Turku PET Centre Modelling report TPCMOD0026 2003-10-30
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# Using GLLS to overcome bias problem

Generalized linear least squares (GLLS) is an unbiased algorithm for parameter estimation of nonuniformly sampled biomedical systems. The bias is removed iteratively from initial solution received with a linear minimisation algorithm. The method has been proposed by Feng et al. [Feng et al. 1996, 1998, 1999].

## GLLS

When using GLLS, we assume that a linear continuous dynamic system can be described with *n*th order differential equation of the form

$$y^{(n)}(t) + a_1 y^{(n-1)}(t) + \cdots + a_n y(t) = b_1 u^{(n-1)}(t) + \cdots + b_n u(t), \qquad (1)$$

where y(t) is system output and u(t) is system input and $a_1..a_n$ and $b_1..b_n$ are the model parameters. If all initial conditions are assumed to be zero, then the expression (1) can be integrated into form

$$y(t) = -a_1 \int_0^t y(t)dt - a_2 \int_0^t \int_0^l y(l)dt^2 - \cdots - a_n \int_0^t \int_0^t \cdots \int_0^t y(t)dt^n + b_1 \int_0^t u(t)dt + \cdots + b_n \int_0^t \int_0^t \cdots \int_0^t u(t)dt^n .$$

Model parameters are then solved with some linear least square method from equation

$$y = X\theta + \varepsilon,$$

where

$$X = \begin{bmatrix} \int_0^{t_1} y(t)dt & \cdots & \int_0^{t_1} \cdots \int_0^{t_1} y(t)dt^n & \int_0^{t_1} u(t)dt & \cdots & \int_0^{t_1} \cdots \int_0^{t_1} u(t)dt^n \\ \int_0^{t_2} y(t)dt & \cdots & \int_0^{t_2} \cdots \int_0^{t_2} y(t)dt^n & \int_0^{t_2} u(t)dt & \cdots & \int_0^{t_2} \cdots \int_0^{t_2} u(t)dt^n \\ \vdots & & \vdots & \vdots & & \vdots \\ \int_0^{t_m} y(t)dt & \cdots & \int_0^{t_m} \cdots \int_0^{t_m} y(t)dt^n & \int_0^{t_m} u(t)dt & \cdots & \int_0^{t_m} \cdots \int_0^{t_m} u(t)dt^n \end{bmatrix}$$

and $y = [y(t_1), y(t_2), \ldots, y(t_m)]^T$, where $y(t_1), \ldots, y(t_m)$ are measured activities at times $t_1,\ldots,t_m$. After attaining the initial solution the problem is altered and solved iteratively to whiten the noise. The coefficient matrix of the new problem $r = Z\theta$, is

$$Z = \begin{bmatrix} \sum_{i=1}^{n} \lambda_i^{n-1} y_i(t_1) & \cdots & \sum_{i=1}^{n} y_i(t_1) & \sum_{i=1}^{n} \lambda_i^{n-1} u_i(t_1) & \cdots & \sum_{i=1}^{n} u_i(t_1) \\ \sum_{i=1}^{n} \lambda_i^{n-1} y_i(t_2) & \cdots & \sum_{i=1}^{n} y_i(t_2) & \sum_{i=1}^{n} \lambda_i^{n-1} u_i(t_2) & \cdots & \sum_{i=1}^{n} u_i(t_2) \\ \vdots & & \vdots & \vdots & & \vdots \\ \sum_{i=1}^{n} \lambda_i^{n-1} y_i(t_m) & \cdots & \sum_{i=1}^{n} y_i(t_m) & \sum_{i=1}^{n} \lambda_i^{n-1} u_i(t_m) & \cdots & \sum_{i=1}^{n} u_i(t_m) \end{bmatrix},$$

where $\lambda_{1,\ldots,}\lambda_n$ are roots of polynomial $s^n + \hat{a}_1 s^{n-1} + \cdots + \hat{a}_n$ and $\hat{a}_1, \cdots, \hat{a}_n$ are the estimates of $a_1, \cdots, a_n$. Data vector is transformed into vector

$$r = \left[ y(t_1) - \sum_{j=1}^{n} \hat{a}_j \sum_{i=1}^{n} \lambda_i^{n-j} y_i(t_1),\ y(t_2) - \sum_{j=1}^{n} \hat{a}_j \sum_{i=1}^{n} \lambda_i^{n-j} y_i(t_2), \cdots, y(t_m) - \sum_{j=1}^{n} \hat{a}_j \sum_{i=1}^{n} \lambda_i^{n-j} y_i(t_m) \right].$$

Problem $r = Z\theta$ is solved iteratively until $s^n + \hat{a}_1 s^{n-1} + \cdots + \hat{a}_n \to s^n + a_1 s^{n-1} + \cdots + a_n$. Usually one or two iterations are enough to reach satisfactory results.

## Usage in Turku PET Centre

We were hoping to use this method for reference region input models, but it seems that these formulas were developed only for plasma input models since only these models satisfy equation (1). When a model is transformed to have reference region input formula

$$K_1 C_P(t) = R_1 \frac{dC_R(t)}{dt} + k_2 C_R(t)$$

is substituted in place of plasma input function. Here $C_P$ (=u(t)) denotes concentration in plasma and $C_R$ concentration in the reference region. Substitution leads to differential equation, where input and output curves have equal order of differentiation. Equation (1) does not support these kinds of models. Possibilities for making a more common version of GLLS will be explored.

## References


1. Feng et al.: *An unbiased Parametric Imaging Algorithm for nonuniformly Sampled Biomedical System Parameter Estimation*, IEEE Trans. on Med. Im. Vol 15, NO. 4, August 1996.
2. Feng et al.: *Generalized Linear Least Squares method for Fast Generation of Myocardial Blood Flow Parametric Images with N-13 Ammonia PET*, IEEE Trans. on Med. Im. Vol 17, NO. 2, April 1998.
3. Feng et al.: *GLLS for optimally sampled continuous dynamic system modelling: theory and algorithm*. Comp. Meth. and Prog. In Biomedicine 59, 31-34, 1999.