Research chair on Brain Trauma: Progress report

This document describes the projects worked on and respective progress obtained by Bavo Kempen, PhD student, working with Bart Depreitere MD PhD, funded by the research chair on brain trauma to ameliorate brain trauma outcomes.

Brief introduction

The unfortunate inevitability of traumatic brain injury (TBI) occurrence and our domains of expertise motivates us to focus on the timely detection and prevention of so called secondary injuries, while the patient is hospitalized and treated in the intensive care unit (ICU). Secondary injuries occur over time due to a cascade of pathophysiological processes triggered by the initial mechanical injury and have been shown to be detrimental to patients' short –and long – term outcomes. Responsible for the occurrence of such secondary injuries is the dynamic impairment of cerebrovascular autoregulation which results from the primary mechanical injury (Figure 1).

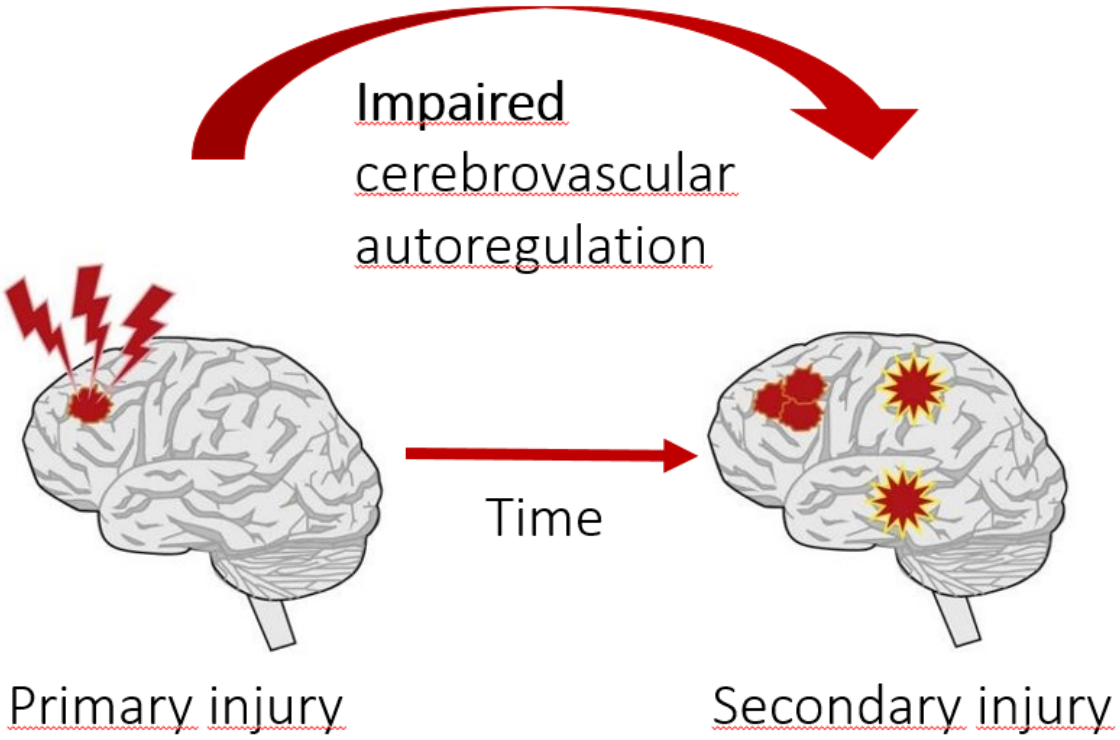

Figure 1: Development of secondary injuries triggered by the inital primary injury.

Cerebrovascular autoregulation is a crucial mechanism for healthy brain functioning since it is responsible for maintaining an adequate cerebral blood flow (CBF) over changing cerebral perfusion pressures (CPP) (Figure 2). Consequently, the impairment of this mechanism leads to an inadequate CBF which results in neuronal cell death due to a lack of oxygen and nutrients (ischemia) with a significant detrimental effect on the patients' outcome and chance of survival. To date, no monitor exists to dynamically assess and detect the state of autoregulation of patients while this information could be invaluable to clinicians at the bedside to ensure an adequate CBF and as such detect and prevent detrimental secondary injuries.

PhD project

Develop the **first validated dynamic cerebrovascular autoregulation monitor using peripheral signals routinely monitored in the ICU** utilizing advanced modeling techniques.

