Purpose

The introduction in the clinical practice of anti-angiogenic therapies aiming at preventing tumour growth, spread, and capability of generating metastasis, has highly improved efficacy of cancer treatment [1]. Since the effects of these therapies are early visible on lesion’s functional behaviour and only later on morphology [2], the need for techniques capable to early estimate functional changes inside tissues has quickly increased [3].

Thanks to its high morphological and temporal resolution, CTp has shown to be particularly well-suited for the early assessment of anti-angiogenic therapies efficacy [4]. In fact, this functional imaging technique allows achieving perfusion parameters related to tissue vascularization [5], that have shown to be effective both in tumour diagnosis [6] and prognosis [7]. Moreover, one of the advantages of using CTp over other functional imaging techniques, such as magnetic resonance, is that the concentration of contrast agent (CA) inside tissue is directly proportional to the attenuation of HU values. In the ideal conditions (i.e., without noise), tissue density values before CA arrival (i.e., the baseline attenuation value) should be constant in time. Therefore, after subtracting from each TCC its baseline value, what results is a signal in direct ratio with the CA concentration inside tissue, on which perfusion parameters are computed [8].

The main steps that have to be followed for the computation of CTp perfusion parameters are three:

1. drawing a region of interests (ROI) on the tissue to be analysed and extracting a time concentration curve (TCC) from each voxel
2. subtracting from each TCC its baseline value to obtain the corresponding time attenuation curve (TAC)
3. applying specific kinetic models, and computing methods to each TAC to obtain voxel-based perfusion parameters

Each item of the list is of a fundamental importance to achieve accurate and correct perfusion results. However, while the methods to carry out the first and third tasks have been deeply analysed in the literature [9,10], to the best of our knowledge, the second item has not been studied in the details yet. Indeed, actually, there are no works explicitly facing the issue of how computing baseline values.

In the literature, baseline values have been mainly computed according to two methods. Both these methods are based on the analysis of the first CT image acquired, since it is the one having the highest probability of representing unenhanced tissues (of course, as time goes by, the CA will join the tissue). The most common method to compute baseline extracts its value as the average of liver density values inside the tissue ROI on the first image. In this way, the same global baseline value is subtracted from all the TCCs [11], thus neglecting local variations in tissue densities. Instead, the second method uses voxel-based baseline values that are selected for each TCC as the corresponding density
values in the first CT image acquired [12]. However, the presence of noise and artefacts affecting the first CT image can alter baseline values and lead to incorrect perfusion values.

Several works in the literature report mean density values for normal liver, measured through the use of unenhanced CT scans, around 50–65 HU [13]. Other works extend the range to 30 HU–70 HU [14, 15] or even more. Indeed, in a recent retrospective study involving 48 patients with normal liver who underwent two CT examinations, carried out with two different CT scanners in less than one year, the mean liver density values measured ranged from 9.6 to 63.2 HU and from 20 to 77.2 HU [16], respectively.

Despite CTp has proved to be a useful tool in oncology, the lack of reliability and reproducibility of perfusion results [17] is the main cause delaying its use in the standard clinics. Recently, some steps forward have been taken to try solving these issues. Indeed, some works address the problem of assessing perfusion values reliability [18, 19] and try improving their computation [20]. Moreover, guidelines regarding the set-up of CTp studies have been compiled to improve reproducibility of results [17]. However, some efforts still need to be done to improve the accuracy of perfusion results and, in turn, outcomes reliability and reproducibility.

In this work, we propose a new adaptive method permitting to compute accurate voxel-based baseline values of normal liver in a set of patients with colorectal cancer.
Methods and materials

Patients

The CTp examinations used in this preliminary study were randomly selected from those of "Perfusion IndeX: Evaluation for Liver metastases (PIXEL)", a CTp multi-centre study on liver involving 19 Centres and almost 400 patients. The aim of this multi-centre study is to evaluate the capability of perfusion parameters to predict the onset of hepatic metastases in patients with initially non-metastatic colorectal cancer, before the administration of anti-cancer therapies. 40 examinations pertaining to as many patients who did not develop metastases in the 3-year follow ups were selected from one Centre that took part to PIXEL.

