Universidade de Aveiro
2010
Departamento de Electrónica, Telecomunicações e Informática

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Suporte ao diagnóstico em Acidentes Cardio Vasculares

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Engenharia de Computadores e Telemática (M.I.E.C.T.), realizada sob a orientação científica do Professor Doutor Paulo Miguel de Jesus Dias, Professor Auxiliar do Departamento de Electrónica, Telecomunicações e Informática da Universidade de Aveiro e do Professor Doutor José Maria Amaral Fernandes, Professor Auxiliar do Departamento de Electrónica, Telecomunicações e Informática da Universidade de Aveiro

Dedico este trabalho à minha família.

o júri

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Agradecimentos

Gostaria de agradecer ao professor Doutor Paulo Miguel de Jesus Dias, ao professor Doutor José Maria Fernandes por me orientarem, pela ajuda e disponibilidade demonstrada ao longo do projecto.
Gostaria de agradecer ao Doutor Miguel Cordeiro e ao Doutor Gustavo Santos da equipa de neurologia e neurorádiologia dos Hospitais Universitários de Coimbra (HUC) pela ajuda prestada.

Palavras-chave

Acidentes cardio vasculares, tomografia computorizada de perfusão, imagem médica, volume sanguíneo, fluxo sanguíneo, tempo de trânsito

Resumo

O acidente vascular cerebral é uma das causas de morte mais frequente em todo o mundo e a decisão de tratamento e o resultado final é altamente dependente da qualidade do diagnóstico. Recentemente, a tomografia de perfusão tem sido utilizada com resultados promissores na avaliação de Acidentes Cardio Vasculares (AVCs), principalmente porque esta técnica dá mais informação sobre as alterações hemodinâmicas dentro da área de enfarte.

No entanto, muitos parâmetros diferentes são actualmente usados para analisar os resultados da tomografia de perfusão, tentando integrar a informação temporal que contém. Alguns desses parâmetros são o volume sanguíneo, o fluxo sanguíneo ou o tempo de trânsito por exemplo.

Neste trabalho foi desenvolvido um conjunto de ferramentas que permitem aplicar os diversos métodos encontrados na literatura assim como uma aplicação que nos permite seleccionar os métodos e a forma de os aplicar. Desta forma foi possível investigar e trabalhando com os médicos descobrir os métodos mais promissores, assim como implementar ferramentas para a detecção das ares passíveis de recuperação.

Keywords stroke, computed tomography, perfusion CT, brain imaging, blood volume, blood flow, transit time

Abstract

Stroke is among the most frequent cause of death around the world and the decision to treat and final outcome is highly dependent on the quality of diagnosis. Recently, cerebral perfusion tomography have been used with promising results in the stroke evaluation mainly because this technique gives further information about the hemodynamic changes within the stroke area.
However many different parameters are actually used to analyze the CT perfusion results, trying to integrate the temporal information it contains. Some of these parameters are Blood Volume, Blood Flow or Transit Time for example.
We developed a framework that applies several methods present in literature as well as an application that allows us to select the methods and how to apply them. This made it possible to investigate and working with clinical experts to discover the most promising methods and implement tools for detecting potentially recoverable areas.

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List of Acronyms

AIF ..... Artery Input Function
AUC ..... Area Under the Curve
BBB ..... Blood-Brain Barrier
bSVD ..... block-circulant SVD
CBF ..... Cerebral Blood Flow
CBV ..... Cerebral Blood Volume
CT ..... Computed Tomography
CTA ..... Computed Tomography Angiography
DICOM ..... Digital Imaging and Communications in Medicine
dSVD ..... delay-corrected SVD
FT ..... Fourier Transform
MCA ..... Middle Cerebral Artery
MTT ..... Mean Transit Time
MR ..... Magnetic Resonance
MRI ..... Magnetic Resonance Imaging
PRR ..... Potential Recuperation Ratio
ROI ..... Region of Interest
SMA ..... Simple Moving Average
SVD ..... Singular Value Decomposition
TDC ..... Time-Density Curve
tPA or PLAT ..... Tissue plasminogen activator
TTP ..... Time to Peak

Glossary

AIF (Artery Input Function) – The time concentration curve of artery is many times used as reference.

AUC (Area Under the Curve) – Area under the time concentration curve.

Auto regulation mechanism – The active auto regulation mechanism is a homeostatic mechanism that minimizes the differences in cerebral blood flow when blood pressure changes compensating with vasodilatations.

BBB (Blood-Brain Barrier) – Protective network formed by blood vessels and cells that filter the blood that went into the brain.

bSVD (block-circulant SVD) – Determination of CBF using circular SVD deconvolution.

CBF (Cerebral Blood Flow) – Represents the blood supply to the cerebral vessels in a given time.

CBV (Cerebral Blood Volume) – Represents the percentage of blood per unit volume of tissue.

Circular convolution – Circular convolution can be defined as a convolution of two periodic functions.

Convolution – Convolution is the process of feeding one function through another function, is the product of the signal and the response, the deconvolution is achieved by dividing the convolution by the response data set.

CT (Computed Tomography) – Is a medical imaging method employing tomography created by computer processing.

CTA (Computed Tomography Angiography) – Is a computed tomography technique used to visualize arterial and venous vessels throughout the brain.

Deconvolution – Deconvolution is a process that restores the original signal after convolving data, removing the effect of system response on a signal.

DCMtk – Is a collection of libraries and applications implementing large parts the DICOM standard.

DICOM (Digital Imaging and Communications in Medicine) – Is a standard for handling, storing, printing, and transmitting information in medical imaging

dSVD (delay-corrected SVD) – Determination of CBF using SVD deconvolution correcting the delay of arrival contrast material by shifting the tissue concentration curve in time.

Endothelium – The endothelium is the thin layer of cells that line the interior surface of blood vessels.

Fick's law – The Fick's first law says that a fluid flow from high concentrated regions to low concentration, with a rate proportional to the concentration gradient. The Fick's second law predicts the concentration change in time with diffusion.

First moment of the curve – Equivalent to the centre of gravity of the shape defined by the concentration curve.

FT (Fourier Transform) – Is an operation that transforms one complex-valued function of a real variable into another.

Hounsfield units – Is a quantitative scale for describing radio density.

Ischemia – Is a restriction in blood supply originated by occlusion of vessels.

MCA (Middle Cerebral Artery) – Is one of the three major paired arteries that supplies blood to the brain.

MR (Magnetic Resonance) – Is a medical technique used in radiology.

MRI (Magnetic Resonance Imaging) – Is a medical imaging method used in radiology employing a powerful magnetic field.

MTT (Mean Transit Time) – Represents time between the arterial inflow and venous outflow blood in the brain.

OpenCV – Is a computer vision library.

Parenchyma – Brain tissue distinguishable from supporting structure (bone).

Permeability – Permeability measures how the vessels are permeable to particles of a specific size, that is, let molecules of contrast agent pass through their walls from the intra vascular to extravascular space.

RAW – Raw image file contains minimally processed data.

Reperfusion – Returns the blood supply to the tissue after a period of ischemia

Residue function – Represents the fraction of the contrast material that remains in the tissue at time *t*.

ROI (Region of interest) – The region of interest is the region most favourable to the occurrence of a stroke so that the region is more relevant to observe.

SMA (Simple Moving Average) – Is a filter used to analyze a set of data points by creating a series of averages of different subsets of the full data set.

SVD (Singular value Decomposition) – In linear algebra is an important factorization of a rectangular matrix, with many applications in signal processing and statistics. Is s used to calculate the deconvolution of the concentration values of the artery.

TDC (Time-Density Curve) – Time-Density Curve of contrast material. Also named as time-concentration curve.

tPA or **PLAT** (Tissue plasminogen activator) – Is a protein involved in the breakdown of blood clots.

Thrombolysis – Is the breakdown (*lysis*) of blood clots.

TTP (Time to Peak) – Is the time elapsed between the injection of the contrast material and the appearance of a maximum concentration in the cerebral blood vessels.

VTK (Visualization Toolkit) – Is an open-source, freely available software system (C++ class library) for 3D computer graphics, image processing and visualization.

1. Introduction

1.1. Motivation and context

Stroke [1] is one of the major causes of death around the world. A stroke happens when there's a sudden vessel occlusion – usually with a blood clot – which results in inefficient blood supply and leads to poor oxygenation of brain cells. As a result, cellular activity is perturbed and can lead to cellular death if early reperfusion does not occur. 50% of people who survive suffer of physical limitations [2].

It is possible to distinguish two different areas in stroke. One is the infarct penumbra where cells are affected by the lack of oxygen but still intact and possible to recover with a fast reperfusion, the other is called infarct core where there's a cell death and no recovery is possible. The infarct core begins with a small area and in the course of time it grows to full fill the penumbra area if reperfusion not occurs.

Within a limited timeframe (around 3 hours from the stroke) it is possible to recover the brain tissue in the penumbra with an injection of a tissue plasminogen activator (tPA or PLAT) to destroy blood clots and avoid total tissue loss.

Discriminating the penumbra from the unrecoverable area is important for diagnosis, for that reason, the main clinical issue in the acute stroke management [3-10].

Several imaging tools are currently used to support diagnosis like Computed Tomography (CT) and Magnetic Resonance Image (MRI) [11]. We focus on cerebral perfusion CT (Perfusion Computed Tomography – PCT) because this type of exam uses equipment available in most of hospitals and do not require specialized equipment for monitoring.

1.2. Objectives

The decision to treat a stroke patient and final outcome is highly dependent on the quality of diagnosis. Recently, cerebral perfusion tomography have been used with promising results in the stroke evaluation mainly because this technique gives further information about the hemodynamic changes within the stroke area. From the literature several parameters are proposed to analyze the CT perfusion results and trying to integrate the temporal information it contains. Some of these parameters are Blood Volume, Blood Flow or Transit Time.

The objectives of this work are to implement and evaluate the clinical usefulness of the several methods supported in perfusion CT for stroke acute management. To achieve our objective we will provide an implementation of each of the methods in an open software application integrated within a processing pipeline that will minimize human intervention along the process. This application will support a clinical evaluation supported in both visual and quantified comparison of the methods supervised by a pool of clinical experts. Our ulterior objective is to map the clinical usefulness of the methods to quantified parameters (e.g. establish threshold for specific parameters) to define a guidance model that may help clinicians in their decision process.

1.3. Dissertation structure

This dissertation is divided into the following chapters, excluding this one:

• **Chapter 2 – State of the Art,** presents the background concepts of perfusion CT and the current state in stroke diagnosis. Both the data acquisition and perfusion CT based methods are presented, namely the several perfusion parameters described in the literature.

• **Chapter 3 – Methods Implementation and Application,** presents the processing methods and application. This chapter describes our implementations used to generate the perfusion parameters images and the application processing pipeline applied to obtain the images presented to the clinicians.

• **Chapter 4 – Evaluation** and Results, presents the clinician classification of the several perfusion based parameters and we present the work conclusions.

• **Chapter 5 – References**

• **Appendices –** Methods Implementation describe detail information about the methods implementation and Case Study presents the cases study and the clinical evaluation.

2. State of the Art

2.1. Stroke

The brain is an organ that requires much energy and requires a lot of oxygen to maintain normal cellular activity and energy production. Low oxygenation perturbs cellular activity, in worst stages, leads to cellular death if early reperfusion does not occur. In the absence of oxygen the production of energy is obtained by an anaerobic process with low energy production producing lactic acid that accumulates.

A stroke occurs when a specific brain area has inefficient blood supply usually caused by a sudden vessel occlusion, leading to poor oxygenation of that area and consequently cell death from the ictus site to a peripheral zone. It is possible to distinguish two different areas in stroke. One is the infarct penumbra where cells are affected by the lack of oxygen but still intact and possible to recover with a fast reperfusion, the other is called infarct core where there's a cell death and no recovery is possible. The infarct core begins with a small area and in the course of time it grows to full fill the penumbra area if reperfusion not occurs, as evidence in Figure 1.

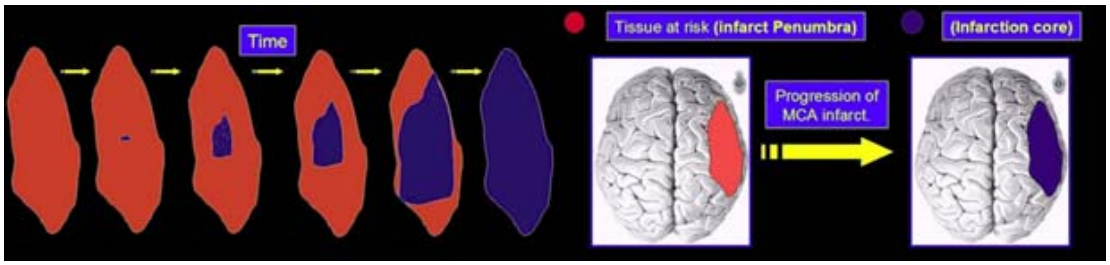

Figure 1 – Stroke progression (adapted from [8]).
The large red area represents the infarct penumbra and the blue area represents the infarct core (small or inexistent at the beginning of the crisis). With time the infarct core grows to full fill the infarct penumbra.

The treatment depends on the size of these areas (Figure 1): if the penumbra and infarct core are similar there is no reason to submit the patient to treatment once it is no longer possible to recover the damaged tissue. For example in Figure 1, if both areas are different the treatment is possible depending on the time elapsed from the stroke. If blue area is small and orange area is big the patient is a good candidate for treatment because the potential ratio recuperation is bigger – large area of reversibly damaged tissue and a small area of irreversibly damaged tissue. Based on the area of penumbra and core is possible to determine the Potential Ratio of Recovery (PRR), PRR is the reason between penumbra size and penumbra size plus core size [12].

In some patients the recovery of cells in the penumbra area is viable up to 12 hours after the stroke [13-14]. The areas are compared with similar regions in the opposite cerebral hemisphere [9]. The recovery process of tissue in penumbra area depends on the existence of an active auto regulation mechanism, auto regulation mechanism is homeostatic mechanism that minimizes the differences in cerebral blood flow when blood pressure changes [15] compensating with vasodilatation, enabling the delivery of oxygen to cells, maintaining the viable recovery during a certain period of time but not in normal operation [8].

Thus the phrase "time is brain" as said by Gomez [16] refers to the fact of increase irreversibly damaged tissue area over time. Reperfusion of tissue at risk with a therapeutic window around 3 hours can lead to a complete regeneration of brain activity [7]. A late treatment can also cause a brain hemorrhage due to the destruction of the endothelium – a thin cellular layer that lines the inside of blood vessels [2, 8-9].

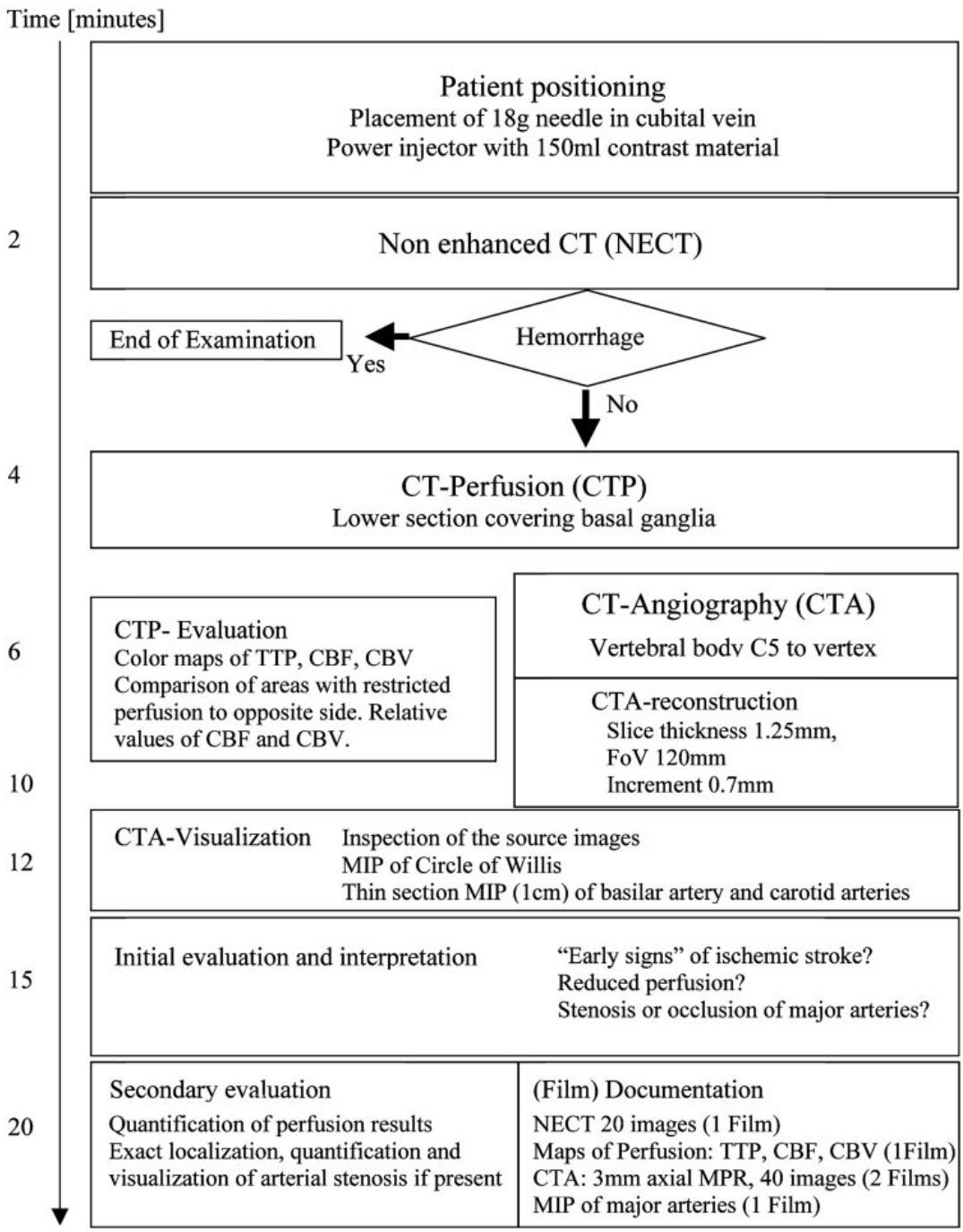

Figure 2 – Protocol for evaluating stroke patients.
Protocol for assessing the patient state using multi-section computed tomography and the average time necessary to perform each step (adapted from [7]).

In the next sections we present the several methods used in stroke diagnosis using Computed Tomography following the Figure 2.

2.1.1. Critical Stroke Management Using Computed Tomography

The first exam to be made to the patient in stroke clinical management is a regular Computed Tomography (CT) without contrast material (non enhanced Computed Tomography in Figure 2). This method is faster than others and allow to see the entire brain and discriminate what kind of pathology the patient has (stroke, hemorrhage, tumours or infections). A typical CT uses 60 slices and each slice has 4 to 8 mm of thickness.

However typical CT does not reveal sufficient information about extending or resilience of damage cells. Often a perfusion CT is started followed by a CT angiography (Figure 2 – to 2 minutes) [7, 17] is used using a contrast material to provide information about the physiological hemodynamic level capillary while ensuring better discrimination of brain structures. The drawback of perfusion CT is that it cannot be used in cases of hemorrhage or other lesions since it could aggravate the situation of the patient.

2.1.2. Computed Tomography Angiography

As in perfusion CT, Computed Tomography Angiography (CTA) also uses a contrast material that makes the blood vessels opaque to X-ray and allow measuring vessels volumetric capacity. After data reconstruction the generated 3D image shows the occlusion site and allows determines the type and cause of stroke [7, 18].

2.1.3. Perfusion Computed Tomography

The brain Perfusion Computed Tomography (PCT) is a functional study of the brain by making data acquisition typically using several slices over time, used for treatment and investigation of patients with stroke. Cerebral perfusion uses a non diffusible iodated contrast material that is injected in brain vessels and enables tracing the blood flows along time. Perfusion CT uses normally a non diffusible contrast material composed by relatively large molecules that remain within the intravascular environment. The transposition of the Blood Brain Barrier (BBB) by the marker is normally associated to structural damages and should result in abnormal perfusion parameters. Using a non diffusible tracer it is possible to simplify the quantification process because not imply knowing its diffusible concentration [9]. The downside is the existence of some contraindications for the use perfusion CT and iodinated contrast material namely in the presence of renal failure or diabetes [13, 19].

As in other perfusion based methods such as MRI perfusion, perfusion CT measures the concentration of contrast material along time in the tissues generating a Time-Concentration Curve for each voxel (Figure 3) from time of injection to time of contrast material leave the system resulting in three-dimensional perfusion maps for overall brain perfusion [20].

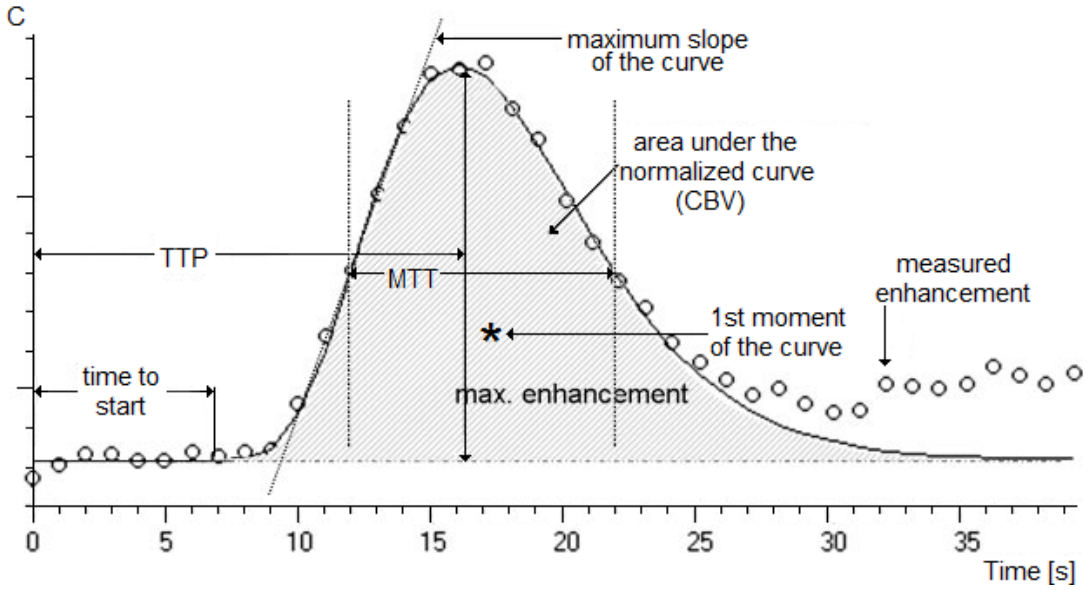

Figure 3 – Time concentration curve.
This curve is obtained by measuring the concentration (C) of the contrast material in a given brain position (voxel) over the time (adapted from [7, 21-22]).

From the Time-Concentration curve several parameters can be extracted to characterize the hemodynamic blood flow. The usual parameters are Cerebral Blood Flow (CBF), Cerebral Blood Volume (CBV), Mean Transit Time (MTT), Permeability and Time To Peak (TTP). The velocity of blood flow is correlated with arterial blood pressure.

CBV is the percentage of blood per unit volume of tissue. In infarct penumbra CBV is usually normal or high due to auto-regulation mechanism but low in the infarct core. CBF represents the time a certain amount of blood takes to pass the cerebral blood vessels and arrive to the veins, in infarct penumbra and infarct core this value is low because of the artery obstruction. MTT is the time between the arterial inflow and venous outflow blood in the brain. Permeability measures how the vessels are permeable to particles of a specific size: it indicate that molecules of contrast agent pass through the walls of the vessels passing form the intra vascular to extra vascular space. TTP is the time elapsed between the injection of the contrast material and the appearance of a maximum concentration in the cerebral blood vessels [7-9, 17, 22-26].

In Figure 3, time to start also called baseline is the portion of the curve that has constant values before contrast material arrive to artery and vessels due to pulmonary recirculation. After the contrast material leaves the system, slight increase occurs (around 32s in Figure 3) corresponding to the recirculation of the marker.

Regardless of the clinical relevance of some of these measures [7, 17] their actual use lacks an independent and reproducible validation namely because the measurement process and algorithms often depends on closed commercial applications use or in human expertise making it difficult to compare objectively the different methods [27-29].