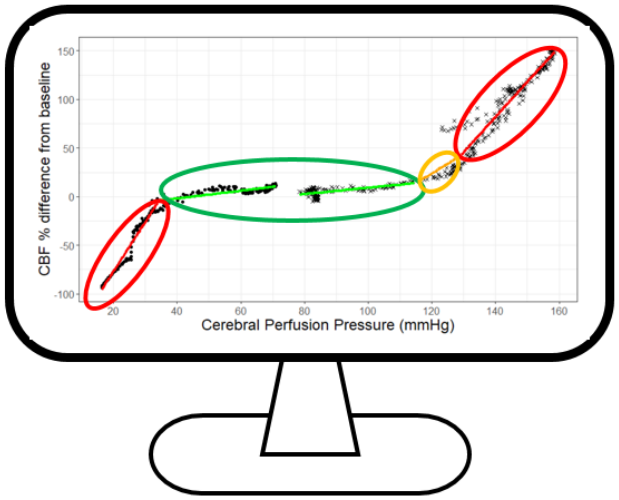

Figure 2: Cerebrovascular autoregulation curve. Green is the intact zone of cerebral perfusion pressures with a stable cerebral blood flow. Orange and red indicate inadequate cerebral blood flow and impaired autoregulation.

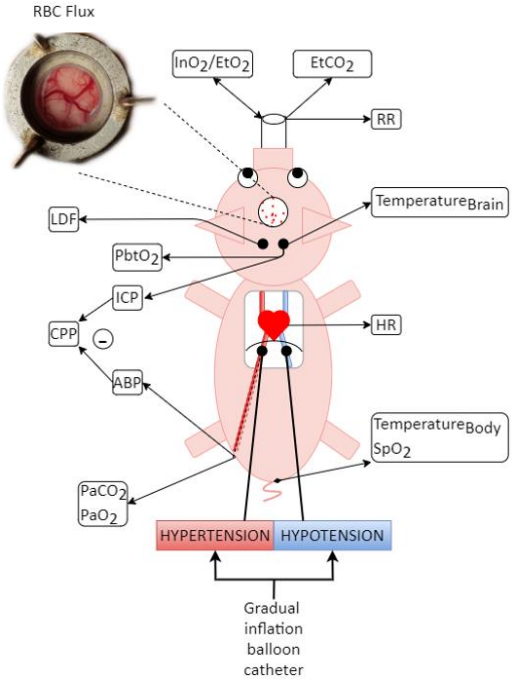

Figure 3: Experimental setup cerebrovascular autoregulation experiments.

To do so, colleague researchers have gathered over the past years as part of other work a large lab animal data set in which the researchers induced nonpharmacologically hypo – or hypertension which can impair autoregulation while mimicking an ICU environment and monitoring CBF (RBC flux and LDF). This data set is unique and one of its kind, which puts me in a privileged position to develop a dynamic autoregulation model using state of the art machine learning techniques.

Data set curation

The application of machine learning techniques to data sets necessitated an initial study of the data set and each of the signals' characteristics. Hence, I studied in depth individual signals dynamics to evaluate the possibilities using "ensemble empirical mode decomposition".

Following the conclusions from the latter study and an extensive additional exploratory data analyses I developed an automated data preprocessing pipeline which results in a well-defined data set with autoregulatory state projected on the multimodal time series.

Modelling strategies

Three modelling methodologies were identified after extensive literature study that could be used to model autoregulation from peripheral data to detect when and where autoregulation is impaired.

1) Use representation learning model architectures (e.g., variational autoencoders) to learn an optimal representation of cerebrovascular autoregulation from the peripheral signals (not including CBF)
    a. Reconstruction error based classification
    b. Latent space based classification

2) Simulate dynamically the autoregulation curve (Figure 2)
    a. Predict CBF trend changes based on peripheral signal input using deep learning
    b. Simulate the autoregulation curve using (a) and peripheral signals dynamically with a hierarchical Bayesian model

Insofar, modelling strategy (1a) has shown promising results, in that, from peripheral time series input data we managed to accurately detect the state of autoregulation in subsequent classification. To do so, we developed a deep learning model that can accurately reconstruct data governed by intact autoregulation dynamics. Moverover, the model is on the other hand bad at reconstructing time series data governed by impaired autoregulation. The error and uncertainty of the prediction we can quantify which makes us able to decide whether autoregulation is intact or not as shown in Figure 4.

