Linear Modelling of Cerebral Autoregulation System Using Genetic Algorithms

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Abstract. Cerebral autoregulation (CA) represents the brain's capacity to maintain the cerebral blood flow constant, independent of the activities realized by an individual. There are pathologies like Alzheimer, vascular dementia, ischemic stroke, subarachnoid haemorrhage and severe brain injury, where a degradation of CA can be found. Despite limited understanding of its physiological basis, assessment of CA is relevant for diagnosis, monitoring and treating some of these pathologies. CA modelling is done by using mean arterial blood pressure (MABP) as input and cerebral blood flow velocity (CBFV) as output; the standard model used is transfer function analysis, although CA has been modelled with support vector machines (SVM) and other methods. In this work a resistive-capacitive model (R-C) is presented where parameters can be estimated from MABP and CBFV signals through Genetic Algorithms (GA), comparing its discrimination capacity against SVM models. Signals from 16 healthy subjects were used with 5 min of spontaneous variations (SV) and 5 min breathing oxygen with 5% of CO_2 (hypercapnia). Results show that both models can capture CA and the degradation induced by hypercapnia. Using the autoregulation index (ARI), the R-C model discriminates with a ROC area of 0.89 against 0.72 from SVM, thus representing a promising alternative to assess CA.

Keywords: Cerebral autoregulation · Genetic algorithms · R-C model

1 Introduction

Human brain is sensitive to changes in its blood supply, where low cerebral blood flow (CBF ischemia) could lead to loss of consciousness or even death after few minutes. On the other hand excessive CBF could generate damage on the vessels and cerebral tissue through intracranial hypertension or even hemorrhage. The mechanism that controls the level of blood flow in the brain (associated to the energy consumption) independently of changes in MABP is known as cerebral autoregulation (CA). In patients with Alzheimer, vascular dementia, ischemic brain stroke, and severe head injury, a degradation of CA has been reported, but detailed modelling of this system remains

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challenging. In the 80s, the appearance of transcranial Doppler [1] opened up the possibility of CA assessment through maneuvers to induce changes in MABP of the subject to get an autoregulatory response [2–5]. These maneuvers are not always applicable therefore models that can captures CA at rest, based on spontaneous variations (SV), for example using transfer function analysis (TFA) have been widely used [3, 6, 7] other non-linear models such as neural networks, Wiener-Laguerre and SVM [3, 8, 9] had allowed improvements in performance and the comprehension of this phenomenon during SV. CA is often evaluated through the response of a theoretical inverse step of MABP, measuring the recovering of CBFV levels by using an autoregulation index ARI [10]. The lack of more physiological information related to the understanding of CA, and the high complexity of black box models such as SVM, makes it attractive to present a new model that parameterizes resistive and capacitive components (R-C), which could provide greater understanding of the underlying physiology, by using genetic algorithms (GA). To evaluate CA, the subject breathes oxygen with 5% of CO_2 which produces CA degradation by the effect of CO_2 over the vessels [2, 11]. Considering data of healthy subjects that inhaled CO_2, two hypotheses arise: first, a GA allows learning human cerebral autoregulation pattern by using a resistive-capacitive model. Second, GA applied over a resistive-capacitive model can discriminate between a normal and degraded status of cerebral autoregulation, with a ROC area greater than the one from a linear SVM.

2 Methods

2.1 CA Modelling by Using SVM

CA modelling through black box approach is implemented by using SVM under the concept of "support vector regression" in which is done an estimation of CBFV $\widehat{v}(t)$ values, based on MABP $p(t)$ using a finite impulse response (FIR) structure:

$$\widehat{v}(t) = f(p(t), \ldots, p(t - n_p)) \tag{1}$$

CBFV estimation $\widehat{v}(t)$ is given by a static SVM with n_p inputs, corresponding to the delays number of the model. Each segments signal (SV and under CO_2) is normalized and divided in two, one part for training and the other for validation (balanced cross validation). Trainings are done for each subject with hyper parameter's configurations for SVR, with its proper validation. For hyper parameter's configurations C, ν and n_p a grid search is realized and using a Linear Kernel, same behaviour as TFA [6] to compare under similar conditions. Estimated $\widehat{v}(t)$ and measured $v(t)$ are compared through correlation coefficient and Mean Squared Error (MSE) per each training. Finally models are selected through normalized inverse MABP step response criteria where the model selected is the one with higher correlation coefficient in prediction that satisfies the physiological response of CA as shown in Fig. 1.