In perfusion CT it is necessary select the region most favourable to the occurrence of stroke, being the area that is more relevant to observe, because the currently equipment doesn't permit to see the entire brain [7, 17, 25].

In comparison with other techniques such as Magnetic Resonance Imaging (MRI), perfusion CT is more widespread. The perfusion CT has several advantages within the clinical environment and in the stroke management limited clinical decision time:

- It is acquired in equipments that are commonly available in hospitals;
- Does not require specialized equipment for monitoring when compared with MR;
- Does not require to know if the patient contains metals or implanted devices such as pacemakers – an advantage when compared with MR;
- Only takes a few minutes, not requiring the patient to quiet for a long time;
- The exam can be performed with a low rate injection of contrast material and allows simultaneously collection data for CT Angiography (CTA);
- Regarding diagnostic, perfusion CT provides rapid detection of anomalies and allow the distinction between infarct penumbra (recoverable) and infarct core (no recoverable).

The main downside is that this method has a poor coverage area of the brain (typically 4 slices and 5-10 mm of thickness) and is not free of radiation since it uses X-ray instead of MR that is free of radiation [9, 17, 22].

More information about data acquisition can be found in these papers [7, 14, 26, 30].

2.2. Perfusion Related Parameters: Methods and Models

Most of the perfusion related parameters used in perfusion CT were initially defined by Leon Axel in 1980 [20] adapting the theory of fluid flow to the tomography data. Among them the more relevant in the literature and in clinical diagnose are the Cerebral Blood Volume (CBV), Cerebral Blood Flow (CBF), Mean Transit Time (MTT), Permeability and Time To Peak (TTP).

These perfusion parameters are often expressed quantitatively (e.g. ml/g) (see [7, 9, 20]). However providing reliable quantitative values may be difficult since they depend on many non-controllable external conditions such as blood pressure, patient movements. For that reason most clinical experts prefer to perform visual comparison of perfusion parameters between different brain areas, typically the brain hemispheres.

2.2.1. Cerebral Blood Volume

Cerebral Blood Volume (CBV) is a functional parameter corresponding to the percentage of blood per unit volume of brain tissue. It is closely related to variations of the size of blood vessels. Under normal conditions the CBV are between 4 and 5 $ml.g^{-1}$ (amount per 100g of tissue). When a cerebral stroke occurs, CBV is usually higher in penumbra because of the blood accumulation from neighbouring territories and the auto regulation mechanism that causes vasodilatation but low in the infarct core because the blood supply was compromised [7-9, 17].

Given a certain amount of contrast material m (mg) and knowing the concentration c (mg / ml) in a fluid, it is possible to obtain the total volume V (ml) of the solution using the following formula:

$$c = \frac{m}{V} \qquad \text{Eq. 1}$$

A typical simplification is to assume only a single inflow and outflow for the contrast material. This assumption does not consider recirculation and consider that the contrast leaves the system at the end.

Knowing the quantity of tracer administered and its concentration and generalizing the equation Eq. 1, it is possible to calculate the volume and flow between the inflow and outflow site. If the tracer is injected at a constant rate i (mg/s) in a fluid with a steady flow F (ml/s), the concentration c (mg/ml) at equilibrium is given by:

$$c = \frac{i}{F} \qquad \text{Eq. 2}$$

This model does not consider the recirculation and the equilibrium are not achieved.

For that reason other methods do not assume such stability and rely in modelling the concentration as a function of time. A very common model is to consider that the concentration at the outflow is a function of time $c(t)$ that increases to a peak and returns to zero (as depicted in Figure 3). In a short period of time Δt, the amount of tracer that leaves the system is given by $F.c(t).\Delta t$. Assuming that the amount of injected contrast material – sum (or in the limit the integral when $\Delta t \rightarrow 0$) – that leaves the system must be equal to the original amount of tracer introduced into the system (in absence of recirculation) we achieve the formulation in Eq. 3.

$$m = \int_0^\infty F.c(t)dt \qquad \text{Eq. 3}$$

m being a known, $c(t)$ can be calculated, assuming a constant flow as in Eq. 4:

$$F = \frac{m}{\int_0^\infty c(t)dt} \quad \text{Eq. 4}$$

The integral represents the area under the concentration curve in function of time.

Considering *h(t)* (distribution function) the fraction of tracer that leaves the system per unit time, *F* the fluid flow and *c(t)* the concentration in the fluid, according to the equation Eq. 3 we have:

$$h(t) = \frac{c(t)}{\int_0^\infty c(t)dt} \quad \text{Eq. 5}$$

Assuming a flow *F* coming to the brain tissue, the amount of contrast material flowing in arteries is a product of *F* integral and artery concentration $c_a(t)$. The amount of contrast material administered and leaving the system must be equal, since the concentration in tissues is a fraction *f* of the intravascular concentration. Thus we obtain the following equalities (Eq. 6 and Eq. 7):

$$c_t = f.c_v \quad \text{Eq. 6}$$

$$\int_0^\infty F.c_a(t)dt = \int_0^\infty F.c_v(t)dt = \frac{1}{f}\int_0^\infty F.c_c(t)dt \quad \text{Eq. 7}$$

If the flow is constant, the equation Eq. 7 cancels out and we get the equation Eq. 8.

$$f = \frac{\int_0^\infty C_t(t)dt}{\int_0^\infty C_a(t)dt} \quad \text{Eq. 8}$$

The integral of the concentration indicates the fractional vascular volume (CBV), this volume represents the ratio between the area under the concentration curve of the contrast material $C_t(t)$ through the brain tissue (parenchyma) and the area under the curve of the artery $C_a(t)$ or vein $C_v(t)$, if Blood Brain Barrier (BBB) is still intact the results are the same. The integral can be replaced by a sum as we are in discrete time [20, 31].

$$\text{CBV} = \frac{\int_0^\infty C_\text{t}(t)dt}{\int_0^\infty C_\text{a}(t)dt} = \frac{\int_0^\infty C_\text{t}(t)dt}{\int_0^\infty C_\text{v}(t)dt} = \frac{\sum_0^\infty C_\text{t}(t)}{\sum_0^\infty C_\text{a}(t)} = \frac{\sum_0^\infty C_\text{t}(t)}{\sum_0^\infty C_\text{v}(t)} \quad \text{Eq. 9}$$

In another method proposed by Klotz and König [31], CBV is determined using only maximum concentration values in tissue and vein, according to equation Eq. 10.

$$\mathrm{CBV} = \frac{\max C_{\mathrm{t}}(t)dt}{\max C_{\mathrm{v}}(t)dt} \qquad \text{Eq. 10}$$

2.2.2. Cerebral Blood Flow

Cerebral Blood Flow (CBF) represents the time a certain amount of blood takes to flow through the brain vessels and arrive to the veins, in infarct penumbra and infarct core the CBF is low because of the artery obstruction.

Normal values of CBF are between 50 and 60 $ml.g^{-1}.min^{-1}$. The CBF is controlled by changes of the diameter of blood vessels and remained relatively constant due to the auto regulation mechanism. With values below 35 $ml.g^{-1}.min^{-1}$ (50 to 60% of normal) protein syntheses in neurons is terminated due to lack of energy. In this state the cells survive while the CBF is maintained. Less than 20 $ml.g^{-1}.min^{-1}$ (30 to 40% of normal) cellular metabolisms can not be maintained, this tissue is not neurologically functional but is recoverable. If this continues (low CBF threshold of ischemia) for 2 to 3 minutes, the cells begin to die and thus becomes impossible to recover, defined as penumbra or tissue-at-risk. For values below 10 $ml.g^{-1}.min^{-1}$ (<20% of normal) cell death occurs. These values refer to amounts per 100g of tissue [7, 17].

CBF can be obtained using Fick's method, calculating the derivation of time-concentration curve for a given Region of Interest (ROI). The Fick's law analyze the diffusion of a fluid between high concentrated regions to low concentrated over time.

This method relies on the assumptions of single blood inflow and outflow and uses equation Eq. 11 to estimate the CBF where parameter t_{max} represents the instant of maximum slope (maximum derivation in upslope segment of the curve, see Figure 3) of the concentration curve. If the maximum tissue slope is reached before venous outflow starts $C_v(t_{max}) = 0$ and equation Eq. 11 turns into equation Eq. 12.

$$CBF = \frac{dC_t(t_{\max})/dt}{C_a(t_{\max}) - C_v(t_{\max})} \qquad \text{Eq. 11}$$

$$CBF = \frac{dC_t(t_{\max})/dt}{C_a(t_{\max})} \qquad \text{Eq. 12}$$

This method doesn't require correction for recirculation of contrast material and the results are obtained from a short period of time, however, it is more susceptible to noise and require pre-processing to reduce noise [13, 26, 31-32].

The CBF can also be seen as the ratio between the maximum derivative in upslope segment of the curve and the difference between the concentration on artery and vein when maximum slope occurs. The maximum slope is an estimate of blood speed ($ml.g^{-1}.min^{-1}$) and is calculated as a difference between the value in current time and previous time.

Another method widely used for calculating the CBF is based on deconvolution. Deconvolution is a process that restores the original signal after convolving data. Convolution is the process of feeding one function through another function. More information can be found in books of signal processing [33-34].

The main advantage is that, by using this method, it is possible to achieve good CBF estimation with smaller administration rates of contrast material since delay and dispersion of the contrast material is corrected using the residue function.

Deconvolution based methods based on Singular Value Decomposition (SVD) (or standard SVD – sSVD [35]) in most commercial applications. This method is less sensitive to variations in vascular anatomy because of the assumption of the single point of input and output blood. The deconvolution can also be obtained mathematically by the method of Fourier transform (Laplace transform and Z transform) [13, 30].

The variation of contrast concentration tissues can be described in function of Arterial Input Function (AIF – $C_a(t)$), the residue function ($R(t)$) and CBF, The $\otimes$ represents the convolution (extern product).

$$C_t(t) = C_a(t) \otimes R(t) \cdot CBF \qquad \text{Eq. 13}$$

The residue function $R(t)$ represents the fraction of the contrast material that remains in the tissue at time t. The CBF is proportional to the maximum height of the residue curve. The final CBF in each voxel is the maximum value of $R(t)$ [13, 35-38]. In our implementation, we compute $R(t)$ using SVD.

According to Ostegaard et al. [37] the tracer concentration over time in the venous outflow can be obtained by convolution of the artery concentration variation over time with a probability density function $h(t)$. However this function is rather sensitive to noise.

$$C_v(t) = C_a(t) \otimes h(t) \equiv \int_0^t C_a(\tau) h(t-\tau) d\tau \qquad \text{Eq. 14}$$

$$R(t) \equiv \left[1 - \int_0^t h(\tau) d\tau \right] \qquad \text{Eq. 15}$$

By definition $h(t)$ is a probability density function where $R(0) = 1$ and $R(t) > 0$ and is a decreasing function.

Since the concentration analysis performed for small and regular time intervals Δt, we can consider the residue function and arterial flow as constant and can use the following approach (Eq. 16 or Eq. 17):

$$C(t_j) = \int_0^{t_j} C_a(\tau).R(t-\tau)dt \approx \Delta t \sum_{i=0}^{j} C_a(t_j)R(t_j - t_i) \quad \text{Eq. 16}$$

Or

$$\Delta t \begin{bmatrix} C_a(t_0) & 0 & \cdots & 0 \\ C_a(t_1) & C_a(t_0) & \cdots & 0 \\ \cdots & \cdots & \ddots & 0 \\ C_a(t_{N-1}) & C_a(t_{N-2}) & \cdots & C_a(t_0) \end{bmatrix} \cdot \begin{bmatrix} R(t_0) \\ R(t_1) \\ \vdots \\ R(t_{N-1}) \end{bmatrix} = \begin{bmatrix} C_t(t_0) \\ C_t(t_1) \\ \vdots \\ C_t(t_{N-1}) \end{bmatrix} \quad \text{Eq. 17}$$

For simplification we can assume:

$$A \cdot b = c \quad \text{Eq. 18}$$

Where *b* is the value of the residue function and *c* is the concentration in tissue.

In the next paragraphs we explain how to determine CBF using the SVD. The equation Eq. 18 is solved using SVD. The method uses three matrices: V, W and U^T. W is a diagonal matrix, V and U^T are orthogonal matrices, U^T denotes a transpose matrix. The matrix and its inverse can be defined as:

$$A \cdot b = c \Leftrightarrow b = A^{-1} \cdot c \quad \text{Eq. 19}$$

$$A = U \cdot S \cdot V^T \quad \text{Eq. 20}$$

$$A^{-1} = V \cdot 1/S \cdot U^T = V \cdot W \cdot U^T \quad \text{Eq. 21}$$

$$b = V \cdot W \cdot U^T \cdot c \quad \text{Eq. 22}$$

Ostegaard et al. [37] assumes that $c_a(t)$ and $R(t)$ varies linearly with time, and the elements a_{ij} matrix A are:

$$a_{ij} = \begin{cases} \Delta t\left(C_a(t_{i-j-1}) + 4C_a(t_{i-j}) + C_a(t_{i-j+1})\right)/6 & 0 \le j \le i \\ 0 & otherwise \end{cases} \quad \text{Eq. 23}$$

This method is widely used for the calculation of inverse matrices because the matrix W is diagonal (diagonal values are zero or near to zero) making easier the calculation of the inverse matrix [35, 37-38].

However the delay in arrival of contrast material in brain tissue may cause an underestimation of CBF in order to try to correct the delay is possible using a SVD method with delay-corrected SVD (dSVD).

This method corrects the delay by shifting the tissue concentration curve in time. First the beginning of the upslope curve of time-concentration *c(t)* is determined then, t_d is the delay between the artery concentration curve and brain tissue curve (when the maximum derivation in concentration curve is achieved), *c'(t)* is the corrected concentration curve (Eq. 24).

$$C'(t) = C(t + t_d) \qquad \text{Eq. 24}$$

There is another method also using SVD that uses circular SVD (circular deconvolution) instead linear, this method is called block circulant SVD (bSVD). Circular convolution is a convolution of two periodic functions; a multiplication of two sequences is equivalent to the circular convolution of the two sequences in the time domain. More information can be found in books of signal processing [33].

The matrix A is an N×N matrix and for using bSVD we need an L×L matrix D, where L≥2N and using zero-padding [35, 38].

$$d_{i,j} = \begin{cases} a_{i,j} & , \quad \text{j} \le \text{i} \\ a_{L+i-j,0} & , \quad \text{otherwise} \end{cases} \qquad \text{Eq. 25}$$

Using the Fourier Transform (FT) the equation Eq. 14 becomes to Eq. 26. $F\{\ \}$ denotes the Fourier Transform and $F^{-1}\{\ \}$ the inverse Fourier Transform, F_t represents the tissue blood flow (CBF).

$$F\{C_v(t)\} = F_t \cdot F\{C_a(t) \otimes R(t)\} = F_t \cdot F\{C_a(t)\} \otimes F\{R(t)\} \qquad \text{Eq. 26}$$

The residue function can be calculated by the following equation:

$$R(t) = F_t^{-1} \cdot F^{-1}\left\{\frac{F\{C_v(t)\}}{F\{C_a(t)\}}\right\} \qquad \text{Eq. 27}$$

According to Zaharchuk [39]:

$$CBF \cdot R(t) = F^{-1}\left\{\frac{F\{C_v(t)\}}{F\{C_a(t)\}}\right\} \quad \text{Eq. 28}$$

This approach is very sensitive to noise, however a filter can be used to attenuate noise [37]. More information can be found in references [33, 37, 39].

2.2.3. Mean Transit Time

The Mean Transit Time is the average time necessary for the blood to flow through the brain.

Using the first moment of the curve (see Figure 3), MTT can be calculated using the equation Eq. 29.

$$\bar{t} = \frac{\int_0^\infty t \cdot C(t)dt}{\int_0^\infty C(t)dt} \quad \text{Eq. 29}$$

With *t=0* when the tracer enters into system and the concentration *c(t)* was measured at the outflow, so we have the ratio between the volume *V* and the flow *F* (Eq. 30)

$$\bar{t} = \frac{V}{F} \quad \text{Eq. 30}$$

Considering the instantaneous injection of tracer, the MTT is related to CBF, by Eq. 30 we obtain:

$$\bar{t} = f\frac{V}{F} \quad \text{Eq. 31}$$

The MTT can be defined as a density function, where *h(τ)* represents a probability density function – transport function [37].

$$MTT = \frac{\int_{-\infty}^{\infty} \tau.h(\tau)d\tau}{\int_{-\infty}^{\infty} h(\tau)d\tau} \quad \text{Eq. 32}$$

Another method proposed by Axel [20] of approximating the MTT considers the area of the curve divided by its height according to the equation Eq. 33, where *height* is the difference between C_{max} and C_{min} for each voxel.

$$\bar{t} = \frac{\int_0^\infty C(t)dt}{height} \Rightarrow \frac{\sum_0^\infty (C(t) - C_{\min}(t))}{C_{\max}(t) - C_{\min}(t)} \quad \text{Eq. 33}$$

At time *t=0* the concentration is zero but the equipment give us other value, for artery voxel *C(t=0) ≈ 800 HU* – Hounsfield units, because of that is necessary to translate the concentration curve to zero [20-21].

According to Phillips the MTT can also be defined as the width of curve at half of the maximum value [22]. To estimate the width of the curve it is necessary determine the average perfusion value between in the upward and downward concentration curve slopes is used as reference. This value is used to determine the points in both curve slopes that will be used to calculate the time difference that is the actual estimation of the MTT (see Figure 3).

We found in literature (see Smith [40]) more methods for the determination of MTT, described as a ratio between the integral of tissue concentration curve and the maximum value of the tissue curve.

$$MTT = \frac{\int C(t)dt}{C_{\max}(t)} \quad \text{Eq. 34}$$

2.2.4. Blood Flow and Transit Time Relationship

The CBF and MTT are inversely proportional: if the flow decreases the same amount of blood will take more time to flow through the brain.

The Central Volume Principle is based on a concept of transit time, injecting a bolus of tracer, the particles will take different paths and transit time; correlating the CBV, CBF and MTT [41].

Based on Central Volume Principle (Eq. 35) CBF can also be defined by the ratio of CBV and MTT [36], many authors support this method [35, 37, 40].

$$CBF = CBV / MTT \Leftrightarrow MTT = CBV / CBF \quad \text{Eq. 35}$$

The delay in arrival of contrast material in brain tissue (compared to the arrival time of the artery) may cause an underestimation of CBF and overestimation of MTT if it is calculated using Central Volume principle, the CBV almost does not change because the shape of the curve maintains the same [35, 38].

2.2.5. Permeability

Permeability measures how the vessels are permeable to particles of a specific size – that is, let them pass through their walls from the intra vascular to extra vascular space (space between cells and vessels), microvascular permeability is expressed in $ml.100cm^{-3}.min^{-1}$. Permeability Surface (PS) is given in ml/cm^3. In a normal brain permeability is equal to the CBV. After a stroke, permeability increases linearly over time because the Blood Brain Barrier (BBB) begins to be destroyed and became permeable to the contrast material, leading to accumulation of contrast agent outside the vessels; this effect is showed in Figure 4 [39, 42].

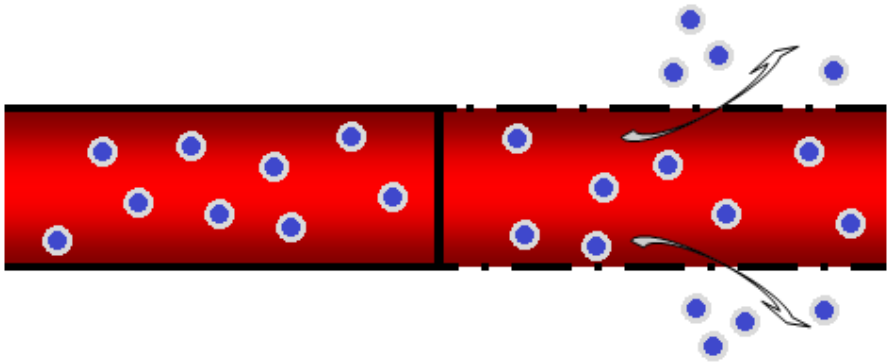

Figure 4 – Representation of permeability in two capillaries.
Intact Blood Brain Barrier (BBB) on left - not permeable and disrupted BBB on right - permeable to the contrast agent (adapted from [42]).

The contrast material flow through the parenchyma enabling the detection of changes in the density of brain tissue, it is maintained in an intravascular environment while the BBB is intact. The velocity of blood flow is correlated with arterial blood pressure. Patients with high permeability of BBB should not be treated with thrombolytic agents to avoid hemorrhages [23, 43-44].

The determination of Permeability Surface (PS) uses a two compartment model; one compartment represents intravascular space where the blood flows and other compartment consist by intracellular and extravascular extracellular spaces (see Figure 5). More information about the compartment model can be found in [39, 45].

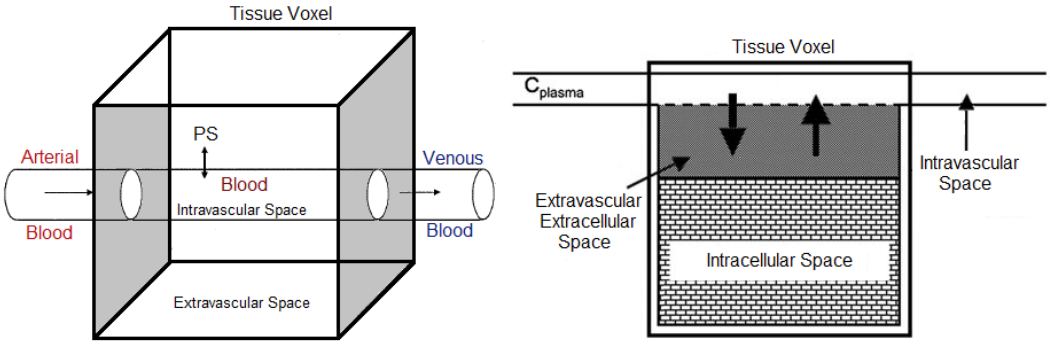

Figure 5 – Permeability Surface - two compartment model (adapted from [39, 45]).

Patlak et al. [46] have developed a graphical analysis technique based on the compartment model and linear regression developed a graphical analysis technique used to evaluate the concentration of contrast material in the blood. Using the formula for the Patlak plot we can obtain the PS using equations Eq. 36 to Eq. 38. In formula Eq. 36, *C(t)* represents the dynamic enhancement of a tissue voxel, $C_a(t)$ represents the dynamic enhancement of a reference blood vessel – the artery, CBV is the fractional Blood Volume, the parameter t_{max} represents the instant of maximum slope of the concentration curve and HU is Hounsfield units [47].

$$C(t_{\max}) = PS \times \int_0^t C_a(t)dt + CBV \times C_a(t_{\max}) \rightarrow PS = \frac{C(t_{\max}) - CBV \times C_a(t_{\max})}{\int_0^t C_a(t)dt} \quad \text{Eq. 36}$$

$$C(t) = HU_{brain}(t) - HU_{native\ brain}(t) \quad \text{Eq. 37}$$

$$C_a(t) = HU_{blood}(t) - HU_{blood\ brain}(t) \quad \text{Eq. 38}$$

In Zaharchuk [39], permeability is defined as a flow of contrast material normalized for surface area, concentration gradient and time. In equations Eq. 39 and Eq. 40 P is the Permeability (cm/s), S is the Surface area per unit mass (cm^2/g), M is the tissue Mass (g), $C_{plasma} - C_{EES}$ is the concentration difference between the two compartments ($mmol/cm^3$), because of dependency between P and S, these parameters appear together like PS product, originating equation Eq. 40, where ρ is the brain density ($\rho = 1.04$ [40]) and v_e is the EES volume fraction [39].

$$\frac{dC_{tissue}}{dt} = P \cdot S \cdot M \cdot (C_{plasma} - C_{EES}) \quad \text{Eq. 39}$$

$$\frac{dC_{tissue}}{dt} = PS\rho(C_{plasma} - (C_{tissue} / v_e)) \quad \text{Eq. 40}$$

2.2.6. Time To Peak

Time to Peak (TTP) is the time elapsed between the injection of the contrast material and the appearance a concentration peak in the cerebral blood vessels. This parameter is inversely related to the CBF since the reduction of blood flow leads to an increased time required to reach peak concentration in brain tissue. On the other side it is directly related to MTT since the increase TTP mean a bigger time necessary to the tracer leave the system.

Phillips [22] ignore the delay by subtracting the time between the start of injection and reach the cerebral tissue, but others authors [7, 21] doesn't ignore the time to start.

