Semi-automatic segmentation of core and penumbra regions in acute ischemic stroke: preliminary results

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Abstract – Acute ischemic stroke is one of the most prevalent vascular diseases in the world. The early diagnosis of perfusion deficits is preferable due to the limited therapeutic window (3h), for the application of thrombolytics. For early diagnosis, it is necessary to calculate perfusion maps which will allow the physician to identify the two ischemic regions: core, irreversible ischemic tissue; and penumbra, salvageable tissue. Perfusion computed tomography (PCT) is a convenient method for diagnosis of perfusion deficits. The goal of this work is the development of a semi-automatic software for the segmentation of both ischemic regions in PCT images. We implemented an algorithm called Local Statistics (LS) that obtains a regional mean and standard deviation extracted from a sample delineated by the user on the region of interest (core or penumbra) of a specific perfusion map. The algorithm expands the selected region accepting boundary pixels from an 8-neighbourhood only if they pertain to the interval defined by the distribution parameters obtained from the sample. The process stops when all boundary pixels on the last ischemic region obtained do not satisfy the acceptation criteria. The segmentation results were compared with the manual segmentation performed by a clinician (CB), considered as the reference standard for our work. Visual inspection showed that the software provided similar results to the manual methodology. Implementation of quantitative performance metrics is needed for an accurated validation of our method.

Keywords: *ischemic stroke, core, penumbra, perfusion computed tomography, segmentation.*

I. INTRODUCTION

Computed tomography (CT) is an inexpensive and widely available imaging technology that is probably more feasible in the acute patient than magnetic resonance because it suffers less from motion-related artifacts and has fewer contraindications [1].

Perfusion CT imaging has the advantage of assessing both reversible and irreversible ischemia by generating parametric maps of cerebral blood volume (CBV), cerebral blood flow (CBF), and contrast mean transit time (MTT) [2]. Here we use the software *stroketool-ct* to calculate these perfusion maps.

As the therapeutic window for thrombolysis is small, it is crucial to perform rapid postprocessing of the PCT images, including the generation of perfusion maps and the segmentation of the ischemic regions.

No freely available software for the segmentation of core and/or penumbra ischemic region was found in review of the literature. The scarce availability of publications regarding segmentation of ischemic regions using PCT is puzzling, and in contrast to other imaging modalities. To the best of our knowledge, only Baumgartner et al. applied a partitioning (k-means) and a density based clustering algorithm to CBF, CBV and time to peak (TTP) maps in order to identify and segment clusters of normal and apparently ischemic parenchyma [8].

This paper is organized in the following manner: we present the software (*stroketool-ct*) used to obtain the perfusion maps in Section II; the methodology used to develop the LS algorithm is presented in Section III; the LS algorithm is explained in Section IV; the experimental results and the limitations of the proposed segmentation algorithm are discussed in Section V. Finally, in Section VI we present the conclusion and future works.

II. PERFUSION MAPS CALCULATED BY STROKETOOL-CT SOFTWARE

The basic principle of a dynamic CT time series is to scan the same image slice repeatedly (every e.g. 1 second) over a period (e.g. 60 seconds) while injecting a contrast agent. Using a multi slice CT imager it is possible to scan more than one slice simultaneously. *stroketool-ct* software allows for the calculation and

analysis of perfusion images based on dynamic contrast enhanced CT investigations of the human brain. The package is free to download for research purposes only. *stroketool-ct* analyses the signal intensity time curves pixel by pixel to create color coded perfusion image maps [3].

A. Calculation algorithms

stroketool-ct uses singular value decomposition (SVD) algorithms to deconvolute the pixel based time curves with the arterial input function (AIF) [4].

Central equation of the calculation of relative CBF, relative CBV and MTT is:

$$C_v(t) = F \int_0^t C_a(\tau) R(t - \tau) \, d\tau \qquad (1)$$

where $C_v(t)$ = contrast agent concentration within a given volume, F = tissue flow, $C_a(t)$ = contrast agent concentration of arterial input and $R(t)$ = residue function.

