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Reproducibility of Computed Tomography perfusion parameters in hepatic multicentre study in patients with colorectal cancer

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Abstract

Objective: The Computed Tomography perfusion (CTp) is a promising tool in oncology to characterize tissue hemodynamics, but the difficulty to achieve reproducible perfusion parameters in several organs, with different methods, contributes to hamper the clinical translation of CTp. The goal of this study is to setup a new approach aiming at achieving multicentre reproducibility of blood flow (BF) values in liver.

Methods: 75 patients from two Centres (A and B) underwent an axial liver CTp, including arterial and portal phases. A dedicated workflow addressing modelling and computational aspects was implemented, including a novel two-stage strategy to separate the dual-input contributions of hepatic signals, thus allowing to compute independently both Maximum Slope (MS) and Deconvolution (DV) on the same contributing signals.

Results: 95% of patients in A and B showed an excellent voxel-based Pearson correlation ($\rho \geq 0.96$) between MS and DV BF values, with very low coefficients of variation ($CV = 0.11$ in the worst case). The good concordance is confirmed for the whole cohorts, in single Centres and both, where

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R^2=0.97, $\rho \geq 0.97$, $\rho_s \geq 0.96$, $ICC \geq 0.78$ and CV=0.25 are the worst values. Compared with eighteen recent articles, these represent by far the best outcomes.

Conclusion: The excellent patient- and cohort-based reproducibility of BF values achieved independently by MS and BV confirms the effectiveness of the approach presented.

Significance: Our approach can be used to improve the reproducibility in other CTp multicentre studies, in liver as well as in other organs, with even different clinical questions, and represents a marked step forward towards CTp standardization, favouring the investigation of imaging biomarkers.
Key Words: Signal processing, deconvolution, computed tomography, oncology, reproducibility.

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1. Introduction

In the last years, tumour treatments have been greatly improved by exploiting target therapies, which allow attacking cancer cells by preserving healthy ones, as in case of the antiangiogenic drugs. The formation of new blood vessels from existing ones (i.e. neoangiogenesis) is a key process of the rising cancers that, as their volume raises 3 mm^3, over-express pro-angiogenic factors to favour their growth, by increasing the amount of pathways available for the transport of nutrients and oxygen [1]. Dependently on tumour aggressiveness, the new vessels grow chaotically, in a disorganized structures hindering the efficacy of classical cytotoxic therapies. To this purpose, the antiangiogenic drugs are employed to reshape the abnormal structures of tumour vasculature, try restoring the normal blood flow and oxygenation status, thus possibly enhancing the activity of citotoxins, usually thwarted by disorganization of tumour vessels [2].

The functional changes induced by these drugs occur much earlier than morphological ones, this making classical morphological imaging techniques unfit for assessing their efficacy. To this purpose, functional imaging, such as dynamic contrast-enhanced Magnetic Resonance (DCE-MRI) and Computed Tomography (DCE-CT, also referred to as CT perfusion, CTp) [3], can provide a functional assessment of tumour vasculature coupled with morphological depiction [2]. A series of scans performed before, during, and after the intravenous injection of a Contrast Agent (CA) allows imaging its flow through the tumour Region of Interest (ROI) and measuring tissue perfusion after recovering the Time-Concentration Curves (TCCs) of the CA [4].

Perfusion parameters are widely used to derive image-based biomarkers to assess anti-angiogenic drug response and the Blood Flow (BF) is among the most common perfusion parameters considered to early detect tumour changes in diverse anatomic districts [5]. While DCE-MRI offers a higher spatial resolution than CTp, the latter has an excellent temporal resolution that makes it preferable for quantitative dynamic analysis. However, at present CTp is not standardized in the clinical routine for most of anatomic districts (e.g., lung, liver, kidney) due to several types of artefacts jeopardizing the reliability of perfusion values and preventing their reproducibility. Nevertheless, CTp is still drawing interest, with more than 120 scientific works in the last years (according to PubMed database) addressing CTp applications in liver [6], head and neck [7], lungs [8], abdomen [9], and kidneys [10]. Three wide European multicentre liver CTp studies exist (SARAH [11], PiXEL [12], and PROSPeCT [13]), enrolling more than 300 patients each, to evaluate promising image-based biomarkers in predicting tumour development and patient prognosis. Moreover, in recent *omics* imaging applications that integrate information derived from clinics and structural and functional imaging, CTp can play a key role to enrich processes of tumour diagnosis, management, and clinical decision making [14]. However, although some work has been done to measure [15] and enhance parameters reliability through the improvement of TCC signals [16], the analysis of artefacts from motion [17], acquisition and beam hardening [18], some difficulties still remain to have different methods and software used in CTp yielding comparable results [19]. Many studies report variations of up to 30% between perfusion values, depending on the computing methods chosen [20]. On the other hand, very few methodological studies deal with how to improve CTp reproducibility and even less [21] focus on the modelling aspects rather than on the computational ones. In this regard, Deconvolution (DV) and Maximum Slope (MS) are well-established and widely used perfusion methods, independent from each other. In particular, DV relies on the whole TCC signal, acquired throughout the CA kinetics phase being studied, and exploits the input-output relationship of the model, describing its dynamics, which reflects upon the generated perfusion parameters. Instead, MS exploits one TCC sample only, in its ascent phase (in one or two distinct time instants, based on the number of inputs), thus permitting perfusion analyses referred to the CA first-pass, hence requiring the shortest acquisition times as possible. Therefore, attaining a common agreement between MS- and DV-based CTp parameter values is necessary to achieve the reproducibility of results [22], to improve the effectiveness of