As we can see on Figure 6 the delay only provokes the addition of padding to the values of TTP image.

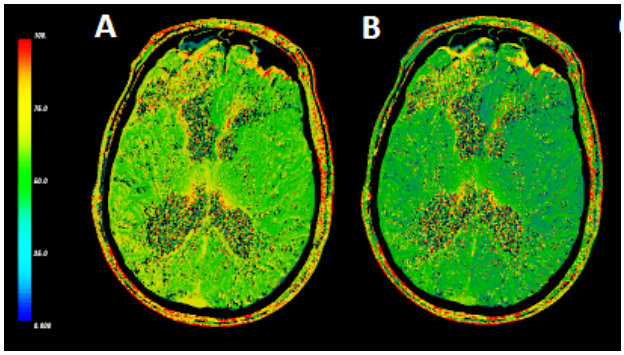

Figure 6 – The perfusion parameters estimation methods for TTP.
In A the delay isn't ignore and B we remove the delay.
These images have the same clinical information.

2.2.7. Mismatch and Penumbra Detection

According to Murphy et al. [14] the multiplication of CBF by CBV (Eq. 41) results in a better separation of the penumbra area and core area because of the matching between CBF and CBF in these two areas decrease. In core area both parameters combined (low CBF and low CBV) by other hand in penumbra area we have a mismatch (low CBF and normal or high CBV). With this we have low values in infarct core and high value in infarct penumbra.

$$CBF \times CBV \qquad \text{Eq. 41}$$

Also using CBV and MTT [48] (Eq. 42) we can view mismatches between them and distinguish infarct penumbra and infarct core.

$$CBV \times MTT \qquad \text{Eq. 42}$$

2.2.8. Recovery Potential Ration

A parameter important to support the diagnosis is the recovery potential by extension of affected area, Wintermark et al [12] defines the Recovery Potential Ratio (PRR) as:

$$PRR = \frac{\text{penumbra size}}{\text{penumbra size} + \text{core size}} \qquad \text{Eq. 43}$$

To apply this method we must select a ROI which is applied to Eq. 43.

3. Methods Implementation and Application

3.1. Pipeline

Our main objectives were to study and implement the perfusion parameters described in the literature and provide a controlled comparison environment for visual clinical assessment where the human intervention was kept to a minimum. With that in mind we developed a framework to calculate and display the perfusion parameters using an automatic processing pipeline for data visualization namely automatic visualization settings a window levels or colour scales (lookup tables). This ensured that, regardless of the method considered, the final visualization results will not be user dependent and quantified measure can be mapped directly to original data.

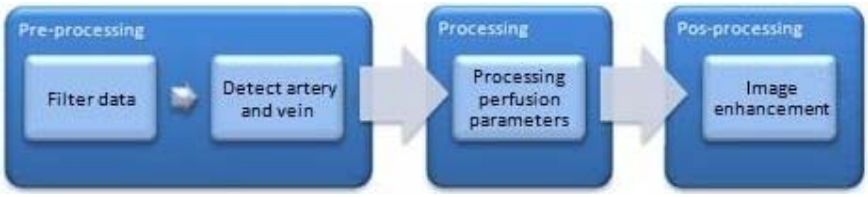

Figure 7 – Generic pipeline.

The pipeline starts with an initial filtering of the image data to minimize the presence of noise due to acquisition, patient movements or other effects like the one of data discretization or sampling [26, 38]. The following step is to detect the two main perfusion references: the artery – blood input – and the vein – blood output. This detection is based on the high contrast perfusion values and concentration curve signature of both artery and veins two reference voxels are automatically selected to be used as static reference along the following stages. Based on the reference voxels we process the several perfusion parameters and enhance the final images using some post-processing methods (Figure 7).

3.2. Pre-processing

The pre-processing step prepares data for the processing of perfusion parameters. In this section we will explain the several filtering methods and the automatic selection of the two reference voxels (one for artery and one for vein).

All methods that are present in this section are summarized in Table 1.

3.2.1. Simple Moving Average

Simple Moving Average (SMA) is a filter applied in time to the input data to minimize noise (Figure 8). It uses a time window that is applied to the current time. The result value is an average of surrounding values inside the window.

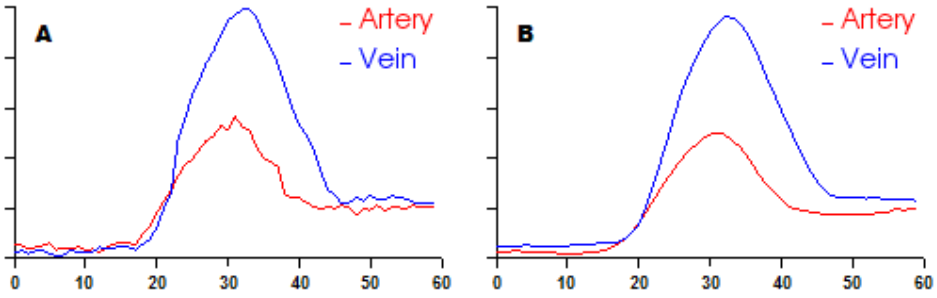

Figure 8 – Time concentration curve for artery and vein using SMA filter. Original data in A and using SMA filter for each voxel in B.

It has two modes of application, the first applies the filter for each voxel over time (Figure 9 – B), the second mode applies the filter to adjacent voxels in the same slice over time (Figure 9 – C), the filter is applied in 3 dimensions (width * height * time). The difference between these two methods is not significant for the voxels being analyzed however using the 2nd mode we smooth spatiality the image since information around the voxel is used resulting in a loss of definition (Figure 9 – F).

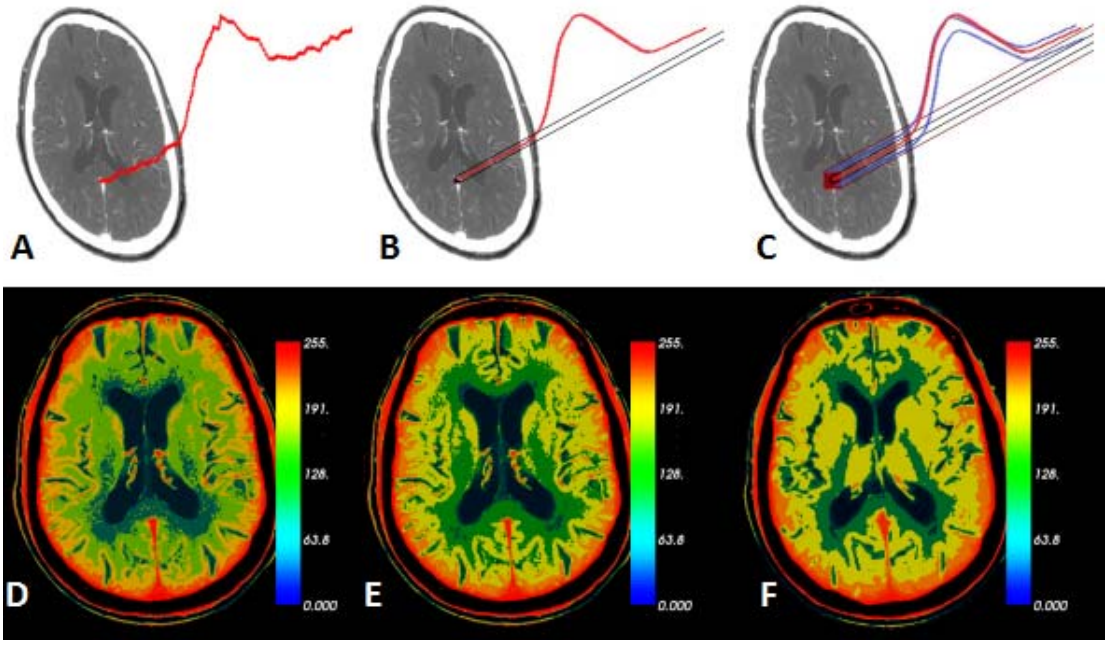

Figure 9 – Concentration curve and the changes by applying different types of filters. Without any filter (A) and CBF image (D); Application of the filter to a single voxel over time (B) and CBF image for that filter (E); Application of the filter to adjacent voxels in the same slice over time (C) and CBF image for that filter with low definition (F).

This filter, while simple, showed good results and with low processing time in 1st mode, around 1 minute.

3.2.2. Moving Median

Moving Median is a filter applied in time to the input data to minimize noise (Figure 10). It uses a time window that is applied to the current time. The result value is a median of surrounding values inside the window.

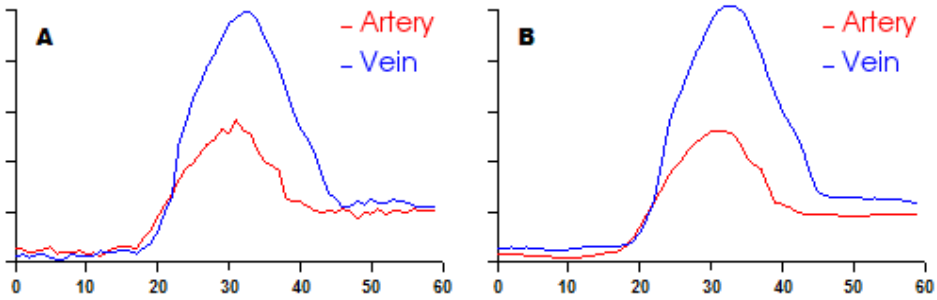

Figure 10 – Time concentration curve for artery and vein using moving median filter. Original data in A and using Moving Median filter for each voxel in B.

The operating procedure is similar to the previous method (see 3.2.1 Simple Moving Average).

This filter needs to sort data before to determine the median value and because that it is slow, takes about 45 minutes in 1st mode.

3.2.3. Smooth Curve

This method applies a gaussian filter for each voxel over time (Figure 9 – B). For each voxel it uses a gaussian curve fitting. This method is adequate since the shape of the curve is similarly to a gaussian curve. In fact, the results are very similar to the SMA filter but with much larger processing time, take about 2 hours (Figure 11).

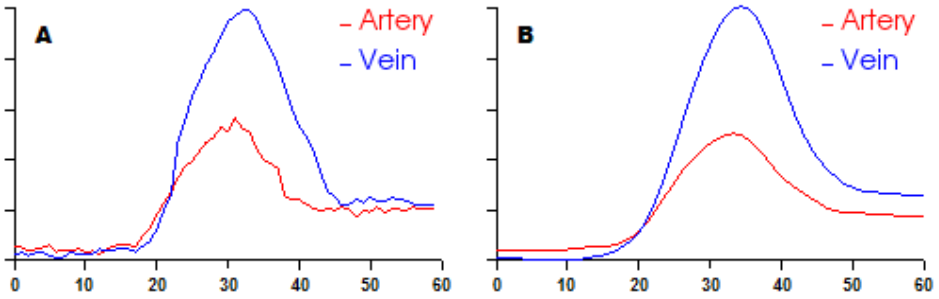

Figure 11 – Time concentration curve for artery and vein using smooth curve filter. Original data in A and using smooth curve fitting filter for each voxel in B.

3.2.4. Delay corrected

In some patients the tracer arrive to the tissue brain with some delay comparing to the concentration curve of artery reference (see Figure 12), this delay may influence the results of some parameters (principally the CBF – delay-corrected SVD methods). This correction should be applied before processing the data [35].

This method corrects the delay by shifting the tissue concentration curve in time [35] (Eq. 24).

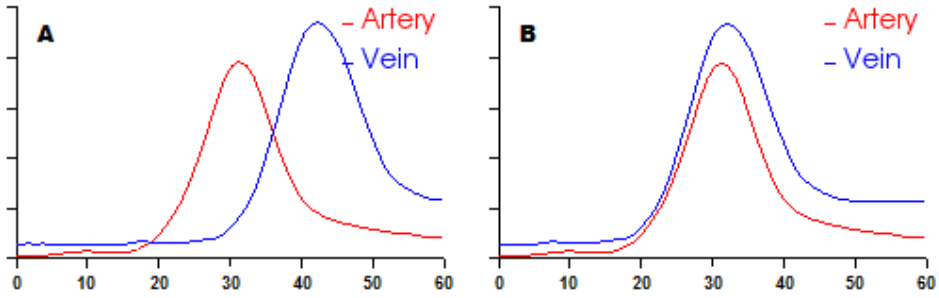

Figure 12 – Time concentration curve for artery and vein using delay corrected filter. Data without delay corrected in A and using delay corrected filter in B.

3.2.5. Bone Identification

In terms of the perfusion parameters calculation bone is non-relevant and can be excluded from the calculation process to improve the overall efficiency of the processing. Supported on the time modulation of the brain tissue correlated with artery perfusion, using the artery concentration curve, one can clearly identify bone. In Figure 13, it is possible to se the reference values voxels where the concentration is oscillating (Figure 13 – B) or versus the always high values over time found in the bone (Figure 13 – A), in Figure 13 – C the

concentration variation can not start with high values, at time 0 should be like curve B. The curve Figure 13 – D represents noise or artefacts from the machine. Through this process is possible to identify the voxels to exclude bone from the processing or remove by masking them.

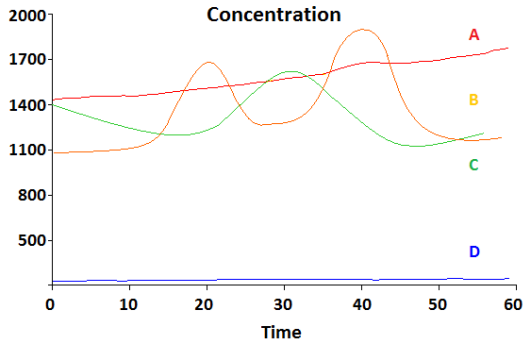

Figure 13 – Concentration curve in invalid reference voxels.

For proper use of this method the selection of artery and vein must be correct since the values in these voxels are used as references.

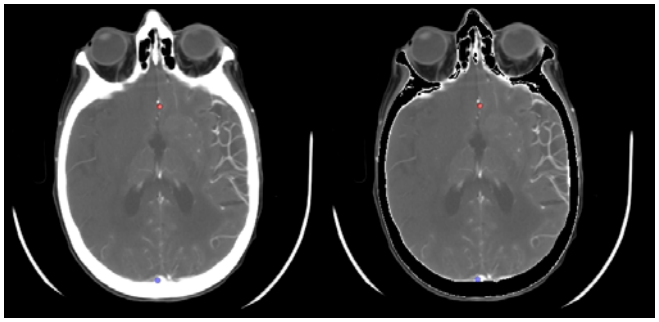

Figure 14 – Bone removal filter.
Original CT image on left and CT image filtered using bone removal filter on right.

This method still needs some improvements since many non interesting voxels are not filtered (for example non-brain voxels within the range or bones) as we can see on Figure 14. However it is a good first approximation to the area of interest (the brain) and helps the analysis by neurologists.

3.2.6. Removing Unwanted Voxels

Two main categories of unwanted voxels exist: artefact of the CT machine - head support signature - and bone.

For removing the bone, a binary mask is used; combining the bone segmentation (3.2.5 Bone Identification) and the original image, removing the unwanted voxels by a close operation (dilate and erode). To avoid some noise originated by the mask creation and for an accurate result we shrink the mask (erode operation). The mask is applied to all voxels by multiplying each voxel of the CT image by a correspondent voxel on mask. The overall process is depicted in Figure 15.

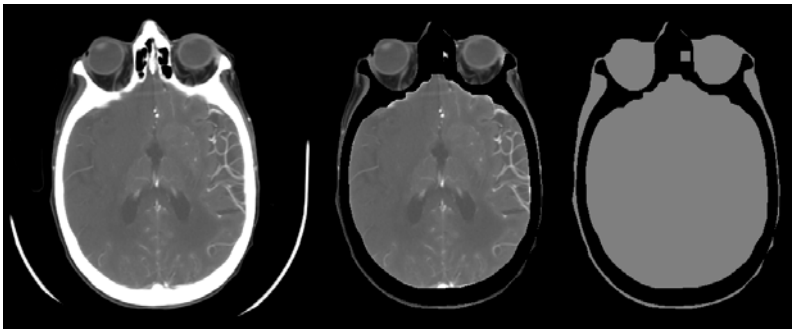

Figure 15 – Filtering unwanted voxel.
Original CT image on left, CT image filtered on centre and the used mask on right.

The disadvantage of this method is not considering the patient movements because it is applied from the first image; however it is a good method for removing bone.

3.2.7. Time Variation Filter

This filter tries to improve the previous filter (Removing Unwanted Voxels) and analyze the voxel tracer concentration (Figure 16). Applies a mask using morphological operations (see 3.2.6 Removing Unwanted Voxels), after that the concentration variation of contrast material over time is analyzed. Each voxel only can cross the average value (between the minimum and maximum concentration value of reference voxel – artery) two times (unlike Figure 13 – B), in ascending section and descending section of the curve, if the voxel do not respect that that voxel are removed.

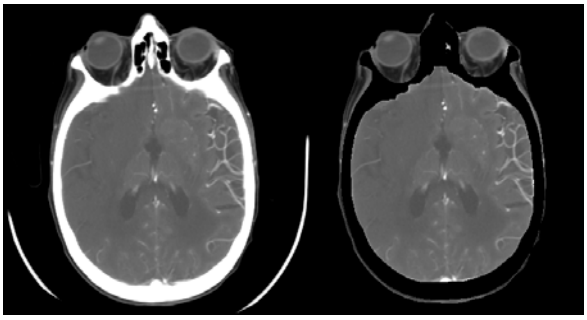

Figure 16 – Time variation Filter.
Original CT image on left and CT image filtered using a time variation filter on right.

This method tries to overcome the disadvantages of others methods removing all voxels that not respect a gaussian pattern, is a good method of extracting the bone too. If the patients move probably the concentration curve is irregular and the voxel will be removed.

3.2.8. Summary of Filters

The Table 1 summarizes all filters developed and possible to use.

Type of filter	Filter process	Method/ Description
Curve smoothest	Simple Moving Average	Smoothes the concentration curve using a moving average. Application over time and 3D. Fast method.
	Moving Median	Smoothes the concentration curve using a median value. Application over time and 3D. Slow method.
	Smooth Curve	Smoothes the concentration curve using OpenCV function. Application over time. Slow method.
Delay corrected		Corrects the arrival time of contrast material.
Cleaning image	Bone Identification	Removing voxels whose values out of range. Not remove some voxels with irregular concentration variation and maintain brain outliers.
	Removing Unwanted Voxels	Applying an image mask to the input data. Remove almost all artefacts but do not contemplate patient movements.
	Time Variation Filter	Applying an image mask to the input data. Removes voxels that not respect a gaussian pattern and maintain brain contours.

Table 1 – Overview of filters.

3.3. Processing

The implementation of several methods used in the literature for determination of perfusion parameters are demonstrated in section 2.2 (Perfusion Related Parameters: Methods and Models), the results and the evaluation made by the clinical experts are in the section 4.1 (Results).

Beside the usual perfusion parameters presented before (CBV, CBF, MTT) we also develop to additional measure (methods) that may provide additional information that can be of interest:

- Transit time
- Concentration Amplitude of the Contrast Material

3.3.1. Transit Time

Transit Time (TT) represents the time that blood takes to flow through the brain. It is calculated by determining, for each voxel, the maximum concentration and the time that maximum occurs. The obtained image has the same dimension of perfusion CT image making it possible navigate though images along time and visualize, for the current time, the voxels with maximum concentration (see Figure 17).

In Figure 17, the red colour represents a maximum concentration, at 32 when the contrast material concentration rises to a peak in the artery (A) and at 38 when the contrast material concentration rises to a peak in the vein (V). The green colour represents voxels where the maximum concentration not yet occurred. The blue colour represents voxels where the maximum concentration already occurred. From 32 seconds to 38 seconds changes in colours can be associated with changes flow namely when green voxels became red (maximum concentration achieved) or when red become blue (the contrast material leaves the brain cells).

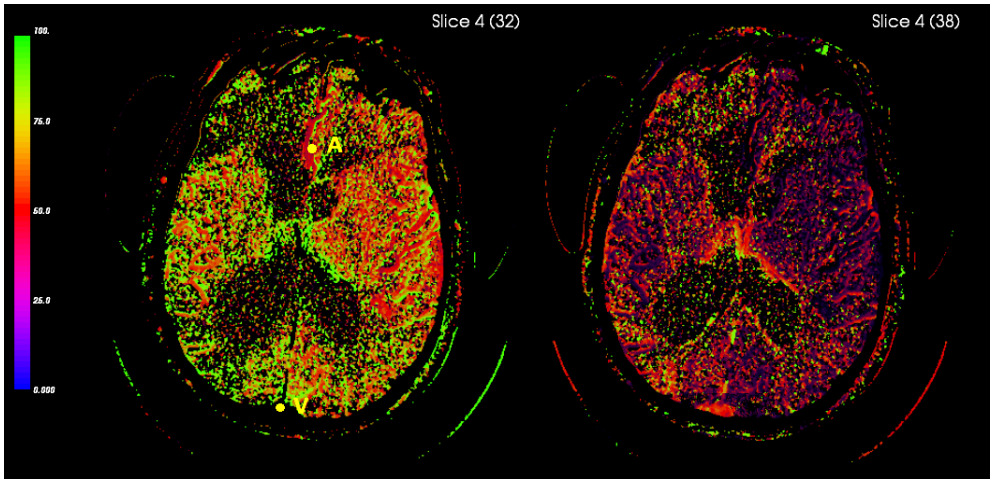

Figure 17 – Blood Transit Time

These preliminary results were attractive for the clinical experts because they gives similar and complementary information that obtained by MTT transmits the notion of time.

3.3.2. Concentration Amplitude of the Contrast Material

Concentration Amplitude of the Contrast Material represents amplitude of variation of the contrast material. The objective of this method was to identify voxels where the contrast material concentration doesn't change, indicating that the region is damage (see Figure 18).

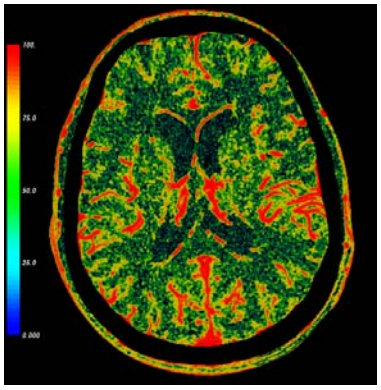

Figure 18 – Concentration variation of the contrast material**.**

3.3.3. Summary of Perfusion Parameters

The Table 2 summarizes all perfusion parameters developed and possible to use.

Perfusion Parameter	Method	Equation	Description
CBV	Artery	Eq. 9	The ratio between the area under the concentration curve of the contrast material and the area under the artery curve.
	Vein	Eq. 9	The ratio between the area under the concentration curve of the contrast material and the area under the vein curve.
	Max Vein	Eq. 10	The ration between the maximum concentration value in tissue and vein.
	Max Artery		The ration between the maximum concentration value in tissue and artery.
CBF	sSVD	Eq. 17 to Eq. 23	Determination of CBF using singular values (SVD).
	dSVD	Eq. 24	Determination of CBF using delay-corrected SVD
	bSVD	Eq. 25	Determination of CBF using block circulant SVD
	Fick	Eq. 11	Uses maximum derivation, the ratio between the tissue and the difference between artery and vein.
	Max Derivation	Eq. 12	Uses maximum derivation, the ratio between the tissue and artery.
	Central Volume	Eq. 35	The ratio between each voxel in CBV and MTT image.
MTT	Axel	Eq. 33	The area under the curve divided by its height.
	Phillips		Width of curve at half of the maximum value.
	Smith	Eq. 34	The ratio between the area under the concentration curve of the contrast material and the maximum value of the curve.
	Central Volume	Eq. 35	The ratio between each voxel in CBV and CBF image.
Permeability	Artery	Eq. 36	Determination of Permeability Surface
TTP	Phillips		The time elapsed between the injection and the appearance a peak.
Transit Time	Transit Time		Determines the maximum concentration and the time that occurs.
Concentration Amplitude	Concentration Variation of the Contrast Material		Determines the amplitude of variation of the contrast material
PRR	Potential Recuperation Ratio		Determines the potential recuperation ratio of the patient using CBV and other method

Table 2 – Overview of perfusion parameters.

3.4. Post-processing

The post-processing step is used to improve the contrast and enhance the processed images. This section will present the several methods we tested. All methods that are present in this section are summarized in Table 3.

3.4.1. Normalization

This section will present the several methods of normalize data that we can use.

