

Patient-Specific CFD Simulations of Side-Hole Catheters for Transarterial Liver Cancer Embolisation: Effects of Hole Size and Radial Orientation on Particle Distribution

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Remark on the Oral Presentation

This master's dissertation is part of an exam. Any comments formulated by the assessment committee during the oral presentation of the master's dissertation are not included in this text.

Abstract

Hepatocellular carcinoma ranks as the third leading cause of cancer-related deaths globally. One available treatment is transarterial radioembolisation, which involves injecting radioactive microspheres directly towards the tumour site, utilising the unique arterial blood supply of liver cancers to enhance treatment impacts while protecting surrounding healthy tissue. The success of this treatment is greatly influenced by clinical factors, including the patient's specific hepatic vascular structures, particle injection rates, and catheter type. These elements contribute to substantial variability in treatment outcomes. This thesis aims to optimize embolic particle delivery using computational fluid dynamics to better align particle distribution with blood flow patterns. To achieve this, a side-hole catheter design will be employed to enhance this alignment and mitigate the effects of clinical variables, leading to more predictable treatment outcomes and improved tumor targeting. In particular, this research assesses both standard end-hole microcatheters (SMC) and side-hole catheters (SHC) with closed frontal endings featuring various side-hole diameters. Utilising Ansys Discovery, distinct catheter geometries were developed and incorporated into a patient-specific hepatic arterial model to simulate particle trajectories and fluid dynamics. A mesh sensitivity analysis was conducted to identify the optimal volume mesh. The simulations encompassed steady-state and transient analyses, exploring how catheter type, side-hole diameter, and catheter orientation influence particle distribution. Results from catheter designs developed using Ansys Discovery aligned with expectations regarding particle spread and distribution, with the Discovery-based workflow preserving the native geometry with a surface-area deviation of only 0.0003% from the original segmented model. However, outcomes in key metrics such as Matching Deviation Index (MDI) and Targeting Deviation Index (TDI) depended on the side-hole orientation. The MDI, which measures the alignment of particle distribution with blood flow, indicated superior performance for SHC compared to SMC. SHC with smaller side-holes (0.2 mm) exhibited higher variability between orientations (2.53%) due to distinct injection streams close to arterial walls. The TDI, reflecting medical performance by aligning particle distribution with tumour perfusion, consistently favoured SHC with larger side-holes (0.4 mm), demonstrating less orientation dependency (0.89% variability compared to 2.84%). These findings were extended to transient simulations, showing a 12-fold increase in particle spread. Transient simulations consistently produce lower MDI and TDI values. SHC 0.2 had the best MDI due to the highest uniform particle spread, but this also led to diminished targeting specificity, resulting in the poorest TDI. This thesis demonstrates the potential of the side-hole catheter design to mitigate parameter sensitivity and align the treatment planning better with the actual treatment.

Keywords: Ansys Discovery, Catheter design, Hepatocellular carcinoma, Particle distribution, Transarterial therapy

Patient-Specific CFD Simulations of Side-Hole Catheters for Transarterial Liver Cancer Embolisation: Effects of Hole Size and Radial Orientation on Particle Distribution

Marnix Christiaens, Jessie Duquesne, Jana Zeebroek, Geert Maleux, and Charlotte Debbaut

Abstract—Hepatocellular carcinoma ranks as the third leading cause of cancer-related deaths worldwide. One available treatment is transarterial radioembolisation. It is a targeted therapy involving the injection of radioactive microspheres directly into the tumour-feeding arteries, exploiting the unique arterial blood supply of liver tumours to enhance therapeutic effectiveness while preserving healthy tissue. However, treatment outcomes vary greatly due to clinical factors including patient-specific vascular anatomy, catheter type, particle injection velocities, and catheter orientation. This thesis addresses the optimisation of embolic particle delivery through computational fluid dynamics modelling, evaluating standard end-hole (straight with a frontal opening) and novel side-hole catheter (closed frontal tip with lateral openings) designs with varying side-hole diameters (0.2 and 0.4 mm). Using Ansys Discovery (Ansys Inc., USA), a detailed patient-specific hepatic arterial model was developed to simulate and analyse particle trajectories under both steady-state and transient conditions. Results indicated that side-hole catheter designs improved alignment of particle distribution with blood flow, with larger side-hole diameters (0.4 mm) showing superior consistency in key metrics such as Matching Deviation Index and Targeting Deviation Index compared to smaller side-hole diameters (0.2 mm). Additionally, transient simulations demonstrated increased particle dispersion, suggesting improved predictive accuracy in clinical scenarios. This research underscores the potential of optimised catheter designs to reduce variability in clinical outcomes, enhancing the predictability and effectiveness of liver cancer treatments.

Index Terms—Ansys Discovery, Catheter design, Hepatocellular carcinoma, Particle distribution, Transarterial therapy

I. INTRODUCTION

HEPATOCELLULAR carcinoma (HCC) represents the most prevalent type of primary liver cancer and is recognised as the third leading cause of cancer-related deaths worldwide, as well as the sixth leading cause in both the European Union and North America in 2022, according to the WHO [1]. Its incidence is particularly pronounced in regions such as Eastern Asia, North-Western Africa, and Southeast Asia, primarily attributable to elevated rates of hepatitis B and C infections [2]. The prognosis for individuals diagnosed with HCC remains unfavourable, with a notably low five-year survival rate of approximately 19.6% in the United States as of 2020 [3]. Historically, HCC has been closely associated with viral hepatitis; however, in Western countries, its incidence increasingly correlates with non-alcoholic fatty liver disease (NAFLD), driven by a rising prevalence of obesity and diabetes [4]. Furthermore, liver cirrhosis often

manifests as a precursor or comorbidity to HCC, complicating the management of the disease, particularly liver surgery, due to reduced hepatic reserve and coagulopathy [3].

