MODELING OF TUMOR CONSPICUITY IN HEPATIC CT IMAGES: COMBINED COMPARTMENT AND VASCULAR MODELS

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ABSTRACT

The aim of this work is to simulate dynamic CT scan of the liver, in normal tissue and in a hypervascular tumor. Two models are developed: a physiological vascular model for the main vessels, until arterioles and venules, and a compartment model for parenchyma enhancement. Combining these two models allows us to compute locally the contrast product concentration, all along the propagation, after injection in the hepatic artery and the portal vein. In the second step, a density representation of the organ is created and CT scans are simulated by using the standard reconstruction algorithm – filtered back-projection. As a final step, enhancement curves are extracted from the obtained images, showing very good agreement with real hepatic enhancement in CT.

1. INTRODUCTION

In CT examinations after infusion of a contrast agent, the tissues enhancement varies with time: it increases when the contrast agent is present in vessels and interstitial liquid, and then decreases when it is eliminated. Normal and pathological parts of an organ have different dynamics of enhancement. Radiologists try to use the best injection protocol and to find the best acquisition conditions to detect the pathological processes, either visually or by means of image analysis tools. The injection rate, concentration, number of phases combined with the acquisition time, slice thickness and resolution create a complex multi-parameters system, whose optimization is not easy.

In case of the liver tumors, this optimization is still more complicated, because the acquisition time which guarantees the greatest conspicuity is strongly dependent on the particular perfusion of this organ: a dual blood supply, by the Hepatic Artery (HA) and the Portal Vein (PV) leads to a complex dynamic of enhancement.

In this paper, we propose a method to simulate the liver enhancement in dynamic CT, and its application to the *Hepatocellular Carcinoma* during the arterial and the portal phases. Two combined models are first used to generate the liver in three dimensions, and the contrast product propagation in it: *i)* a physiological vascular model to simulate the HA, PV and HV and contrast agent propagation in this network and *ii)* a 3 compartments model to simulate the parenchyma enhancement by studying the contrast product diffusion from the smallest vessels (arteriole, venule) to the extra-cellular space.

2. METHOD

2.1. Physiological vascular model

In our computational model detailed in [9], the liver is constituted of parenchyma and vessels. The macrovascular network is made of 3 trees (HA, PV, HV), whose growth is simulated, considering at each growth cycle, the geometric (length, caliber) and heamodynamic properties (blood flow, and pressure). This model is used to simulate local pathological changes, like hyper-vascularisation due to a tumor development (vascular modifications are mainly arterialization and capillarization). The contrast product propagation, in normal or tumoral tissues is calculated, by using all the vessels characteristics. These 3 vascular trees are connected at the level of macro-functional units ("macro-cell"). A macro-cell is made of parenchyma and very small vessels, whose geometry is not considered, but whose enhancement has to be known, in order to simulate realistic CT images. It is at this level that compartment modeling intervenes: each macro-cell is replaced by an independent compartment model.

2.2. Compartment model of the microcirculation

Several compartment models have already been proposed to simulate vessels/tissue exchanges ([1], [2], [10]). However, most of them are global and not local. Some of them do not consider the three hepatic trees, or are focused on contrast product molecules exchanges without taking into account liquid movements. But the main new

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characteristic of the model we propose is to generate directly CT images and not only enhancement curves. The compartment model we propose is represented in Figure 1, where entries, compartments, exchanges and outputs are displayed (with corresponding variables).

The model entries are the two blood supplies coming from the hepatic arteriole, and the portal vein. They are characterized by their flows $Q_{ha}(t)$ and $Q_{pv}(t)$ and contrast product concentrations, $C_{ha}(t)$ and $C_{pv}(t)$.

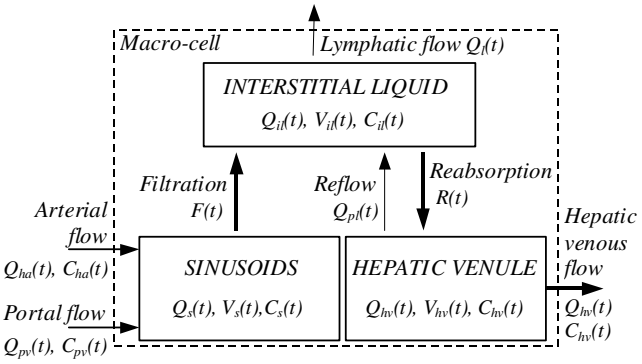

Figure 1: Compartment model of the hepatic microcirculation

The model is made of three compartments:

