**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

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

where \( y(t) \) is system output and \( u(t) \) is system input and \( a_1, a_2, \ldots, a_n \) and \( b_1, b_2, \ldots, b_n \) are the model parameters. If all initial conditions are assumed to be zero, then the expression (1) can be integrated into form

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

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

\[
y = X\theta + \epsilon,
\]

where

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

and \( y = [y(t_1), y(t_2), \ldots, y(t_m)]' \), 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
\[
Z = \begin{bmatrix}
\sum_{i=1}^{n} \lambda_i^{-1} y_i(t_1) & \cdots & \sum_{i=1}^{n} \lambda_i^{-1} y_i(t_s) & \sum_{i=1}^{n} \lambda_i^{-1} u_i(t_1) & \cdots & \sum_{i=1}^{n} u_i(t_s) \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
\sum_{i=1}^{n} \lambda_i^{-1} y_i(t_n) & \cdots & \sum_{i=1}^{n} \lambda_i^{-1} y_i(t_n) & \sum_{i=1}^{n} \lambda_i^{-1} u_i(t_n) & \cdots & \sum_{i=1}^{n} u_i(t_n)
\end{bmatrix},
\]

where \( \lambda_1, \ldots, \lambda_n \) are roots of polynomial \( s^r + \hat{a}_r s^{r-1} + \cdots + \hat{a}_0 \) and \( \hat{a}_r, \ldots, \hat{a}_0 \) are the estimates of \( a_r, \ldots, a_0 \). Data vector is transformed into vector

\[
r = \begin{bmatrix}
y(t_1) - \hat{a}_r \sum_{i=1}^{n} \lambda_i^{-r} y_i(t_1),
\vdots
y(t_n) - \hat{a}_r \sum_{i=1}^{n} \lambda_i^{-r} y_i(t_n)
\end{bmatrix}.
\]

Problem \( r = Z \theta \) is solved iteratively until \( s^r + \hat{a}_r s^{r-1} + \cdots + \hat{a}_0 \to s^r + a_r s^{r-1} + \cdots + a_0 \). 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

\[
K_i C_i(t) = R_i \frac{dC_i(t)}{dt} + k_i C_i(t)
\]

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**