphi_2(y) \left(\int_{-\infty}^{\infty} \varphi_1(x-y)dx \right) dy = \mu_1 \int_{-\infty}^{\infty} \varphi_2(y)dy + \int_{-\infty}^{\infty} y\varphi_2(y)dy = \mu_1 + \mu_2.$$

Now, taking into account (16), we obtain

$$\sigma_3^2 = \int_{-\infty}^{\infty} (x-\mu_3)^2 \left(\int_{-\infty}^{\infty} \varphi_1(x-y)\varphi_2(y)dy \right) dx =$$

$$= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} (x-y-\mu_1+y-\mu_2)^2 \varphi_1(x-y)\varphi_2(y)dxdy =$$

$$= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} (x-y-\mu_1)^2 \varphi_1(x-y)\varphi_2(y)dxdy +$$

$$+2\int_{-\infty}^{\infty}\int_{-\infty}^{\infty} (x-y-\mu_1)(y-\mu_2)\varphi_1(x-y)\varphi_2(y)dxdy +$$

$$+ \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} (y-\mu_2)^2 \varphi_1(x-y)\varphi_2(y)dxdy =$$

$$= \int_{-\infty}^{\infty} \varphi_2(y) \left(\int_{-\infty}^{\infty} (x-y-\mu_1)^2 \varphi_1(x-y)dx \right) dy +$$

$$+2\int_{-\infty}^{\infty} (y-\mu_2)\varphi_2(y) \left(\int_{-\infty}^{\infty} (x-y-\mu_1)\varphi_1(x-y)dx \right) dy +$$

$$+ \int_{-\infty}^{\infty} (y-\mu_2)^2 \varphi_2(y) \left(\int_{-\infty}^{\infty} \varphi_1(x-y)dx \right) dy =$$

$$= \sigma_1^2 \int_{-\infty}^{\infty} \varphi_2(y)dy + 0 + \int_{-\infty}^{\infty} (y-\mu_2)^2 \varphi_2(y)dy = \sigma_1^2 + \sigma_2^2.$$

Now we describe the suggested method of estimating the parameters α and β in the gamma model. Recall that, without loss of generality, we can assume that $K(t)$ and $u(t)$ are integrable and

both integrate to one. Let μ_f and σ_f^2 be the expectation and the variance of the probability density $f(t)$. Then $\alpha = \mu_f^2/\sigma_f^2$ and $\beta = \mu_f/\sigma_f^2$. Define

$$\mu_K = \int_0^\infty tK(t)dt, \quad \mu_u = \int_0^\infty tu(t)dt \tag{18}$$

and

$$\sigma_K^2 = \int_0^\infty (t-\mu_K)^2 K(t)dt, \quad \sigma_u^2 = \int_0^\infty (t-\mu_u)^2 u(t)dt. \tag{19}$$

Due to Lemma,

$$\mu_f = \mu_u - \mu_K, \quad \sigma_f^2 = \sigma_u^2 - \sigma_K^2$$

and hence

$$\alpha = \frac{(\mu_u - \mu_K)^2}{(\sigma_u^2 - \sigma_K^2)}, \quad \beta = \frac{\mu_u - \mu_K}{(\sigma_u^2 - \sigma_K^2)}. \tag{20}$$

Now we use the plug-in principle in the following form. Suppose that the points $t_1, \ldots, t_n$ form a uniform grid with step size h, and that this grid covers a region such that one may neglect the functions $K(t)$ and $u(t)$ outside this region. One can estimate the parameters μ_K, μ_u, σ_K^2 and σ_u^2 replacing integrals in (18) and (19) by the corresponding integral sums, i.e. as follows

$$\hat{\mu}_K = h\sum_{i=1}^n t_i K(t_i), \quad \hat{\mu}_u = h\sum_{i=1}^n t_i u(t_i)$$

and

$$\hat{\sigma}_K^2 = h\sum_{i=1}^n (t_i - \hat{\mu}_K)^2 K(t_i), \quad \hat{\sigma}_u^2 = h\sum_{i=1}^n (t_i - \hat{\mu}_u)^2 u(t_i).$$

Replacing the parameters of the functions $K(t)$ and $u(t)$ in (20) by the corresponding estimators, we obtain the following estimators of α and β:

$$\hat{\alpha} = \frac{(\hat{\mu}_u - \hat{\mu}_K)^2}{(\hat{\sigma}_u^2 - \hat{\sigma}_K^2)}, \quad \hat{\beta} = \frac{\hat{\mu}_u - \hat{\mu}_K}{(\hat{\sigma}_u^2 - \hat{\sigma}_K^2)}.$$

3.2 Nonparametric estimation

Gamma densities have quite a special form. They are all unimodal and skewed to the right. This can be in contradiction with the real behavior of an estimated density. Then it is reasonable to use a nonparametric approach, which in our case consists in numerical solution of equation (12), that is a convolution equation of the first kind. Nevertheless, parametric approximations can still be useful in this case. For example, the can be used for selection of the regularization parameter, which is the most difficult part of the solution. Ushakova (2008) suggested to use parametric estimation of the measurement error for selecting the regularization parameter. Here we consider an alternative method. The idea of the method consists in estimation of some functional of smoothness of the estimated density using a parametric approximation. The regularization parameter is chosen from the equality of this functional of the regularized solution and parametric approximation.