multicentre trials and favouring the CTp standardization. A first worthy attempt has been accomplished in [23], where a match between perfusion maps computed with MS and DV was achieved, on a reduced number of patients, just for visual purposes, with perfusion values min-max normalized, separately for MS and DV.

The goal of this work is to develop a new approach aiming at achieving a numerical reproducibility of blood flow (BF) values in liver, tested in a multicentre study. In particular, we face the CTp reproducibility issue by addressing the choice of the *model*, the *kinetics phase* of CA, the *method* used to compute the voxel-based perfusion parameters. To this purpose, we considered the two most populous Centres of PIXEL and dealt with the simplest operating conditions for all these three aspects, by (a) choosing a one-compartmental model (Sect. 2.2), (b) analysing the first passage (Sect. 2.4), and (c) adopting MS and DV as the computational methods whose perfusion results have to be compared, being the former the simplest to compute and the latter the most precise one [24]. After describing in Sect. 2.5 how input and output signals were modelled, we provided details on MS and DV computation in Sect. 2.6 and proposed, in Sect. 2.7, a novel two-stage algorithm to separate the dual-input contributions on hepatic CTp signals, to be used by both MS and DV for the independent computation of perfusion parameters. The methodology for the assessment of MS and DV numerical reproducibility is presented in Sect. 2.8. In Sect. 3, this study analyses for the first time the correlations achieved separately on the single patients, followed by a discussion on results achieved on the whole cohorts, which are compared with the state of the art. Concluding remarks are given in Sect. 4.

2. Materials and methods

2.1. Patients and CTp protocol

This multicentre study involves 75 patients with colorectal cancer and normal liver, belonging to the two centres of PIXEL (15 French Centres, 315 enrolled patients) [12], aiming at evaluating the predictive role of the perfusion parameters in the onset of liver metastases within three years from cancer diagnosis. In particular, Centre A (54) and Centre B (21) were chosen because they are the most populous ones. All patients underwent an axial CTp liver examination, including the portal vein trunk and the right hepatic parenchyma, during which they were asked to breathe slowly. Acquisitions

started contemporaneously with a bolus-injection of 40 ml of iodinated intravascular CA, at a speed of 5 ml/s, with a concentration of 350 mgI/ml, followed by 20 ml of physiological solution. CT tube current and voltage were kept at 100 mA and 80 kV, respectively, with 1 s rotation time (100 mAs exposure). The CTp protocol lasts for 2 min, yielding 60 scans (every 1 s for the first 30 s, and 3 s after), each consisting of 8 sections of 5-mm thickness. The patients included (75) were those patients for which the portal vein were visible in the whole sequence.

2.2. Physiological and kinetic models

CA kinetics in CTp studies reflects the dynamics of vascular microcirculation, and the analysis of TCCs has been proved to provide useful information on tissues' angiogenesis degree. During the ascending phase of the TCCs, the CA is washed into the vascular compartment, then it reaches its maximum concentration in correspondence of the peak of the TCCs, before being washed out during the descending phase. However, during the dominant descending phase of the TCCs, lower concentrations of CA are still washed into the compartment due to the blood plasma recirculation [25]. Indeed, the way CAs propagate throughout the biological pathways also depends on the chemical and physical properties of the CA themselves, chosen on the basis of the hemodynamic properties under investigation, and can be described by several models. Based on whether CA remains within the intravascular space or moves towards the extravascular and extracellular lumen, different mono- or multi-compartmental models of increasing complexity exist for representing the tissue exchange sites [26]. These compartmental models split up the exchange site in interacting multiple chambers, each of them obeying the mass conservation law expressed by a differential equation. In addition, the liver is a dual-input organ and as such it was considered in this work, in a single-compartmental model without any reference to the extravascular and extracellular spaces. In practice (Fig. 1), the input of the system is the lin-

Figure 1: Hepatic dual-input one compartmental model

ear combination of the arterial ($C_A(t)$) and the portal ($C_P(t)$) blood plasma concentrations, while the output is the venous concentration ($C_{out}(t)$). $C_A(t)$ and $C_P(t)$ are weighted in input by the Hepatic Perfusion Index (HPI), so that the total input blood plasma concentration $C_{in}(t)$ is expressed by Eq. 1:

$$C_{in}(t) = \mathrm{HPI} \cdot C_A(t) + (1 - \mathrm{HPI}) \cdot C_P(t) \tag{1}$$