The inclusion criteria for patients in PIXEL were:

• age > 18 y.o.
• having colorectal cancer
• absence of liver metastases
• absence of previous cancer pathologies

Exclusion criteria can be resumed as follows:

• presence of liver metastases at the time of cancer diagnosis
• having chronic liver diseases
• receiving chemotherapy before undergoing liver CTp
• undergoing cancer colorectal surgery before liver CTp
• being allergic to CA
• suffering from renal impairment
• being pregnant

Acquisition protocol

A first unenhanced spiral scan was carried out on the liver to identify the correct region that had to be analysed. Right after, an axial CTp acquisition was performed in order to include the portal vein trunk and the right hepatic parenchyma. The image acquisition started at the same time as the administration of 40ml of iodinated CA, with a concentration of 350mgI/ml, at 5ml/s. The CA bolus was followed by 20ml of physiologic solution. Patients were asked to breathe shallowly during the two minutes of the CTp acquisition. The CT tube current and voltage was kept fixed at 100mA and 80kV, respectively, with 1s rotation time and exposure of 100mAs. The tissue was acquired every 1s during the first 30s and every 3s for the remaining 90s, this yielding 60 scans, each composed of 8 sections of 5mm thickness.
ROI selection

In each CTp examination, a ROI has been drawn on a central section of the liver. The whole tissue ROI had to lay within the liver borders, possibly, far from liver margins, so as to avoid partial volume effects in all the images of the CTp sequence. Moreover, the ROI had to exclude big vessels, such as portal vein or hepatic artery. Then, a second ROI had to be drawn on a supplying vessel (e.g., the aorta). An example of these two ROIs is reported in Fig. 1 on page 12.

Fig. 1: ROIs of examination ID1 drawn on the aorta (in the red colour) and on normal liver (in the blue colour), avoiding big vessels.
Baseline computation

The main problems related to baseline computation are:

1. deciding how many time instants to include, that is which are the time instants before CA arrival
2. setting up a proper processing method

As regards the second point, we simply perform an average operation on the data point selected in 1). Hence, the main core of the algorithm is to find out BP. While the first point of BP is naturally chosen as the first time instant, the real problem is to find out what the ending point (EP) is.

The algorithm to find out voxel-based EP values is an adaptive iterative algorithm subdivided into four steps:

1. looking for the possible time instants of ending baseline
2. iterative TCC fitting
3. computing TCC’s fitting error index
4. selecting the time instant corresponding to EP

While the first data points of each TCC certainly belong to BP and EP has to be found, in order to speed up the algorithm we selected the proper TCC portion on which looking for baseline EP. Both the extremities of this interval of possible EPs were selected in a conservative way to preserve all the possible solutions. In particular, the starting point of the interval (SI) is selected as the time instant of CA arrival in aorta. In this way, since CA cannot reach tissue before passing through the arterial input vessel, all the TCC data points before SI certainly belong to BP and therefore are excluded from the dataset of possible EPs. SI is automatically selected as the last local minimum before the aortic peak. Fig. 2 on page 12 reports an example of SI chosen stemming from the aortic TCC of examination ID2.
Fig. 2: The aortic curve (in the red colour) and one TCC of the examination ID2 (in the blue colour) are shown. Selected SI is pointed out by the green vertical line. The green marker on the aortic TCC highlights the last local minimum of this curve before it starts enhancing.

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While SI is assumed to be the same for all the TCCs (because it is extracted from the aortic signal that is the same for all the tissue voxels), EI is kept variable. In particular, EI is selected for each voxel as the time instant corresponding to the tissue TCC peak. This allows the algorithm to adapt the research of EP to the most appropriate signal portion, dependently on the time taken by CA to join that specific tissue voxel. In this way, EI always represents one of the points surely localised after the arrival of CA in the corresponding tissue voxel. This permits to include in the interval all the data points that could correspond to EP and to exclude those data that have been acquired after the arrival of CA inside tissue. Fig. 3 on page 13 reports an example of EI selected on a TCC randomly chosen from data of examination ID2.
Fig. 3: One TCC of the examination ID2 (in the blue colour) is shown together with the green vertical line pointing out the selected SI. The blue marker points out the position of the peak of the TCC, while the blue line highlights EI, accordingly.