Normalize to Range Values

This method allow a better comparison between several perfusion parameters or image because it normalizes all images to the same range values, this range can be configured [49]. In Figure 19, the image is normalized to the range [0,1].

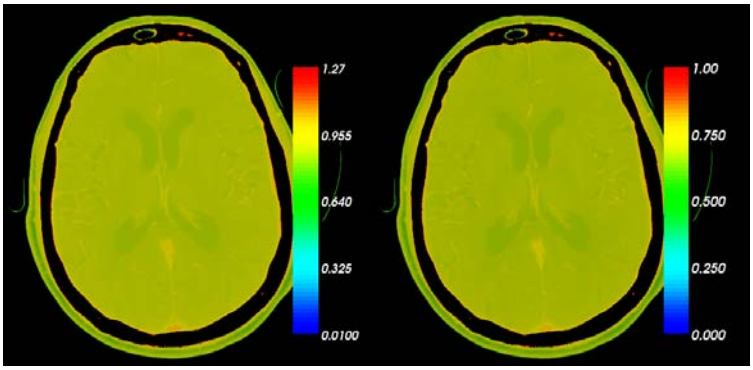

Figure 19 – Normalize image to range values.
Original image on left and image normalized on right.

Normalize to Zero Mean

This method normalize input image with zero mean [49], determines the average value of the image and centred all values around this value (shift down all values *average* value). In Figure 20, the image is normalized to zero mean.

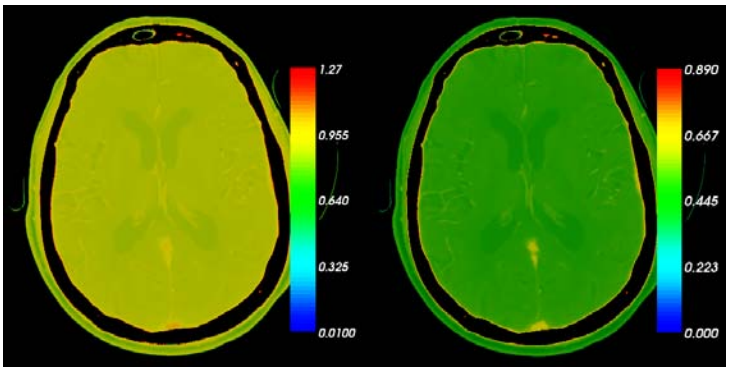

Figure 20 – Normalize image to zero mean.
Original image on left and image normalized on right.

Normalize to Zero Mean and Unit Standard Deviation

This method normalize input image with zero mean and unit deviation, [49], determines the average value and the standard deviation of the image and centred all values around the average value and with a unit standard deviation. In Figure 21, the image is normalized to zero mean and unit deviation.

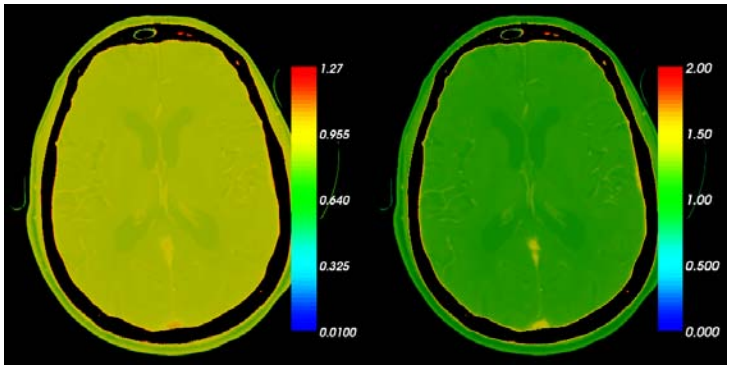

Figure 21 – Normalize image to zero mean and unit deviation.
Original image on left and image normalized on right.

Saturate image

This method saturate the input image with a given range values. Values bigger than *high* value are saturated at *high* and values lower than *low* value are set to *low*. In Figure 22 , the image is saturate to [0,1].

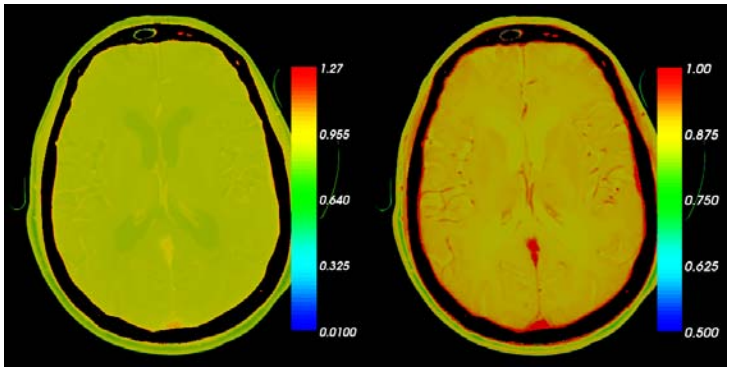

Figure 22 – Saturate image to range values.
Original image on left and saturated image with range [0.5 ; 1.0] on right.

Window Level Correction using Artery as Reference

This method truncates the image with the maximum value corresponding to the maximum value obtained in artery voxel (in image not in the concentration curve) and the minimum is a global minimum in the image (different to zero) (see Figure 23). By using an automatically generated reference we maintain a clear map between transformed and original perfusion values.

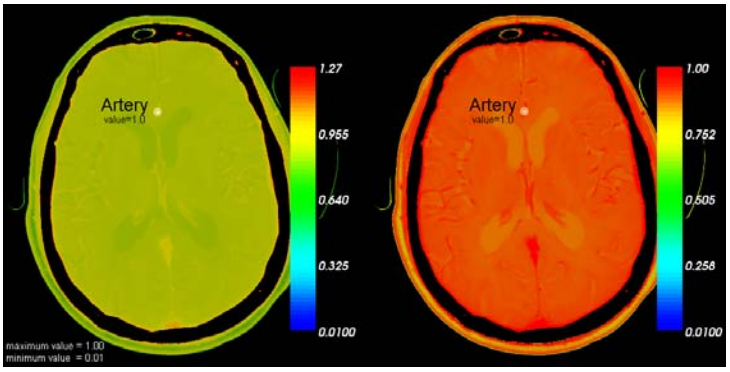

Figure 23 – Window level correction using artery as reference.
Original image on left and range correction image using window level correction [0.01 ; 1.0] on right.

3.4.2. Equalization

To enhance visually the different brain tissues (e.g. gray vs. white matter) and structures (e.g. brain tissues and ventricles) – expected to present different values regardless of the perfusion parameter in consideration – we also applied a histogram equalization method. The result of this step is emphasized in Figure 24.

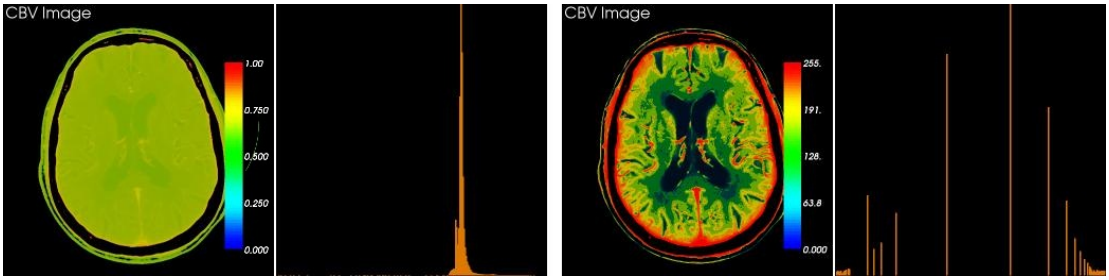

Figure 24 – Equalized image and histogram distribution.
Comparison between CBV before and after post-processing: initial CBV image (left) and after histogram equalization (right). The histogram distribution is also presented for both images.

3.4.3. Enhance the Image

This section will present the several methods to enhance the contrast of the image. These methods were applied only after the image equalization. These methods are not linear transformations and change the values in order to enhance visually characteristics of the images that can be later correlated to specific brain structures or areas such as the infarct penumbra. Our objective was to explore if using any of these transformation it was possible to highlight visually the infarct penumbra and infarct core; try to achieve results similar to those used by clinical experts.

Quadratic

This method applies a quadratic function in each voxel (Figure 25) using the equation Eq. 44. V is a voxel value.

$$V' = V^2 \qquad \text{Eq. 44}$$

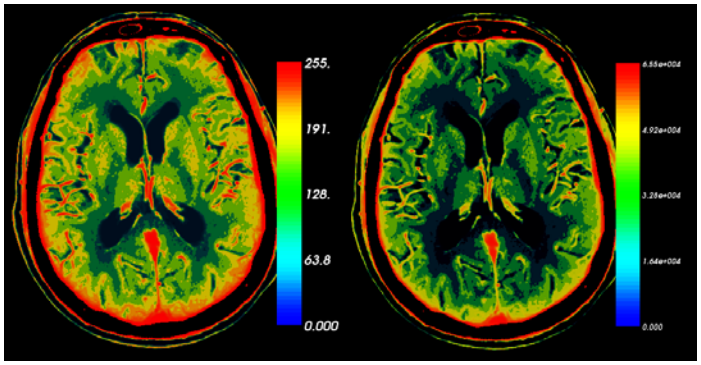

Figure 25 – Quadratic function filter.
Comparisons between an image with histogram equalization (left) and with a quadratic function filter (right).

Exponential

This method applies an exponential function in each voxel (Figure 26) using the equation Eq. 45. V is a voxel value and a is an adjustable parameter.

$$V' = e^{V/a} \qquad \text{Eq. 45}$$

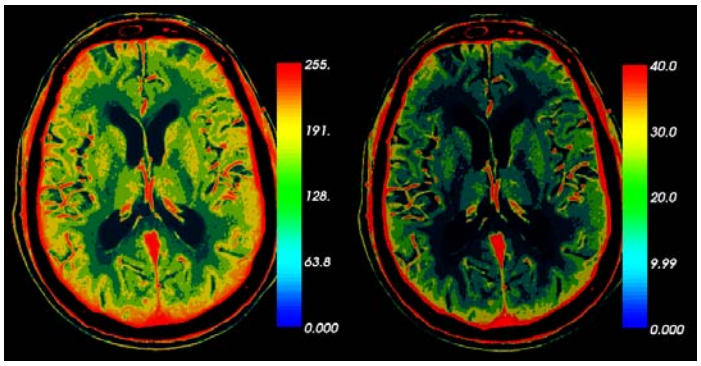

Figure 26 – Exponential function filter.
Comparisons between an image with histogram equalization (left) and with an exponential function filter (right).

Logarithm

This method applies a logarithmic function in each voxel (Figure 27) using the equation Eq. 46. V is a voxel value and a is an adjustable parameter.

$$V' = a \times \log(V) \qquad \text{Eq. 46}$$

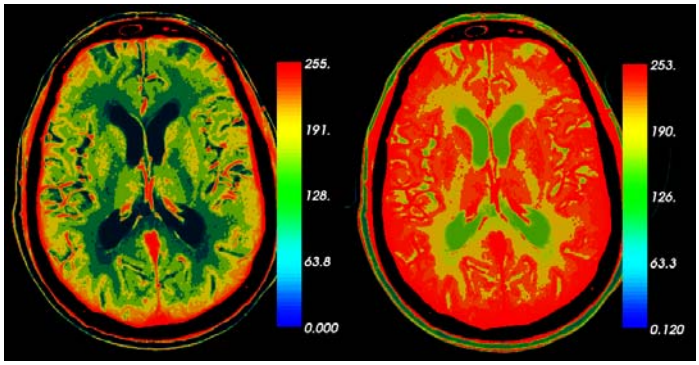

Figure 27 – Logarithmic function filter.
Comparisons between an image with histogram equalization (left) and with a logarithmic function filter (right).

Logistic

This method applies a logistic function in each voxel (Figure 28) using the equation Eq. 47. V is a voxel value, a is an adjustable parameter, t_0 is the time when occurs the inflection curve and *lim* is the superior limit.

$$V' = \lim/(1 + e^{-a(V - t_0)}) \qquad \text{Eq. 47}$$

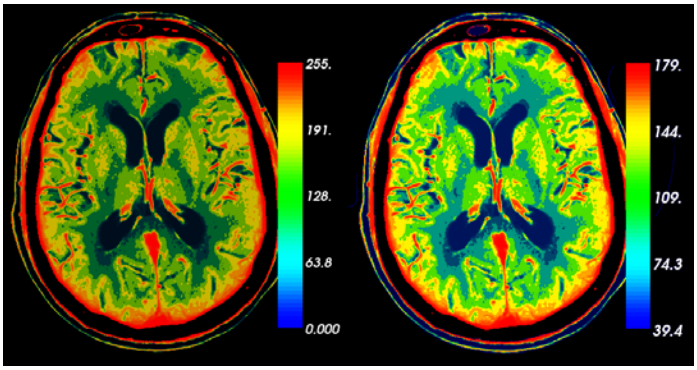

Figure 28 – Logistic function filter
Comparisons between an image with histogram equalization (left) and with a logistic function filter (right).

3.4.4. Summary of Post-Processing Methods

The Table 3 summarizes all post-processing methods developed and possible to use.

Post-processing Method	Description
Normalize to Range Values	Allow a better comparison between several perfusion parameters or image because normalize all images.
Normalize to Zero Mean	Normalize input image with zero mean.
Normalize to Zero Mean and Unit Standard Deviation	Normalize input image with zero mean and unit deviation.

Saturate image	Saturate the input image with a given range values.
Artery Correction	The image is truncated with the maximum value corresponding to the maximum value obtained in artery voxel.
Equalization	Equalize the image using a histogram distribution.
Quadratic	Application of a quadratic function. This method should be applied after equalization method.
Exponential	Application of an exponential function. This method should be applied after equalization method.
Logarithm	Application of a logarithm function. This method should be applied after equalization method.
Logistic	Application of a logistic function. This method should be applied after equalization method.

Table 3 – Overview of post-processing methods.

3.4.5. The Pipeline Discussion

The final implementation of the processing pipeline for perfusion CT was based on the steps described in Figure 29.

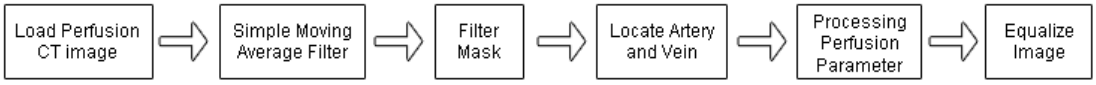

Figure 29 – Implemented pipeline

The first step used a Simple Moving Average (SMA) filter chosen among others like Moving Median, Smoothing filters. This selection was a good trade-off between simplicity and results. Preliminary tests with a 7 seconds window centred in the current time (t-3, t+3) shows that SMA can remove noise and smooth with low processing time.

After filtering the data, the non-brain tissues (e.g. bone) were extracted using a mask prior to the perfusion parameters calculations using as reference the values for both artery and vein contrast calculated earlier. For visualization purpose an equalization was applied to the image (Figure 29) followed by a normalization in order to produce all final images within the same range of values. In our case the range of 0 to 100 was used.

In the application, it was allowed to apply further non-linear transformation based on the Quadratic, Exponential, Logarithm or Logistic functions.

In Figure 30 is depicted the consequence of change the order of non-linear transformations (e.g. logistic function) in the pipeline for a CBV image in order to achieve the ground truth image. In A we have the original CBV image, with equalization in B, in C is the CBV image when applied the transformation function before equalization, D the transformation function is applied after the equalization and E is the ground truth.

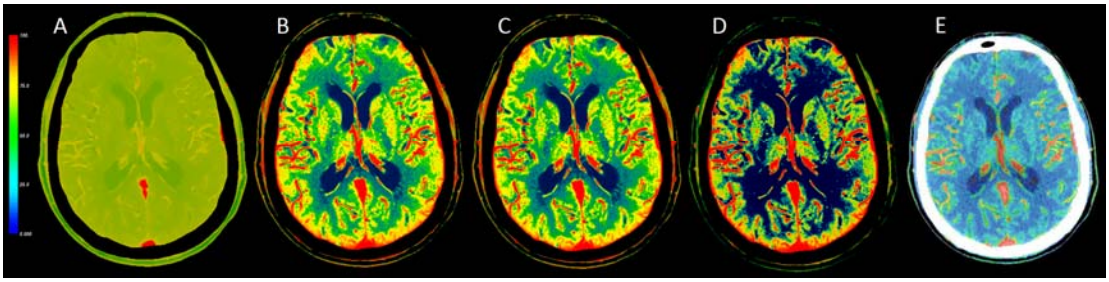

Figure 30 – Application of a logistic function on CBV image.
Original image (A); Equalized image (B); Application of transformation before equalization (C); Application of transformation after equalization (D); Reference image (E).

3.5. Additional Tools

Along the application development several auxiliary methods needed to be implemented to support the processing of the data. Among them are:

- An automatic method to find the artery and the vein
- Calculated the mismatch between two parameters based on combination of both or on combined threshold strategy.

3.5.1. Find Artery and Vein

The correct location of an artery and vein is crucial for determining the values of reference used in the calculation of several perfusion parameters. The method implemented is automatic but not 100% effective. For that reason, in the application the user can still select manually the artery and vein reference voxels. The method assumes boundaries in which both the artery and the vein can be found. It is assumed that the coordinate X of artery and vein varies between a quarter of image width and three quarters of image width, the coordinate Y of artery is located in upper half image and the vein in bottom half image, according to the Figure 31.

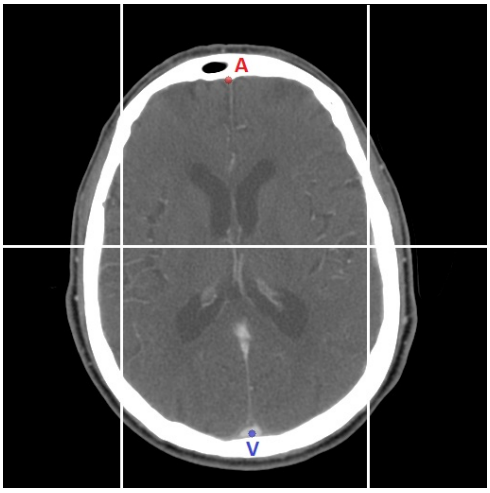

Figure 31 – Limits of location of artery and vein.

According to Figure 31 it is possible to assume that the artery and vein is located always in the same regions, even if the head is inclined and can be in different slices.

3.5.2. Mismatch

Although most of our attention has been spent with individual perfusion related parameters it is possible to combine two or more of the previous parameters and look for combined patterns that have a clinical value. According to the literature we have two types of mismatch: one that combines two images through a mathematical relation (e.g. by multiplying) and established threshold on the transformed image, the other based on combining visually the information based on intersecting areas defined through parameter related thresholds. In both cases, it is expected that it is possible to detect the infarct penumbra and infarct core by exploring the threshold values and/or the mathematical transformations.

Multiplying images

According to Murphy [14] the multiplication of CBF by CBV results in a good separation of the penumbra area and core zone once both parameters combine in the stroke area, with major variation in the penumbra (Figure 32).

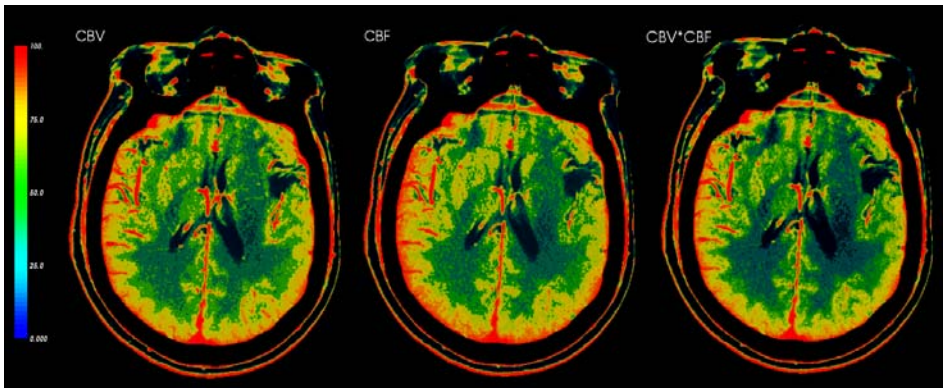

Figure 32 – CBV×CBF operation.

It is also possible to multiply the CBV by MTT [48] that results in a better separation of the penumbra area and core zone once both parameters combine in the stroke area (Figure 33). It is necessary to determine the CBV and MTT image previously.

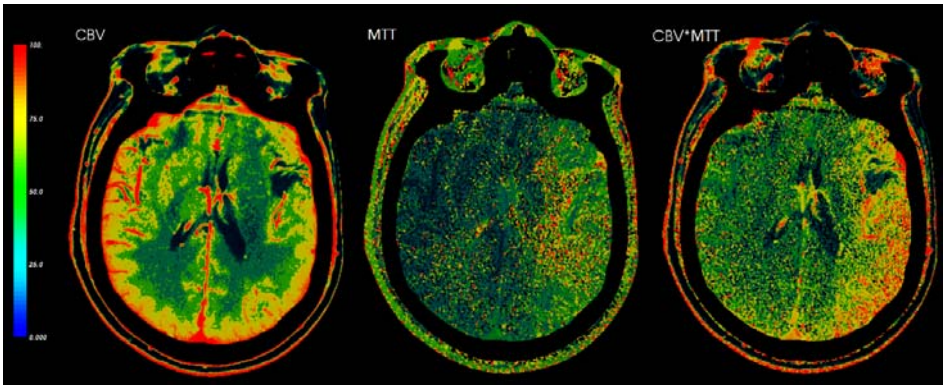

Figure 33 – CBV×MTT operation.

Combining Visually Images

On discussion with the neurologists and knowing that Siemens ® generate a mismatch image similar to what we are looking for, we developed a tool in the application that enables the mismatch of CBV vs. CBF, MTT and TTP based on setting threshold for each of the parameters used.

In Figure 34, CBV and TTP were combined (both parameters were normalized to the range 0 to 100). The penumbra is defined by CBV below 50 and TTP upper 50. The infarct core is defined by CBV lower than 25 and TTP upper than 50.

These thresholds can be defined using the track bars (Figure 39 – J) and it is possible to put overlap image over CT image (Figure 34 – right).

In the Overlapping image we have a mask when the three conditions are true, on CT image yellow area is the penumbra area (CBV high and CBF low) and blue are infarct core (CBV and CBF low).

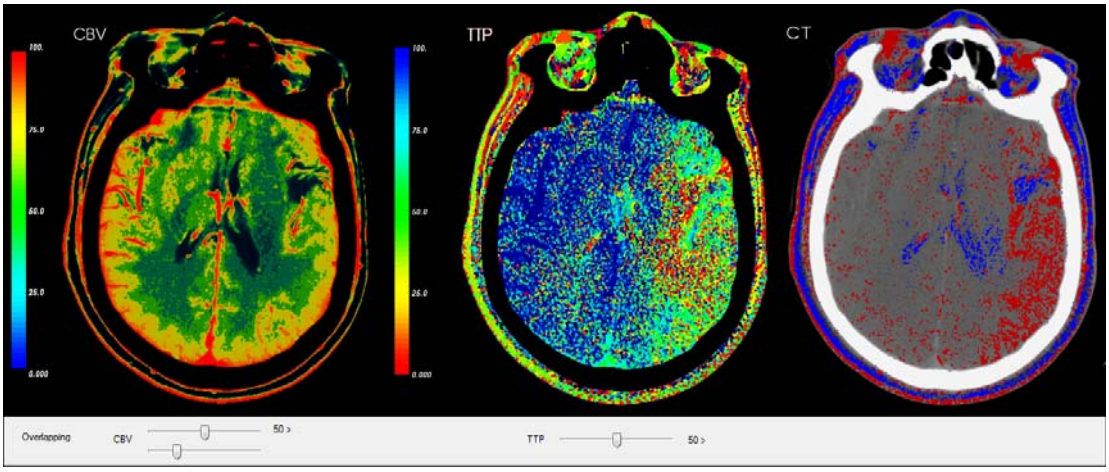

Figure 34 – Mismatch areas.
CBV image on left, TTP image on centre and overlap the mismatch over CT image on right.

As referred previously, it also possible to combine CBV with MTT, CBF or TTP (3.7 Graphic User Interface, Figure 40 – B). Indirectly we are combining mathematically related parameters as MTT is proportional to TTP and inversely proportional to CBF.