Hence, while $C_{out}(t)$ is exiting the compartment, the concentration of CA still inside the compartment is represented by $C_T(t)$. In addition, due to the dual-input supply, the concentration $C_T(t)$ is the sum of two contributions $C_{T_A}(t)$ and $C_{T_P}(t)$ (Eq. 2), due to $C_A(t)$ and $C_P(t)$, respectively:

$$C_T(t) = C_{T_A}(t) + C_{T_P}(t) \tag{2}$$

Finally, hemodynamic analyses can be further classified depending on whether the first-passage kinetics only is considered or recirculation is also included. While the latter case allows more perfusion parameters to be computed, at the expense of a longer CTp protocol, the former one owns a lower complexity, resulting very attractive in CTp studies, and this is the choice adopted in this work. In fact, first-pass analysis can be carried out on shorter examinations, which entail a lower dose to patients, besides being compliant with breath-hold and reducing artefact from motion [27], accordingly.

2.3. Data preparation

In each CTp examination, a central representative slice is selected and two regions of interest (ROIs) are first drawn, on the aorta and the liver, respectively. The ROI placement procedure on liver is carried out with a great care, excluding large vessels, such as portal vein or hepatic artery. Then, a ROI outlines the portal vein and it is aligned over time, on each sampling instant, to compensate for motion in the subsequent CTp scans [17]. For both vessels, one mean TCC ($C_A(t)$ and $C_P(t)$, respectively) is achieved from the whole ROIs while, from the tissue, single voxel-based TCCs ($C_T(t)$) are extracted and kept, after excluding voxels undergoing dynamic artefacts [18] and performing a 3D edge preserving filtering. Finally, after an accurate baseline removal [28], a preliminary non-parametric fitting of the real TCCs is performed to up-sample the signal from 30 s on, to the end of the acquisition, so to have a uniform sampling frequency of 1 Hz.

2.4. Extracting the first-pass signal

Focussing on first-pass kinetics, we needed to extract from the vascular and tissue TCCs the contribution due to the first passage only. Some simulation studies show that the CA kinetics limited to the first passage is represented by a TCC decaying to the baseline, after its peak [29]. Moreover, it is known that when considering short CA bolus injections, the recirculation contributes to TCCs mainly after its peak is reached, in the aorta as

well as in the abdominal vessels supplying the liver [30]. As far as the hepatic single-compartment model is concerned, the CA vascular kinetics can be reasonably applied on tissue hemodynamics, yet more in the absence of altered vascular pathways (e.g., due to angiogenesis or diseases), yielding a CA recirculation flooding the tissue after the maximum CA concentration is reached. Therefore, the main problem is to find out enough TCC samples expectedly belonging to the first-pass phase, that could be successively used in a parametric fitting model to extract a complete first-pass signal from the real tissue TCC. In practice, while the left bound of the interval is known (i.e., the first acquired sample t_0), what lacks is the last first-pass interval sample. Based on all the considerations above, we found reasonable choosing the time instant halfway between the peak time (t_p) and the washout time (t_w), when the outflow is maximum. Hence, we first performed a signal denoising for each patient through a smoothing spline [31], computed over all the acquired n samples, setting the smoothing parameter $\lambda = 0.7$ [32], also on the basis of preliminary tests. Then we computed the derivative on these smoothed signals, thus achieving t_p (when it has 0-value) and t_w (when it has its minimum). It is worth noting that if different values of λ can affect the goodness of fit, the effects on t_p and t_w are almost negligible. Finally, for each TCC $[t_0, (t_p + t_w)/2]$ represents the time interval whose samples are considered as belonging to the first-pass phase.

2.5. Models of vascular and tissue signals

The fitting procedure of both vascular and tissue signals was carried out by adopting two widely used parametric models, the Lagged Normal (LN) [33] and the Gamma Variate (GV) [34] functions, respectively, similarly to what done in [23]. The fitting procedure was performed using the Interior Point [35], a constrained nonlinear optimization algorithm implemented in the *fmincon* function of Matlab© (MathWorks Inc, Natick, MA, USA).

2.5.1. The Lagged Normal function

The LN model has been parametrized with the specific aim of describing the dispersion of an indicator in arterial or, in general, large vessels [36]. According to the differential Eq. 3:

$$f(t) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}(\frac{t-t_c}{\sigma})^2} - \tau \frac{df(t)}{dt} \tag{3}$$

the model combines two contributes. The first term refers to a Gaussian function of unit area, representing a random distribution of transit times around the central time, t_c, with σ as standard deviation. The second term is a first-order exponential process included in order to consider the evidence of skewness in experimental dye-indicator curves attained in mixing chambers. Then, τ is the time constant of the first-order decay. Eq. 3 can also be represented by means of three more practical parameters enabling data-driven criteria of selection, the Relative Dispersion (RD), the skewness (s), and the mean time (t_m), which allow expressing the three LN parameters, as reported in Eqs. 4, 5, and 6:

$$\tau = RD \cdot t_m \cdot \left(\frac{s}{2}\right)^{\frac{1}{3}} \tag{4}$$

$$\sigma = \sqrt{(RD \cdot t_m)^2 - \tau^2} \tag{5}$$

$$t_c = t_m - \tau \tag{6}$$

For normalization purposes, Eq. 3 is finally scaled by the global factor AUC (area under the observed curve). Hereafter, we will refer to the vascular TCCs, $C_A(t)$ and $C_P(t)$, as their LN-fitted version (Fig. 2 (a)).