The blood volume is calculated by the area under the contrast agent concentration time curve normalized to the arterial input:

$$CBV = \frac{\int_0^t t \, C_v(\tau) \, d\tau}{\int_0^t C_a(\tau) \, d\tau} \qquad (2)$$

The mean transit time follows from the central volume theorem:

$$MTT = \frac{CBV}{F} \qquad (3)$$

B. Perfusion maps

For the accurate interpretation of perfusion maps it is crucial to understand the definitions of CBV, CBF, and MTT (Figure 1) as follow [5]:

Cerebral blood flow is defined as the volume of blood moving through a given unit volume of brain per unit time. CBF has units of ml of blood per 100g of brain tissue per minute (ml x 100 g^{-1} x min^{-1}).

Cerebral blood volume is defined as the total volume of blood in a given unit volume of the brain. This definition includes blood in the tissues, as well as blood in the large capacitance vessels such as arteries, arterioles, capillaries, venules, and veins. CBV has units of milliliters of blood per 100g of brain tissue (ml x $100g^{-1}$).

Mean transit time is defined as the *average* of the transit time of blood through a given brain region. The transit time of blood through the brain parenchyma varies depending on the distance traveled between arterial inflow and venous outflow.
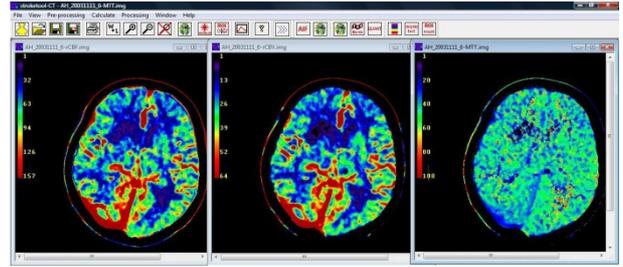

Figure 1. From left to right, perfusion maps: CBF, CBV, and MTT.

III. VISUAL SEGMENTATION OF ISCHEMIC AREAS

Core identification: studies have shown that the absolute CBV (with a threshold at 2.0 ml x 100 g^{-1}) most accurately reflects the acute infarct core. Clinicians manually identify this region by observing the matched decrease in both CBV and CBF parameters.

Penumbra identification: there are two documented methods in the literature regarding the visual identification of penumbral region performed by clinicians:

1) Identification through CBV and CBF mismatch: penumbral regions are characterized by a mismatch between CBF and CBV; namely, CBF is reduced and CBV is maintained or elevated above contralateral values [6].

2) Identification through CBV and MTT mismatch: the mismatch between the area of abnormal CBV and the relative MTT gives an accurate delineation of the tissue at risk of infarction [7].

IV. LOCAL STATISTICS (LS) ALGORITHM

The LS algorithm was developed using the Windows Microsoft® Visual Studio C++ platform. The inclusion of the algorithm within the *stroketool-ct* software was implemented through a macro plug in resource.

The LS algorithm tried to reproduce the clinical approach described in Section III. Therefore, the LS algorithm segments the core region in the CBV map and the penumbra region on the CBF or MTT maps, without using mismatch with CBV map. For this, minimal user interaction is required through the selection of a region of interest that will be used by the LS algorithm as a seed (sample) that will grow according to an acceptance criteria applied to its 8-neighbourhood. For each ischemic region, the sample will be selected on its corresponding perfusion map: CBV (for core) and; CBF or MTT (for penumbra) depending on the chosen approach. Figure 2 shows the fluxogram of the LS algorithm and is described in detail in the following paragraphs.