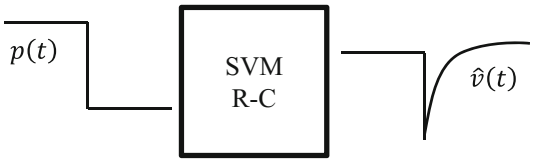

Fig. 1. Theoretical response from trained SVM/R-C models to an inverse MABP step.

Responses $\hat{v}(t)$ per each subject from models are evaluated by using an autoregulatory index ARI [10], with values from 0 (absence of autoregulation) to 9 (best autoregulation).

2.2 Proposed Model Resistive-Capacitive R-C

The standard for cerebral autoregulation modelling is based on TFA [6, 12], which behaves as high pass filter over signals, obtaining parameters such as gain, coherence and phase. Knowing this, the use of a resistive-capacitive circuit is proposed, implementing a second-order high pass filter. MABP represents the voltage input $p(t)$ and CBF corresponds to the input current $v(t)$ to C_1 capacitor as shown in Fig. 2.

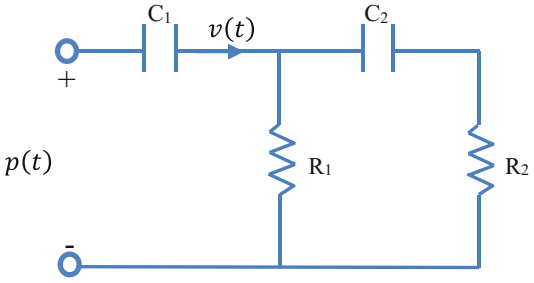

Fig. 2. Proposed model for cerebral autoregulation with resistive-capacitive components.

In this hydraulic-electric analogy, to convert CBF into velocity (CBFV), a standard diameter of 3 mm for middle cerebral artery is considered. The resistive components of the model are measured in mmHg s/ml (cerebrovascular resistance) and capacitive components in ml/mmHg (possibly compliance of the vessels). The combination of the four component's values is presented as an optimization problem, where the MSE is minimized in a frequency band from 0–0.2 Hz (where CA phenomenon is present) [12], comparing CBF estimated and measured. This is a linear model, therefore the complete signal is used for simulations (SV or CO_2), without normalizing them to estimate CBFV. Literature shows ranges of values for resistive and capacitive components for normal subjects [13], but for CA degradations using CO_2 are unknown. Numerical approaches require initial conditions near the optimum to converge and avoid local minimums, therefore the use of Genetic Algorithms is proposed (GA) since they have been used in electrical circuit design [14–16], as well as hydraulic design

problems [17], similar to the R-C model proposed. Using this heuristic, a grid is implemented to establish different ranges for the initial conditions per each component of the model, where each element of the initial population of the GA is a tuple composed of random values (within feasible physiological ranges) following a uniform distribution for R_1, R_2, C_1 and C_2 with which the simulation of the circuit will get a CBFV estimated per each tuple. GA will have a finish condition given by the number of generations of the algorithm or by not finding a difference greater than the millionth part in the MSE. Per each combination of initial conditions for the model, the best model from GA is obtained. To evaluate their learning of CA pattern, an inverse MABP step is applied to the model, with its maximum and minimum values got from the subject's signal, and a model's response is obtained by measuring CBFV (Fig. 1). Following the same selection process than SVM and calculating ARI after that.