2.5.2. The Gamma Variate function

The GV model [37] exploited for tissue TCCs fitting, is described by Eq. 7:

$$f(t) = K(t - t_0)^{\alpha} \cdot e^{-\frac{(t-t_0)}{\beta}} \tag{7}$$

where K is a global scale factor, expressed by Eq. 8

$$K = f(t_{max}) \cdot t_{max}^{-\alpha} \cdot e^{\alpha} \tag{8}$$

and, moreover, α and β are shape and scale factors, respectively, depending on t_{max}, the time when the GV peak value occurs (Eq. 9)

$$t_{max} = \alpha \cdot \beta \tag{9}$$

In its turn, Eq. 9 is achieved by setting the first derivative of Eq. 7 to zero. The cost function minimizes the squared Euclidean norm of residuals computed between the early non-parametric and the GV fittings, within the first-pass phase [38]. Hereafter, we will refer to tissue TCCs, $C_T(t)$, as their GV-fitted representation (Fig. 2 (b)).

Figure 2: Parametric fitting models for patient ID1 of Centre A of $C_A(t)$ and $C_P(t)$ (a) and $C_T(t)$ (b), herein illustrated between the time interval $t \in [0 \div 119]$ s.

2.6. Perfusion computation methods

Compartmental analysis for first-pass studies is generally carried out either exploiting the Fick's principle applied to a single-compartment or through the study of the impulse response function of the compartment itself, without any assumption regarding the underlying biological tissue structure and diffusion processes. We exploit these two approaches to compute CTp parameters by implementing MS and DV, respectively. In particular, MS assumes the conservation of mass under the assumption of no venous outflow (needed to fulfil the one-compartment hypothesis) [39], DV is grounded on the Indicator Dilution Theory (IDT), under the assumption of system linearity and time-invariance [40]. In case of dual-input organs, some perfusion parameters, BF included, arise from the partial contributions provided by each input. For instance with liver, the total BF is expressed as the sum of arterial (aBF) and portal (pBF) contributions [41], according to Eq. 10:

$$\mathrm{BF} = \mathrm{aBF} + \mathrm{pBF} \tag{10}$$

2.6.1. Maximum Slope (MS)

In the standard single-input model, the equation is (Eq. 11):

$$\frac{dC_T(t)}{dt} = \frac{\mathrm{BF}}{V_T}[C_{in}(t) - C_{out}(t)] \tag{11}$$

where C_{in} is usually the arterial blood plasma C_A and V_T is the tissue volume. A minimum transit time exists before the injected CA reaches the venous circulation, when it is assumed to be still inside tissue. Therefore, under the assumption of no venous outflow, $C_{out} \approx 0$, Eq. 11 can be simplified as follows (Eq. 12):

$$\frac{dC_T(t)}{dt} \approx \frac{\mathrm{BF}}{V_T} C_{in}(t) \tag{12}$$

This also implies that $C_T(t)$ reaches its maximum slope in the correspondence of the maximum value of $C_{in}(t)$. Assuming V_T as a normalization factor represented by a constant volume unit, BF can be expressed in ml/min/100 g and given by Eq. 13 [4]:

$$\mathrm{BF} \approx \frac{\frac{dC_T(t)}{dt}|_{max}}{C_{in}(t)|_{max}} \tag{13}$$

In the hepatic dual-input model, MS formulation has to be extended to include aortic and portal contributions, according to Eq. 14:

$$\mathrm{BF} \approx \frac{\frac{dC_{T_A}(t)}{dt}|_{max}}{C_A(t)|_{max}} + \frac{\frac{dC_{T_P}(t)}{dt}|_{max}}{C_P(t)|_{max}} \tag{14}$$

However, under the MS approach $C_{T_A}(t)$ and $C_{T_P}(t)$ cannot be analytically separated. Commonly (as in [23]), they are approximated according to Eqs. 15 and 16 [42]:

$$C_{T_A}(t) \approx C_T(t)|_{t\in[0,C_S(t_{max}))} \tag{15}$$

$$C_{T_P}(t) \approx C_T(t)|_{t\geq C_S(t_{max})} \tag{16}$$

where $C_S(t)$ is the mean TCC extracted from the spleen and t_{max} is the time instant when its peak occurs.

2.6.2. Deconvolution (DV)

When exploiting the DV method, the output function $C_{out}(t)$ is conceived as the convolution of the input function $C_{in}(t)$ with the impulse response function of the system, $h(t)$. Instead, when referring to $C_T(t)$, it can be most usefully described by the impulse residue function $R(t)$, representing the CA *remaining into* the tissue (Eq. 17) [43]:

$$C_T(t) = C_{in}(t) \otimes R(t) \tag{17}$$

According to what described in [44], BF can be estimated as the initial (or maximum) value of $R(t)$ (Eq. 18):

$$\mathrm{BF} = R(t)|_{max} \tag{18}$$

To compute perfusion parameters, $R(t)$ can be recovered through deconvolution starting from $C_T(t)$ and $C_{in}(t)$.