The objective is to determine the infarct core and penumbra area and calculate the Potential Recuperation Ratio (PRR). PRR is the ratio between the infarct penumbra area and the sum of infarct penumbra and infarct core area; and it is calculated for each slice. For an accurate result it is necessary to remove the ventricles from the image, to do that we analyse the large connected areas (blobs) or use a ROI.

The use of the values referred above was chose empirically.

Using the determination of mismatch by the overlapping the CBV and CBF image on CT and analyzing the infarct core and penumbra areas it is possible to calculate the PRR, for do that it is necessary to remove the ventricles from the image for an accurate result. On Figure 35 it is possible to see the infarct core (blue) and penumbra (red) and the PRR results for each slice.

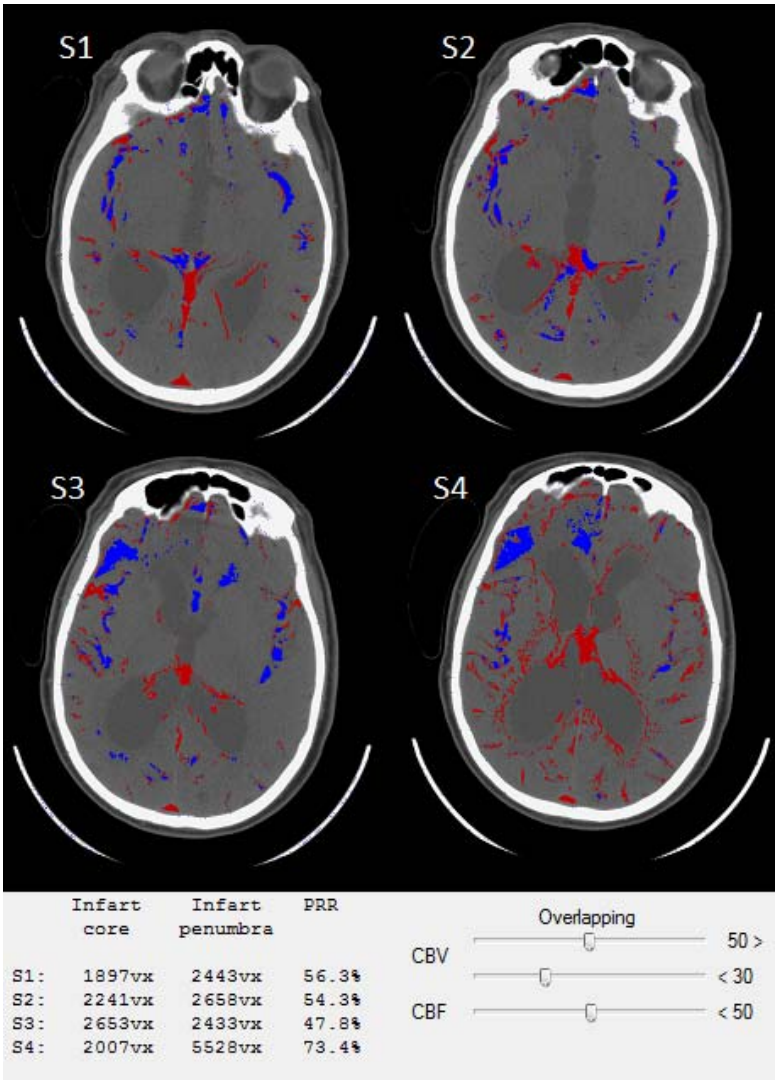

Figure 35 – Mismatch between CBV and CBF.
Mismatch overlapped on CT image and the PRR results, for each slice.

Other Trial Methods with Mismatch

A common way to compare in imaging is to establish two ROI and then perform a quantified comparison. We develop two automatic approaches to compare the contrast between brain areas: one using symmetrical circular ROI and other comparing two hemispheres.

In the circular ROI comparison we predefined a radius (this value can be configured and is 28 pixels in the example below) and used a symmetry axis passing both the artery (A) and vein voxel (V). For a ROI1 in P a ROI2 centred in P' was calculated (see Figure 36).

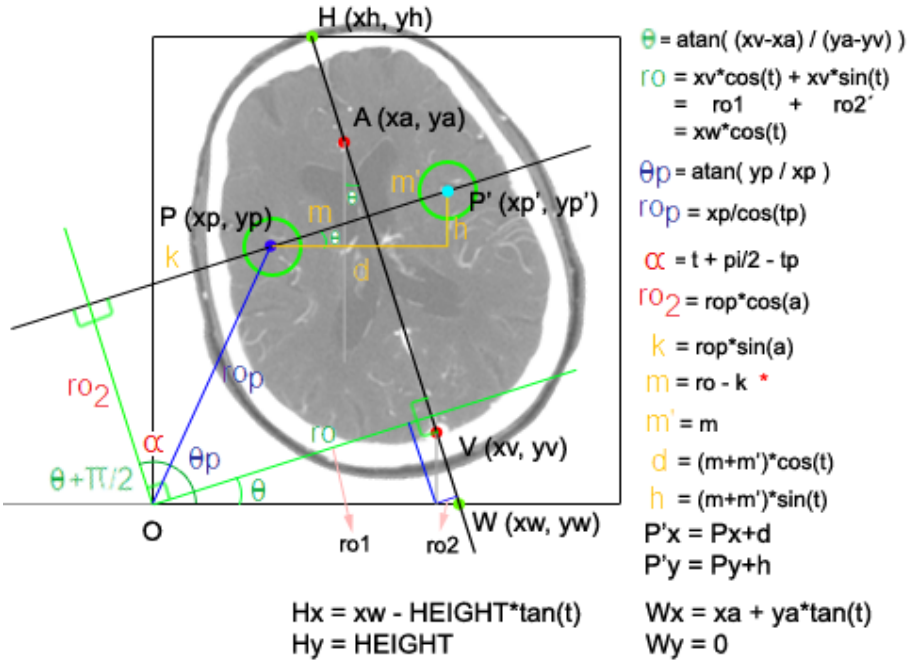

Figure 36 – Relevant points and axis in CT image (artery, vein and symmetry axis).

The matching is applied in a selected slice and a perfusion parameter image (CBV, …). For each ROI (green circle) is created a distribution histogram with the values in the ROI, according to the number of bins specified, these values are stored in a matrix for further processing and analyzing, determining the mismatch bin by bin according to the equation Eq. 48, b_n and b_k are the bins that has more values in the ROI 1 and 2 respectively (Figure 37).

$$matchR1 = \frac{ROI1b_n}{ROI2b_n}, matchR2 = \frac{ROI1b_k}{ROI2b_k} \quad \text{Eq. 48}$$

$$mismatch = 1 - match \quad \text{Eq. 49}$$

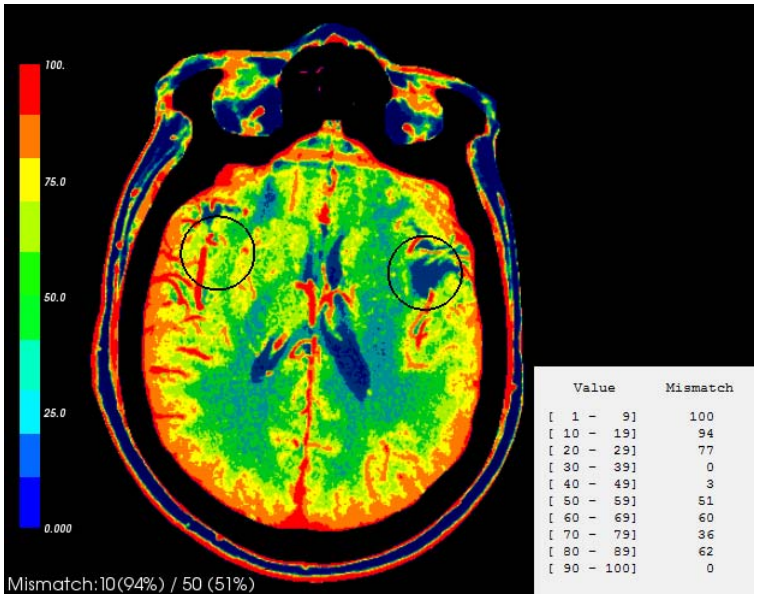

Figure 37 – An example of mismatching – quantitative mismatch for a selected ROI.

In Kudo [35] the selection of ROI in an image is done using a circle (see Figure 37).

In Figure 37, 10 bins were in the perfusion histograms that corresponded to 10 colour levels in the colour scale. In the example for the blue area (0 – 9) we have a mismatch of 100% meaning that on one hemisphere does not exist any voxels in that range.

If we not intend to do this process we can use a simplified method using the method output, calculate the most relevant bins mismatch and the value associated; ##/## – the first value is the match for ROI1 and the second for ROI2.

In Figure 37 we have *bin.x (mismatchROI1%) / bin.y (mismatchROI2%)*, in this example we have a result of 6.49, match of 6% – mismatch of 94% (100-6) for ROI1 and a match of 49% – mismatch of 51% (100-49) for ROI2. 94 correspond to the second bin (10 – 19) and 51 to the sixth bin (50 – 59), according to the table in Figure 37, so we will have 10 (94%) / 50 (51%).

When comparing both hemispheres we used a symmetry axis defined by *H* (height) and *W* (width) in Figure 36. The matching is applied in a selected slice and image, the result is the amount of contrast material in right side of the image divide by left. The quantity of tracer is determined using the minimum contrast in artery as reference, we consider that has tracer if the value is bigger than 10% of the artery value.

Figure 38 present the results of this process. The image shows only the contrast material for all slices and when concentration in artery is maximum, the values in bottom left corner is the matching for each slice. As we can see it is important to remove the outliers, otherwise we will have inaccurate results.

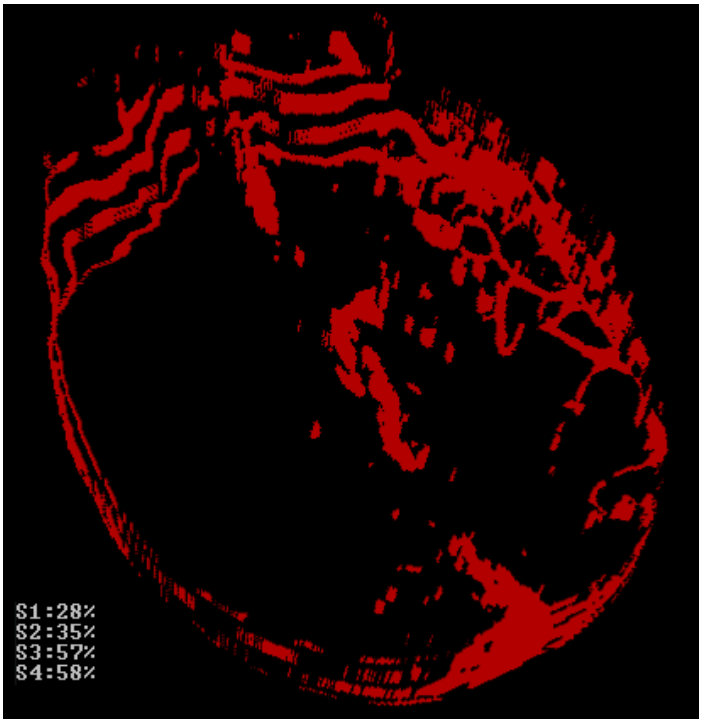

Figure 38 – An example of matching – quantitative mismatch for each hemisphere.

In this example (Figure 38), for slice 1 (S1) we have 28% of mismatch, it means that the left side of the image has more 28% contrast material that the right side.

3.6. Application

We developed a framework to perform quantified comparisons between the different methods described in the literature for perfusion related parameters methods.

An application is essential for using the framework and selecting the several methods to use. The application allows us to select the perfusion parameters, filters and the type of enhancement and others possibilities.

3.6.1. Used software

We had many languages and tools available for developing an application, like C++, C#, MFC, KWWidgets, etc. We developed using C# in Visual Studio 2008 ® with framework .NET 3.5; this choice was based in the simplicity and rapidity for developing an interface. Another advantage is the existence of a large documentation making the development easier.

For the visualization purpose we could use several libraries (OpenGL, VTK, etc…). We used the Visualization Toolkit (VTK) version 5.0.1, this is a free library used for visualization systems and image processing. It is developed in C and can be integrated in other languages using wrappers (for example the VTK for .NET).

Our application also uses other libraries like OpenCV 1.0 and DCMtk 3.5.4. OpenCV is a free library used for computer vision and has a lot of optimized algorithms. DCM Toolkit (DCMtk) is a collection of libraries that implements a large parts of DICOM standard [50-54].

Because we already has code written in C++ (the framework) through the use of a Dynamic-Link Library (DLL) containing most of the algorithms developed. This DLL make possible the use of the original C++ code in C# without further adaptation and possible the reutilization of the framework by other applications that may be developed in the future.

The framework was documented using the Doxygen and the documentation is available in web (html) and eBook (PDF) format.

The final application also allows to read directly RAW and DICOM files. For RAW images, the user needs to provide to the interface data properties (like pixel spacing, etc.) regarding DICOM files, the information is read directly from the files. In any case, it is necessary ensure that we have only one perfusion CT exam in the current folder. The software works only with 4 slices since this is the most common Perfusion CT resolution actually, but the framework is ready for others resolutions.

3.6.2. DICOM

DICOM is an acronym for Digital Imaging and Communications in Medicine. This is a Medical Imaging Format developed to help the visualization and distribution of medical images, like CT or MR but also a network communications protocol. DICOM file have a header with information about the patient (personal information like name, age, etc.), the operator, modality type and data properties. Each file holds a single image and the header unlike others formats. The DICOM format is the standard commonly used for medical images [55].

3.6.3. RAW

In order to simplify the reading process of file it is possible to convert DICOM into raw data. To perform the conversion we use the application *dicom2* [56]. RAW format simplify the manipulation of images since there is no header embedded but just the actual image data. However the user needs to provide the data properties in another way.

This format is simple because does not exist a header, so the file only contains image data, because that we need to specify the data properties when we read a file.

This format is commonly used because many libraries cannot interpret the complexity of DICOM.

3.7. Graphic User Interface

This section gives an overview the application used for processing perfusion parameters and the user interface (see Figure 39).

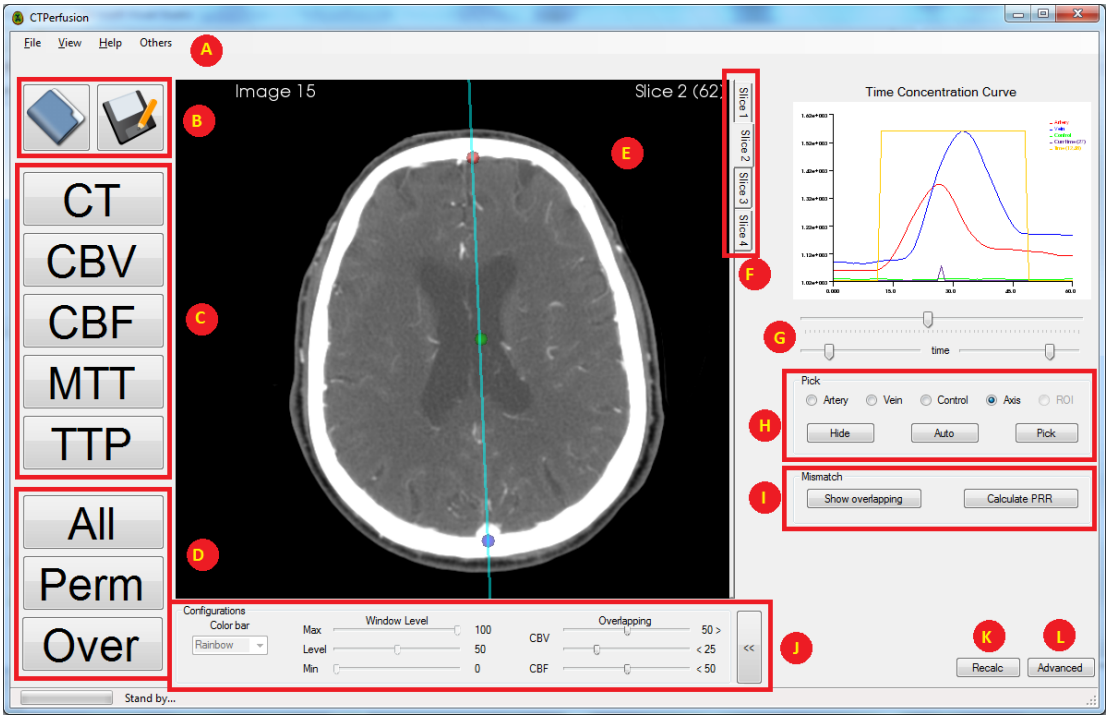

Figure 39 – Main window application.

- A – Menu strip. This menu display some basic options (Open, Close, …), perfusion parameters (CBV, CBF, …), help options and advanced options. Unhide all buttons allows to access to advanced options (explain later).
- B – These buttons allow us to *Open/Close* CT files and *Save* the image display in E.
- C – These buttons show the common perfusion parameters (CBV, CBF, …); other methods are available in advanced options (L or *Others* → *Open Control Window*).
- D – These buttons show other images. *All* show 4 images (CBV, CBF, MTT or CT) in E. It is possible to define these 4 images. *Perm* show permeability image. *Over* show overlap image, this image overlap the intersection of CBV bigger than value in J and CBF lower than value in J on CT image.
- E – Render area for show images. A double click in this area will open a full screen window with the image under analysis.
- F – This tab control permits to change slice image.

- G – Time control. The upper track bar selects the current time and the two lower track bars select the range time in which perfusion parameters are calculated. The graph is a representation of the concentration variation of artery, vein and control voxels. Current time is also displayed.
- H – This panel controls the pick options. *Hide* the points or axis in the screen, *Auto* make an automatic selection of artery and vein, using the radio buttons it is possible to chose what to pick and using the button *Pick* we can pick a point in E.
- I – This button permit to see the overlap image over CT image (left) and calculate PRR (right).
- J – In this panel we can define what lookup table to use and define the window and level visualization. It is possible to define the overlapping parameters (high and low CBV and low CBF or high TTP/MTT). The button « permit us to hide (or show if ») the lateral right panel.
- K – *Recalc* button clear all data, reload the original CT image (not the files), filter data and show a CT image.
- L – *Advanced* button allows us to access the advanced menu (explain later).

In the previous image (Figure 39 – A) using the tools bar we have some functionalities.

- File – In the file button it is possible to open, close, save data image or exit the program. The program can read DICOM, RAW files or a single binary file (.dat), also it is possible to write an image (JPEG, PNG, RAW) the image we saw in the viewer but we also can save as a single binary file (.dat) the CT image with the filters or other processing what we already made.
- View – In this button we can generate all images we want, however some methods only are available if we unlock them (Others → Unhide all buttons).
- Tools – This button only was available if we unlock them (Others → Unhide all buttons), here we can *Customize* some functionalities of the application, like define the image we have when we saw 4 images (button *All*) or which methods or files to use for determining perfusion parameters (this option is unavailable after the files reading), also is possible to do that in Advanced option after read the input CT images. In *Options* we can (only) see the image properties, like pixel spacing and image dimensions.
- Help – The *How do I* (or F1) button show this information and the *About…* help.
- Others – Here we can access to the advanced options if the data set is loaded or show/hide buttons.

The button *Advanced* (Figure 39 – L) accesses to an advanced control window (Figure 40).

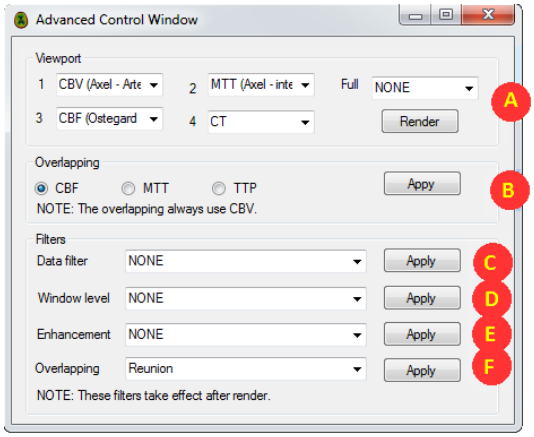

Figure 40 – Advanced control window.

- A – In this section it is possible to select what image are present in each viewport (*1* to *4*) or one image on full viewport (*Full*), after we press *Render* the images are rendered. It is possible to select one CBV among 4 methods, one CBF among 7 methods, one MTT among 3 methods, and other methods (CT, TTP, Permeability, Histogram, CBV×CBF, Transit Time, Overlap, Concentration variation) (see 2.2 Perfusion Related Parameters: Methods and Models).
  Note: If we choose one method for more than one viewport, the same image will be displayed; this is if we select *CBV_1* for viewport 1 and *CBV_2* for viewport 2 the two viewports will display the *CBV_2* image.
- B – It is possible to define what image is used with CBV to generate the overlap image (CBF, MTT or TTP).
- C – It is possible to choose what filter is used, this option only takes effect if we press *Apply* and *Render* CT image (A) or press K in Figure 39 (see 3.2 Pre-processing).
- D – In *Window Level* we can choose what method to use for image enhancement (see 3.4 Post-processing). This option only takes effect if we press *Apply* and *Render* an image.
- E – In *Enhancement* we can choose what method is used for image contrast improvement (see 3.4 Post-processing). This option only takes effect if we press *Apply* and *Render* an image.
- F – It is possible to choose what kind of overlapping we have, *Intersection* or *Reunion*. If we choose *Intersection* the overlap image only contain data when the three conditions in J (Figure 39) are true, if we choose *Reunion* the overlap image contain data when one conditions in J (Figure 39) are true. This option only takes effect if we press *Apply* and *Render* an image.

It is possible to customize (Figure 41) some options, for that we need to unhide some options (*Others* → *Unhide all buttons*) and open customize window (*Tools* → *Customize*).

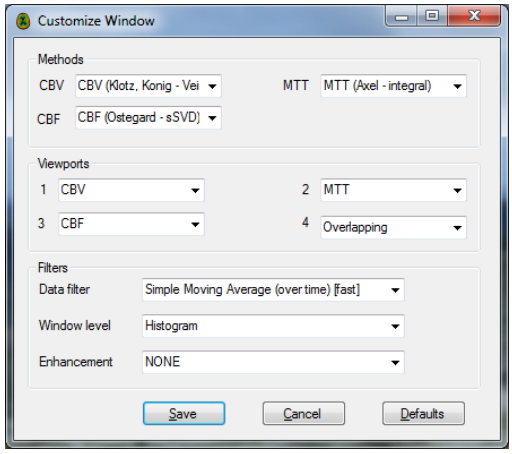

Figure 41 – Customize window.

This window is similar to Figure 40.

We also developed an independent application (ReadDICOM) exclusively for manipulation of DICOM files (Figure 42), the application was developed in C# and uses DCMtk 3.5.4 and VTK 5.0.1 libraries [51-53].

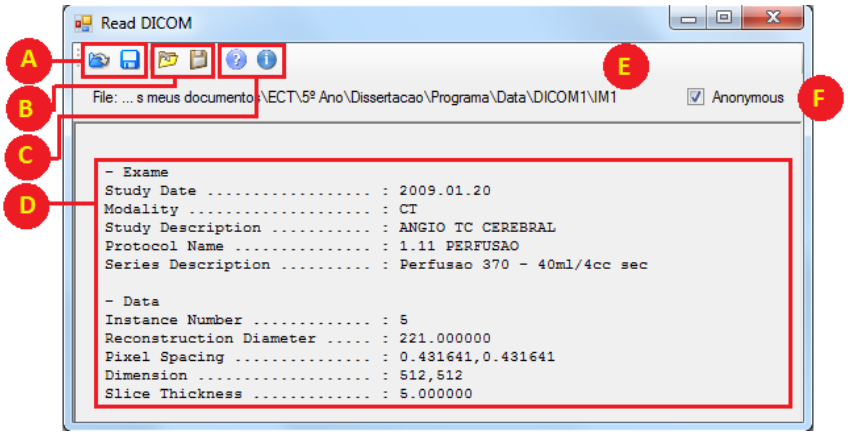

Figure 42 – Read DICOM.

- A – Open the header of a DICOM file. Save the visible header information (D) as text file.
- B – Open the content (image) of a single file or several files, in DICOM or RAW format. If the files are DICOM the header will be shown. Save the read data as single binary file.
- C – *Help* button (or F1) show this information and the information button show the *About*... help.

