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# THE IMPACT OF INJECTION TIMING AND LOCATION ON MICROPARTICLE DELIVERY FOR TUMOR TARGETING IN A PATIENT-SPECIFIC LIVER

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## INTRODUCTION

Hepatocellular carcinoma (HCC), the most common form of primary liver cancer, is one of the leading causes of cancer-related deaths worldwide. In 80-90% of HCC patients, cirrhosis is present [1].

The preferred treatment for unresectable HCC is transarterial chemo- or radioembolization (TACE or TARE). During these therapies, microparticles are injected in the hepatic arteries to selectively damage tumor tissue through a combination of embolization and a secondary chemotherapeutic effect (TACE), or through emission of high-intensity beta radiation (TARE) [2]. The goal of these transarterial therapies is to maximize the dose delivered to tumor tissue and limit the offsite-toxicity delivered to healthy tissue.

However, the impact of clinical parameters (e.g. the injection's location and timing) and microparticle characteristics (e.g. size and density) on the particle distribution is unclear. Therefore, computational fluid dynamics (CFD) may help to understand this impact and potentially use these parameters to improve the clinical outcome [3].

To date, Childress et al. [4] studied the impact of injection timing during the cardiac cycle in two simplified literature-derived hepatic arterial geometries. However, Aramburu et al. [3] noted that the geometry has a significant impact on the particle distribution. Therefore, we previously studied the impact of particle size, density and injection location in two patient-specific hepatic arterial geometries [5].

In this study, the impact of injection timing will be investigated for two axial injection locations in a patient-specific geometry.

## METHODS

*Geometry & meshing.* The liver geometry was obtained by combining vascular corrosion casting and micro-CT imaging of a cirrhotic human liver (see [6] for more details). The hepatic network was segmented and 3D reconstructed using Mimics and 3-matic software (Materialise, Leuven, Belgium). A volume mesh containing $9 \cdot 10^6$ tetrahedral elements and three prism boundary layers was created in ICEM CFD (Ansys Inc., Canonsburg, USA).

*CFD.* Blood flow (continuous phase) was modeled using a density of 1060 kg/m³ and a modified Quemada model for viscosity. The mass transport of particles (discrete phase) in the fluid phase was calculated in a Lagrangian framework using the Discrete Phase Model (DPM) in Ansys Fluent (Ansys Inc., Canonsburg, USA). The presence of a moderate tumor (565 ml) was modeled in liver segment IV (outlets 1-6, see Fig. 1) using outflow percentage boundary conditions (ranging between 1.25 and 27.75%) based on the arterial perfusion distribution methodology proposed by Aramburu et al. [7]. At the inlet, a transient flow waveform was specified, with a cycle length of 0.8 s and cycle-averaged flow of 481.2 ml/min. The fluid time step was alternated between $1 \cdot 10^{-3}$ and $5 \cdot 10^{-4}$ s depending on convergence conditions. Particles with a diameter of 40 µm and a density of 1600 kg/m³, mimicking SIR-Spheres (Sirtex Medical Australia) used for TARE, were released from the inlet (see '1' in Fig. 1; simulation 1 (Sim1)), and from a second axial injection location near the second bifurcation (see '2' in Fig. 1; Sim2). Seven (Sim1) or six (Sim2) cardiac cycles were run, and particles were released every 0.01 s during the third cycle (1.6 s-2.4 s).

## RESULTS

For each injection timing, Particle Release Maps (PRMs) were generated. As shown in Fig. 1, PRMs are visualizations of the injection plane cross-section, showing where particles should be injected to reach certain exit branches (ideally, the tumor-perfusing branches (TPB)). In Composite Particle Release Maps (CPRMs), particles are colored according to their target specificity throughout the cycle, where *e* indicates for which % of the selected injection timings particle fates

corresponded with exit through a TPB (see Fig. 2B & 3B). Here, 16 evenly-spaced injection timings between 1.60s and 2.35s were selected, comparing particle fates from one injection timing to their nearest-neighbor fates at other timings.

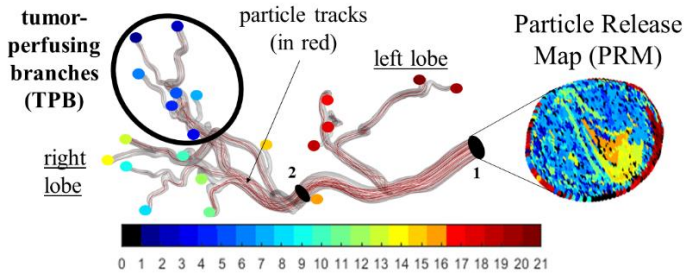


**Figure 1: A Particle Release Map (PRM) shows where particles should be injected to reach the tumor.**

In Fig. 2A-3A, the PRMs are given for injections at several injection timings (t = 1.60s, 1.80s, 2.00s, 2.20s) at the inlet and at the second bifurcation, respectively. As is clear, the PRM patterns vary significantly between the two axial locations. Moreover, the tumor targeting zone (shown in blue, outlets 1-6 in Fig. 1) varies significantly throughout the cycle. However, injection typically lasts for several cardiac cycles. Therefore, in Fig. 2B-3B, the corresponding CPRMs are given, with the green cells ($e$ > 80%) indicating the cross-sectional injection locations where particles exit through a TPB for >80% of the cycle. These zones can be considered as ideal zones to position the catheter tip throughout the whole cycle.