Eq. 17 can be represented in its matrix form, according to Eq. 19:

$$\mathbf{Ax} = \mathbf{b} \tag{19}$$

where $\mathbf{A} \in \mathbb{R}^{n\times n}$ and $\mathbf{b} \in \mathbb{R}^n$ represent $C_{in}(t)$ and $C_T(t)$, respectively, with n the number of the TCC samples. Performing deconvolution means solving an inverse problem, whose best solution is given by Eq. 20:

$$\min_{\mathbf{x}} \|\mathbf{Ax} - \mathbf{b}\|_2 \tag{20}$$

However, $\mathbf{A}$ is known to be ill-conditioned and to regularize it we chose the circular truncated singular value decomposition (cTSVD) [45], since circular regularization is a well-established technique for CTp, allowing for time delays between the vascular input and the tissue curves [46]. In order to prevent aliasing in circular deconvolution, $C_{in}(t)$ and $C_T(t)$ are first zero-padded for $L = 2n$ samples. Then, the circular square matrix $\mathbf{A^c} \in \mathbb{R}^{L \times L}$ is implemented according to Eq. 21 [47]:

$$\mathbf{A^c}_{i,j} = \begin{cases} C_{in}(t_{i-j+1}), & \text{for } j \leq i \\ C_{in}(t_{L+i-j+1}), & \text{for } j \text{ ¿ } i \end{cases} \tag{21}$$

The cTSVD solution is achieved by SVD decomposition of $\mathbf{A^c}$, so that its inverse matrix $\mathbf{A^{c-1}} = \mathbf{V\Sigma U^T}$, where $\mathbf{\Sigma}$ is the diagonal matrix of the singular values sorted in descending order, and $\mathbf{V}$ and $\mathbf{U}$ contain the left- and the right-singular vectors, respectively. In order to reduce the oscillation of the solution, the less representative singular values in $\mathbf{\Sigma}$ must be removed and we chose the last 5%-threshold, a value commonly used in several studies [48].

2.7. Computation of perfusion parameters

Both MS and DV requires $C_{T_A}(t)$ and $C_{T_P}(t)$ to compute perfusion parameters. In order to avoid approximating the two contributions according to Eqs. 15 and 16, we decided to compute $\mathrm{BF_{MS}}$ analytically, employing the same signals as DV, this also expectedly improving reproducibility. The two contributions $C_{T_A}(t)$ and $C_{T_P}(t)$ arise from $C_{in}(t)$ of Eq. 1 that, substituted into Eq. 17 leads to Eq. 22:

$$C_T(t) = (\mathrm{HPI} \cdot C_A(t) + (1 - \mathrm{HPI}) \cdot C_P(t)) \otimes R(t) \tag{22}$$

and, if split into two addends, yields Eqs. 23 and 24:

$$C_{T_A} = \mathrm{HPI} \cdot C_A(t) \otimes R(t) \tag{23}$$

$$C_{T_P} = (1 - \mathrm{HPI}) \cdot C_P(t) \otimes R(t) \tag{24}$$

As one can see, in order to compute $C_{T_A}(t)$ and $C_{T_P}(t)$, both HPI and $R(t)$ are needed. To this purpose, we implemented a two-stage procedure, made of an initialization (Init) and a computation (Compute) block, outlined in Fig. 3. The first, sequential, block aims at providing a very preliminary estimate of HPI and $R(t)$, used to initialize the second block, whose purpose is

Figure 3: Two-stage procedure made of initialization (Init) and computation (Compute) blocks. Initially, $\text{HPI}^{[e]}$ is estimated through convolution ($\otimes_{min}$), stemming from an ideal model of $R(t)$ (i.e. $R(t)^{[i]}$), minimized against $C_T(t)$. Then, by exploiting $\text{HPI}^{[e]}$, $R(t)^{[r]}$ is first achieved via deconvolution ($\otimes^{-1}$), then fed to the Compute block, where the estimates of $\text{HPI}^{[r]}$ and $R(t)^{[r]}$ are iteratively refined until convergence (i.e., until the mean residuals computed between two subsequent estimates of $R(t)^{[r]}$ reach a plateau).

iteratively refining HPI and $R(t)$, until convergence is reached. In particular, we started in the first block by estimating the voxel-based HPI values ($\text{HPI}^{[e]}$) *via* convolution ($\otimes_{min}$), from Eq. 22, which is directly minimized against $C_T(t)$ using an *ideal* model of $R(t)$ (i.e., $R(t)^{[i]}$). Then, $\text{HPI}^{[e]}$ is employed to deconvolve Eq. 22, now achieving voxel-based estimations of $R(t)$ on *real* data (i.e., $R(t)^{[r]}$), which is fed to the second stage to achieve an early estimate of the *real* HPI (i.e., $\text{HPI}^{[r]}$). The subsequent refinements of $R(t)^{[r]}$ and $\text{HPI}^{[r]}$ are iteratively performed minimizing the mean residuals of $R(t)^{[r]}$ ($\mu[R(t)^{[r]}]$) computed between two subsequent estimates. The mean curve computed over all 75 patients (Fig. 4(a)) shows a **L**-like curve shape, similar in each patient,