- ✓ "Sinusoids": blood arriving in the sinusoids is mixed with contrast product with concentration $C_s(t)$ and goes through the capillary wall into the extra cellular space (interstitial liquid) with a flow $F(t)$.
- ✓ "Interstitial liquid": the plasma and the contrast product molecules can go out of this compartment by two possible ways: hepatic venules, with a flow $R(t)$, and lymphatic capillaries with a flow $Q_l(t)$. In this compartment, the liquid has a $C_{il}(t)$ concentration.
- ✓ "Hepatic venules": blood goes out of the liver by the hepatic veins, with a blood flow Q_{hv}, but the reflow from the hepatic venules into the extra-cellular space ($Q_{pl}(t)$) is also integrated in the model [2], [4]. The contrast material concentration is $C_{hv}(t)$.

As the macroscopic vascular model does not currently take into account the lymphatic circulation, the lymphatic flow from the extra-cellular space ($Q_l(t)$), and the venous circulation ($Q_{hv}(t)$) constitutes in fact only one output: the hepatic venous flow.

In order to study concentration variations in the different compartments, exchanges are formalized by differential equations.

At the sinusoids compartment level, contrast product concentration follows Eq. 1, in which the compartment volume is $V_s = 57ml$ [6]:

$$V_s \frac{dC_s(t)}{dt} = C_{ah}(t)Q_{ah}(t) + C_{vp}(t)Q_{vp}(t) - C_s(t)F(t) \qquad (1)$$

The interstitial liquid compartment is characterized by Eq. 2 where the volume has been set to $V_{il} = 524ml$.

$$V_{il} \frac{dC_{il}(t)}{dt} = C_s(t)F + C_{hv}(t)Q_{pl} - C_{il}(t)(R + Q_l) \qquad (2)$$

In the same way, the exchanges concerning the hepatic venule compartment are summarized in Eq. 3, where $V_{hv} = 15ml$ [6].

$$V_{hv}.\frac{dC_{hv}(t)}{dt} = C_{il}(t).R(t) - C_{hv}(t).(Q_{pl}(t) - Q_{hv}(t)) \qquad (3)$$

Following data are used for the hepatic micro-circulation simulation [5], [7]: $Q_{ha} = 15Lh^{-1}$, $Q_{pv} = 78.6Lh^{-1}$, $F = 93.6Lh^{-1}$, $R = 78.6Lh^{-1}$, $Ql = 19.6Lh^{-1}$, $Q_{pl} = 4.6Lh^{-1}$, $Q_{hv} = 74Lh^{-1}$.

The flows Q_{pl} and Q_{hv} are calculated by supposing that the liver volume is constant (same quantity of fluid entering and going out), what is reflected in Eq. 4 and 5.

$$Q_{net} = F + Q_{pl} - R - Q_l = 0 \qquad (4)$$

$$Q_{pl} + Q_{hv} - R = 0 \qquad (5)$$

Contrast product can only diffuse in the extracellular space, whose volume is about 51% of the liver volume [1]. About 88% of this space (45% of the total liver volume) are occupied by interstitial liquid, and 12% (6,1% of the total volume) by blood, with 80 % in sinusoids (4,8% of the total volume) and 20% in the hepatic vein (1,3% of the total volume). The global contrast product concentration of the hepatic tissue can then be calculated, given these volumes:

$$C(t) = 0.048 \cdot C_s(t) + 0.45 \cdot C_{il}(t) + 0.013 \cdot C_{hv}(t) \qquad (6)$$

Runge-Kutta method is used to solve the resulting differential equations system:

$$\begin{pmatrix} \dot{C}_s(t) \\ \dot{C}_{il}(t) \\ \dot{C}_{hv}(t) \end{pmatrix} = \begin{pmatrix} -F/V_s & 0 & 0 \\ F/V_{il} & -(R+Q_l)/V_{il} & Q_{pl}/V_{il} \\ 0 & R/V_{hv} & (Q_{pl}+Q_{hv})/V_{hv} \end{pmatrix} \begin{pmatrix} C_s(t) \\ C_{il}(t) \\ C_{hv}(t) \end{pmatrix} + u(t) \qquad (7)$$

Where $u(t)$ is the following vector:

$$u(t) = \begin{pmatrix} C_{ha}(t).Q_{ha}/V_s + C_{pv}(t).Q_{pv}/V_s \\ 0 \\ 0 \end{pmatrix} \qquad (8)$$

2.3. Connection with the macro vascular model

Each macro-cell is replaced by an independent compartment model whose entries (arterial and portal blood flows and concentrations) depend on the corresponding data in the macro vascular model. Their profiles are deduced from the contrast product propagation in the vessels until the arteriole and venule [3].