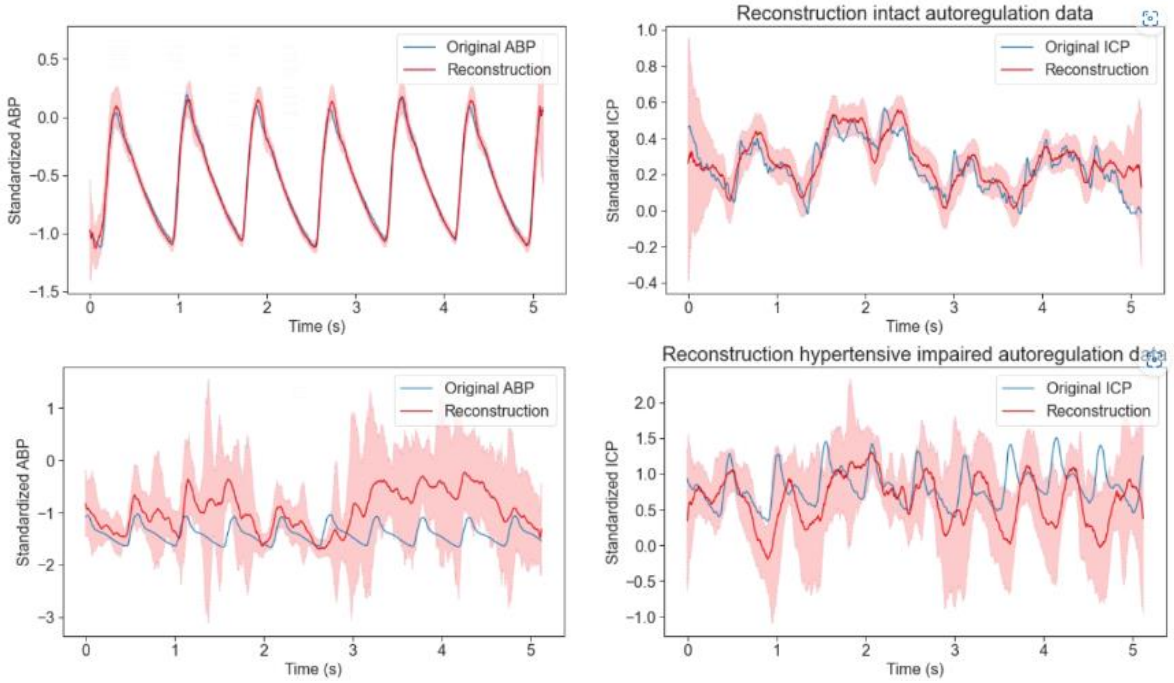

Figure 4: Original ABP and ICP signal and their reconstruction by a neural network trained solely on data derived from intact autoregulatory phase. Blue line represents the initial input, red line the optimal mean reconstruction and red shade the uncertainty of the latter reconstruction. The top two plots should reflect good reconstruction whereas the bottom two plots intentionally bad reconstruction. This distinction in reconstruction error is quantified by negative log likelihood, a measure of prediction error and uncertainty, and could allow us to automatically decide whether autoregulation is intact or impaired.

If instead we train the model on all the different data types that are governed by intact and the distinct types of impaired autoregulation (1b), we can show that the latent space of the model organizes itself in such a way that we can use these features to determine in what type of autoregulatory state we are (Figure 5).