- D – The header of a DICOM file.
- E – The name of the file opened.
- F – The *Anonymous* check box can be used to protect privacy since it hides private information of the patient.

An interesting feature of this program is the possibility to read and present the information of the header file. This option is interesting for debug since it provides easily information about the type of exam.

4. Evaluation and Results

The perfusion CT parameters were calculated for five exams, for each dataset the CBV, CBF, MTT and permeability using the implemented methods. Based on these several combinations between CBV and CBF (or MTT, TTP) used to try to define the penumbra and infarct core based on mismatch technique. In this process we used the application described earlier: pre-processing with Simple Moving Average, extraction of non brain tissues with mask filter, artery and vein detection and, after performing calculations, image equalization. In the process few or non user intervention were allowed other window level adjustments and the user could select the voxel references (artery and vein) when explicitly stated.

To perform the evaluation we used the following process for each parameter:

- An image was generated for each of the implemented methods.
- A figure containing all the images was generated and presented a code that allowed mapping the figure to the method.
- This figure was presented to two clinical experts (one neurologist and one neuradiologist) that gave a mark between 0 and 10 being 0 for no relevance for diagnosis, 10 for relevant for diagnosis – at least as good as the one provided by the CT equipment (in this case a GE equipment).

In the Hospitais da Universidade de Coimbra (HUC) the clinical experts uses clinical software from General Electric ® (GE) that generate perfusion images. We use the GE results to evaluate and compare our results.

The results given by the clinical experts for each of the parameters are presented in the appendix B.

4.1. Results

4.1.1. CBV

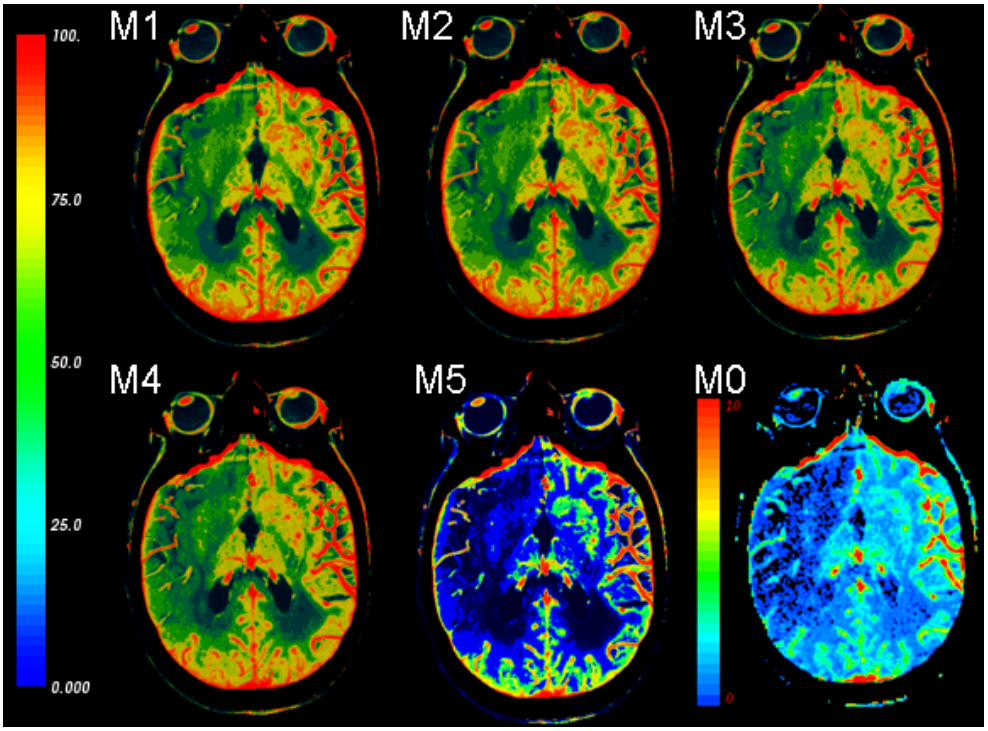

Figure 43 – The CBV perfusion parameters for case study 2.
M1 and M2 using Axel method (Eq. 9) using artery as reference in M1 and using vein as reference in M2; M3 using Klotz and König method (Eq. 10, using vein as reference); M4 using an adaptation of Eq. 10 that uses artery as reference; M5 is the same as M3 but with manual window level correction and applying a logistic function after equalization; M0 ground truth image (GE image).

In CBV (Figure 43), the images were generated using the raw methods without user intervention (M1 to M4); M5 image was generated with manual window level correction and applying a logistic function after equalization (Eq. 47) (see Appendix B for details). According to the clinical experts all methods generated are equivalent. In some cases (in presence of penumbra) we enhanced the image (e.g. M5) to visually converge to the GE results (M0) while maintaining the clinical evaluation of the not enhanced method.

4.1.2. CBF

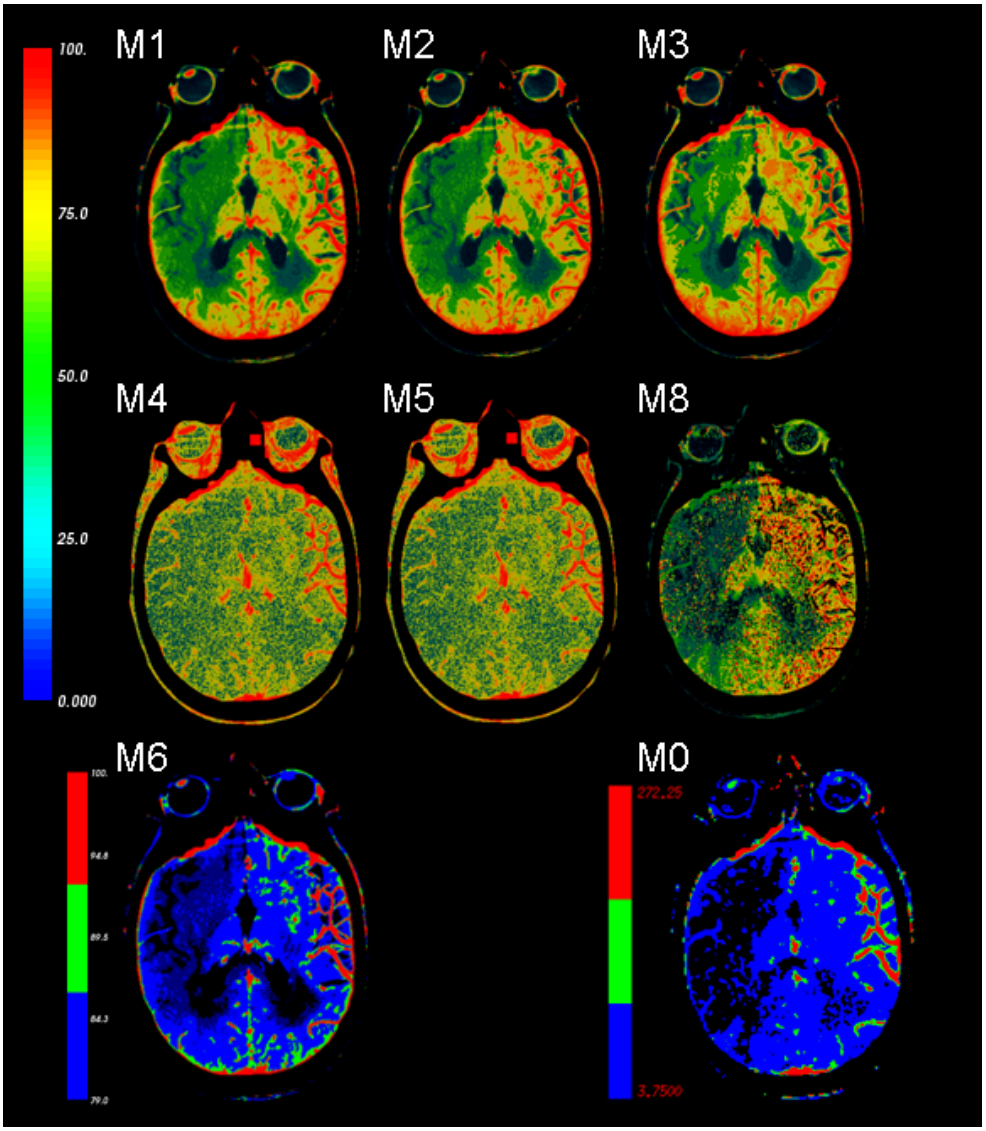

Figure 44 – The CBF perfusion parameters for case study 2.
M1 using sSVD method (Eq. 17 to Eq. 23); M2 using dSVD method (Eq. 24); M3 using bSVD method (Eq. 25); M4 using Eq. 12; M5 using Fick's method (Eq. 11); M8 using Central Volume Principle (CBV M3 – Figure 43 and MTT M10 – Figure 45); M6 the same as M1 but with manual window level correction and using other lookup table; M0 ground truth image (GE image).

In CBF (Figure 44), the images were generated without user intervention using the methods described earlier (M1 to M5 and M8); in M6 image was generated with manual window level correction and using other lookup table (see Appendix B for details).

According to the clinical experts the first two CBF methods (M1 and M2) show good results but not as good as the original GE (M0). With adjustments performed in M7 (window level and change the lookup table), the previous methods were considered equivalent to GE images (M0). The main change was the lookup table change, more similar to what the clinical experts are accustomed to see (Figure 51 – F)

4.1.3. MTT and TTP

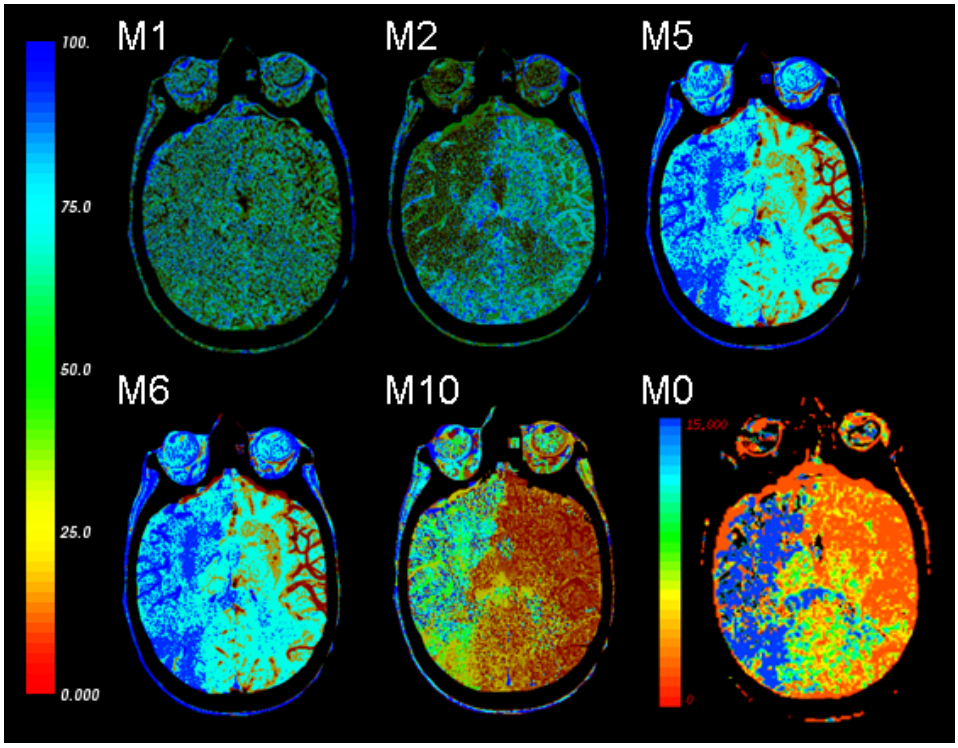

Figure 45 – The MTT perfusion parameters for case study 2.
M1 using Axel method (Eq. 33); M2 using Fillips method; M5 using Central Volume Principle (CBV M3 – Figure 43 and CBF M1 – Figure 44); M6 using Central Volume Principle (CBV M3 – Figure 43 and CBF M2 – Figure 44); M10 using TTP; M0 ground truth image (GE image).

In MTT (Figure 45), the images were generated without any user intervention (see Appendix B). For MTT there was no consensual answers, both methods M5 and M6 generated good results. Patients without a significant delay between arterial and venous flow of contrast material curve signature (as in this case study) M5 and M6 are similar otherwise M6 is the best. TTP image (M10) was considered equivalent to GE MTT image (M0). It is worth to reinforce that both MTT and TTP are correlated as seen in section 2.2.6 (Time To Peak).

4.1.4. Permeability

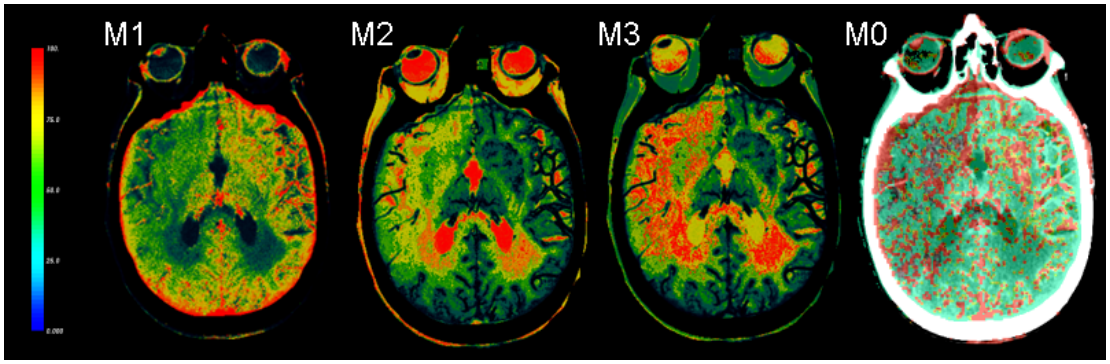

Figure 46 – The Permeability for case study 2.
M1 Permeability using Eq. 36 and CBV M3; M2 is the same as M1 but with equalized CBV; M3 the same as M1 but with equalized CBV and applying a logistic function after equalization; M0 ground truth image (GE image).

Analyzing the results of permeability and according to the clinical experts, M3 (Figure 46 – M3) give us better results. Sometimes we don't have the GE image for comparing, but according to the clinical experts our results have more definition, however the result is not consensual (see Appendix B).

4.1.5. Mismatch and Penumbra Detection

Combining Visually Images

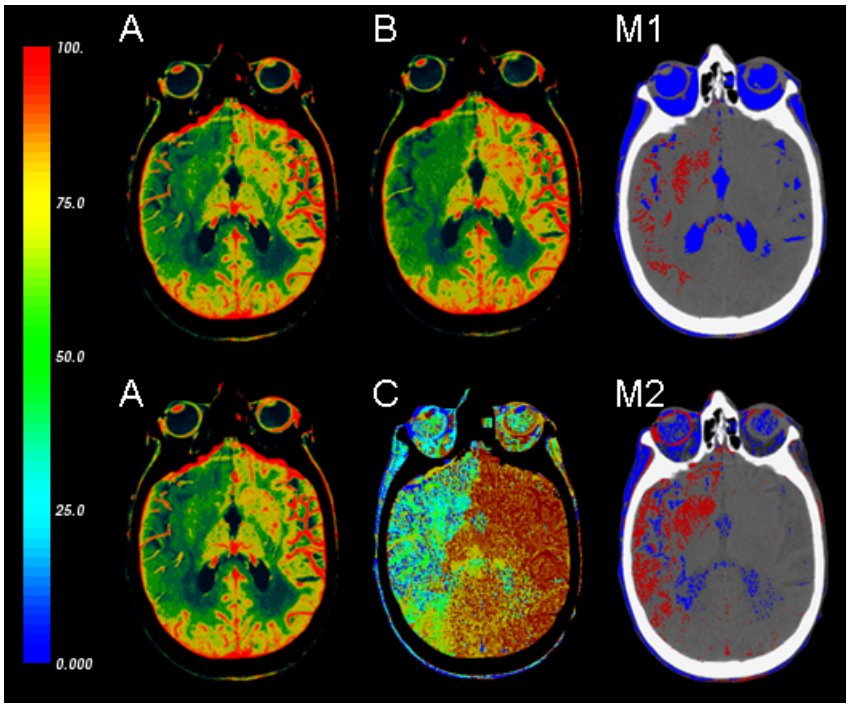

Figure 47 – The Mismatch for case study 2.
A CBV M3 using Klotz and König method (Eq. 10, using vein as reference); B CBF M1using sSVD method (Eq. 17 to Eq. 23); M1 Mismatch between CBV (A) and CBF (B) overlapped on CT image; C TTP using Phillips method; M2 Mismatch between CBV (A) and TTP (C) overlapped on CT image.

In our opinion this is an interesting method that many systems don't implement (Figure 47), usually the default parameters give us good results, CBV less than 25 and CBF (or TTP) bigger than 50 for infect core – blue; CBF and CBF (or TTP) bigger than 50 for infarct penumbra – red. If it is necessary we can adjust these thresholds for a better visualization of infarct penumbra. However these are preliminary results and according to the clinical experts are not possible to distinguish clearly the infarct penumbra and core (see Appendix B).

For mismatch detection we need to equalize the images before the mismatch calculation.

Multiplying images

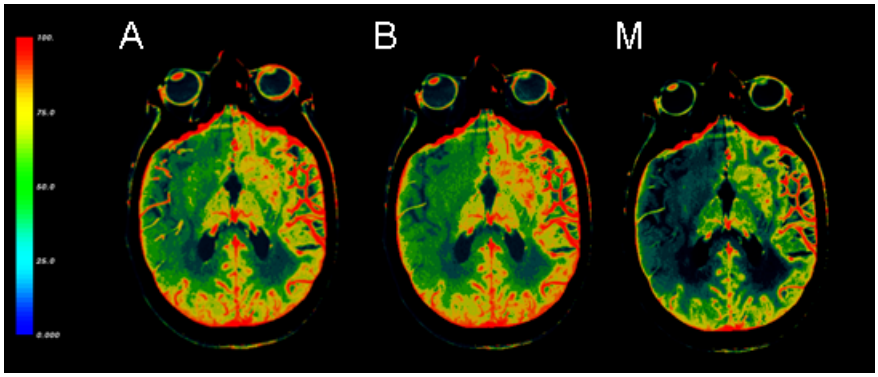

Figure 48 – The Mismatch areas by multiplication for case study 2.
A CBV M3 using Klotz and König method (Eq. 10, using vein as reference); B CBF M2 using dSVD method (Eq. 24); M Mismatch areas (M5) between CBV (A) and CBF (B).

Using this method it is possible to identify the two areas (infarct penumbra and core) but is not clear. These are preliminary results and needs more tests and improvements (see Appendix B).

For mismatch detection we need to equalize the images before the mismatch calculation, but the final image is not equalized.

4.2. Discussion

According to our results it is possible to establish a rank among the method for each of the perfusion CT parameters. For CBV no clear distinction was found between all methods when no adjustment was used. For CBF the best method is the Ostergaard method (sSVD – M1) using adjustments (method M6 or M7); For MTT the best methods are (Central Volume Principle – M6), Phillips method (TTP/MTT – M10 or M11);

For permeability no clear conclusion is possible as it is more complex method and still new in the clinical practice, nevertheless, according the Lin method with equalized CBV (M3) gives good results.

The mismatch results are only preliminary results and needs more tests and improvements for a correct usage.

In general, in the opinion express by neurologists through the queries (in Appendix B), our results produce results that are clinically comparable to the General Electric ® (GE) results. Nevertheless, as seen in some cases, the manual adjustment of window levels may improve our results as in some cases the brain asymmetry patterns are very subtle and only with expert supervision is possible to identify them.

It was clear the influence of the lookup table in the clinical expert classification, specially if they converge to the ones usually displayed in clinical environment – in this case default lookup tables in GE equipment.

Some of the implemented methods such as Transit Time, PRR and Concentration Variation of the Contrast Material method where not evaluated due to their limited or no use in clinical practice – mainly to limited availability in standard equipments.

5. Conclusions

Our main objective was to implement the main methods used to calculate perfusion related parameters found in the literature reproduce that have clinical relevance and assert their clinical usefulness.

We achieve a framework that, besides the methods implementation, allowed a standardized way to process and display the results with little or no human intervention to allow keeping a map of transformations between original perfusion data and the visualized data. This work resulted in a publication in the International Conference on Image Analysis and Recognition [57].

Through the use of automatic methods such the one to detect the artery and vein references, combined to simple pre-processing (smoothing) and post-processing (equalization) we were able to provide a visualization that is clinically useful with limited user intervention. In other words we were able to provide a reproducible baseline representation that enables the visual comparison of different methods – critical to have a clinical comparison using standard inter-rater agreements evaluation (e.g. [27]). However, as expected, the fine tuning using tools such window levels or lookup tables can improve the impact in the clinical appreciation of the images as it was clear is some of the analysed cases. For that reason it is possible to keep track of these optimizations in order to support their relation with clinical scores.

In the process we also tested some other approach either using image enhancement (e.g. exponential function) or a combined approach of existing parameters (e.g. mismatch) that seem to have some potential although no clear conclusion can be drawn from the results.

It is our opinion that this work can have an impact in clinical practice with special emphasis in the acute stroke management by contributing to define which methods are more clinically relevant and, in consequence, quantify relevant stroke related features like the penumbra or unrecoverable brain tissues. The present work will support quantified comparisons between different method and help assessing the method's real clinical.

5.1. Future Work

The current work needs further evaluation and testing by the clinical experts. The current version of the application is good for research but is not suitable for clinical usage or testing as it still presents too many options useful for research but confusing and unintuitive for a clinical user. A simplified version of the application with the most promising methods indicated by the clinical experts might be useful to converge to a useful clinical tool in real clinical environment. Simultaneously, this could be a valuable tool to gather information about the methods usage, the most common and useful settings and help devising which factors or settings are more crucial in the clinical decision process

In a professional application an interesting functionality would be the integration between this application and others applications that neurologists and radiologists already use and additional auditing tools.

According to the neurologists an interesting feature and understudied (one paper found in Russian [58]) is apply the Perfusion CT to the brainstem and analyze the results using the methods here described.

All work was oriented for using CT images, if we allow the user to select the type of exam (CT, MRI, …) and the properties of the image (e.g. number of slices) the application could be more useful. A promising method could be the usage of Arterial Spin Label (ASL), ASL is the tagged by magnetization of molecules of water before it enters into the brain by Magnetic Resonance (MR) for the determination of perfusion parameters and infarct penumbra detection. This method (ASL) is safer because is free of radiation (MR) and is not necessary to inject any contrast material [39, 59].

For the determination of PRR and penumbra area we used a simple method that extracts the bone and the ventricles, however using other tools it is possible to remove blobs more accurately [60] and more efficiently. A better approach would be use a ROI for selecting where calculate PRR using tools for draw the ROI according to the user desire.

Regarding permeability and mismatch detection, further work is needed since preliminary results do not convinced the clinical experts. Transit Time, PRR and Concentration Variation of the Contrast Material also needs more investigation since, due to limited availability of clinical experts, several implemented methods and tools were not tested yet.

Using the bone as reference it is possible to reduce noise in CT image, the values on bone are supposed to change.

In terms of performance this application could be improved using multithreading in the methods (e.g. using one thread for each slice), in terms of behaviour and functionalities the application could be tested with more users (e.g. neurologists, radiologists). The application, as it is now, can generate all methods in all conditions; it could be improved if we restrict to the more promising methods improving the performance and stability of the application.

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Appendix A: Methods Implementation

In this section we present more details of the implementation of filters and perfusion parameters described in the thesis to facilitate the use or improvement of the application in the future.

Filters and Pre-Processed Methods

Simple Moving Average

This filter smoothes the concentration curve to reduce the noise using an average value, our implementation (*SimpleMovingAverageTime()*) uses a configurable time window and it is possible to define the application mode (see 3.2.1 Simple Moving Average). Usually we used a 7 seconds window and operate in mode one.

Moving Median

This filter smoothes the concentration curve to reduce the noise using a median value, our implementation (*MovingMedianTime()*) uses a configurable time window and it is possible to define the application mode (see 3.2.2 Moving Median). Usually we used a 7 seconds window and operate in mode one.

Smooth Curve

This filter smoothes the concentration curve to reduce the noise using the function *cvSmooth()* of the OpenCV [50], our implementation (*smoothImage()*) uses a configurable time window and it is possible to define the application mode (see 3.2.3 Smooth Curve). Usually we used a 7 seconds window and operate in mode one.

For each voxel it is created a vector with all values along time, the OpenCV smoothes the values according to a gaussian curve, this works well because it is expected the shape of the curve is similarly to a gaussian curve.

