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A tool to visualize and analyze perfusion data: Development and application of the R package "CTP"

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ABSTRACT

Background and objective: Computed tomography perfusion (CTP) is a widely used imaging modality especially in neuroimaging. Despite this, CTP is often prohibitive due to the dearth of free/open-source software. This could have wide-ranging implications for instruction and research. We have implemented an online-available CTP tool built and run completely within the R computing environment.
Methods: Called from within R, the user can select one of four different methods to construct a cerebral blood flow (CBF) map: (1) max-slope (2) singular value decomposition (3) block circulant singular value decomposition or (4) oscillation minimization singular value decomposition. The four methods are compared against a digital CBF phantom.
Results: All four methods generate a CBF map, with the oscillation minimization technique giving the most accurate map.
Conclusions: We have constructed an easily accessible teaching and research tool to create a CBF map and made it freely available. We hope this tool will help facilitate understanding of the methods involved in constructing perfusion maps and be a valuable resource to future researchers.

1. Introduction

Of the two major classifications of stroke (hemorrhagic and ischemic), ischemic is the most prevalent [1]. During an ischemic stroke, blood supply to the brain is either temporarily or permanently reduced or occluded. If the location of an ischemic stroke can be detected early, a treatment plan can be quickly developed to break the clot using thrombolytic drugs. It is therefore important to visually identify where a stroke is occurring and the extent of the damage to the brain tissue. This is where brain perfusion is of great use.

Perfusion is defined as the process of delivering blood to a tissue via a capillary bed. Despite this straightforward definition, perfusion itself is difficult to measure, especially in the brain. Thus we are limited to estimating perfusion. This is also not an easy endeavor. Radiological brain imaging provides two tools to help estimate the delivery of blood to the brain: dynamic susceptibility contrast perfusion-weighted imaging, taken from an MRI, or computed tomography (CT) perfusion. There is variability in both the image acquisition parameters across different scanners and in the mathematical models for calculation perfusion, which are typically vendor specific; however, the image acquisitions are standardized, and the input data are constant across machine vendors. The method used to estimate various parameters of perfusion does not depend on the type of machine used to acquire the data, therefore from this point forward we will focus the discussion around CT perfusion.

Computed Tomography Perfusion (CTP) is an imaging technique first described twenty-five years ago [2]. This was initially done with single section CT scanners and progressed into multisection CT scanners [3]. With the advent of 256 slice (and higher) CT scanners, it is now possible to perform CTP on the entire brain, but this is still relatively rare due to the advanced machines needed [4]. During this procedure, a bolus of contrast is injected into a patient while a preselected area of tissue is repeatedly scanned while the bolus passes through the arteries and veins. As the contrast arrives to the brain tissue, it increases the "brightness" (often called "attenuation") of the tissue, measured in Hounsfield Units (HU). This is typically used to obtain one image per second [3]. This relationship between attenuation and time can be plotted on a Time-Attenuation Curve (TAC).

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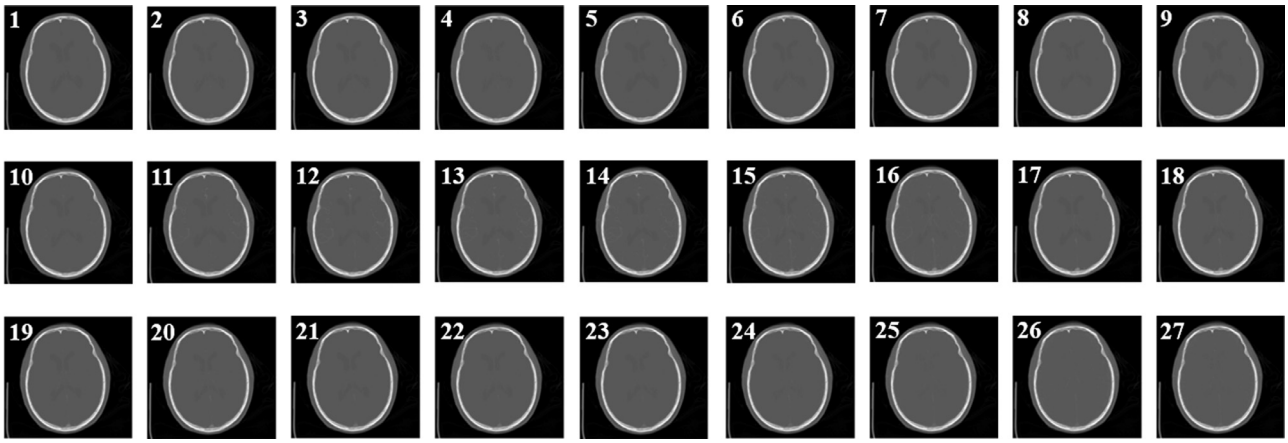

Fig. 1. Original grayscale images of single slice CTP data taken at 27 one second intervals from a 72 year-old male. These are the raw data images used to construct the CBF map shown in Fig. 3A.