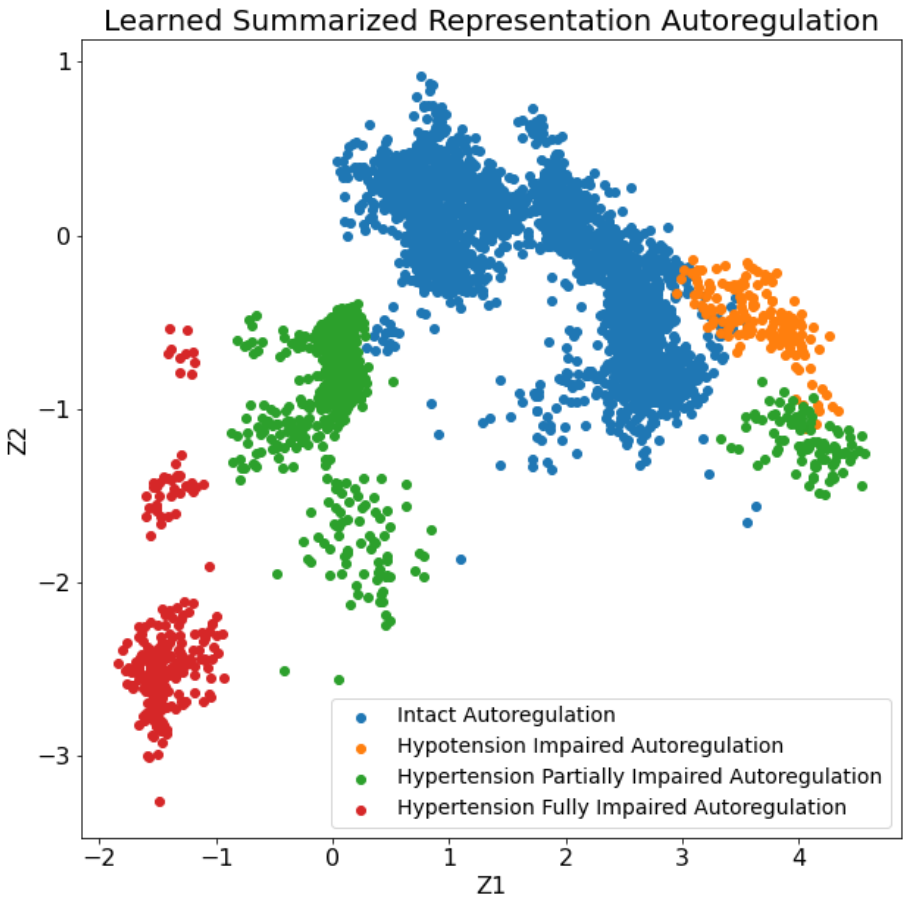

Figure 5: Learned summarized representation of autoregulatory states in the latent space of a variational autoencoder model. Distinct cluster formed which can be used to classify and determine in which autoregulatory state we are.

Notwithstanding the very promising results insofar, the selected deep learning models will be iteratively improved in the near future.

Work on approach 2 is currently paused for now, as extensive studying on 2a) has proven to be a difficult challenge, which will be resumed when approach 1 has been concluded.

Side project 1: KidsBrainIT

KidsBrainIT was a large international multicenter study in which monitoring data from children aged 2 to 16 years was gathered over multiple years. My role in this study was to analyze the data and apply existing algorithms and visualization techniques. In essence, the visualization technique associates the concept of ICP dose, a combination of ICP intensity and the duration of that intensity, with outcome as measured on the Glasgow outcome scale (GCS). The goal of the study was to 1) validate the ICP dose response plot, 2) construct for the first time the CPP dose response plots for the pediatric population, 3) evaluate the validity of the CPPopt algorithm using a multiverse analysis approach. The main focus of these studies were on the visualization technique as it will have a direct impact on patient treatment.

1) We reproduced and thus validated the ICP dose response plot in the pediatric population, from which the resemblance with the original ICP dose response relation found on a dataset gathered more than two decades ago is remarkable (Figure 6). Two instrumental conclusions from this work are that: 1) Pediatric traumatic brain injury patients in general benefit from low ICP values, 2) The current cutoff point often used by clinicians to keep ICP below 22 mmHg is not strict enough for the pediatric population which cannot tolerate the same ICP insult intensity as the adult population, 3) too low CPP overrules relationship of ICP dose and outcome.

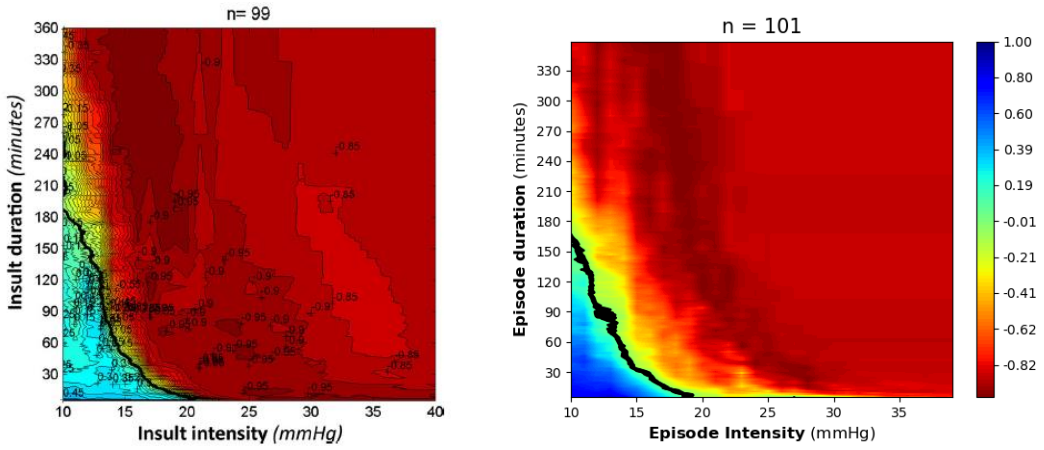

Figure 6: Intracranial pressure insult intensity – duration association with Glasgow outcome scale. Red area indicates a relationship of insult intensity and duration with negative outcome whereas the blue area indicates a relationship of insult intensity and duration with positive outcome. Left, original insult intensity – duration plot produced by Guïza et al. (2015) using the Edinburgh – Newcastle data set. Right, the reproduced insult intensity – duration plot based on the novel KidsBrainIT data set. The plot can be read as follows, ICP values of 20 or above will always result in negative outcome for the patient, an ICP value of 10 however, can be maintained for approximately 150 – 170 minutes until a negative outcome is expected.