Core Segmentation:

The user selects the "core segmentation" macro plug in option and loads the CBV perfusion map (step 1) where a sample of the ischemic region (**Seed**) is manually delineated (step 2) for the obtention of statistic parameters that will guide the region growing process: mean (μ_{seed}), standard deviation (σ_{seed}) and delta (δ_{seed}). The value of delta (δ_{seed}) is calculated as 20% of the difference between the maximum and the minimum

intensity values of the sample. The segmented ischemic region (**Ischemia**) is initially equal to **Seed** (step 4). An auxiliary structure (**Edge**) is used to store pixels that come from the search space defined by pixels pertaining to the edge of **Ischemia**. Expansion is attained selecting a pixel (**pixel_edge**) from **Edge** (step 7) and assessing its 8-neighbourhood. The ischemic region is expanded (step 12) if the neighbours that do not pertain to **Ischemia** (8-neigh) have a mean intensity ($\mu_{8\text{-neigh}}$) within the interval $[\mu_{seed} - \sigma_{seed} - \delta_{seed}, \mu_{seed} + \sigma_{seed} + \delta_{seed}]$. At the end of the iteration, the **Edge** structure contains the accepted neighbours (step 13) whose neighborhood will be assessed in further iterations. The auxiliary structure is emptied deleting the pixel in consideration (**pixel_edge**, (step 8). The algorithm exits the loop when no pixels remain on **Edge** (step 6). Finally, the obtained segmentation is displayed and saved as a mask (**core mask**) that will be used in the next stage.

Penumbra Segmentation:

The steps for penumbra segmentation are almost the same as those described previously. One difference is that the user selects the "penumbra segmentation" macro plug in option and chooses the perfusion map (CBF or MTT) together with **core mask**. The only addition is on step 9 where neighbours cannot pertain to **core mask**, a requirement to keep the core and penumbra ischemic regions separated.
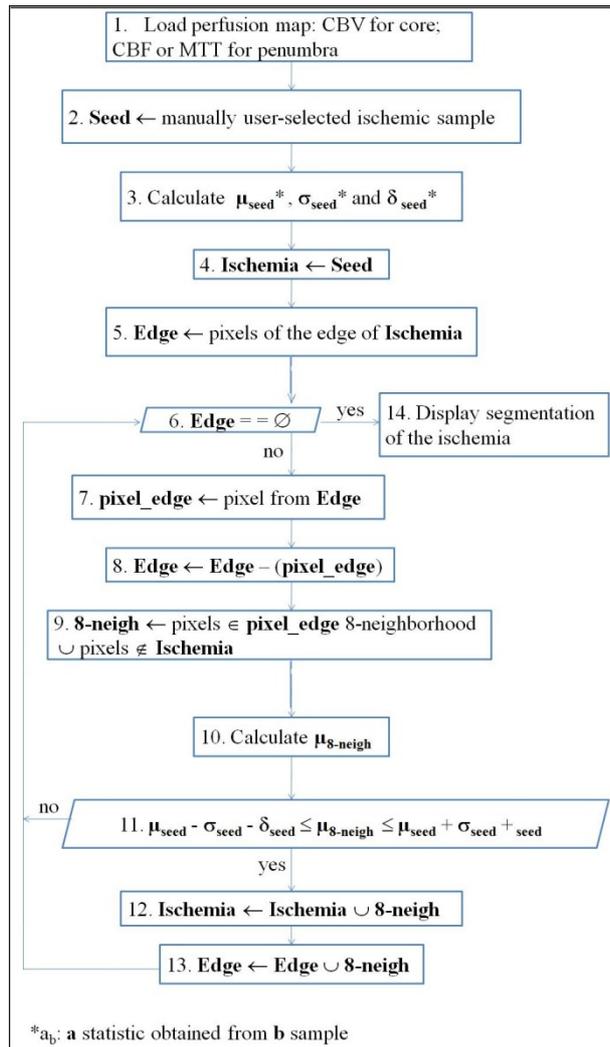

*a_b: **a** statistic obtained from **b** sample

Figure 2. Local Statistics algorithm fluxogram.

V. RESULTS AND DISCUSSION

A small sample (n = 6) of PCT images were postprocessed with the LS algorithm. The results presented here are preliminary. In this section, we present a set of images that come from the same patient to illustrate the segmentation results obtained for core (CBV map) and penumbra (CBV and MTT maps). These images were chosen because they are good examples of both the efficiency and the limitations of the LS algorithm. These characteristics were evaluated through a qualitative comparison with another set of images showing the manual segmentation (of the same ischemic regions) performed by a clinician.