Normal macro-cells are supplied by two vessels (arteriole and venule) whereas those of hypervascular tumor are perfused only by the arteriole (portal entry of the corresponding compartment models is set to zero).

Compartments' volumes have been adapted to the mean volume of a macro-cell (total hepatic volume divided by the number of macro-cells).

3. RESULTS

3.1. Enhancement of hepatic macrovascular network

Before injecting the contrast product at the entry of the macro-vascular trees, the growth of a hypervascular tumor (e.g. *Hepatocellular Carcinoma*) was simulated in the liver, leading to a localized hypervascularization.

To generate the injection profiles, we used the concentration values from [8], corresponding to the evolution of hepatic artery and portal vein concentrations with time, during 3 minutes. A spline interpolation between the main points extracted from these enhancement curves provides a continuous curve of enhancement variations with time (figure 5), which is necessary for the differential equations system resolution.

The contrast product propagation is then computed, in all the vessels of HA, PV and HV. The geometrical (length, radius) and haemodynamical (pressure, flow) properties of all the vessels are used to evaluate, at each time *t*, the contrast product concentration in the vessels[3]. An illustration of this propagation in 3D is given on Figure 2.

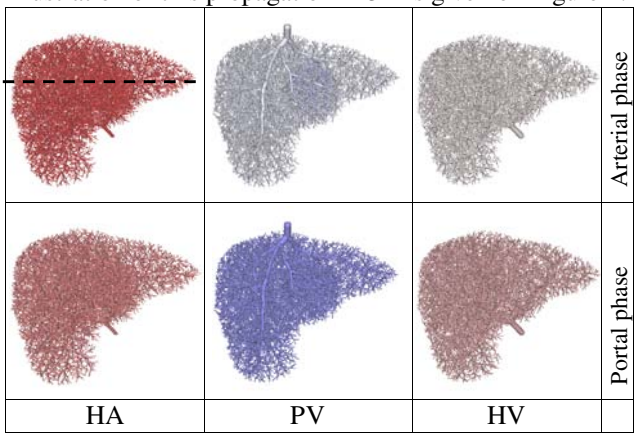

Figure 2: The contrast product propagation in simulated hepatic vascular trees with a localized hyper-vascularization. Vessel intensity is proportional to the quantity of contrast material.

3.2. Parenchyma enhancement

3.2.2. Enhancement curves from concentration

The compartment model we propose has been used to generate enhancement curves (in normal and tumoral case) after injection in HA and PV. In this test, enhancement values are obtained directly from concentrations by multiplication by a constant coefficient. These curves are close to real liver enhancement, showing a rapid concentration rise in the tumor (supplied only by HA) followed by a similar increase in normal tissue (supplied by both HA and PV), and a slower decrease in both of these vessels, tending to an equilibrium between normal and tumoral tissues. We also implemented models proposed by Materne [10] and Bae [1], and showed that our model has a comparable behavior.

3.2.3. Enhancement curves from simulated CT scans

The time evolution of the parenchyma enhancement is assessed at the microvascular level, by replacing each macro-cell of the macrovascular model by a compartment model, leading to a total number of compartment models around 12000.

At each moment (second) of the contrast product propagation, a 3D array is generated, in which each voxel is characterized by a density, depending i) on its situation (vessel of the macrovascular network and/or parenchyma), and ii) especially on its contrast product concentration, estimated by the method presented in section 2. Given this 3D density representation, the classical CT reconstruction algorithm (filtered backprojection) is applied to synthesize slices, whose resolution and thickness can be set.

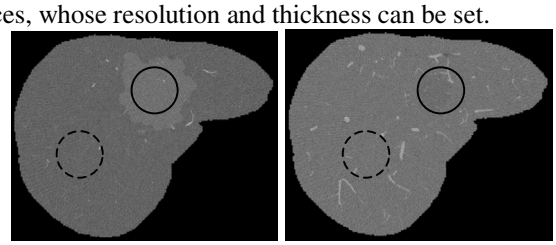

Figure 3: Simulated hepatic CT scans. On left arterial phase (the contrast product is essentially in HA; hyperdensity of the tumor) and on right portal phase (the contrast product also in PV; iso- or hypodensity of the lesion).

