# Modelling cerebral blood flow autoregulation in humans

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*Abstract* – **Better understanding of the determinants of cerebral blood flow (CBF) and the interpretation of clinical measurements can benefit from quantitative modelling of CBF regulatory mechanisms and their interaction with other haemodynamic variables such as intracranial pressure and blood gases. Mathematical models have been able to reproduce many known phenomena and to extract relevant parameters for patient management. "Black-box" models, chiefly transfer function analysis, are easier to apply in a clinical setting, but cannot separate the contributions of the myogenic, metabolic, or neurogenic regulatory mechanisms from that of the vascular bed and other intracranial elements. Future work should emphasize i) multivariate system identification approaches and, ii) closer collaboration between the mathematical and "black-box" schools of modelling to enhance the benefits of these distinct approaches.**

## I. INTRODUCTION

In humans, cerebral blood flow (CBF) is regulated by a number of different mechanisms, including pressure-autoregulation, which tends to maintain CBF relatively constant when cerebral perfusion pressure (CPP) is varied by changing either arterial blood pressure (ABP) or intracranial pressure (ICP) [1-3]. Control of CBF is normally effected by changes in cerebrovascular resistance (CVR) resulting from vasoactive regulation of the diameter of small cerebral vessels. This can be achieved by myogenic, metabolic, or neurogenic mechanisms [1].

Cerebral autoregulation can be disrupted in a number of conditions, such as prematurity, birth asphyxia, severe head injury, stroke, and hypertension [1,2]. Different approaches to modelling autoregulatory mechanisms have been adopted to support diagnosis and patient monitoring. Modelling is also a tool to investigate the physiology of cerebral autoregulation, and to identify the contribution of other variables, such as ICP, $pO_2$, $pCO_2$, mental activation, haematocrit, intracranial compliance, CSF balance, and sympathetic stimulation, which have been shown to influence CBF [1,2]. This paper reviews the main approaches that have been adopted for modelling cerebral autoregulation in humans and identifies future directions for research in this area.

## II. METHODOLOGY

Fig. 1 provides a framework to discuss the different modelling approaches that have been applied to studies of cerebral autoregulation. The CVR of the vascular bed can be regulated by myogenic, metabolic or neurogenic mechanisms. The metabolic pathway is stimulated by changes in tissue $CO_2$ or by the balance between $O_2$ supply and demand. "False autoregulation" can result from changes in CPP due to fluctuations in cerebral blood volume (CBV) that can influence ICP due to the finite compliance of the closed skull. Models can also be classified as either static or dynamic. The latter treats ABP, CBF, and CVR as a function of time whilst the former corresponds to steady-state solutions [2,4,5].

## III. VASCULAR BED

The simplest model for the vascular bed, which has been adopted by some authors, is a single element, adjustable CVR in static models [6-10]. This approach assumes that the instantaneous ABP-CBF relationship goes through the origin. Analysis of real pressure-flow (velocity) relationships though indicates that flow or velocity reaches zero for ABP > 0. This phenomenon has been modelled by assuming the existence of a critical closing pressure (CrCP) in the cerebral circulation [11-14].

More elaborate models of the cerebral vascular bed were proposed by several authors in both static and dynamic models. In general, these models involve multiple compartments with lumped parameters for resistances only [15-16], or resistances and compliances [17-27]. As a particular case, [28] performed simulations with a 34 segment model that can be regarded as a reasonable approximation to a distributed parameter model.

System identification, or "black-box" approaches, such as transfer function analysis, theoretically allow for models of the vascular bed of a much higher order and complexity than that provided by a limited number of compliant elements [2]. One limitation of these techniques though, is that usually they cannot separate the contribution of the vascular bed from that of the autoregulatory mechanisms and the other feedback loops represented in Fig. 1.

## IV. AUTOREGULATORY MECHANISMS

In static models, and also in some of the dynamic ones, autoregulation is simulated by simply introducing a dependence of the type CVR = *f(*ABP or CPP*)*. Often, a non-linear static function $f(\cdot)$ is extracted from published experimental results [6,9,15,16,22,25,26]. These models can be said to be purely "myogenic" as CVR depends exclusively on ABP or CPP. Although such models contribute little to improve understanding of autoregulatory mechanisms, they can help to interpret clinical data or to support more general studies of the cerebral circulation. In a similar vein, [28] introduced myogenic autoregulation by simply adjusting small vessel diameters for different levels of systemic ABP.