Let $\varphi(x)$ be a function of a real variable. One of several appropriate characteristics of the smoothness level is the total variation

$$V(\varphi) = \sup \sum_{i=1}^{n-1} |\varphi(x_i) - \varphi(x_{i+1})|$$

where the sup is taken over all natural n and all collections $-\infty < x_1 < \ldots < x_n < \infty$. If $f(x)$ is differentiable, then

$$V(\varphi) = \int_{-\infty}^{\infty} |\varphi'(x)| dx.$$

Slightly changing the right hand side of this equality, we obtain a functional having very similar properties, in particular characterizing the smoothness level, but which is more convenient analytically. Namely, define

$$W(\varphi) = \int_{-\infty}^{\infty} (\varphi'(x))^2 dx.$$

Denote the Fourier transforms of the functions $K(t)$, $z(t)$ and $u(t)$ by $\tilde{K}(\omega)$, $\tilde{z}(\omega)$ and $\tilde{u}(\omega)$ respectively. A regularized solution has the form (see for example Tikhonov and Arsenin, 1977)

$$f_\delta(t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \frac{\tilde{K}(-\omega)\tilde{u}(\omega)e^{-i\omega t}}{|\tilde{K}(\omega)|^2 + \delta M(\omega)} d\omega,$$

where $M(\omega)$ is an even nonnegative function such that $M(0) \geq 0$, $M(\omega) > 0$ for $\omega \neq 0$ and $M(\omega) \geq c > 0$ for large enough $|\omega|$, satisfying some regularity conditions (see Tikhonov and Arsenin (1977) for details), and $\delta > 0$ is the regularization parameter.

The regularization parameter δ is selected as follows. First, using the gamma approximation, estimate $f(t)$ parametrically. This can be done for example using the method described in the previous subsection. Let $\hat{\alpha}$ and $\hat{\beta}$ be the corresponding parameter estimates. Suppose that $\hat{\alpha} \geq 2$. Denote the parametric estimate of $f(t)$ by $\hat{f}(t)$, i.e.

$$\hat{f}(t) = \frac{\hat{\beta}^{\hat{\alpha}}}{\Gamma(\hat{\alpha})} t^{\hat{\alpha}-1} e^{-\hat{\beta}t}.$$

The parameter δ is selected from the condition

$$W(f_\delta) = W(\hat{f}).$$

After some algebra, we obtain

$$W(\hat{f}) = \frac{\Gamma(2\hat{\alpha}-3)\hat{\beta}^3(\hat{\alpha}-1)}{[\Gamma(\hat{\alpha})]^2 2^{2\hat{\alpha}-2}}.$$

Due to the Parseval identity,

$$W(f_\delta) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \frac{|\omega|^2 |\tilde{K}(\omega)|^2 |\tilde{u}(\omega)|^2}{(|\tilde{K}(\omega)|^2 + \delta M(\omega))^2} d\omega.$$

Thus δ is a solution of the equation

$$\frac{1}{2\pi} \int_{-\infty}^{\infty} \frac{|\omega|^2 |\tilde{K}(\omega)|^2 |\tilde{u}(\omega)|^2}{(|\tilde{K}(\omega)|^2 + \delta M(\omega))^2} d\omega = \frac{\Gamma(2\hat{\alpha}-3)\hat{\beta}^3(\hat{\alpha}-1)}{[\Gamma(\hat{\alpha})]^2 2^{2\hat{\alpha}-2}}.$$

It is easy to see that the left hand side of this equation is a monotone (decreasing) function of δ, having derivatives of any order. Therefore, numerical solution of this equation is a simple problem.

If $\hat{\alpha} < 2$, then $\int_0^\infty (\hat{f}'(t))^2 dt = \infty$, and this method cannot be directly used. In this case, it can be modified by replacing $\hat{\alpha}$ by 2.

3.3 Remarks

In this work, we studied estimation of the distribution of the intracellular delay in the situation of a treatment with a protease inhibitor, on the basis of model (9)–(11) or, more precisely, of equation (11). This kind of functions can, however, be estimated in other situations and on the basis of other models. For example, the delay can be taken into account in a model of the interaction between HIV and the immune system. Then the delay distribution will be involved in a model different from the one considered here, while the main equation will still be a convolution equation of the first kind. Therefore, despite the difference between models, the estimation procedure is similar to the one described above.

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