The segmentation performed by the LS algorithm (Figures 3 and 4) is similar to the one drawn by the clinician albeit showing a more scattered pattern. This can be partially explained by an obvious advantage of the LS algorithm over manual segmentation that consists on the possibility of creating any type of boundaries, either smooth or sharp, according to the real ischemic region. Manual delineation is limited by the precision of the user and the interface.

Figure 4 shows that the LS algorithm segmentation expands beyond natural anatomical boundaries. This occurs because the manual segmentation identifies the region of the ventricle as an anatomical frontier for the ischemic delineation. As this knowledge is not embodied within the LS algorithm the low intensities in the ventricle are interpreted as core region. Being deterministic, the LS algorithm expansion stops only when no pixels on the edge of the segmented area pass the acceptance condition.
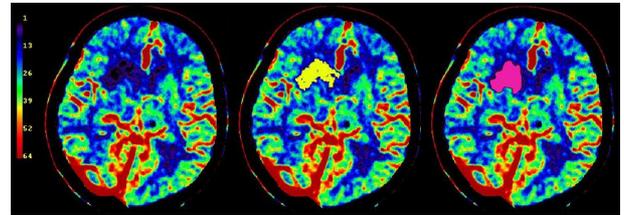

Figure 3. From left to right: CBV perfusion map, core segmentation obtained by LS algorithm (yellow), and core segmentation obtained by the reference standard (pink).
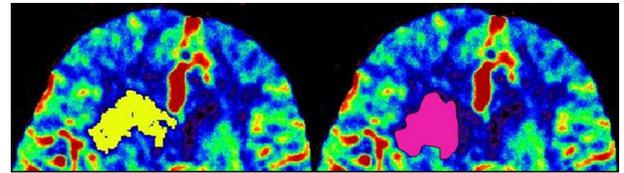

Figure 4. Core segmentation on CBV perfusion map (zoom of Figure 3): in yellow, obtained by the LS algorithm (left); in pink, drawn by the clinician (right).

In manual delimitation continuous free-hand areas are commonplace. In contrast, the automatic algorithm grows the segmented area depending on the statistics obtained from the user-selected sample so that regions with mean intensities lower or higher than intensities of the interval of acceptance criteria do not enter the segmentation. Figures 5, 6, and 7 show how this rejection of pixels with mean intensities out of the interval of acceptance created "islands" of different

sizes. Whether, this is a problem or not depends on whether it is a real underlying physiological phenomena or not. The penumbra is a result of direct autoregulatory responses to maintain CBF by dilating the precapillary vessels in response to decreased perfusion pressure [6]. For this reason, it may be counterintuitive to accept small and very small regions as luxury perfusion (white circle in Figure 6). The physiology of the penumbra including the autoregulatory phenomena and the luxury perfusion remain subjects to be studied.
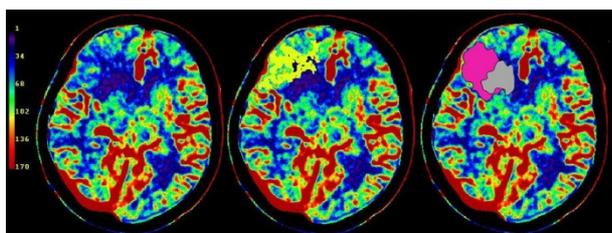

Figure 5. Left from right: CBF perfusion map, penumbra segmentation by LS algorithm (yellow), and manual penumbra segmentation (pink). The core (gray) was previously drawn by the clinician in Figure 3 and here illustrates that penumbra usually surrounds the core region.
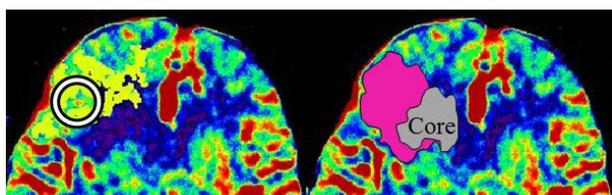