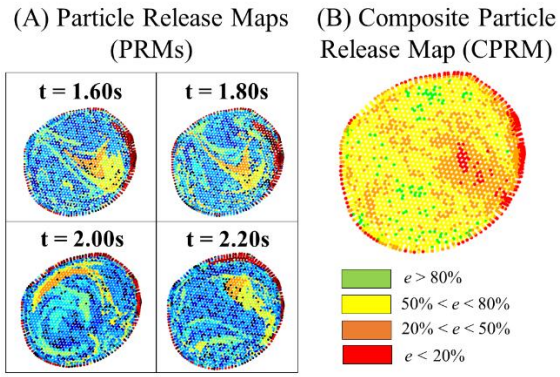


**Figure 2: (A) PRMs and (B) CPRM for the inlet injection.**

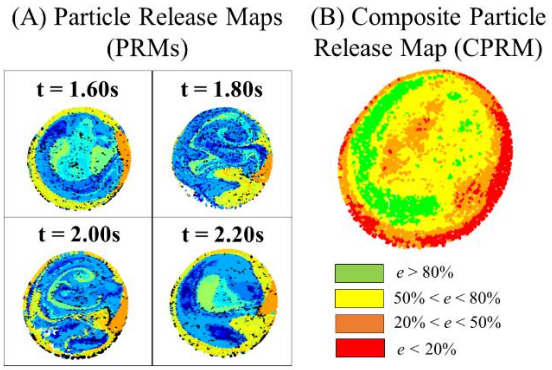


**Figure 3: (A) PRMs and (B) CPRM for injection near the second bifurcation.**

For the inlet, these ideal locations are distributed over the whole cross-section (4% of total particles displayed). However, for the injection location near the second bifurcation, the ideal cross-sectional injection locations are less spread out and form a much larger, more clearly delineated injection zone (16.8% of total particles).

## DISCUSSION

Childress et al. [4] constructed CPRMs for their two idealized hepatic arterial geometries (with only 5 and 3 outlets, no tumors modeled). They noted that for their basic 5-outlet geometry there was little variation between the PRMs for different injection timings, and that clear targeting zones could be distinguished in the CPRM for each exit branch. Interestingly, they noted that the variation was much higher for their 3-outlet geometry, and that there were no clear targeting zones in the CPRM. This implies the importance of the arterial geometry.

In this study, a much more complex, patient-specific arterial geometry was considered (with 21 outlets). As shown in Fig. 2, the variation between the PRMs was large for different injection timings. The CPRMs in Fig.2B & 3B show that for inlet injections there was no clear tumor targeting zone (green), while for injections at the second bifurcation the targeting zone was much clearer. This suggests that the results do not only depend on the arterial geometry, but also on the axial injection location. These results support our hypothesis that injection locations closer to the tumor make it easier to target the tumor.

The strengths of the study lie in (i) the consideration of a complex, patient-specific cirrhotic liver geometry, (ii) the direct comparison of two axial injection locations, and (iii) the modeling of a realistic cancer scenario with increased arterial perfusion in the TPB.

The limitations lie in considering only surface injections. The next step in the workflow includes modeling of the catheter, releasing a targeted injection from the suggested targeting zone (green, Fig. 2B-3B) and investigating the impact of catheter presence on the local hemodynamics and downstream particle distribution. Moreover, a wider range of axial injection locations and particle properties (i.e. size, density) should be studied for their impact on the CPRMs.

Judging from Fig. 2B-3B, there might be a trade-off between the choice of axial and cross-sectional location: far away from the tumor, the ideal targeting zones are minimal, implying that the cross-sectional injection location needs to be very precise; while, closer to the tumor, the ideal targeting zones are larger, and the location of the catheter tip matters less. Since accurate intra-arterial positioning of the catheter tip may prove to be a complex task, the ideal targeting zone should be maximized as much as possible.

In conclusion, the CPRM, studied on a wider scale of injection locations and particle properties, can be a helpful tool in selecting the most optimal injection conditions (i.e. those which maximize the ideal targeting zone) for efficient patient-specific tumor targeting.

## ACKNOWLEDGEMENTS

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