Autoregulatory Model Comparison and Optimisation Methodology

Martin Shaw, Ian Piper, and Michael Daley

Abstract Cerebral pressure autoregulation (AR) is a process by which blood flow is kept constant over a specific cerebral perfusion pressure (CPP) range. There have been a number of advances in recent years in the monitoring and modelling of this physiological variable; however, there has been very little work done on the comparison or optimisation of some of the existing models in clinical use today: pressure reactivity index, highest modal frequency techniques and compartmental modelling. Presented here is a methodology for the comparison and optimisation results for these main AR models. By simple mathematical manipulation of the original modelling end points each model can be converted into a form that is directly comparable to the others. Using a standardised data set with known gold standard AR status indications, the models can then be readily assessed. As a consequence each of the models can then be optimised to maximise specificity and sensitivity.

Keywords CBF autoregulation • Intracranial pressure • Mathematical modelling • Head trauma

Introduction

The application of mathematical modelling to the detection of specific events, such as loss of cerebral blood flow autoregulation, or to the prediction of clinical outcome have been investigated in a number of specific patient populations. Although some success has been achieved with time-series modelling in specific disease areas, there has not been a systematic study comparing different modelling approaches within a given population of patients.

Cerebral autoregulation is the process by which cerebral blood flow is constantly maintained over varying cerebral perfusion pressure. It is important to the treatment and outcome of TBI patients as the treatment planning might vary depending upon whether or not autoregulation is intact. The non-surgical management of patients with traumatic brain injury (TBI) focuses upon the prevention of secondary insults such as drops in blood pressure (BP) or increased intracranial pressure (ICP). The latter (raised ICP) is of particular concern as increases in ICP will decrease cerebral perfusion pressure (CPP = BP – ICP) and can lead to decreases in cerebral blood flow (CBF). Cerebral autoregulation is a physiological mechanism that maintains CBF constant in the face of changing CPP although it can become impaired following brain injury. Currently, there is considerable clinical interest in using an index of autoregulation (AR) in the management of raised ICP and reduced CPP and to this end a number of mathematical models to predict the state of the AR process have been proposed.

Model Comparison

Literature on approaches to comparing these types of models, in terms of their relative accuracy, is sparse. This could be attributed to the difficulty in comparing physiological models that include known autoregulatory parameters with other models that focus primarily on generating an indexed autoregulatory status using a "black box" approach regardless of the underlying physiology. Another difficulty concerns the lack of high quality data upon which to compare models. Without high-frequency "gold standard" data on autoregulatory status, any model could be placed at a disadvantage during such a comparison; furthermore, a major problem in model comparison concerns the range of tests that can be used for comparison with test choice key to the

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meaningful comparison of the models. One approach we propose would be to perform model comparison on a related statistic, but not necessarily one that is originally generated by any of the models. For example, by taking two models, one of which outputs a direct measure of autoregulation via an index and a second model that outputs a time series trend for intracranial pressure, both of these could generate a third statistic to a known value for autoregulation. This could then be used as the basis for a direct comparison of the models.

Study Aims

This paper reports on the results of our application of this approach to autoregulation model comparison focused upon three models. First, the pressure reactivity index (PRx) [2], second, the highest modal frequency (HMF) [3] analysis, and third, a reworked Ursino model [6].

For each model a normalised autoregulatory parameter will be generated to ease comparison and a high-resolution data set will be used to ensure that all model comparisons are not biased by data sampling rate. We also report on analyses leading to the best choice for model comparison statistics and finally a method of optimising the data window size to yield the best performance of a given model for estimating the status of autoregulation. Models will be compared in terms of performance at detecting baseline autoregulation status from a data set generated from an experimental model of autoregulation disruption based upon pial vessel imaging before and after fluid percussion injury. Models will also be compared against each other as well as before and after application of our data window size optimisation method.

Methods

Reworked Ursino Model

Ursino's original model is a two-compartment model where autoregulation can be thought of as a combination of three processes affecting arterial-arteriolar compliance for a given percentage change in CBF. The first process is the autoregulatory gain, the next is the static sigmoidal autoregulatory response function and the last component is a low pass transfer function. The gain parameter G is essentially a continuous index for cerebral autoregulation. With this in mind Ursino's original model has been rearranged to predict G.

HMF Autoregulatory Predictor

The HMF method [3] using a technique called modal analysis found that when cerebral arterial flow regulation is intact, changes in the highest modal frequency (HMF) are inversely related to changes in cerebral perfusion pressure (CPP). In contrast, when the arterial-arteriolar vascular bed demonstrates autoregulatory impairment, i.e. when CBF shows a CPP dependency, changes in HMF are directly related to changes in CPP.

PRx

The PRx, or pressure reactivity index, described by Czosnyka et al. [2] is a moving Pearson's correlation between ABP and ICP. This method looks at the amount of correlation between the two variables and the decision on whether there is pressure reactivity or not is based on a pressure-passive model. If the correlation is positive, i.e. the ICP is reacting passively, with ABP, then it can be assumed that the subject is not autoregulating and vice versa.