Various quantities, called perfusion parameters, from these TACs are used to evaluate the amount of blood available to be used by the brain. These are derived from an "inflow" TAC gathered from a major artery and a TAC from each voxel of brain tissue to be mapped. Essentially, the most basic measurements are flow and volume, denoted by Cerebral Blood Flow (CBF) and Cerebral Blood Volume (CBV). Two other additional measures are sometimes reported: Time To Peak (TTP) and Mean Transit Time (MTT). TTP is the time from the start of injection until maximum contrast in reached. TTP can be easily calculated empirically without any estimation techniques. CBV is a fairly straightforward calculation consisting of the area under the curve (AUC) of the tissue TAC divided by the AUC of the arterial TAC. MTT is defined as the mean time between the arterial inflow and venous outflow and has a direct relationship to both CBV and CBF. This will be discussed later. MTT and CBF estimation vary tremendously depending on the method used for the estimation. The perfusion parameters can then be graphed regionally for every voxel and provided with a color map. The perfusion parameter most widely applied and the most easily understood, conceptually, is CBF. It is, arguably, the most important. If we can map where blood flow decreases or stops, we can see where an infarct (or stroke) occurs.

The estimation techniques vary across vendors of the postprocessing software [5–7,7,8]. The variability of the estimation of CBF and CBV are of great consequence. For example, a decrease of 10–15 mL/100 g/min can signal that blood is having difficulty perfusing an area, implying there is a blockage and giving information to the clinician on where intervention should occur. So the estimation of these different perfusion parameters matters tremendously. In addition, most of the software are proprietary and expensive ($50,000 as a conservative estimate) making it difficult for researchers to evaluate and further improve estimation methods. Thus there is a need for a learning and analysis tool for these perfusion data.

In this paper, we present an open source tool in the R computing environment [9] that we have developed which may be used to help clinicians and other researchers explore the perfusion results from their data. We illustrate this novel tool for evaluating different methods for perfusion estimation and showcase the application of the tool. This paper is organized as follows: a brief introduction to different perfusion parameter estimation techniques, a description of the simulation (called a phantom in imaging studies), software implementation and usage, results from both the simulation study and in vivo CT data, and finally a discussion of limitations and future directions of the software.

2. Methods

2.1. Techniques for estimating perfusion parameters

The essence of the problem of estimating the perfusion parameters can be distilled down to this question: how can we arrange the series of images shown in Fig. 1, consisting of 27 sequential grayscale CT images measured at one second intervals, to represent CBF? We will briefly discuss the different methods for accomplishing this with the goal of comparing and contrasting the accuracy and performance of the methods.

Three of the most important measures when trying to determine the amount of salvageable brain tissue are the CBF, CBV, MTT. They provide clinicians with visually identifiable areas of the brain that are either fully dead, or potentially salvagable. CBF is, arguably, the most important as it provides information to help answer whether blood is flowing to the brain. For any particular pixel/voxel, this is defined mathematically as the simple fraction

$$CBF = \frac{CBV}{MTT} \tag{1}$$

and CBV can be calculated by

$$CBV = \frac{\int_0^T C_t(t)dt}{\int_0^T C_a(t)dt} \tag{2}$$

where, T is the maximum time observed, $C_t(t)$ is the TAC for brain tissue and $C_a(t)$ is the TAC for the artery [10,11]. The majority of the work involves calculating the CBF (or, conversely, the MTT), and there are two mathematical approaches in deriving the CBF: methods not based on deconvolution and methods based on convolution.

Non-deconvolution methods

Methods not involving deconvolution – finding the solution to a convolving equation – were the first to be considered for calculating CBF and first described by Miles et al. [2]. The main attraction is that these can be calculated quickly. At the core, these methods are based on the Fick principle of conservation of mass for cardiac output. In its strict form this requires TACs for arterial (C_a), venous (C_v), and tissue (C_t):

$$C_t(t) = CBF \cdot \int_0^T (C_a(t) - Cv(t))dt \tag{3}$$