Figure 6. Penumbra segmentation (zoom of Figure 5): the white circle is detaching the islands of pixels that do not fulfill acceptance criteria used by LS algorithm (left); reference standard segmentation (right).
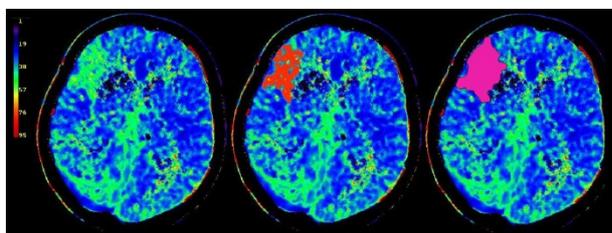

Figure 7. From left to right: MTT map, penumbra segmentation performed by the LS algorithm and the manual segmentation based on CBV and MTT mismatch.

It is evident in all examples that the LS algorithm is more efficient in selecting pixels on the edge. This can be attributed to the fact that the clinician does not have a fine precision mouse control to draw the sharp boundaries of the ischemic region with fidelity.

VI. CONCLUSIONS

We presented a deterministic algorithm to perform the segmentation of ischemic areas in brain PCT images. The algorithm has limitations, including persistence of islands with different intensity values inside the segmented areas that are not included in the core or penumbra. However, these islands may correspond to preserved tissue due to a compensatory brain response. Future investigation on this subject is necessary, both from a physiological point of view and for a new technical approach. The utilization of a non-

deterministic algorithm could bypass small intensity walls that should be interpreted as injured tissue.

In general, the shape of the segmentation is very similar to the one provided by the reference standard. Albeit preliminary, we consider the performance of the algorithm is satisfactory as it is not intended to substitute clinician judgment but rather to be used as an auxiliary tool for the identification of ischemic regions. We are quantifying the false negative/positive true negative/positive rates to evaluate performance of the LS algorithm. The quantification of anatomical and physiological information from the ischemic regions (volume, flow, and area) is also necessary to make this tool more useful as a support for diagnosis that will lead the most appropriate treatment for the patient.

This computational segmentation of core and penumbra is novel. In the context of scarce literature related to segmentation of brain PCT images, this preliminary work makes a substantial contribution the state of the art in this area.

REFERENCES

[1] R. R. Moustafa, J.C. Baron. "Imaging the penumbra in acute stroke". Current Atherosclerosis Reports, Vol. 8, pp. 281-289, (2006).

[2] M. W. Parsons, E. M. Pepper, G. A. Bateman, Y. Wang, and C. R. Levi. "Identification of the penumbra and infarct core on hyperacute noncontrast and perfusion CT". Neurology, Vol. 68, pp. 730-736, (2007).

[3] H.J Wittsack. "stroketool-ct manual", pp. 16 -17 (2006). Web: www.digitalimagesolutions.de

[4] JD Eastwood,. MH Lev, TAzhari,. T-Y Lee, D P Barboriak, D M. Delong, C Fitzek, M Herzau,. M Wintermark,. R Meuli, D Brazier, and J M. Provenzale. "CT perfusion scanning with deconvolution analysis: pilot study in patients with acute middle cerebral artery stroke". Radiology, Vol. 222, pp. 227-236, (2002).

[5] RG González, J A Hirsch; W J Koroshetz, MH Lev, P Schaefer. *Acute Ischemic Stroke: Imaging and Intervention* .1st Edition. Berlin: Springer-Verlag, p. 92, (2006).

[6] K A Miles, J D Eastwood, M Koenig. "Multidetector Computed Tomography in Cerebrovascular Disease: CT Perfusion Images". 1st Edition. London: Informa Healthcare, p 63, (2007).

[7] EM Teasdale, S Aitken. "Multidetector CT in neuroimaging an atlas and pratical guide". 1st Published. Oxford. Clinical Publishing Ltd, p. 67, (2009).

[8] C Baumgartner, K Gaustsch, C Böhm, S Felber. "Functional cluster analysis of CT perfusion maps: a new tool for diagnosis of acute stroke?". Journal of Digital Imaging, Vol. 18, pp. 219-226, (2005).