

GLOBAL SENSITIVITY AND IDENTIFIABILITY ANALYSIS APPLIED TO A MODEL PREDICTING BAROREFLEX REGULATION DURING HEAD-UP TILT

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ABSTRACT

Mathematical modeling has long been used for prediction of biological phenomena, but practical use of mechanistic models for data analysis is not as common. One of the major obstacles is the lack of practical methods for model based data analysis. This study presents methods for predicting global sensitivities of model outcomes to model parameters and shows how global sensitivities can be used for predicting sets of globally identifiable parameters. These methods will be applied to analyze dynamics in a model designed to predict baroreceptor regulation of heart rate during head-up tilt (HUT).

Keywords: Global sensitivity analysis; Global parameter identifiability; Baroreflex regulation of heart rate; Head-up tilt.

1. INTRODUCTION

The baroreflex control system, part of the autonomic control system, is responsible for the regulation of the blood pressure and thus for organ perfusion, which is especially important in the brain. Dysfunctional autonomic regulation is associated with postural hypotension and syncope, which has negative impact on quality of life. This problem is often observed (Brignole 2001), yet few methods are available for analysis of clinical data routinely recorded in the laboratory.

The baroreceptor reflex system consists of a number of elements: Stretch sensitive baroreceptors in the wall of the carotid sinus stimulate firing of afferent nerves, which are integrated primarily in the nucleus of the solitary tract. At this location several stimuli are integrated causing modulation of parasympathetic and sympathetic outflow, which in turn determines release of neurotransmitters enabling modulation of heart rate. Several models have investigated this process (Ottesen and Olufsen 2011), though few have been successfully used for analysis of clinical data.

This paper discusses a model adapted from previous studies that predicts the heart rate, global sensitivity analysis and parameter identification. Global

sensitivities will be calculated as the average of the local sensitivities over the entire parameter space. The latter will be computed using a quasi-random Monte Carlo method based on Sobol's algorithm (Joe and Kuo 2003). Sensitive parameters will be further analyzed to predict a set of parameters that are globally identifiable. The latter requires prediction of correlations among model parameters. Two methods will be used for this part: analysis of pairwise correlations (Olufsen and Ottesen 2012) and a method that combines a principal component analysis (PCA) with analysis of orthogonality (Li, Henson and Kurtz 2004).

Sensitivity and identifiability techniques developed here will be applied to analyze measured blood pressure from a healthy young adult undergoing a head-up tilt table test.

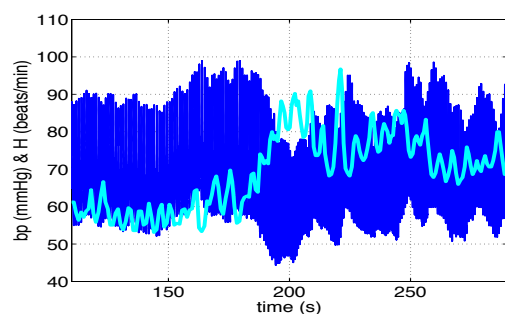


Figure 1: Blood pressure (bp) [mmHg] and heart rate (H) [beats/min] recorded during HUT. The displayed data are from a young healthy adult.

2. MATHEMATICAL MODEL

The mathematical model developed in this study incorporates the parts of the baroreflex feedback system that modulates heart rate. The model (shown in Figure 2) is an extension of previous a previous model (Olufsen, Tran, et al. 2006).

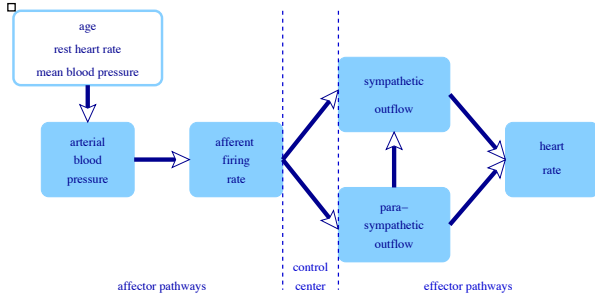


Figure 2: A schematic view of the model components included to predict baroreflex regulation of heart rate during HUT.

In summary, the model uses blood pressure data along with information about the subjects' age, gender, resting heart rate, and mean blood pressure as inputs to predict heart rate.