The OpenCV function is intensively used and many copy operations is performed, because that this method is very slowly compared to Simple Moving Average and Moving Median. In fact, the bigger difference between this method (Smooth Curve) and SMA is the processing time.

Delay Corrected

This method (*delayCorrected()*) corrects the delay by shifting the tissue concentration curve in time [35], is initially calculated the beginning of the upslope curve of time-concentration *c(t)* with a margin of 5% of the peak of the curve and correction time t_d is the difference between the time of artery curve and brain tissue curve, *c'(t)* is the corrected concentration curve (see 3.2.4 Delay corrected).

Bone Identification

This method (*filterImages()*) removes voxels that are located out of the head and bone voxels, values bigger than maximum of artery or vein and less than 20% of minimum of artery or vein, voxels where the concentration is oscillating (Figure 13 – B) or always high over time (e.g. bone) (Figure 13 – A) are removed too (see 3.2.5).

Removing Unwanted Voxels

This filter (*filterMask()*) uses a binary image (mask) with 4 slices. For the mask creation it is used morphological operations from OpenCV library [50] (see Appendix A – Create Mask). This process is accomplish in two phases, the first we remove the head support signature (two white lines out of the head – may not exist), for do that we opening the image with erode (*cvErode()*) and dilate (*cvDilate()*) functions, the second phase is removing the bone. Combining the bone segmentation and the original image removing the unwanted voxels by a close operation on the image, with dilate and erode. To avoid some noise originated by the mask creation and for an accurate result we shrink the mask (erode operation).

The application of the mask is done by multiplying each voxel of the CT image by a correspondent voxel on mask (see 3.2.6 Removing Unwanted Voxels).

Time Variation Filter

This filter (*filterHybrid()*) uses a binary image (mask) with 4 slices and analyze the concentration variation of contrast material. For the mask creation it is used morphological operations (see Appendix A – Create Mask), finally we analyze the concentration variation

over time, each voxel only can cross the average value (between the minimum and maximum concentration) two times, in ascending section and descending section of the curve, using the range values of artery as reference, if the voxel do not respect that that voxel are removed (see 3.2.7 Time Variation Filter).

Find Artery and Vein

Using CT data we locate the artery and vein (*locateArteryVein()*) it is crucial for several perfusion parameters.

Using the first image (baseline) of each slice we create a mask that remove non brain tissues, voxel whose value is greater than 1200 (like Figure 13 – A) and lower than 800 (like Figure 13 – D), the process will be explain later (Appendix A – Create Mask).

The reference voxel (artery and vein) must be respect some limitation like have a single centred maximum concentration (unlike Figure 13 – B) and the first value (in baseline) shouldn't be greater than 1200 (unlike Figure 13 – A and C) or lower than 800 (unlike Figure 13 – D).

This method gives us the artery and vein position, but also the maximum and minimum value of this reference voxels. Se more information on section 3.5.1 Find Artery and Vein.

Summary Table

Type of filter	Filter process	Method/ Description
Curve smoothest	Simple Moving Average	SimpleMovingAverageTime() Smoothes the concentration curve using a moving average. Application over time and 3D. Fast method.
	Moving Median	MovingMedianTime() Smoothes the concentration curve using a median value. Application over time and 3D. Slow method.
	Smooth Curve	smoothImage() Smoothes the concentration curve using OpenCV function. Application over time. Slow method.
Delay corrected		delayCorrected() Corrects the arrival time of contrast material.
Cleaning image	Bone Identification	filterImages() Removing voxels whose values out of range. Not remove some voxels with irregular concentration variation and maintain brain contours.

	Removing Unwanted Voxels	filterMask() Applying an image mask to the input data. Remove almost all artefacts but do not contemplate patient movements.
	Time Variation Filter	filterHybrid() Applying an image mask to the input data. Removes voxels that not respect a gaussian pattern and maintain brain contours.
Find Artery and Vein		locateArteryVein() Locate the artery and vein for the determination of perfusion parameters.

Table 4 – Detailed overview of filters methods.

Processing Methods

Cerebral Blood Volume

Using the equation Eq. 9 we create two functions for generate CBV image. One (*CBV_Artery()*) uses artery as reference, the CBV is the ratio between the sum of tissue concentration and artery concentration. A second method (*CBV_Vein()*) uses vein as reference, the CBV is the ratio between the sum of tissue concentration and vein concentration. It is necessary to determine the artery or vein position previously.

Using the equation Eq. 10 we create a function (*CBV_maxV()*) for generate CBV image that uses vein as reference, the CBV is the ratio between the maximum of tissue concentration and vein concentration. Like as Eq. 9 we try to use artery as reference in Eq. 10 for generate CBV using maximum of tissue concentration (*CBV_maxA()*). It is necessary to determine the artery or vein position previously.

The CBV was truncated to the value of reference voxel because the reference voxel is in the artery or vein and has the biggest value of CBV.

In order to reduce noise or delay injection theses methods can uses the time when the concentration curve is significant, ignoring the arrival and reperfusion time.

See section 2.2.1 (Cerebral Blood Volume) for more information.

Cerebral Blood Flow

Using the equation Eq. 11 we create a function (*CBF_Fick()*) for generate CBF image, CBF is the ratio between the maximum derivation in upslope segment of the curve and the difference between the concentration on artery and vein when maximum slope occurs. Using the equation Eq. 12 we create a function (*CBF_maxD()*) for generate CBF image considering that $C_v(t_{max}) = 0$. It is necessary to determine the artery or vein position previously.

According to Figure 3 the maximum slope is achieved around 10-15 seconds and this value is non negative, in order to reduce noise a cut off threshold is used, this threshold is the range values in artery – referenced voxel.

Using the equations Eq. 17 to Eq. 23 we create a function (*CBF_sSVD()*) for generate CBF image, the determination of singular values it was used OpenCV library [50] is necessary determine the matrix A, c, W, U^T, V and finally the matrix b. The value of CBF is the maximum of residue, the matrix resulting from A×c.

Using deconvolution and through the equation Eq. 24 we create a method (*CBF_dSVD()*) that corrects the delay by shifting the concentration curve in time, is initially calculated the beginning of the upslope curve of time-concentration *c(t)* with a margin of 5% of the peak of the curve and correction time t_d is the difference between the time of artery curve and brain tissue curve, *c'(t)* is the corrected concentration curve [35].

Using circular SVD, called block circulant SVD (bSVD), we create a method (*CBF_bSVD()*) to calculate CBF using this technique.

One problem inherent to the utilization of SVD is the change in blood or brain concentration to be reduced when compared to the noise, in order to minimize this effect (oscillation of *R(t)*) the diagonal elements of S that are below a cut-off threshold level of 20% of the maximum value are set to zero [35]. It is necessary to determine the artery and vein position previously.

Using the equation Eq. 35 we create a method (*CBF_CentralVolume()*) for determination of CBF, in that case it is necessary to determine the CBV and MTT previously, after that it is a ratio between each voxel in each image.

In order to reduce noise or delay injection theses methods can uses the time when the concentration curve is significant, ignoring the arrival and reperfusion time.

See section 2.2.2 (Cerebral Blood Flow) for more information.

Mean Transit Time

Using the equation Eq. 33 we create a function (*MTT_Axel()*) for generate MTT image. It is necessary to determine the maximum and minimum concentration tissue previously and after that obtain the height, for each voxel. The minimum value acquired from the machine is approximately 800.

Using the Phillips method we create a function *MTT_Phillips()* for generate MTT image, empirically we can assume the minimum with is on the reference voxels.

Using the equation Eq. 35 we create a function (*MTT_CentralVolume()*) for generate MTT image. It is necessary to determine the CBV and CBF previously, after that it is a ratio between each voxel in each image.

In order to reduce noise or delay injection theses methods can uses the time when the concentration curve is significant, ignoring the arrival and reperfusion time.

See section 2.2.3 (Mean Transit Time) for more information.

Permeability

Using the equation Eq. 36 we create a method (*PERM_Artery()*) for generate Permeability image. It is necessary to determine the CBV image and the artery position previously. If the CBV image is previously equalized guarantees better results.

In order to reduce noise or delay injection theses methods can uses the time when the concentration curve is significant, ignoring the arrival and reperfusion time.

See section 2.2.5 (Permeability) for more information.

Time to Peak

Using the Phillips method we create a function (*TTP()*) for generate TTP image. It is necessary to determine the artery position previously because is used for determining the time delay if we intend to ignore the delay. The inflow blood is at the artery, so the TTP in other voxels is bigger than a cut-off threshold of 15% in the artery.

In order to reduce noise or delay injection theses methods can uses the time when the concentration curve is significant, ignoring the arrival and reperfusion time.

See section 2.2.6 (Time To Peak) for more information.

CBV Multiply by CBF or MTT

According to Murphy the multiplication of CBF by CBV results in a good separation of the penumbra area and core zone once both parameters combine in the stroke area, with major variation in the penumbra. It is necessary to determine the CBV and CBF image previously.

It is also possible to multiply the CBV by MTT results in a better separation of the penumbra area and core zone once both parameters combine in the stroke area. It is necessary to determine the CBV and MTT image previously.

The function for do that is *MUL()*, the multiplication id done voxel by voxel.

Transit Time

Transit Time (*TransitTime()*) represents the blood circulation in the brain, for each voxel is determined the maximum concentration and the time that maximum occurs. This image has the same dimension of perfusion CT image, so it is possible to navigate in time. It is created a matrix where each cell have the time where occurs the maximum concentration of a correspondent voxel. The TT image has a value of 50 where the maximum concentration occurs, using a configurable time window it is possible to define the time with where we see some data, for the time before the maximum concentration the value is less than 50 and for the time after the maximum concentration the value is bigger than 50.

Using a correct lookup table (Figure 51 – G) it is possible view voxels where the maximum concentration to within a time window.

If we use another lookup table we only see the voxel where the maximum concentration occurs, without values inside the time window, only when the voxel has a value of 50.

Potential Recuperation Ratio

This method (*calculatePRR()*) calculate the potential recuperation ratio of the patient using CBV and other method (e.g. CBF, MTT, TTP) – preferential TTP.

Using CT image we create a mask only with brain voxel – inside the skull. For the mask creation it is used flood method (*cvFloodFill()*) from OpenCV library [50] by selecting the image centre as seed. Using the two input images and the mask we can define the infarct core using thresholds (from CBV and the other image).

We tried to remove the ventricles by analyzing the large connected areas, using flood process for an accurate result, after that we generate an image with infarct penumbra and infarct core, also is calculated the number of voxels in infarct core and penumbra and the PRR for each slice.

Concentration Variation of the Contrast Material

This method (*concentrationVariation()*) creates an image where each voxel represents the amplitude of variation of the contrast material. Each voxel takes the difference between the maximum and minimum value of the tissue concentration curve.

Summary Table

Perfusion Parameter	Method	Equation	Description
CBV	CBV_Artery()	Eq. 9	The ratio between the area under the concentration curve of the contrast material and the area under the artery curve.
	CBV_Vein()	Eq. 9	The ratio between the area under the concentration curve of the contrast material and the area under the vein curve.
	CBV_maxV()	Eq. 10	The ration between the maximum concentration value in tissue and vein.
	CBV_maxA()		The ration between the maximum concentration value in tissue and artery.
CBF	CBF_sSVD()	Eq. 17 to Eq. 23	Determination of CBF using singular values (SVD).
	CBF_dSVD()	Eq. 24	Determination of CBF using delay-corrected SVD
	CBF_bSVD()	Eq. 25	Determination of CBF using block circulant SVD
	CBF_Fick()	Eq. 11	Uses maximum derivation, the ratio between the tissue and the difference between artery and vein.
	CBF_maxD()	Eq. 12	Uses maximum derivation, the ratio between the tissue and artery.
	CBF_CentralVolume()	Eq. 35	The ratio between each voxel in CBV and MTT image.
MTT	MTT_Axel()	Eq. 33	The area under the curve divided by its height.
	MTT_Phillips()		Width of curve at half of the maximum value.
	MTT_Smith()	Eq. 34	The ratio between the area under the concentration curve of the contrast material and the maximum value of the curve.
	MTT_CentralVolume()	Eq. 35	The ratio between each voxel in CBV and CBF image.
Permeability	PERM_Artery()	Eq. 36	Determination of Permeability Surface
TTP	TTP()		The time elapsed between the injection and the appearance a peak.
CBV×CBF	MUL()	Eq. 41	The multiplication of CBV by CBF
CBV×MTT	MUL()		The multiplication of CBV by MTT

Transit Time	TransitTime()		Determines the maximum concentration and the time that occurs.
Concentration Amplitude	concentrationVariation()		Determines the concentration variation of the contrast material
PRR	calculatePRR()	Eq. 43	Calculate the potential recuperation ratio and mismatch image

Table 5 – Overview of perfusion parameters.

Post-Processing Methods

The post-processing stage improves the contrast on the images without any manual adjustment by the users.

The methods Normalize to Range Values,

Normalize to Zero Mean and Normalize to Zero Mean and Unit Standard Deviation uses an adaptation of ivorix library [49] (see 3.4.1 Normalization).

Equalization

The equalization method (*equalization()*) uses the OpenCV [50] library for calculate histogram information for visualization purposes. The histogram uses 256 bins (because unsigned char data type is used), for equalize image using a histogram we need to calculate the histogram H by *cvCalcHist()* for each slice, in the image (Figure 24) we a large black area where the values are zero, so it is necessary to remove them from the histogram, after that we normalize and compute the integral (sum of all bins – Eq. 50) of the histogram, finally transform the image using H' as a look-up table (Eq. 51).

$$H'(i) = \sum_{j=0}^{i} H(j) \quad \text{Eq. 50}$$

$$dst(x, y) = H'(src(x, y)) \quad \text{Eq. 51}$$

This method (equalization) should be applied at the end of the pipeline, however if we intend to apply some visual changes (e.g. Quadratic, Exponential, Logarithm or Logistic functions) it is necessary make the equalization before that (see 3.4.3 Enhance the Image).

See section 3.4 (Post-processing) for more information.

Summary Table

Post-processing Method	Method	Description
Normalize to Range Values	norm_max_min()	Allow a better comparison between several perfusion parameters or image because normalize all images.
Normalize to Zero Mean	norm_zm()	Normalize input image with zero mean.
Normalize to Zero Mean and Unit Standard Deviation	norm_zmuv()	Normalize input image with zero mean and unit deviation.
Saturate image	satureImages()	Saturate the input image with a given range values.
Window Level Correction using Artery as Reference		The image is truncated with the maximum value corresponding to the maximum value obtained in artery voxel.
Equalization	equalization()	Equalize the image using a histogram distribution.
Quadratic	quadratic()	Application of a quadratic function. This method should be applied after equalization method.
Exponential	exponential()	Application of an exponential function. This method should be applied after equalization method.
Logarithm	logarithm()	Application of a logarithm function. This method should be applied after equalization method.
Logistic	logistic()	Application of a logistic function. This method should be applied after equalization method.

Table 6 – Detailed overview of post-processing methods.

Auxiliary Functions

Get ROI

One interesting tool (*GetROI2()*) is the marking the region of interest (ROI), for that it is important get the two points. These two points (ROIs) are in the opposite hemisphere and it is used an axis of symmetry (using artery and vein as points of axis) according to the Figure 36. Given a point *P* using a symmetry axis (formed by *A* and *V*) and trigonometry it is calculated a point *P'*.

Axis Point

Given two reference points like artery and vein this method determines axis points (*GetAxisPoint()*), point *H* and *W* in Figure 36.

Create Histogram Image

This method creates a histogram image (Figure 49) to assess the chromatic distribution, for do that is necessary to calculate and scale the histogram for each slice. The histogram has 256 bins and each bin is represented by a rectangle whose height represents the frequency.

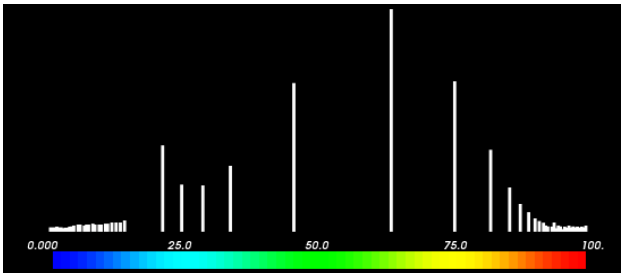

Figure 49 – Histogram image example.

Create Mask

This method (*createMask()*) creates a mask image with 4 slices used for data filter. For the mask creation it is used morphological operations from OpenCV library [50]. We need to remove some artefacts from the CT image, artefacts of the CT machine.

For removing the bone, a binary mask is used, combining the bone segmentation (3.2.5 Bone Identification) and the original image, removing the unwanted voxels by a close operation (dilate – *cvDilate()* and erode – *cvErode()*). To avoid some noise originated by the mask creation and for an accurate result we shrink the mask (erode operation). The mask is applied to all voxels by multiplying each voxel of the CT image by a correspondent voxel on mask.

Concentration in reference voxels

This method (*GenXYconcentration()*) create a vector with concentration variation of artery, vein and optionally a control point, the indication of current image a relevant time, with that data we create a XY graph (Figure 50). The *Time* can be used for accurate perfusion parameters.

0	1	…	N-2	N-1	Artery
N	N+1	…		2N-1	Vein
2N		…		3N-1	Control
3N		…		4N-1	Current Time
4N		…		5N-1	Time

Data structure of data vector

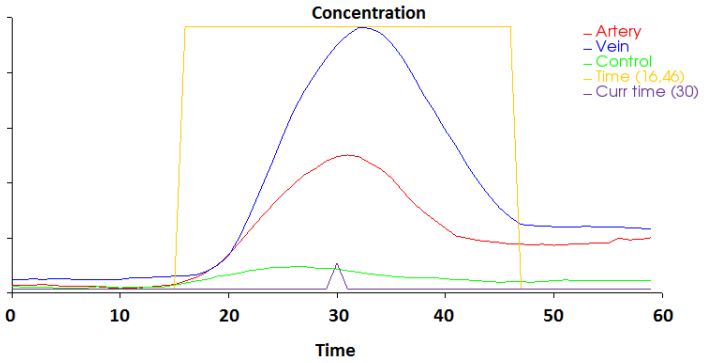

Figure 50 – XY graph with reference voxels concentrations.

Lookup Tables

For a better contrast image we case use some several lookup tables. It is possible to get all lookup tables implemented (*GetAllLookupTable()* – 41 entries) or the common used (*GetLookupTable()* – 7 entries). The common lookup tables are showed in Figure 51.

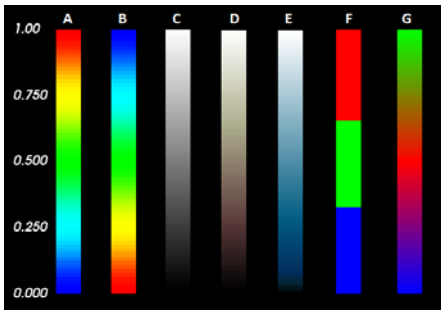

Figure 51 – The common lookup tables.
Rainbow (A), invert rainbow (B), gray scale (C), bone (D), cortex (E), 3 colours (F), centred scale (G).

The reason for we choose these lookup tables are the fact of the neurologists is already familiar with (A-F), the lookup table G is have a different purpose is used only for Transit Time image.

The vector with all colours (*N* pallets and 256 colours) was the next format:

	Colours				Colours			Colours	Colours		
	0	1	. . .	255	0	. . .	255	. . .	0	. . .	255
R	0	4		1020	1024		…	.			
G	1	5	.	1021	…	.	…	.			
B	2	6	.	1022	…	.	…	.			
A	3	7	.	1023	…	.	…				1024N-1
	0				1			. . .	N-1		
	Pallets										

Determination of Range Image

This is a simple method (*DetermineMaxMin()*) widely used in the application because it is necessary know the range values in image for stretching the image values and other functions. This method gives a *high* and *low* value in the current slice, if the slice number is zero the range value is for all slices.

Reference Pick Point

Given a pick point in CT image, artery and vein position it is determined (*PickerCT()*) a new reference point, the artery or vein point is replaced by the point picked depending on closest point.

IO Functions

It is necessary to use some IO functions (Table 7) for read and write data and manipulate DICOM/RAW files.

Method	Description
LoadDataPropDICOM()	Load data properties from a DICOM file.
getImageNumber()	Get sequence number of image from a DICOM file.
isPerfusionDICOM()	Verify if the file is a perfusion DICOM file.
getDICOMData()	Get data image as an array of shorts and image number from a DICOM file.
getDICOMHeader()	Get DICOM header file as an array of chars.
readRAWImagesSet()	Read as an array of shorts a set of RAW images.
readDICOMImagesSet()	Read as a short array a set of DICOM images.
WriteDataFile()	Write image as an array of shorts to a binary file.
ReadDataFile()	Read image as an array of shorts from a binary file.
WriteJPGImage()	Write a JPEG images from an array of doubles.
WritePNGImage()	Write a PNG images from an array of doubles.

Table 7 – Input/Output methods.

Documentation

The framework and the application was documented using the Doxygen and the documentation is available in web (html) and eBook (PDF) format.

Appendix B: Case Study

In this section we present all the images used in the clinical experts' evaluations (perfusion parameters, mismatch, etc.) for all the six available patients. We also present the tables resulting of the evaluations of these images by clinical experts.

The following legend (Table 8) presents for each perfusion parameter the several implementations that were evaluated.

Legend

Method	Acronym	Description
CBV	M0	Ground through image (GE image).
	M1	Axel method (Eq. 9) using artery as reference.
	M2	Axel method (Eq. 9) using vein as reference.
	M3	Klotz and König method (Eq. 10, using vein as reference).
	M4	Adaptation of Eq. 10 that uses artery as reference.
	M5	The same as M3 but with window level correction and applying a logistic function after equalization. Window = 30; Level = 10. Function: max = 103.7; a = 0.1; t0 = 67.
CBF	M0	Ground through image (GE image).
	M1	sSVD method (Eq. 17 to Eq. 23).
	M2	dSVD method (Eq. 24).
	M3	bSVD method (Eq. 25).

	M4		Maximum derivation (Eq. 12).
	M5		Fick's method (Eq. 11).
	M6		The same as M1 but with window level correction and using other lookup table. Window = 21; Level = 45
	M7		The same as M1 but with window level correction and using other lookup table. Window = 35; Level = 30.
	M8		Central Volume Principle (CBV M3 / MTT M10).
MTT	M0		Ground through image (GE image).
	M1		Axel method (Eq. 33).
	M2		Fillips method.
	M3		The same as M1 but with window level correction. Window = 80; Level = 0.
	M4		The same as M2 but with window level correction. Window = 80; Level = 0.
	M5		Central Volume Principle (CBV M3 / CBF M1).
	M6		Central Volume Principle (CBV M3 / CBF M2).
	M7		Central Volume Principle (CBV M3 / CBF M3).
	M8		Central Volume Principle (CBV M3 / CBF M4).
	M9		Central Volume Principle (CBV M3 / CBF M5).
	M10		Time to Peak. Window = 100; Level = 0.
	M11		The same as M10 but with window level correction. Window = 60; Level = 10.
Permea-bility	M0		Ground through image (GE image).
	M1		Permeability using Eq. 36 and CBV M3.
	M2		The same as M1 but with equalized CBV.
	M3		The same as M1 but with equalized CBV and applying an exponential function. Function: a = 21.72.
Mismatch	Thresholds	M1	Mismatch between CBV M3 and CBF M1 overlapped on CT image. (CBV: 50; 30. CBF: 50)
		M2	Mismatch between CBV M3 and CBF M2 overlapped on CT image. (CBV: 50; 30. CBF: 50)
		M3	Mismatch between CBV M3 and CBF M1 overlapped on CT image. (CBV: 50; 30. CBF: 70)
		M4	Mismatch between CBV M3 and TTP (MTT M10) overlapped on CT image. (CBV: 50; 30. TTP: 50)
		M5	Mismatch between CBV M3 and TTP (MTT M10) overlapped on CT image. (CBV: 50; 30. TTP: 70)
	Multiplication	M1	Multiplication of CBV M3 by TTP.
		M2	Multiplication of CBV M3 by TTP without equalization at last step.

		M3	Multiplication of CBV M3 by CBF M1.
		M4	Multiplication of CBV M3 by CBF M1 without equalization at last step.
		M5	Multiplication of CBV M3 by CBF M2 without equalization at last step.
		M6	Multiplication of CBV M3 by CBF M3 without equalization at last step.