Model Comparison and Optimisation

We used a high-quality data set for model comparison, which consisted of six piglets with a cranial window preparation and a fluid percussion injury model with ICP, ABP and middle cerebral artery (MCA) flow velocity data collected at 250 Hz. The protocol included a number of ABP challenges both before and after injury. A cranial window preparation using pial artery imaging allowed the pial vessel diameter to be measured before and after BP challenge as well as before and after fluid percussion injury. A pressure-passive increase in pial vessel diameter was used as an indication of autoregulation impairment. Across all six animals there were 57 measures of autoregulation: 25 intact and 32 impaired. This data set was prepared so that there were a similar number of calculated results for each model based on a prediction for the autoregulatory state every 6 s. The points at the start of each BP challenge were selected for comparison, to minimise the system compromise from the challenges themselves. For all of the comparison data we selected only the first hour of data before and after fluid percussion injury with the intention that this should make the testing more comparable to a binary intact verses impaired status.

The choice of comparison methodology was driven by the data set and we have selected the Matthews correlation coefficient (MCC) method as the fairest model comparison test. To compare the models using the MCC, two approaches

Table 1 Model predictive ability using Matthews correlation coefficient (MCC)

Model	Baseline MCC	Optimised MCC	Optimised window (min)
PRx	0.09	0.25	66
HMF	0.09	0.55	72
Ursino	0.3	n.a.	n.a.

PRx pressure reactivity index, *HMF* highest modal frequency

Table 2 Intermodel comparisons using MCC

Intermodel comparison	Baseline MCC	Optimised MCC
PRx compared with the HMF	–0.5477226	0.4714045
PRx compared with modified Ursino	–0.75	n.a.
Modified Ursino compared with HMF	0.7302967	n.a

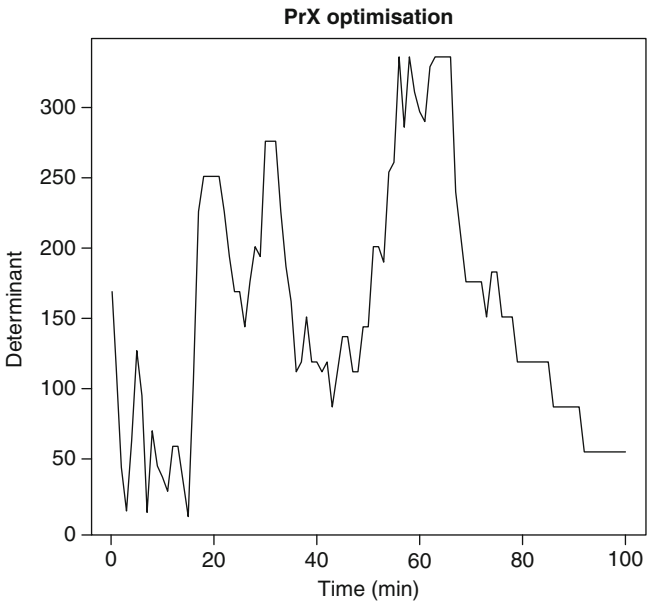

Fig. 1 Pressure reactivity index (*PRx*) model confusion matrix determinant vs window size

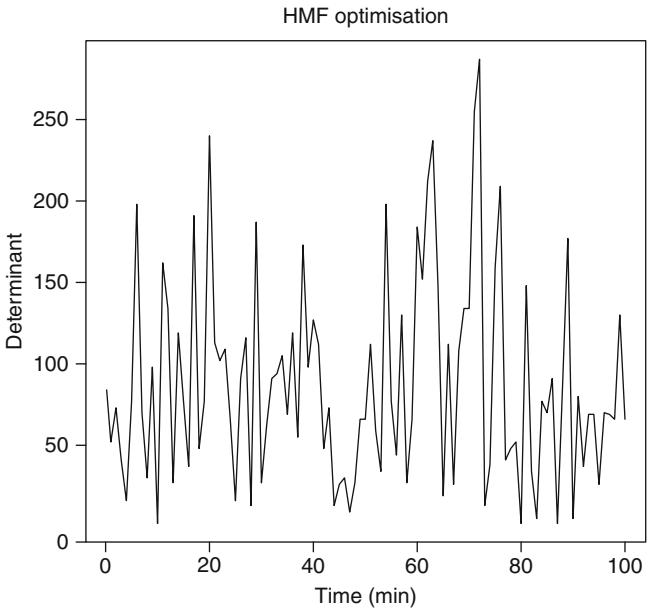

Fig. 2 Highest modal frequency (*HMF*) model confusion matrix determinant vs window size

were used. The first was to base the MCC against the known autoregulatory status derived from the pial artery window of the piglet. This will give an MCC figure both before and after the optimisation. The second was to compare each of the models against each other to produce a relative inter-model comparison.