First, the firing rate (n) of the baroreceptors n is predicted by

$$(1) \quad \frac{dn}{dt} = k_i \frac{dp}{dt} \frac{n(M-n)}{(M/2)^2} - \frac{n-N}{\tau_i}, \quad n = \sum n_i,$$

where n_i is the firing rate of the baroreceptor of type i , M is the maximum firing rate and N is the threshold firing rate, dp/dt is the rate of change of blood pressure, k_i is a constant determining how sensitive the receptor is to changes in blood pressure, and τ_i is a time constant that determines the rate at which the firing rate decays to the threshold value.

Parasympathetic and sympathetic outflows are predicted as

$$(2) \quad T_p = \frac{n}{M}, \quad T_s = \frac{1-T_{p,d}}{1+\beta T_p},$$

where β is a constant controlling the relationship between the parasympathetic T_p and the sympathetic T_s outflow. $T_{p,d}$ is the delayed parasympathetic outflow given by

$$(3) \quad T_{p,d} = c \int_{-\infty}^t (t-s)^D e^{-\alpha(t-s)/t_d} T_p(s) ds,$$

where D and α , an integer and a real number, determines the shape of weight function for the signal, t_d is the time for the largest effect, and c is a normalization constant determined from D and t_d . This formulation is different than what is found in the literature. It has the advantage of easier numerical implementation and reflecting a distributed delay, which by the authors is believed to be more physiologically correct than a discrete delay.

The concentration of the neurotransmitters acetylcholine C_a and noradrenaline C_n are predicted from

$$(4) \quad \frac{dC_a}{dt} = \frac{T_p - C_a}{\tau_a}, \quad \frac{dC_n}{dt} = \frac{T_s - C_n}{\tau_n},$$

where τ_a and τ_n are time constants. Finally, the build up of electrical potential (ϕ) in the pacemaker cells of the heart is determined by

$$(5) \quad \frac{d\phi}{dt} = H_0 (1 - M_a C_a + M_n C_n),$$

where H_0 denotes the default depolarization rate when no neurotransmitters impact the system, and M_a , M_n denote the sensitivity to the neurotransmitters. From this expression the heart rate can be calculated, assuming that each heartbeat corresponds to an increase in the potential build up by 1.

3. SENSITIVITY ANALYSIS

Classically, sensitivities can be calculated as

$$(6) \quad S(t; \theta) = \frac{\partial y(t; \theta)}{\partial \theta},$$

where y denotes the model output (heart rate) and θ the model parameters. For linear (in the parameters) models, sensitivities can be predicted analytically, but for nonlinear models this relation is typically predicted by linearizing around current values of the parameters. For a model that depends nonlinearly on the parameters the sensitivities will change depending on the parameter values. This can produce challenges since the sensitivities are important both for determining which parameters are identifiable and for estimating parameter values that allows accurate prediction of the data. One way to get more precise information about the sensitivity is via prediction of global sensitivities, which estimate how the model output vary as an average over the parameter space. A possible approach for predicting global sensitivities is via Sobol's global sensitivity indices, which builds on an analysis of variances (ANOVA) (Kiparissides, et al. 2009). Predicting global sensitivities is computational intensive, due to the large number of evaluations of the model output. Oftentimes computational efficiency is of high importance. One method to improve efficiency is to use derivative based global sensitivity measures (DGSM), which are computed by integrating sensitivities over the parameter space (Kiparissides, et al. 2009).

Calculation of DGSM requires computation of local sensitivities, which in this study are predicted from the model and parameter Jacobians. The latter are calculated using finite differences. Both the ODEs representing the model and the local sensitivities are computed numerically using Sundials ODE suite (Serban and Hindmash 2005). Within this software, the numerical integration over the parameter space is carried out using a quasi-random Monte Carlo method. Parameter sets are generated using Sobol's algorithm, and the global sensitivities are computed as the average of the local sensitivities.