Figure 4: (a) The mean curve of $\mu[R(t)^{[r]}]$ referring to whole patients, with the red point highlighting the iteration ($i = 4$) at which a plateau starts; for a sample patient (ID37, Centre A) (b) $\mu[\text{HPI}^{[r]}]$, (c) $\rho_s[\text{HPI}^{[r]}]$ and (d) $\text{ICC}[\text{HPI}^{[r]}]$ are reported.

with a plateau for $\mu[R(t)^{[r]}]$ starting at the red point, the fourth iteration (that is, referring to differences between estimates at i=4 and i=3). As one can infer by the very low standard deviations, this occurs for all patients and because there are no real benefits to wait for convergence, we chose to stop the process and taking $R(t)^{[r]}$ at i=3. This choice was also supported by the concomitant best $\text{HPI}^{[r]}$, as one can see for a representative sample patient (ID37, Centre A) in Fig. 4(b), reporting the evolution of the mean residuals, and by the Spearman coefficient (ρ_s) and the Intraclass Correlation Coefficient (ICC) in Fig. 4(c) and (d), respectively.

Finally, by deconvolving $C_{T_A}(t)$ and $C_{T_P}(t)$ with the corresponding input functions, $C_A(t)$ and $C_P(t)$ respectively, we can compute voxel-based aBF_{DV} and pBF_{DV} values, subsequently summed up to yield the total BF_{DV} value (Eq. 10). Similarly, MS is independently applied to $C_{T_A}(t)$ and $C_{T_P}(t)$ to compute aBF_{MS} and pBF_{MS} *via* central finite-differences, then summed up to achieve BF_{MS}.

2.8. Assessment of results

Few works exist reporting BF values achieved with both MS and DV, and these all refer to only aggregate data, related to the entire cohort. This is the first work in the literature reporting a patient-wise comparison of voxel-based BF values achieved with both MS and DV, besides a cohort analysis to enable a comparison with the state of the art.

For each patient of Centres A and B, *voxel-based* BF values achieved via DV and MS are compared through the Pearson correlation index (ρ), split into five contiguous classes with increasing correlation, in order to permit a more accurate comparison between Centres. In addition, for each patient, median (M) and Median Absolute Deviation (MAD), mean (m), standard deviation (σ), and coefficient of variation (CV) are also computed for DV and MS separately. Moreover, the correlation of all mean BF (BF_m) values achieved via MS and DV is computed at group (G) level, where "group" is meant as the set of patients of either Centres A or B or both (A&B) and assessed through Spearman (ρ_s), Pearson (ρ_{G}), and Intraclass Correlation (ICC) indexes. To this purpose, when addressing the comparison with the literature, these correlations (c) between MS and DV were considered good or very good if $0.80 \leq c < 0.90$ or $c \geq 0.90$, respectively. On BF_m and BF_M distributions, M_{G}, MAD_{G}, m_{G}, σ_{G}, and $\mathrm{CV}_{\mathrm{G}} = \sigma_{\mathrm{G}}/m_{\mathrm{G}}$ were assessed. Finally, a comparison between DV and MS is carried out considering the absolute percentage differences of M_{G} (Δ_M) and m_{G} (Δ_m). Afterwards, we compared our results with other studies', considering all the published works between 2013 and 2019, retrieved from PubMed database including the keywords: "functional CT, perfusion CT, CT-perfusion, deconvolution, maximum slope, CT-based, dynamic contrast-enhanced computed tomography, dynamic contrast-enhanced CT" and excluding: "brain, cerebral, artery, coronary, stroke, cardi, dynamic contrast-enhanced MRI, dynamic contrast enhanced MRI". Finally, 18 works are considered, dealing with different organs and glands, including liver (8), kidney (3), pancreas (3), lung (2), oesophagus (1), lymph nodes (1).

3. Experimental Results

We start presenting the patient-wise MS and DV voxel-based correlations, followed by a comparison of the aggregate results with other studies.

Table 1 resumes the Pearson correlations between BF values computed at

Table 1: Correlation (ρ) of BF between MS and DV in Centres A and B

Centre	Patients						CV_{MS}	CV_{DV}
	Total	ρ=0.99	ρ=0.98	ρ=0.97	ρ=0.96	$0.90 \leq \rho \leq 0.95$		
A	54	37	5	6	3	3	11.6%	10.7%
B	21	15	4	-	1	1	11.3%	11.0%