A temporal sequence of simulated CT scans is analyzed, and the gray level is computed in two Regions of Interest: one in normal parenchyma (figure 3, dotted line) and the second one in the lesion (figure 3 solid line). Relative enhancement (compared to the simulated CT scan before injection) over time is displayed figure 4.

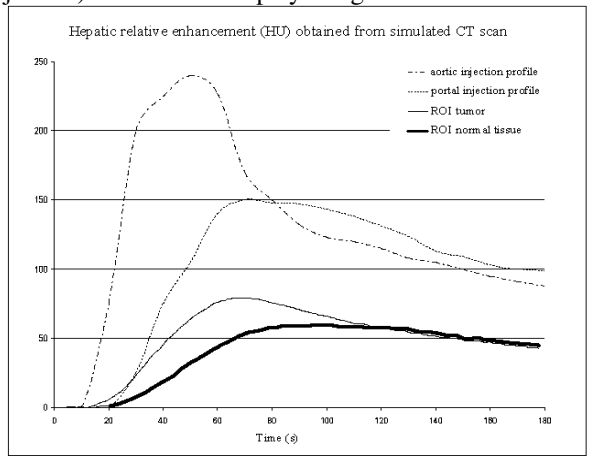

Figure 5: Enhancement curves resulting from simulated CT scans

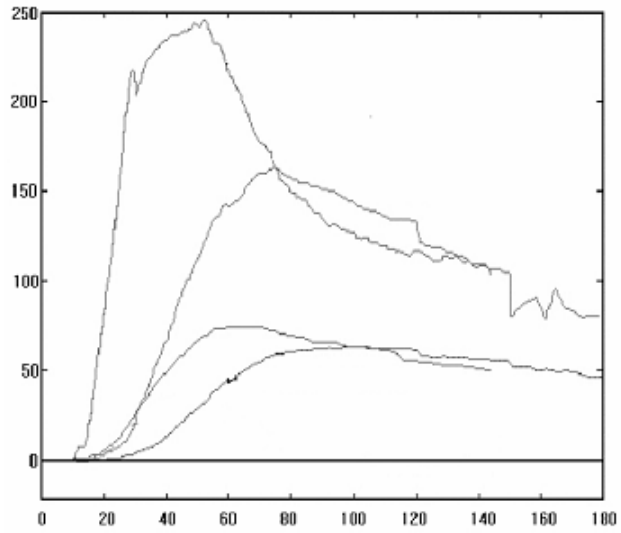

Figure 6: Hepatic enhancement resulting from real CT scans [8]

4. CONCLUSION / PERSPECTIVES

We propose to couple *i)* a physiological model of vessels, able to simulate complex connected vascular trees, taking into account their geometric and haemodynamic characteristics and *ii*) a 3 compartments model that allows us to simulate exchanges between the smallest vessels (capillaries) and interstitial liquid. These two models have been used to follow the contrast product propagation in liver, given the injection profiles into the hepatic artery and the portal vein. The output of these models is 3D arrays, where voxels are composed of quantities of blood, parenchyma and contrast product, varying with time. From these 3D representations, dynamic CT scans are synthesized, every second, during the 3 minutes of contrast propagation through the liver. Hepatic enhancement is measured in these images, in normal tissue and in a hyper vascular tumor whose development has been simulated during the organ growth.

Dynamic enhancement is in very good agreement with real enhancement measured in CT scans. In conclusion, combining these two models, one for the macrovascular trees, and the second one for microvessels, provide a realistic model of dynamic hepatic enhancement in CT.

Such a model can have several clinical applications. First of all, it could be used to ameliorate the tumor detection and characterization by better understanding the respective influence of *i)* physiological properties (vascular density, blood pressure and flow) and *ii)* acquisition parameters (resolution, thickness) on images, and extracted characteristics (like textural features).

Secondly, it could also be useful to optimize the injection and acquisition protocols, which also contribute to a better tumor detection and characterization. With our model, injection profiles as well as acquisition times can be modified, for a particular tumor, in order to know the ones leading to the best tumor conspicuity.

Finally, this model can show advantages in estimation of two important parameters for tumoral process characterization which are the permeability coefficient and extracellular space volume. Indeed, we are able to change locally these parameters, and to observe the repercussion on the dynamic hepatic enhancement. It should also be possible, from time stamp series of CT images (or other modalities), to deduce these two parameters.

5. REFERENCES

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