More specifically, the local sensitivities are calculated by solving the system of ODE

$$(7) \quad \begin{aligned} \frac{dS}{dt} &= J_y S(t, \theta) + J_\theta, \\ S(t, \theta) &= \frac{dy}{d\theta}(t, \theta), \quad J_y = \frac{df}{dy}, \quad J_\theta = \frac{df}{d\theta}, \end{aligned}$$

where $y(t, \theta)$ is the model output of the system with state variables $x(t, \theta)$ described by

$$(8) \quad \begin{aligned} \frac{dx}{dt} &= f(t, x; \theta), \quad x(0; \theta) = x_0, \\ y(t, \theta) &= g(t, x(t); \theta). \end{aligned}$$

In (7-8) J_y denotes the Jacobian and J_θ the parameter Jacobian. If the model consists of k output variables, m parameters that are evaluated at n time steps the local sensitivity matrix can be written as

$$(9) \quad S = \frac{dy}{d\theta} = \begin{bmatrix} \partial y_1 / \partial \theta_1(t_1) & \cdots & \partial y_1 / \partial \theta_m(t_1) \\ \vdots & \vdots & \vdots \\ \partial y_1 / \partial \theta_1(t_n) & \cdots & \partial y_1 / \partial \theta_m(t_n) \\ \vdots & \vdots & \vdots \\ \partial y_k / \partial \theta_1(t_1) & \cdots & \partial y_k / \partial \theta_m(t_1) \\ \vdots & \vdots & \vdots \\ \partial y_k / \partial \theta_1(t_n) & \cdots & \partial y_k / \partial \theta_m(t_n) \end{bmatrix}.$$

Sometimes it might be relevant to calculate relative sensitivities defined by

$$(10) \quad \tilde{S}_{i,j}(t_k) = \frac{\partial y_i}{\partial \theta_j}(t_k) \frac{\theta_j}{y_i(t_k)}.$$

Once, local sensitivities (relative or nonrelative) are computed, the global sensitivities can be found by integration over the parameter space. This is done using Sobol-sequences for sampling parameter sets within the parameter space. For each parameter set local sensitivities are computed. Global sensitivities are then found as an average of the sensitivity matrix calculated at N different points in parameter space, i.e.

$$(11) \quad S_{global}(t_k) = \frac{1}{N} \sum_{i=1}^N S_i(t_k).$$

4. IDENTIFIABILITY AND SUBSET SELECTION

Only sensitive parameters can be identified, but in addition to being sensitive parameters may be correlated (Ipsen, Kelley and Pope 2011). Parameters that are correlated cannot be estimated reliably. However, it may not be trivial to identify parameter correlations globally. In this study, we denote the process of identifying parameters that can be estimated given a model output and corresponding data for subset selection. Parameters not in a subset (i.e., those that are insensitive or correlated) will be kept constant at their *a priori* values,

while the uncorrelated sensitive parameters will be estimated as discussed in section 5.

This study adapts two previously developed methods for prediction of global sets of uncorrelated parameters: the structured correlation method (Olufsen and Ottesen 2012) and the orthogonal sensitivities method (Yao, et al. 2003, Li, Henson and Kurtz 2004). Both are originally developed for local analysis, but will be modified to work with global sensitivities. The structured correlation matrix method is based on finding pairwise correlations of the model Hessian, while the orthogonal method is based on analysis of parameters sensitivities predicted using PCA. With this method, parameters are ranked according to sensitivity from the highest to the lowest. Parameters are added to the subset one-by-one ensuring that the subset remains orthogonal using a process is similar to Gram-Schmidt orthogonalization. Subsets obtained with these methods will be compared and an “optimal” subset will be selected.

4.1. Structured correlation matrix method (SCMM)

The structured correlation matrix method (SCMM) is based on a principle of excluding correlated parameters from the set of parameters until no correlations remain. To evaluate the correlations the *correlation matrix*

$$(12) \quad c_{i,j} = \frac{C_{i,j}}{\sqrt{C_{i,i} C_{j,j}}}$$

is considered (Ottesen and Olufsen 2011). Here $c_{i,j}$ describes the degree of correlation between parameter i and j , with numeric value between 0 and 1. C is the correlation matrix, the inverse of the model Hessian, $C = \mathcal{H}^{-1}$, which is given by $\mathcal{H} = \sigma^{-2} S^T S$. The inversion of the model Hessian requires that S be non-singular. In this study the limiting value γ between correlation and no correlation for c is chosen to be $\gamma = 0.9$. When a correlated pair is found the least sensitive parameter is excluded from the subset, judged by the two-norm of the sensitivity,

$$(13) \quad \bar{S}_j = \sqrt{\sum_{i=0}^n [S_j(t_i)]^2}.$$

Using these measures the procedure can be described:

1. Calculate the correlation matrix c .
2. Find the parameter pair (i,j) with the highest correlation.
3. If $c_{i,j} \geq \gamma$ lock the parameter with the smallest two-norm \bar{S} . If $c_{i,j} < \gamma$ terminate the algorithm.
4. Repeat from 1.