2.3 Subjects and Measurements

Sixteen healthy subjects aged 31.8 ± 8.5 years were studied. None of them had a history of hypertension, diabetes, migraine, epilepsy or any other cardiovascular or neurologic disease. The study was approved by the Leicestershire Research Ethics Committee and informed consent was obtained in all cases [11]. CBFV-measured was recorded in the right MCA with transcranial Doppler (Scimed QVL-120) using a 2 MHz transducer. ABP was measured non-invasively using arterial volume clamping of the digital artery (Finapres 2300 Ohmeda). The signals CBFV-measured and ABP were recorded for 5 min for SV followed by 5 min recording while subjects breathed a combination of oxygen and 5% of CO_2 inducing an hypercapnic status. By using average's heart beat interpolation from CBFV-measured and ABP, CBFV and MABP are obtained, sampled at 5 Hz. To evaluate the proposed hypotheses different measures are used. First an analysis of inverse MABP step response dynamic from models will be realized, followed by repeated measures ANOVA for models between SV and CO_2 conditions using ARI. Finally a ROC curve will be obtained for models RC and SVM to compare their area under the curve.

3 Results

FIR-SVM obtained from a parameter's grid search that learns physiological CA pattern gives the following results shown in Table 1.

Table 1. Statistical mode, mean values, parameter's standard deviation and SVM metrics.

Parameter/metric	SV	5% CO_2
Mode n_p	4 [1–8]	8 [1–8]
C	303.5 ± 986.67	46.25 ± 84.7
ν	0.32 ± 0.59	0.41 ± 0.34
Correlation coefficient	0.59 ± 0.17	0.66 ± 0.18
ARI	6.29 ± 0.79	5.4 ± 1.05

Based on component's values under normal conditions of subjects obtained from [13], an initial condition grid is defined where the ranges for the components are R_1 = [0.5–100]; R_2 = [0.01–1; 1–100]; C_1 = [0.02–2; 2–200]; C_2 = [0.01–1; 1–100] realizing 8 executions of GA based on the initial conditions. Calibrating the GA the size of population changed from 50 to 400, and GA generations from 25 to 175 without finding greater differences in correlation or MSE in prediction, however a population of 300 and 125 generations are selected due present greater classification power between normal and CO_2 conditions as shown in Table 2.

Table 2. Mean values and standard deviation of best R-C models per subject.

Parameter/metric	SV	5% CO_2
R_1 mmHg s/ml	40.22 ± 28.00	19.78 ± 16.03
R_2 mmHg s/ml	5.31 ± 8.8	8 ± 24.13
C_1 ml/mmHg	37.09 ± 50.19	74.07 ± 64.43
C_2 ml/mmHg	7.47 ± 22.79	6.79 ± 19.2
Correlation Coef.	0.53 ± 0.17	0.52 ± 0.19
Correlation Coef. [0–0.2 Hz]	0.53 ± 0.17	0.56 ± 0.22
ARI	5.54 ± 2.01	1.92 ± 2.21

Average Inverse MABP step response to evaluate CA is shown on Fig. 3 for R-C and SVM models, trained with SV and CO_2 signals, in which the suddenly CBFV drop happens at 5 s and stabilize at different levels depending on the signal used in training.

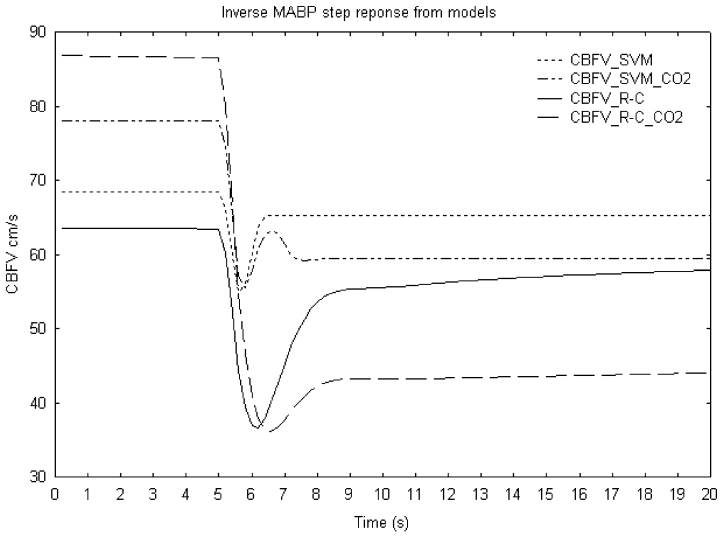

Fig. 3. Inverse average step response from R-C and SVM models adjusted under SV and CO_2 signals.