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After defining the set of possible solutions, we started implementing the part of the algorithm aiming at computing the correct EP. Based on the ideal case (i.e., absence of noise) where the TCC data points belonging to BP are constant, we modelled TCCs' BP with a horizontal line. In particular, we implemented an iterative algorithm considering at each iteration different possible EP, given the first BP point being known. Indeed, in the first iteration, the TCC portion from the first point to SI is fitted with a horizontal line. The ordinate of the fitting line is given by the average values of the TCC data points considered. Then, at each iteration of the algorithm, one more subsequent TCC point is included in the TCC portion that has to be fitted. This iterative fitting process goes on until EI is found. An example of the partial results of this process is reported in Fig. 4 on page 14.
Fig. 4: Red vertical line corresponding to SI. Linear (horizontal) fit of the TCC portions selected during the first five iterations of the algorithm are represented in different colours.

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Now that we have modelled all the possible BPs of the TCC, we need for an index able to evaluate the coherence between the TCC’s data points considered at each iteration and their ideal version represented by their fitting curve. To this purpose, the goodness-of-fit error index $\mu_\#$ presented in [18,19] has been used. $\mu_\#$ is computed as the average of the absolute values of the residuals $\#$, calculated in each data point as the distance between the original data and their fitted version. Consequently, the more the data points are far from the fitted curve, the higher the value of $\mu_\#$. Fig. 5 on page 15 shows an example of the residuals $\#$ referred to BP of a TCC and fitted with a horizontal line. Therefore, $\mu_\#$ was computed at each iteration on the TCC data points considered.
Fig. 5: TCC’s BP (in the blue colour) fitted with a horizontal line (in the red colour) and the residuals $\varepsilon$ for each data point (in the black colour).

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Now, we have all the possible TCC's BP and an index evaluating BP data point coherence with their expected version. Therefore, to select the correct EP, we relied on CA inside tissue quickly increasing TCC's density values from density values of BP, and $\mu_#$ value increases, accordingly. EP is thus in correspondence of the last time instant of BP showing the lowest $\mu_#$. In Fig. 6 on page 16, an example of TCCs and EP, and of the $\mu_#$ values computed at each iteration of the algorithm.
Fig. 6: A TCC of the examination ID1 (a) and the $\mu_e$ values computed at each iteration (b). The green and the blue vertical lines point out the selected SI and EI, respectively. The red vertical line points out the time instant of EP selected by our algorithm.

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Finally, the baseline value of each voxel was computed as the average of the TCC density values referred to the BP. For each examination, the baseline values were represented through the use of colorimetric maps and mean, median, standard deviation, and range values were computed.
Fig. 1: ROIs of examination ID1 drawn on the aorta (in the red colour) and on normal liver (in the blue colour), avoiding big vessels.

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Fig. 2: The aortic curve (in the red colour) and one TCC of the examination ID2 (in the blue colour) are shown. Selected SI is pointed out by the green vertical line. The green marker on the aortic TCC highlights the last local minimum of this curve before it starts enhancing.

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Fig. 3: One TCC of the examination ID2 (in the blue colour) is shown together with the green vertical line pointing out the selected SI. The blue marker points out the position of the peak of the TCC, while the blue line highlight EI, accordingly.

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Fig. 4: Red vertical line corresponding to Sl. Linear (horizontal) fit of the TCC portions selected during the first five iterations of the algorithm are represented in different colours.

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Fig. 5: TCC's BP (in the blue colour) fitted with a horizontal line (in the red colour) and the residuals # for each data point (in the black colour).

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Fig. 6: A TCC of the examination ID1 (a) and the µ# values computed at each iteration (b). The green and the blue vertical lines point out the selected SI and EI, respectively. The red vertical line points out the time instant of EP selected by our algorithm.