4.2. Orthogonal sensitivities method (OSM)

In contrast to SCMM this method is based on the principle of building a subset by adding one parameter at the time. Initially the parameters are ranked by their *importance index*, which for parameter j is given by

$$(14) \quad E_j = \frac{\sum_{i=1}^m |\lambda_i Q_{i,j}|}{\sum_{i=1}^m |\lambda_i|},$$

where m is the number of parameters, and λ_i is the i th eigenvalue and $Q_{i,j}$ the j th eigenvector of the matrix

$$(15) \quad X = \tilde{S}^T \tilde{S}$$

with s denoting the relative sensitivities defined in (10). If n parameters have been selected for the subset θ_s , the *identifiability index* of parameter j is given by $I_j = E_j d_j$, where d_j is the *orthogonality index*. Denoting the column of \tilde{S} corresponding to the l th selected parameter \tilde{s}_{k_l} and assuming that \tilde{s}_{k_l} are linearly independent any vector in the n -dimensional vector field can be represented by

$$(16) \quad \tilde{s} = \sum_{l=1}^n a_{k_l} \tilde{s}_{k_l},$$

where a_k are constants. Consider another parameter h with relative sensitivity \tilde{s}_j , which has not been included in the subset, the objective is to find vector \tilde{s} closest to \tilde{s}_j by determining the coefficients a_{k_l} that solves

$$(17) \quad \min_{a_{k_l}} \frac{1}{2} (\tilde{s}_j - \tilde{s})^T (\tilde{s}_j - \tilde{s}).$$

This is equivalent to solving the linear system

$$(18) \quad \begin{bmatrix} \tilde{s}_{k_1}^T \tilde{s}_{k_1} & \cdots & \tilde{s}_{k_n}^T \tilde{s}_{k_1} \\ \vdots & \ddots & \vdots \\ \tilde{s}_{k_n}^T \tilde{s}_{k_n} & \cdots & \tilde{s}_{k_n}^T \tilde{s}_{k_n} \end{bmatrix} a = \begin{bmatrix} \tilde{s}_j^T \tilde{s}_{k_1} \\ \vdots \\ \tilde{s}_j^T \tilde{s}_{k_n} \end{bmatrix}.$$

Since the \tilde{s}_k are chosen to be linearly independent, the covariance matrix for the selected parameters is invertible and there is a solution for a . Knowing the vector \tilde{s} closest to \tilde{s}_j the orthogonality index is calculated as sine of the angle between them

$$(19) \quad d_j = \sin \left[\arccos \left(\frac{\tilde{s}_j^T \tilde{s}}{\|\tilde{s}_j\| \|\tilde{s}\|} \right) \right].$$

The procedure for ordering the parameters can then be described as follows.

1. Calculate the Importance index. Selected the parameter with the highest value for the subset.
2. Calculate the orthogonality index for the remaining parameters compared to the current subset.
3. Use the orthogonality index d_j with the importance index E_j to calculate the identifiability index I_j .
4. Add the parameter with the highest identifiability index to the subset. Repeat from step 2.

5. RESULTS

The results presented in this section are based on blood pressure data obtained from a Head-Up Tilt experiment.

5.1. Global sensitivities

The calculation of the global sensitivity estimate is based on Sobol's algorithm for integration using 5000 points in the parameter space and the intervals for the parameters given in Table 1. 5000 points was used as a preliminary investigation showed that including more points did not change the results.

The two-norm of the global sensitivity for each parameter is used to rank the parameters from most to least sensitive. This is illustrated in Figure 3.

Parameter	Min. value	Max. value
H_0	0.3	2.0
M_s	1.25	5.0
M_p	0.07	0.28
τ_{ach}	0.1	1.0
τ_{nor}	0.1	1.0
β	3.0	12
κ_1	3	30
κ_2	3	30
κ_3	3	30
τ_1	0.25	1.0
τ_2	2.5	10
τ_3	250	1000
t_d	3.0	12
$T_{par,0}$	0.3	1.0
a	1.5	1.5

Table 1: Intervals defining the parameter space. Intervals are based on the parameter values found by (Olufsen, Tran, et al. 2006).