Each of the models assessed have at their core a window of data over which an analysis or comparison is occurring. For the PRx it is the amount of data used to determine the correlation function, with the HMF it is the collected data over which the slope of the line of the modal frequency changes with time. The modified Ursino model, while it has a window over which data is being processed, does not lend itself well to this method of optimisation so we have focused on optimising only the PRx and HMF models. The optimisation itself is carried out using a quasi-Newton method [4]. This method maximises the determinant of the sensitivity–specificity matrix calculated at a variable window size for each of the models in turn. The use of the determinant is merely for efficiency as there is no need to normalise this to calculate the MCC when optimising to a maximum value. The window sizes involved in the calculations are measured in the number of points used in the calculation.

Analysis and Results

The baseline comparisons are shown in Table 1 and inter-model comparisons in Table 2. From Table 1 the MCC results from the comparison between the model prediction and the known autoregulatory status were for the HMF 0.09 and the PRx 0.09, while the reworked Ursino showed an MCC of 0.3. The inter model comparison results from Table 2 showed slight agreement between the HMF and the reworked Ursino model and a general disagreement between the PRx and the other two models. The calculated optimal window size values for both the PRx and HMF were 60 and 71 min for each of the models respectively (Table 1). These optimal points can clearly be seen in the graphs of window size against determinant (Figs. 1 and 2). Post-optimisation the baseline model comparison can be seen in Table 1 and the inter model comparison between the HMF and the PRx in Table 2.

Table 1 shows that post-optimisation the MCC for the PRx compared with the baseline known AR status is 0.25 and for the HMF it is 0.55, which, if compared with the baseline, shows that there is an increase in predictive power of between 200% and 600% afteroptimisation. From Table 2 it can be seen that the MCC is now equal to 0.47, which is a distinct improvement over the non-optimised result.

Discussion

An important step in any comparative methodology is to standardise the data set on which to compare the models. First, it has to have a known AR state so that one can definitively state whether the status is impaired or intact. Second, it has to be of a high enough temporal resolution to evaluate all of the models so as not to disadvantage the model under comparison. The data set used in the study does meet these key criteria, making it a viable candidate for the analysis; however, the question could be raised whether the end points used are correctly chosen. With this data set [3], as the AR predictions are derived from the pial artery response recorded via the cranial window, there is a small area of observation with a small number of vessels in each case. This could introduce a number of complications, including whether the chosen vessels are representative of the whole pial vasculature and as a consequence may not be a valid global measure of autoregulation. With this data set, the fluid percussion injury model, which has been used in many studies is considered a standard method for impairing AR and has been shown to have a global effect on the physiology [5] even though in the collected data set it is monitored very locally via the pial artery–cranial window methodology. Other considerations with this model, such as the inter-subject variability and vessel variability, have been addressed by Coles et al. [1].

Another key methodological issue is the choice of a comparison test. There are a large number of options available for analysing the prediction data. The first and possibly most crucial piece of information governing the choice of test concerns the output of the models, actual or surrogate, as this influences the basic range of test significantly. If the simple AR prediction, intact or impaired, has been chosen as the surrogate target, then only tests on nominal data will be applicable.

From the results of the model comparisons (Table 1) it is easy to see that with the initial model configurations taken from their respective original papers the predictive accuracy of all of the models is quite poor. This could be attributed in part to the data set used in respect of the variability in the AR assessment with the pial artery–cranial window method, but also the influence of data selection bias in order to reduce BP challenge manipulation interference in the data used for comparison.

As the predictive accuracy is lower than expected for all of these models it leads to the question, could the predictive accuracy of most of these models be increased by the correct choice of window over which the data are sampled and analysed? The results from the optimisation of the HMF and PRx can clearly be seen to have an effect on the predictive ability of the models (Table 1) and the inter-association of the two models (Table 2). With a methodology now in place for both model comparison and optimisation there is a need to validate this approach on an alternative data set, particularly one where there is a longer monitoring period post-injury to allow investigation of optimisation windows beyond that of 2 h. Application of single data set validation techniques like the K-fold cross-validation approach, frequently used in neural network training and testing, would not be appropriate here because of the dependence of autoregulatory status on time post-injury.

Conclusion

This work has provided a methodological approach to optimising data window size for testing models of autoregulation. We have also made a case for the use of MCC as a method of choice for model comparison. In the data set we had available (Piglet data with fluid percussion injury using pial artery visualisation), Ursino's physiological model performed best overall without any form of data window size optimisation. Post-data window size optimisation, only the data-driven models could be compared, of which Daley's HMF model showed better performance than the PRx model as a measure of the status of autoregulation. In view of the large variation observed in the autoregulation status observed with this data set, further model comparison studies with other data sets and methods for testing dynamic autoregulation are warranted.

Conflict of interest statement We declare that we have no conflict of interest.

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