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Results

ROIs area mean and standard deviation were of 23.18±10.3cm$^2$. Average and standard deviation of baseline mean values of all the patients enrolled were of 61.7±10.1HU (range 32÷79HU). In all the examinations, mean and median baseline values are very similar (absolute differences lower than 1HU), this suggesting quite symmetric distributions. The histogram of these absolute differences of the 40 examinations is shown in Fig. 7 on page 21.

![Histogram](image)

**Fig. 7**: Histogram of the absolute differences between mean and median baseline values of the various examinations.

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A representation of the baseline values of each examination is reported in Fig. 8 on page 21. As one can see, range of baseline values (the blue lines represents the sets of
non-null bin values) of each examination are quite similar in almost all the examinations. Averaged baseline values under $40\text{HU}$ have been found in two examinations only and could point out presence of steatosis [21].

**Fig. 8**: Baseline bins of each examination, represented with blue dots, appearing like continuous blue lines. Red markers represent mean baseline values.

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For the sake of completeness, we analyse colorimetric maps (Fig. 9 on page 22) and histograms (Fig. 10 on page 23) of the baseline values achieved with our algorithm in three representative examinations (ID23, ID37, ID38). As one can see, baseline histograms can be of several shapes. For instance, Fig. 9 on page 22 (a) presents a Gaussian-like distribution with a short heavy right-tale (up to 65HU) and a limited range (15.2HU). The histogram in Fig. 9 on page 22 (b) is bimodal, presents a heavy left-tail, and shows the widest range (26.7HU). Instead, the histogram of the last examination, shown in Fig. 9 on page 22 (c), is multimodal but its range (16.4HU) is similar to that of
the first histogram. None of these histograms presents groups or sparse baseline values far from the principal distribution.

![Baseline histograms for patients ID23 (a), ID37 (b), and ID38 (c). The red vertical lines point out the mean baseline value of that examination.](image)

**Fig. 9:** Baseline histograms achieved for patients ID23 (a), ID37 (b), and ID38 (c). The red vertical lines point out the mean baseline value of that examination.

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This is reflected also in the three colorimetric maps (**Fig. 10** on page 23 (a), (b), and (c)) where all the neighbouring voxels assume "continuous" colours in a limited range, this hinting at similar tissue features inside the ROI. By observing the colorimetric maps it is also possible to achieve information about the spatial distribution of baseline values. For instance, all the colorimetric maps are locally highly homogeneous. The presence of a local spatial correlation is demonstrated by the gradual passage of baseline values from lower to higher baseline values that in colorimetric maps results in progressive colour gradients. Since baseline values obtained through using our algorithm are computed in each voxel by using only data pertaining to one TCC, independently from the signal of the neighbour voxels, the local spatial homogeneity of baseline can be considered as a qualitative indicator of algorithm goodness.
**Fig. 10:** Baseline colorimetric maps achieved for patients ID23 (a), ID37 (b), and ID38 (c).

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Fig. 7: Histogram of the absolute differences between mean and median baseline values of the various examinations.

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Fig. 8: Baseline bins of each examination, represented with blue dots, appearing like continuous blue lines. Red markers represent mean baseline values.

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Fig. 9: Baseline histograms achieved for patients ID23 (a), ID37 (b), and ID38 (c). The red vertical lines point out the mean baseline value of that examination.

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**Fig. 10:** Baseline colorimetric maps achieved for patients ID23 (a), ID37 (b), and ID38 (c).

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Conclusion

Accuracy of perfusion parameters computed on CTp images is highly affected by the baseline values selected. In this work, we propose an algorithm to compute baseline values that try improving the two methods mainly used in the literature. Indeed, our voxel-based method to compute baseline values exploits all the data-points pertaining to the signal BP, avoiding to use global baseline values (neglecting local variations) or local baseline values extracted from a single CT image that, as such, are particularly affected by the presence of noise and artefacts.

The spatial coherence shown by all the baseline colorimetric maps hints at a local similarity of tissue features and points out the goodness of our voxel-based algorithm. In addition, the mean baseline values achieved in our study is compliant with values of normal liver reported in the literature. Consequently, our results show that baseline values of normal liver of patients with colorectal cancer are compliant with values of normal liver in healthy subjects reported in the literature.
References