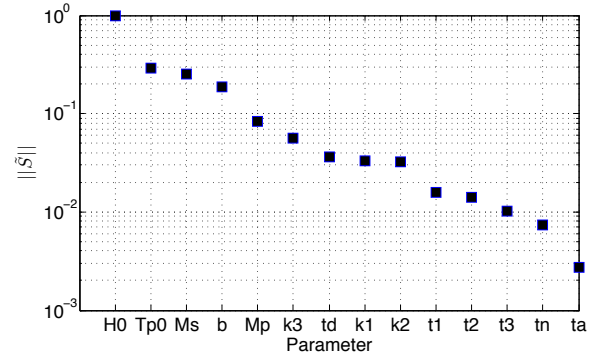


Figure 3: Parameters sorted by two-norm of the global sensitivity. Values have been scaled by the maximum value.

5.2. Subset selection

SCMM and OSM have been used to perform the subset selection. For both methods the global relative sensitivities were used. Furthermore, both analyses were performed without the possibility of including τ_3 in the subset. This parameter reflects a very long timescale in the model on the order of 500 seconds. Hence it is unlikely that this parameter can be determined from data ranging over approximately 700 seconds.

Using SCMM introduced above and a limit for correlations of 0.9 the resulting subset is

$$(20) \quad \theta = \{H_0, \kappa_1, \tau_1, \tau_2, t_d, T_{p0}\}.$$

It is worth noting that this is just one subset one can obtain using structured correlation matrix method. Other variations of the algorithm will lock several parameters at each iteration, lock the most sensitive one, or use another threshold for deciding if a pair of parameters are correlated or not.

Using OSM the parameters have been ranked as shown in Table 2. Setting the limit value of the identifiability index at 0.005 the resulting subset is

$$(21) \quad \theta = \{H_0, M_s, M_p, \kappa_2, \kappa_3, t_d, T_{p0}\}.$$

Iteration	Parameter	E_j	d_j	I_j
0	H_0	—	—	0.910
1	T_{par0}	0.259	0.354	0.092
2	M_s	0.229	0.165	0.038
3	κ_2	0.020	0.672	0.013
4	κ_3	0.040	0.151	0.006
5	t_d	0.007	0.767	0.005
6	M_p	0.075	0.061	0.005
7	κ_1	0.025	0.181	0.004
8	β	0.170	0.020	0.003
9	τ_1	0.012	0.287	0.003
10	τ_3	0.008	0.154	0.001
11	τ_2	0.002	0.231	0.000
12	τ_{nor}	0.000	0.325	0.000
13	τ_{ach}	0.000	0.290	0.000

Table 2: Parameters ordered by the identifiability index of the orthogonal sensitivities method.

It is interesting to see that the two subsets are quite different. Most notably SCMM omits the parameters M_p and M_s , which one would expect to be very important as they appear directly in the differential equation describing the potential, build up (5). Investigating the SCMM correlations in the subset produced by OSM reveals an expected correlation between the parameters H_0 and M_p .

SCMM also finds that the parameters κ_1 and κ_2 are correlated, so the fact that one of these appear in each subset is reasonable. Finally SCMM finds that κ_3 is correlated to T_{p0} , while OSM finds that these are distinguishable. It is possible to obtain different subsets within each method, but these subsets appear to be very different. This difference probably arises due to the fact that one method investigates the sensitivity of the solution to the parameter values (OSM), while the other method utilizes the inverse, the sensitivity of the parameter value to the change in model output.

While the differences are interesting it is also worth noting the parameters shared by the two subsets, H_0 , t_d and T_{p0} . H_0 is a direct scaling of the potential buildup in the model, t_d is the delay associated with the sympathetic nervous system and T_{p0} is the threshold value for the firing rate of the baroreceptors. It seems

very reasonable that both methods should find these parameters to be important and identifiable.

CONCLUSION

Global sensitivities have been calculated using Sobol's algorithm for quasi-random number generation and subset selection performed using two different methods, the structured correlation matrix method (SCMM) and the orthogonal sensitivities method (OSM).

While the two methods for subset selection produced different subsets the parameters shared by both subsets appear to be very important for the model output and thus clearly identifiable.

Future work in this area will include testing the different parameter subsets through optimization against simulated data as well as real data.

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