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**Abstract**

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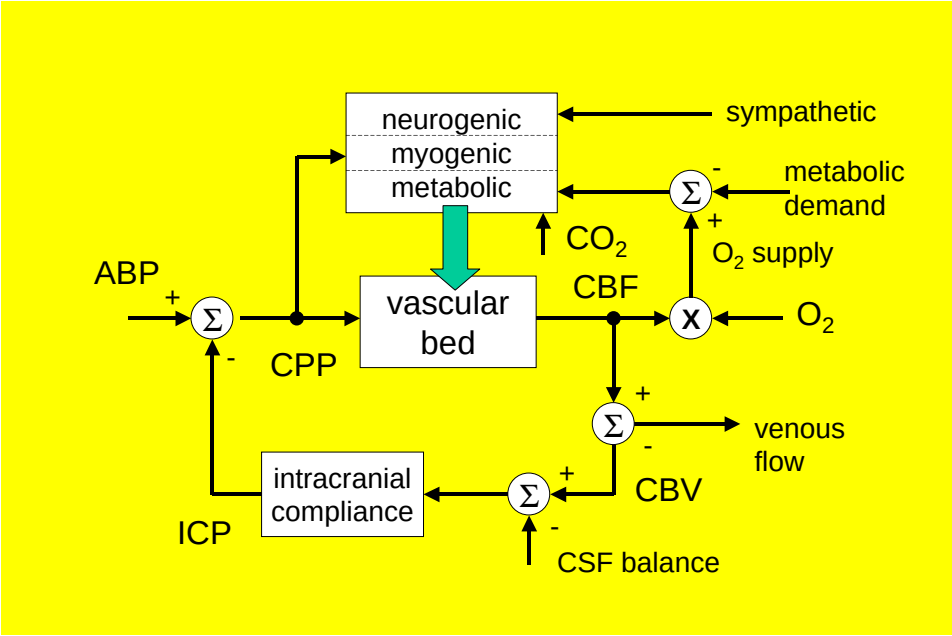


Fig. 1. Simplified block diagram of the main variables and relationships influencing the regulation of cerebral blood flow. See text for abbreviations.

More elaborate, but also purely myogenic models have used linear differential equations to reflect the dependence of CVR on ABP [5,18].

Linear and non-linear differential equations have also been used to model metabolic regulation, by assuming that the rate of change of CVR varies with the displacement of CBF from a set point [17,24]. Models that explain the CBFV amplitude change in transient hyperaemic response tests can also be regarded as simple representations of metabolic regulation [7,8]. Purely metabolic models have also been presented by [10,21], involving the influence of $O_2$ and $CO_2$ on CBF regulation (Fig. 1).

Simultaneous modelling of myogenic and metabolic regulation has been adopted by Ursino et al. in a series of studies [19,20,23,27]. These models have assumed that the diameter of proximal vessels is under myogenic control whilst vasomotion of small vessels and arterioles is metabolically regulated. Recently, the influence of $CO_2$ on CBF and its interaction with autoregulation were also included [27]. The latter aspect was also considered by Wilson [10].

The more complete models of CBF regulation have allowed a better understanding of the role of different variables and parameter values that can influence measurable quantities, such as middle cerebral artery CBFV and ICP. They have also shown that realistic results can be obtained with either a myogenic or a metabolic mechanism, or a combination of both. Wilson [10] has also shown that tissue $O_2$ concentration might well be the controlled variable in the metabolic pathway. On the other hand, these models have not been able to distinguish the relative contribution of the three main possible regulatory mechanisms represented in Fig. 1.