Table 8 – Legend of implementation used.

Patients Images

Patient 1

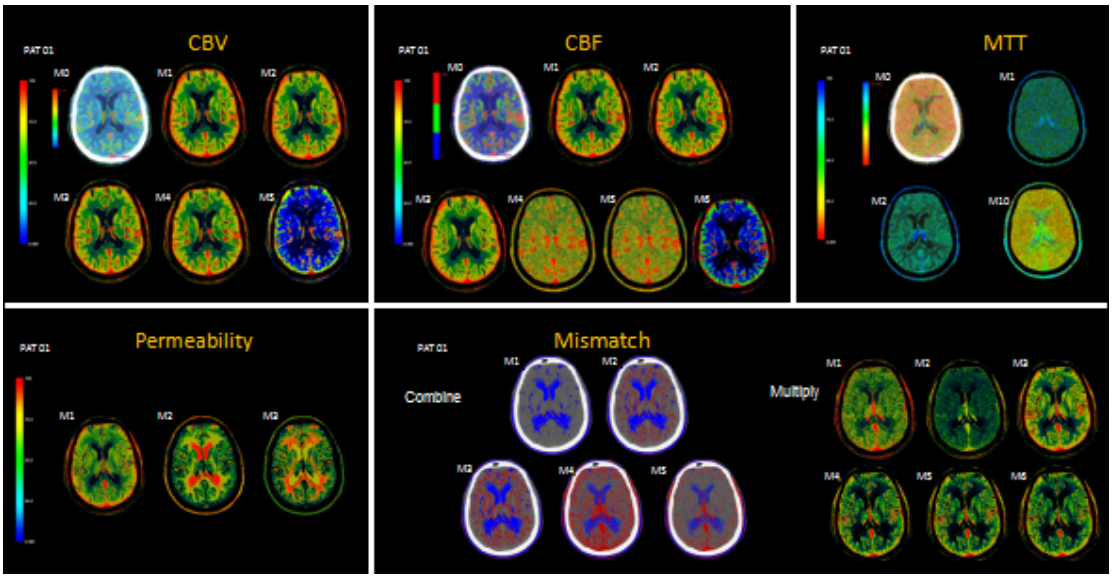

Figure 52 – All relevant methods for patient 1.

Patient 2

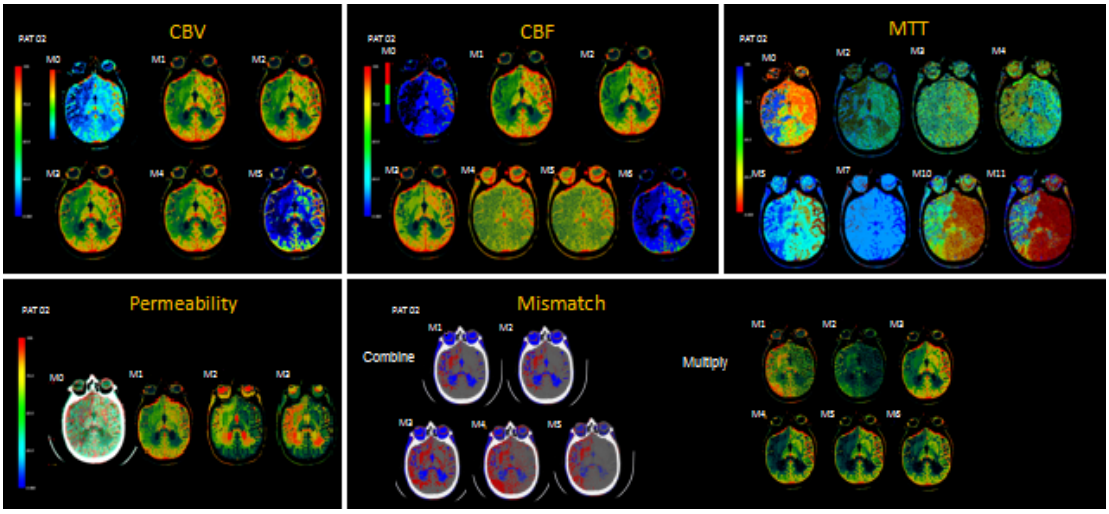

Figure 53 – All relevant methods for patient 2.

Patient 3

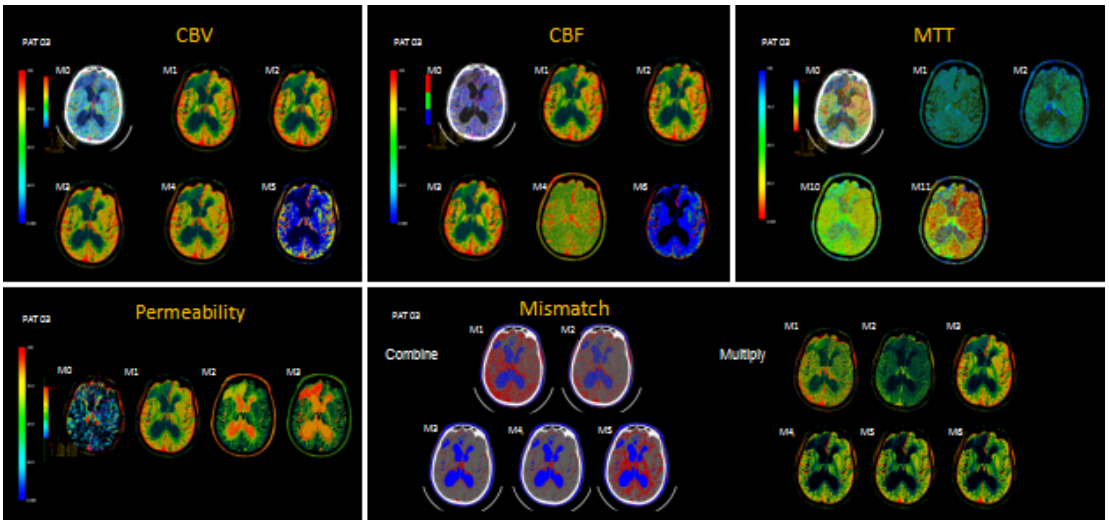

Figure 54 – All relevant methods for patient 3.

Patient 4

The CT images for patient 4 are corrupted and it is not possible to use for processing.

Patient 5

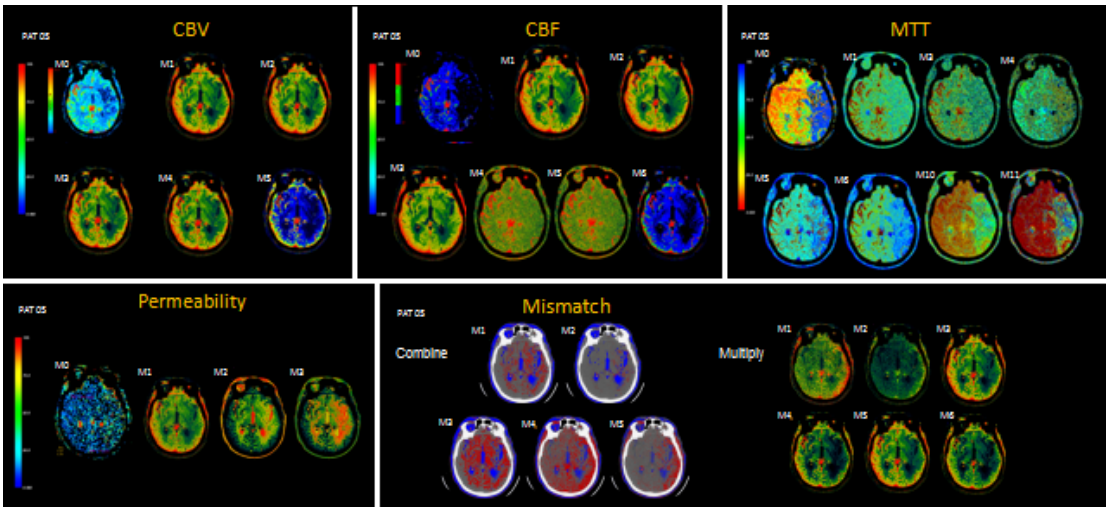

Figure 55 – All relevant methods for patient 5.

Patient 6

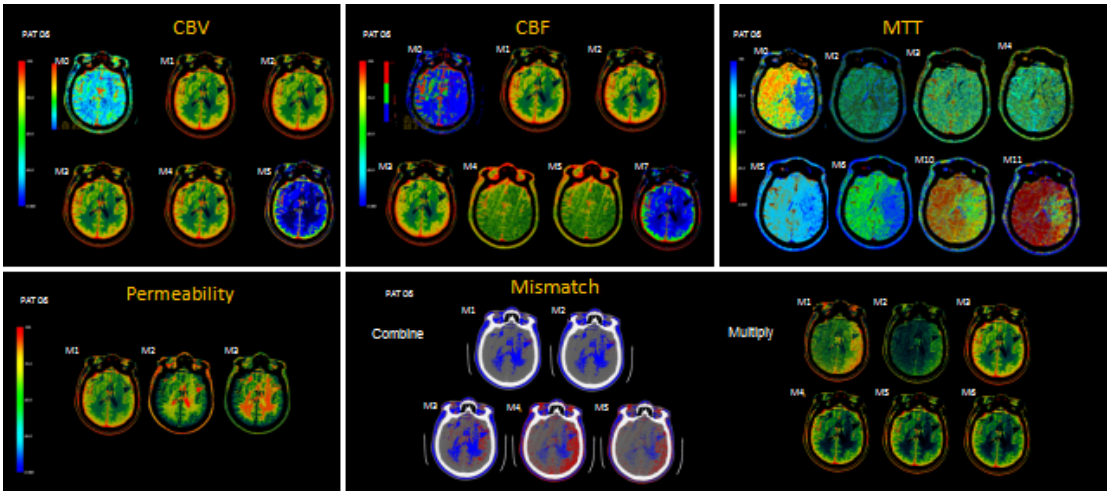

Figure 56 – All relevant methods for patient 6.

Medical results

We made some sessions with the clinical experts for understand the problems and investigate ways to improve the results. We generated several images based on the methods that we developed for each perfusion parameter and patient and asked to the neurologists to evaluate them with a mark between 0 and 10 for each image, the criteria used to evaluate them was based on clinical relevance for diagnosis. See the legend on the top of appendix B. Some methods were not investigated because the results were similar to others or were just noise.

Patient	Marks from clinical expert 1									
PAT 02	M1	M2	M3	M4	M5	M6	M7	M8	M10	M11
CBV	**6**	**6**	**6**	**6**	**9**					
CBF	**7**	**7**	**5**	3	3	**9**				
MTT		4	3	**6**	**9**		**6**		**9**	**9**
Permeability	**4**	**8**	**10**							
Mismatch – comb.	**8**	**8**		**6**	**8**					
Mismatch – prod.	**5**	**6**	**8**	**9**	**9**	**8**				

PAT 05	M1	M2	M3	M4	M5	M6	M7	M8	M10	M11
CBV	2	2	2	2	**7**					
CBF	2	2	2	3	3	**8**				
MTT	**5**		2	2	**7**	**8**	4		**8**	**9**
Permeability	3	3	**6**							
Mismatch – comb.	3	3		3	3					
Mismatch – prod.	1	1	4	5	5	3				

PAT 06	M1	M2	M3	M4	M5	M6	M7	M8	M10	M11
CBV	2	2	3	3	6					
CBF	3	3	2	1	1		7			
MTT		1	1	1	5	**10**	2		**9**	**8**
Permeability	1	3	4							
Mismatch – comb.	1	1	2	**5**	4					
Mismatch – prod.	4	4	1	1	2	2				

Table 9 – Clinical evaluation of generated images – clinical expert 1.

Patient	Marks from clinical expert 2									
PAT 02	M1	M2	M3	M4	M5	M6	M7	M8	M10	M11
CBV	**10**	**10**	**10**	**10**	**10**					
CBF	**10**	**10**	**7**	0	0	**10**				
MTT		**7**	1	**5**	**8**		0		**9**	**9**
Permeability	1	1	1							
Mismatch – comb.	1	1	1	1	1					
Mismatch – prod.	1	1	1	1	1	1				

PAT 05	M1	M2	M3	M4	M5	M6	M7	M8	M10	M11
CBV	3	3	3	3	0					
CBF	1	1	1	0	0	**8**				
MTT	4		2	2	**6**	**7**	0		**10**	**10**
Permeability	3	**6**	**8**							
Mismatch – comb.	1	1	1	1	1					

Mismatch – prod.	1	1	1	1	1	1				

PAT 06	M1	M2	M3	M4	M5	M6	M7	M8	M10	M11
CBV	**9**	**9**	**9**	**9**	**9**					
CBF	1	1	1	0	0		6			
MTT		1	0	1	4	**10**	0		**10**	**9**
Permeability	0	0	0							
Mismatch – comb.	1	1	1	2	1					
Mismatch – prod.	1	1	1	1	1	1				

Table 10 – Clinical evaluation of generated images – clinical expert 2.

Appendix C: Deployment & Installation

Dynamic-Link Library

In this section we present the creation of a Dynamic-Link Library (DLL) in C++ and the usage in C# to facilitate future implementations in Visual Studio ® (or other Windows based application).

We need to create a new project (Figure 57). Click in *File, New, Project…*

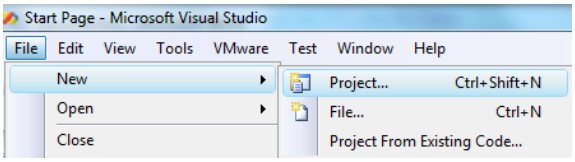

Figure 57 – Creation of a new project.

Select *Win32 Project*, type the name and destination folder, click *OK* and press *Next*. In the second window we select *DLL* radio button in *Application type* and *Empty project* in *Aditional options* and finally click *Finish*, as depicted in Figure 58.

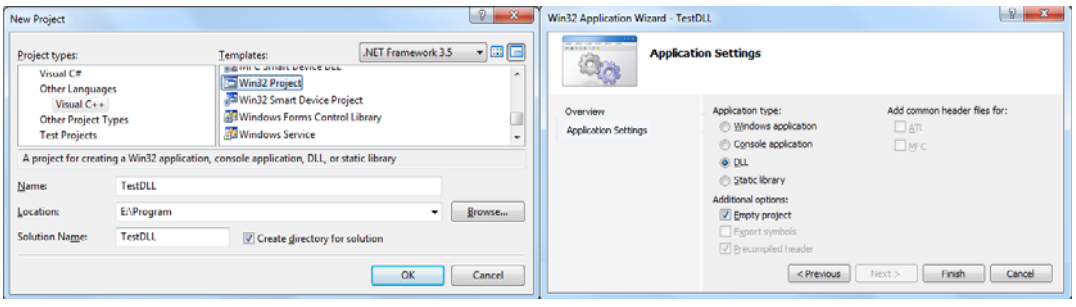

Figure 58 – Creation of a DLL project.

The development process is similar to any other C++ project, in order to create a DLL we need to build the solution project.

Now we present one example of code, the implementation of a class with one method that sum to integers, the exportation in C++ and the import in C#.

Building this project we will have the DLL file and the library file (.lib), the *lib* file is important for know how to invoke the external method (showed in the importation stage).

Exportation in C++

File: funcs.h

```
#ifndef _FUNCS_H_
#define _FUNCS_H_

//user defined macro for DDL exportation
#define DLL_EXPORT __declspec(dllexport)

namespace Nfuncs
{
     class funcs
     {
          private:

          public:
               static DLL_EXPORT int sum(int a, int b);
     };
}

#endif
```

File: funcs.cpp

```
#include "funcs.h"

#include <stdexcept>
#include <iostream>
using namespace std;

namespace Nfuncs
{
     int funcs::sum(int a, int b)
     {
          return a+b;
     }
}
```

Importation in C#

For we import the DLL we need to create a new C# project, windows forms application, for example. The name of the project will be TestForm.

File: main.cs

```
using System;
…

namespace math
{
      …
      public partial class Main : Form
      {
            //import statement
            [DllImport("TestDLL.dll",
                  EntryPoint = "?sum@funcs@Nfuncs@@SAHHH@Z")]
            public static extern int sum(int a, int b);

            …

            private void printSum(int p1, int p2)
            {
            //usage of the extern method
            Console.Writeline( sum(p1,p2) );
            }
      }
}
```

File: TestDLL.lib

The entry point can be found in TestDLL.lib (TestDLL is the project name); to see this entry we need to open the file as text like Notepad++ [61]. This file is a binary file as we can see in Fig. 3 by the non-character pictograms.

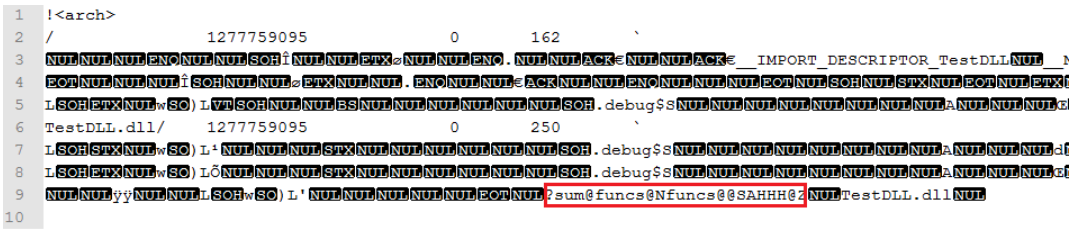

Figure 59 – TestDLL.lib file as text file.

Deployment

In this section we present the deployment process of a C# project to a setup application.

Using the previous project we click with the right button over the solution name (TestForm) and add new *Setup and Deployment* project with setup wizard, as showed in Figure 60.

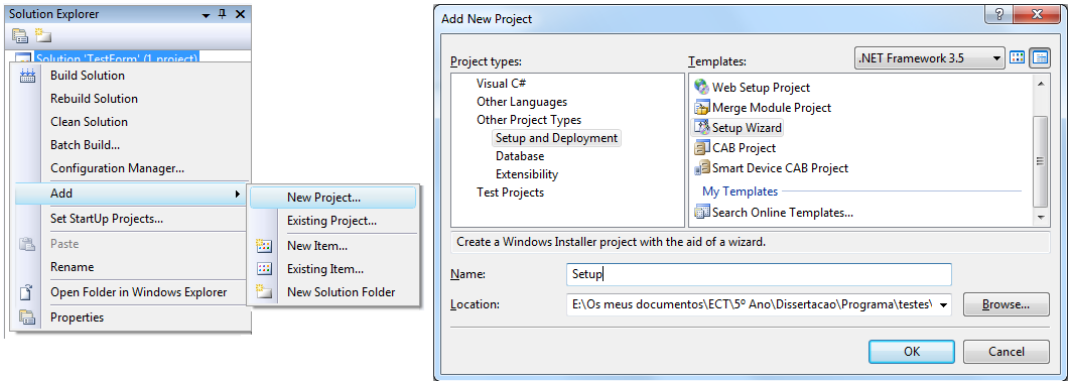

Figure 60 – Add a deployment project to the current solution.

During the process of configuration we select *Create a setup for a Windows application* in *project type*, select *Source files from TestForm* (this example is *TestForm*) in *project outputs*. In *files to include* we can add some additional files like *readme* or help files (not dependencies) and finish the process as showed in Figure 61.

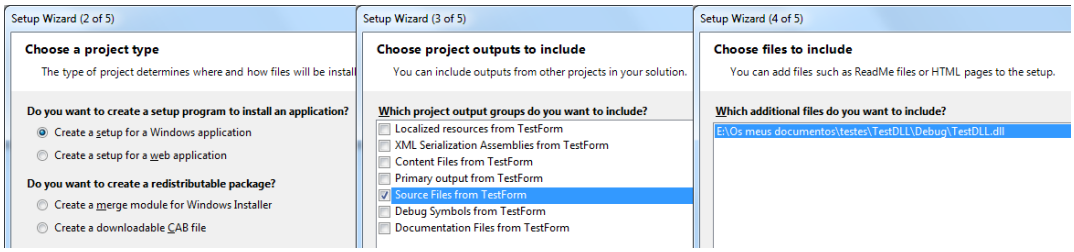

Figure 61 – Adding a setup and deployment project.

After adding the setup project we have two projects in the same solution, as showed in Figure 62 – A. Clicking with the right button over the setup project and click in *View* (Figure 62 – B) we can change the appearance of the setup project. In *File System* we can add folders and shortcuts (Figure 62 – C). In *User Interface* we can add/edit some stage in the installation process pipeline (Figure 62 – D). We are using an external library, so we need to add this file, in *Application Folder* we *Add* an *Assembly* file with the right button.

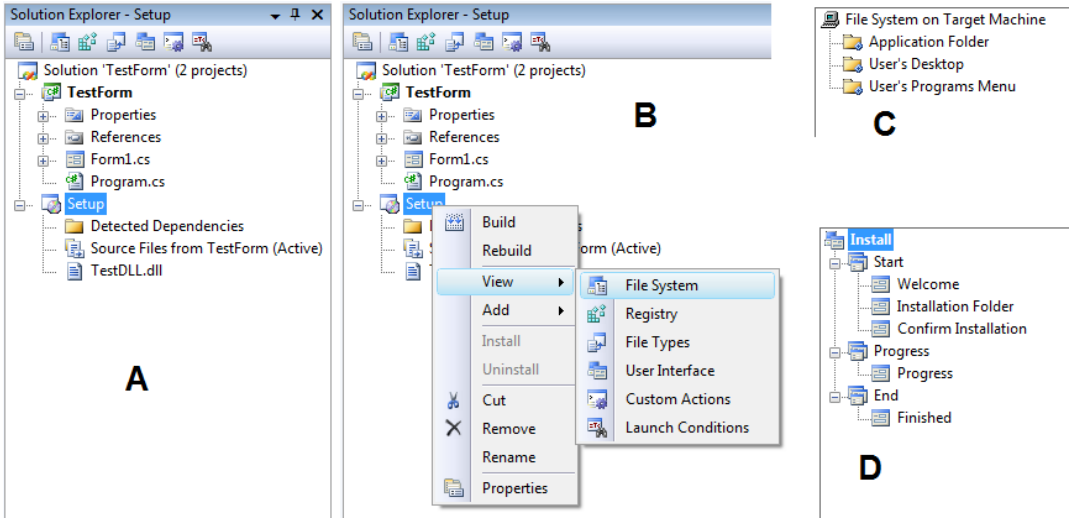

Figure 62 – Several views of the project.
A – Solution explorer; B – Several views; C – File system; D – User interface.

Installation

The installation process is similar to other windows based application. We execute the *setup.exe* and install the application, it is necessary to select the destination folder and click next several times. The splash window is presented in Figure 63.

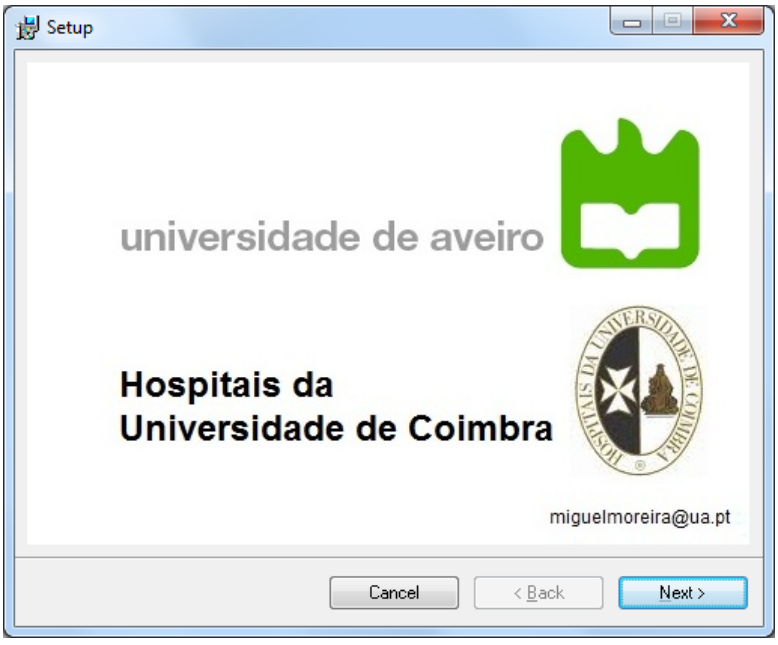

Figure 63 – Splash window.

The prerequisites for the installation of these applications are the framework .NET 3.5 and x86 architecture. The libraries developed also depend of some Visual Studio DLLs.