voxel-level with MS and DV for each patient of Centres A and B, where ρ values are partitioned into 5 contiguous classes. Correlations are excellent, with 95% of patients with $\rho \geq 0.96$ in Centre A as well as in Centre B. These values are yet more significant in the light of the very low mean CVs of all patients for MS (CV_{MS}) and DV (CV_{DV}), suggestive of BF distributions with narrow ranges, with maximum CV_{MS}=11.6% and minimum CV_{DV}=10.7% values in Centre A, for MS and DV, respectively. It is also worth noting that CV_{DV} values are also lower than CV_{MS} ones, this confirming the better precision of DV. Table 2 reports the outcomes of our study (Centres A, B, A&B) and of the most recent literature addressing healthy tissue (H), primary cancer (C), or metastases (m) in different organs and glands. These studies were all single Centres, except for [49], and perfusion parameters were always computed with vendor's Software. The results reported perfusion parameters, correlations, and absolute percentage differences of median and mean BF values achieved with MS and DV, referred to the whole cohorts. As one can see, most of parameters are not computed ('-' points out not available values) and this regards not only voxel-based, but group-wise analyses as well, where the only parameters reported are those deriving from mean (μ_G, σ_G, CV_G), while median-derived parameters are almost never computed. As a matter of fact, this element itself hints at a lack of accurate comparative studies, making our work the most analytical one. Six works reported at least M_G or m_G values for both MS and DV. Apart from the older work in [49], reporting correlation values lower than 0.60, almost all the other correlation indexes are good (¿0.80) or very good (¿0.90), but they are never coupled with low differences between MS and DV BF values, this suggesting at least relevant systematic errors between MS and DV computations. This happens in [59] (ρ_s=0.81, Δ_m=54.6%), [51] (ρ_s=0.86, Δ_m=44.7%), [52] (ρ_s=0.89, Δ_m=44.7%), and even in [50], where ρ_G=0.91, the highest ρ_G value of all the comparing studies considered, derives from Δ_m=51.1%, probably due to a linear correlation having a slope much higher than 1. Also the work in [19] shows very good correlations (ρ_s = 0.85, ICC = 0.83) but, besides

reporting by far the highest σ_{G} in MS computations, not any (absolute percentage) difference is given, nor ρ_{G}, this probably suggesting that neither voxel-based nor global BF values were comparable with DV ones.

As regards our results, Figs. 5(a) and 5(b) highlight the correlation of

(a) (b) (c)

Figure 5: Scatter plots of median BF values computed with MS ($x-axis$) and DV ($y-axis$) in Centre A (a), B (b), and A&B (c), respectively.

BF values computed with MS and DV on the patients of Centres A (54) and Centre B (21). ρ_{G}, ρ_s, and ICC coefficients are very high for Centre A (0.97, 0.96, 0.78) and excellent for Centre B (0.99, 0.98, 0.84), and such an agreement is confirmed (even slightly improved for ICC) by the multicentre analysis of A&B (Fig. 5(c), with 0.97, 0.96, 0.79, respectively). Analogously, as regards m and q values, we can see that increasing the number of patients by adding to Centre A those of Centre B does not improve the slope, but it improves the bias, from q=12.24 to q=10.48. Actually, ICC coefficients for Centres A and A&B are lightly lower than those reported in [19], but it is worth noting that our BF values are associated to the highest precision, as confirmed by the lowest $\mathrm{CV_G}$s, when referring to either MS ($\mathrm{CV_G}$=0.25 and $\mathrm{CV_G}$=0.24, for Centres A and A&B, respectively) and DV ($\mathrm{CV_G}$=0.23 for Centre A and $\mathrm{CV_G}$=0.22 for A&B). The high precision is confirmed also in Centre B, which yields the best $\mathrm{CV_G}$ values, for DV (0.20) and MS (0.22), and the lowest Δ_M=11.2% and Δ_m=11.9%. In addition, also for Centres A and A&B the percentage median and mean differences between MS- and DV-based BF values are incomparably lower than those reported in the studies considered in Table 2, with the "worst" Δ_M=13.5% and Δ_m=15.3% occurring for Centre A&B and A, respectively. These low differences between MS- and DV-based BF values are possible thanks to the almost unitary slope *and* the quite low bias, as confirmed by the intercept (q) values shown in Fig. 5.

The last remarks arise from a comprehensive view of Table 2. It is clear that are very few studies directly addressing the problem of reproducibility of BF values, whether these are computed with either MS or DV, and when the percentage differences were reported, these were around 50% or even more. This is independent on the organ and its healthy status - 13 works deal with primary cancer, two with metastasis and three works only address healthy tissue. All $\mathrm{CV_G}$ referring to MS and DV computation are much higher than ours and it worth noting that the second best $\mathrm{CV_G}$=0.33 [54] and the worst

CV_G=0.79 [60] refer to liver cancer and healthy tissue, respectively. This suggests that the lowest CV_G values of our results do not depend on the healthy status of liver and, more in general, on the organ, but it can be ascribed to the precision and the accuracy of our CTp parameters computation methods, whose results are emphasized by Table 1.