2) We produced for the first time, cerebral perfusion pressure (CPP) dose response plots in a pediatric population, which was already produced for adults in prior work. We concluded that 1) a CPP below 50 mmHg is detrimental for the pediatric population, 2) there exists no zone of constant safe CPP due to dynamic autoregulation impairement, 3) CPPopt is not predictive of mortality nor unfavourable neurological outcome.

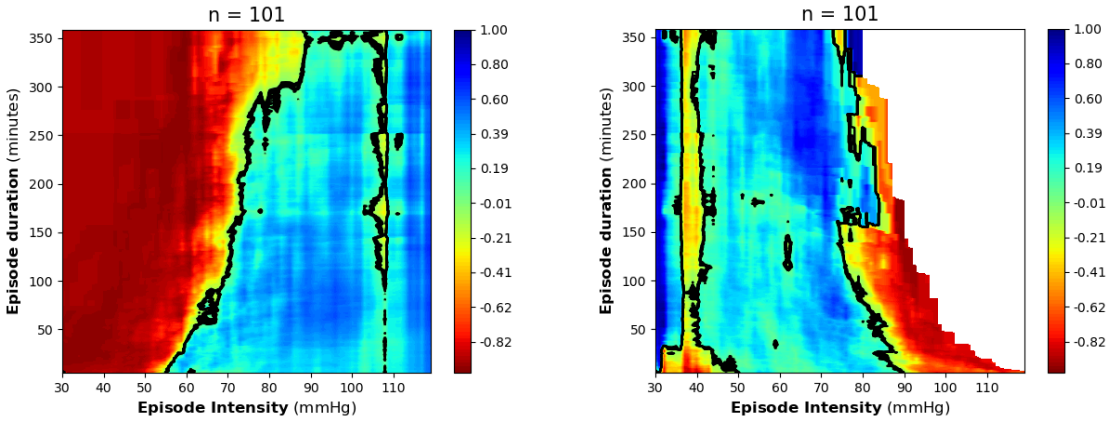

Figure 7: cerebral perfusion pressure insult intensity – duration association with Glasgow outcome scale. Red area indicates a relationship of insult intensity and duration with negative outcome whereas the blue area reflects a relationship of insult intensity and duration with positive outcome. Left plot and right plot are produced by traversing over CPP insult intensity

from low to high and from high to low respectively. CPP measures are different in that way in that, there is not only an upper limit as in ICP but in addition a lower limit. These two plots complement each other to give a total picture.

The KidsBrainIT results outlined above are the main takeaways of this study, with many more conducted analyses supporting them, and will be published in the near future.

Side project 2: Exploratory study in potential genetic predispositions that can lead to more easily impaired autoregulation

A data set was gathered by colleague researchers consisting of 1) extensive monitoring data during their ICU stay, and 2) genetic profile of the patient derived from a blood sample. As such we are investigating whether the genetic profile is related to an increased chance of impaired autoregulation during their stay while controlling for confounders such as injury type.

The study bioinformatics analysis has been performed in which we detected polymorphisms of target genes of which their protein expression is hypothesized to have a relationship with cerebrovascular autoregulation. Concrete relationships with autoregulation have not been mapped yet as this study is still in process of being completed.

Final remarks

As outlined, many projects are being worked on in parallel as outlined above. This brief summary of course does not reflect the complete complexity and time intensity of these projects, however, we are excited to already share some promising results and conclusions with you. The actual PhD project is very challenging in that we are trying to develop the first validated dynamic autoregulation monitor to ameliorate patient outcomes by preventing secondary injuries through personalized blood pressure therapy. As soon as a publication is final, I will of couse disseminate the results in comprehensible format so that the summarized version and its contributions to the traumatic brain injury field will be comprehensible to the readers of your website. Finally, I wish to express my gratitude for the opportunity to work on these very interesting projects that (will) have a significant impact on the field of traumatic brain injury and cerebrovascular autoregulation.

Sincerely,

Bavo Kempen