A repeated measures ANOVA, shows differences for models under both conditions (SV and CO_2) with *p-value = 0.00034*, Fig. 4.

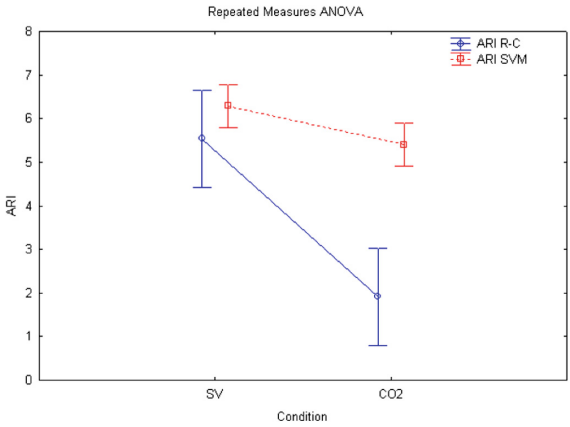

Fig. 4. Repeated measures ANOVA for R-C and SVM models between SV and CO_2

Post-hoc Tukey analysis shows differences for R-C and SVM models *p-value = 0.000186* and *p-value = 0.014* respectively.

Also the area under the ROC curve was calculated where R-C models have 0.89 against 0.73 from SVM.

4 Discussion

SVM achieves an accuracy to estimate CBFV of 0.59 in correlation during SV and slightly higher under CO_2, while R-C model presents a correlation near of 0.53 for both conditions (SV and CO_2). The dynamic of the inverse MABP step response with a drop at 5 s, applied over both models shows a normal autoregulation response for healthy subjects under normal conditions (SV). SVM responses under CO_2 show a behaviour where after the drop it tends to raise and then stabilize, while R-C response during CO_2 drops and keeps in the bottom showing a clear CA degradation.

R-C model's initial conditions grid enables feasible ranges per each component in which the combination allows valid physiological responses, decreasing the number of models to evaluate and giving clarity to the search process.

Repeated measures ANOVA tells that both models present differences among SV and CO_2 conditions. Post-hoc Tukey, shows that despites both models present differences between subject's conditions, R-C models discriminate more markedly with a p-value much lower. Therefore both models can capture CA during SV, but there are differences between models on capturing CA degradations under CO_2. ROC area from R-C model is 17% larger than SVM which validates the better classification power of the proposed model.

Limitations of this work makes it necessary to perform comparisons between R-C model and SVM trained with CBFV under the same frequency band, because the higher correlation of SVM could be given by higher frequencies than the CA phenomenon and therefore out of a range where the information of CA degradation is contained. Considering future works, R-C model could have a physiological meaning from the cerebral haemodynamics perspective, since in Table 2 can be observed a marked difference in the values of R_1 and C_1 among SV and CO_2. Therefore, the components R_1, R_2, C_1 and C_2 could be studied individually or together because of the possibility of classifying subjects in different conditions even better than ARI and improve the understanding of CA. Another approach to be investigated is the use of a non-linear RC model to be implemented and compared against non-linear models previously proposed [3, 8, 9].

5 Conclusions

An R-C model has been presented by using an hydraulic-electric analogy through genetic algorithms to learn the pattern of cerebral blood flow changes in response to fluctuations in arterial blood pressure. This model also discriminates between normal and degraded CA conditions (CO_2) better than SVM, validating both hypotheses proposed in this work. From these results, new clinical applications will allow improvements in differentiating subject's condition through simulations based on measured data from subject/patient, improving comprehension of CA phenomenon in normal as well as pathological conditions.

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