4. Conclusion

The CTp technique is widely employed in oncology in several hospitals, to assess the effects of anti-angiogenic therapies and, more generally, for hemodynamic studies. Nevertheless, the lack of reproducibility of CTp parameter values is among the main reason thwarting CTp diffusion and standardization. So far, it has been given for granted that different software yields different perfusion results, and the literature we reported shows that this is well-founded. In this work we present the approach we developed to compute CTp parameters of liver in a multicentre liver study, according two of the most spread methods, MS and DV. Differently from the other works, instead of using approximations to compute the MS contributions from dual inputs, we devise a two-stage approach that permitted to compute them analytically, using the same signals employed by DV. This yielded a great improvement of MS precision, which allowed achieving excellent *voxel-based* correlations between perfusion values computed with the two methods, and presenting for the first time these results for single patients. Moreover, also considering the outcomes pertaining to whole cohorts, allowing a comparison with the most recent literature, our results overcome those of all these studies, for all the statistical indexes considered. Furthermore such comparison suggests that our results could be quite independent from tissue type or health status. This work is now being extended to other Centres with representative numbers of patients and to other organs that, being mostly single input, require a simplified computation model and, expectedly, could yield even more precise results.

In conclusion, our findings pave the way to the full CTp reproducibility, in liver and other organs, showing that it is possible, and make the approach proposed a promising strategy to purse CTp standardization.

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Table 2: Report of DV- and MS-based BF values in the most recent research studies, addressing healthy tissue (H), primary cancer (C), or metastases (m) in different organs and glands.

Year, Authors	#Pats.	Organ/gland, H/C/m	Correlation MS-DV ρ_G	ρ_s	ICC	$M_G \pm MAD_G$ MS	DV	$m_G \pm \sigma_G$ MS	DV	CV_G MS	DV	Δ (%) Δ_M	Δ_m
[49] (2013, Djuric-S *et al.*)	35	Oes., C	0.55	0.59	-	25.4	74.8	28.6 ± 12.3	78.5 ± 28.0	0.43	0.36	66.0	63.6
[50] (2013, van Elmpt *et al.*)	33	Lun., m	0.91	-	-	-	-	36.5 ± 20.8	74.7 ± 47.7	0.57	0.64	-	51.1
[51] (2015, Kaufman *et al.*)	79	Liv., C	0.86	-	-	-	-	37.8	68.3	-	-	-	44.7
[52] (2016, Schneeweiß *et al.*)	48	Pan., C	0.89	-	0.62	-	-	20.4 ± 9.7	36.9 ± 16.0	0.48	0.43	-	44.7
[53] (2017, Kurucay *et al.*)	36	Liv., C	-	-	-	-	-	-	97.3 ± 45.1	-	0.46	-	-
[54] (2017, Fischer *et al.*)	20	Liv., C	-	-	-	-	-	-	48.3 ± 15.8	-	0.33	-	-
[55] (2017, Tamandl *et al.*)	16	Liv., C	-	-	-	-	-	-	38.5	-	-	-	-
[19] (2018, Deniffel *et al.*)	35	Kid., C	-	0.85	0.83	-	-	134.8 ± 61.9	-	0.46	-	-	-
[56] (2018, Aslan *et al.*)	73	Pan., H	-	-	-	-	-	-	118.6 ± 36.4	-	0.31	-	-
[57] (2018, Kaufman *et al.*)	28	Liv., C	-	-	-	-	-	-	103.6 ± 36.8	-	0.36	-	-
[58] (2018, Horger *et al.*)	23	Lim., C	-	-	-	-	-	41.4 ± 18.8	75.2 ± 36.3	0.45	0.48	-	45.0
[59] (2018, Mains *et al.*)	69	Kid., m	-	0.81	-	466.3 ± 213.4	211.9 ± 80.6	-	-	-	-	54.6	-
[60] (2018, Mulé *et al.*)	16	Liv., H	-	-	-	-	-	-	118.3 ± 92.9	-	0.79	-	-
[61] (2018, Nakamura *et al.*)	36	Liv., H	-	-	-	-	-	-	149.6	-	-	-	-
[10] (2019, Fan *et al.*)	10	Kid., C	-	-	-	-	148.5	-	125.4 ± 70.5	-	0.56	-	-
[62] (2019, Andersen *et al.*)	39	Liv., C	-	-	-	-	-	-	123.9	-	-	-	-
[63] (2019, Kovač *et al.*)	44	Pan., C	-	-	-	-	-	24.0 ± 12.8	-	0.53	-	-	-
[64] (2019, Wang *et al.*)	39	Lun., C	-	-	-	-	-	-	104.9 ± 64.6	-	0.44	-	-
our work-Centre A	54	Liv., H	**0.97**	**0.96**	0.78	95.1±18.2	109.8±19.9	94.3±23.4	111.3±25.3	**0.25**	**0.23**	**13.4**	**15.3**
our work-Centre B	21	Liv., H	**0.99**	**0.98**	**0.84**	90.9±16.1	102.4±16.6	90.0±19.7	102.1±20.7	**0.22**	**0.20**	**11.2**	**11.9**
our work-Centres A&B	75	Liv., H	**0.97**	**0.96**	0.79	94.0±17.6	108.7±19.1	93.1±22.4	108.7±24.3	**0.24**	**0.22**	**13.5**	**14.4**