Modelling the dynamic relationship between ABP and CBF (or CBFV) by means of transfer function analysis, also cannot discern between the distinct autoregulatory mechanisms, since most of the elements in Fig. 1 are assumed to be inside a single "black-box". Nevertheless, this approach provides CBFV step responses to ABP changes that represent a relatively simple method to assess cerebral autoregulation in a clinical setting, using spontaneous fluctuations in ABP [29-36]. Tiecks et al. [5] proposed a second order system to model the relationship between CBF velocity (CBFV) and ABP during transients produced by the sudden release of inflated thigh cuffs. The main objective of the model was to estimate a single parameter, the autoregulation index (ARI), that can reflect the "strength of dynamic autoregulation" [5]. The step response technique also allows a practical way to take into account the interaction between CO2 and cerebral autoregulation [31,34]. CBFV step responses estimated from ABP transients induced by manoeuvres that stimulate the autonomic nervous system, suggest that sympathetic activity does not influence cerebral autoregulation in the normal range of mean ABP [36].

In the frequency domain, transfer function analysis has shown that cerebral autoregulation has characteristic manifestations in the coherence function, amplitude and phase frequency response curves [29,31,32,37-42]. In the frequency range DC-0.1 Hz, an active autoregulation is reflected by a reduction in coherence, as well as in the amplitude frequency response, since CBF variability tends to become more independent of fluctuations in

ABP. On the other hand, in the same frequency band, the phase tends to be positive, indicating that flow leads pressure. This phenomenon can be explained by a simple model in which dynamic adjustments in CVR lag behind perturbations in ABP (myogenic response) or CBF (metabolic control) [2,14,29]. With selective blocking of the different autoregulatory mechanisms in animal experiments, frequency domain analysis might be able to identify their specific contributions in humans in health and disease [43]. In addition, frequency domain analysis applied to some of the mathematical models that have been developed, eg [17-27] would be useful to adjust their time constants and other parameters and to match their responses to human data.

## V. INTRACRANIAL PRESSURE

The ominous consequences of intracranial hypertension, in conditions such as severe brain injury and subarachnoid haemorrhage, have been a strong motivation to develop models that can lead to better management of patients in critical care. Several of the studies mentioned previously have included ICP as one of the model variables [17-20, 23-27]. Seminal work on the pathophysiology of ICP has also been performed by other investigators using both mathematical and "black-box" models, but these studies are not included here as they do not apply to humans or did not take cerebral autoregulation into account. The interplay between ICP and autoregulation is of particular interest. Ursino et al. [20,23,44] have shown that autoregulation needs to be taken into account to explain pressure-volume index (PVI) tests, in addition to the ICP response. Steinmeier et al. [45], have also shown that impairment of cerebral autoregulation can be detected by non-parametric modelling, using cross-correlation analysis between fluctuations in ABP and ICP. More recently, transfer function analysis of spontaneous fluctuations in ABP, CBFV, and ICP has questioned the possibility of characterizing dynamic autoregulation by using $CPP(t)= ABP(t) –ICP(t)$ as the input variable, directly, due to the high correlation observed between oscillations in CBFV and ICP [45,46].

## VI. CONCLUSION

Despite the degree of sophistication achieved by some of the mathematical models of human cerebral haemodynamics that have been proposed, relatively little work has gone into the sub-systems dedicated to model autoregulatory mechanisms. Also, different models tend to focus on different aspects of the cerebral circulation, and more comprehensive models, from the perspective of autoregulation studies, would be obtained by merging the contributions of [10,21,27] for example.

More validation studies of the structure and parameter values of autoregulation models would be highly desirable. One possibility would involve the simulation of frequency-domain analysis in mathematical models, coupled to a sensitivity analysis of its parameters. Studies of this kind could shed light on the specific information carried by coherence functions and amplitude and phase frequency response curves about the different autoregulatory pathways represented in Fig. 1.

The limitations of "black-box" models to discriminate between the vascular bed and its regulatory mechanisms has been mentioned previously. These models can also be quite sensitive to noise and their application to routine clinical practice still requires a more thorough validation of their reproducibility. Further insight into the sub-systems depicted in Fig. 1 could be gained by multivariate modelling, as shown by preliminary studies [34,45,46], but the technical difficulties in this area should not be underestimated [34].

The different limitations of mathematical and "black-box" models could be overcome in part by joining forces to produce hybrid models combining mathematical modelling of relatively well known phenomena with system identification of less well defined components, such as autoregulatory mechanisms. Artificial neural networks are particularly suited for these "grey-box" models [47]

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