The current management of HCC largely depends on the Barcelona Clinic Liver Cancer staging system, which advises treatment choices from surgical procedures in the early stages to systemic therapies in advanced cases [5]. Locoregional treatments, particularly transarterial chemoembolisation (TACE) and radioembolisation (TARE), play a key role in managing HCC. TARE, especially, uses radioactive microspheres like SIR-spheres, resin-based beads, that target and deliver high doses of radiation directly to the tumour location [6]. Transarterial therapies take advantage of the liver's unique arterial blood supply, as tumour tissue mainly receives blood from the hepatic arteries. In contrast, healthy liver tissue is supplied by a combination of about 70% from the portal vein and 30% from the hepatic artery [7]. These transarterial therapies encounter substantial challenges due to variations in patient anatomy and the need to optimise procedural factors, including catheter placement and injection speed [7]. These clinical variables, which affect treatment outcomes, are not entirely controllable, complicating effective management [8].

Previous research has investigated innovative catheter designs to overcome challenges in optimising parameters. Ortega et al. (2022 [9], 2025 [10]) examined the side-hole catheter (SHC) design, which facilitates a more uniform distribution of particles throughout the arterial lumen, thereby aligning particle distribution with blood flow more effectively. This relationship is measured using the Matching Deviation Index (MDI), with lower values indicating better alignment. Enhanced alignment is beneficial due to the liver's distinct vascularisation and tumour hyperperfusion characteristics, which may help reduce the effects of uncontrollable clinical parameters when compared to standard end-hole microcatheters (SMC). Ortega et al. (2022) [9] concluded that an SHC featuring a closed frontal tip and side holes along the catheter wall demonstrated superior performance in simulations with idealised geometry. Ortega et al. (2025) [10] built upon these findings by analysing patient-specific scenarios that varied in cancer situations and radial tip positions, confirming that SHC outperformed SMC in terms of MDI performance and medical outcomes.

Further research conducted by earlier thesis authors Zeebroek (2024) [11] and De Smet (2024) [12] expanded upon these findings, indicating that increased injection velocities

and smaller side-holes resulted in enhanced crossflows, which greatly improved MDI. The dynamics of particle dispersion across various cross-sections were examined as well, detecting a larger particle spread downstream within the arterial network. However, negligible differences in particle spread between SHC designs were found when comparing smaller and larger side-holes, though it was noted that elevated injection velocities markedly enhanced particle dispersion. In contrast, Bomberna et al. (2024) [13] emphasised the strong temporal dependence of particle spread using SMC.

This research seeks to build on earlier findings by introducing a new workflow that maintains segmentation detail while speeding up the process. It will assess how catheter orientation affects particle distribution in steady-state. Furthermore, the steady-state simulation results by Zeebroek will be validated and enhanced using more realistic transient simulations, offering a deeper understanding of how catheter design influences particle distribution and movement. This study highlights the ability of the side-hole catheter design to reduce parameter sensitivity and improve the alignment of treatment planning with actual treatment outcomes.

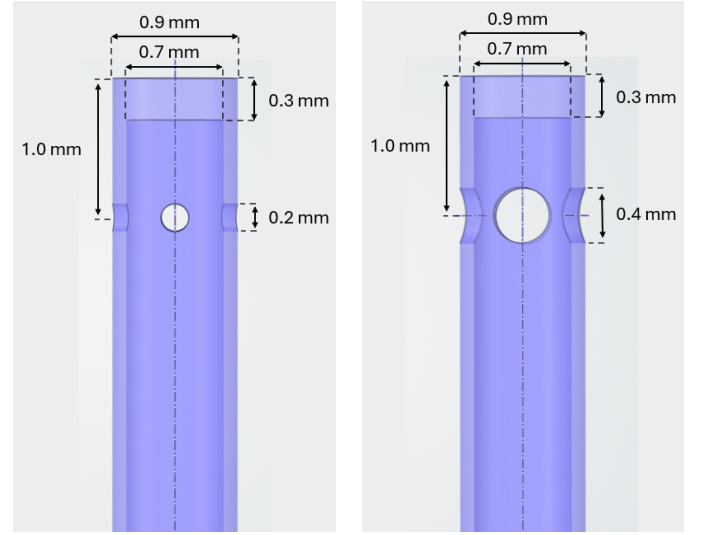
II. MATERIALS AND METHODS

A. Geometry and Mesh Generation

This study utilised a geometric dataset derived from micro-computed tomography (micro-CT) images of hepatic arteries from a patient diagnosed with HCC. The images were captured using a Philips cone-beam CT scanner, featuring a voxel size of 0.655 mm. They involved intra-arterial contrast injections in both branches of the proper hepatic artery. The ethical approval for using these patient-specific scans was granted by the Ethical Committee of the University Hospital Leuven, Belgium [14].

The 3D reconstruction of the hepatic arterial anatomy was previously conducted by Bomberna et al. (2022) [14] using Mimics software (Materialise NV, Belgium). Their segmentation resulted in an arterial geometry comprising one inlet and 48 outlets. To simplify the model, a pruning algorithm was applied, reducing the number of outlets to 17 by systematically removing branches with minimal tumour perfusion and redundant outlets supplying the same tissue regions. Further refinements were made to the arterial geometry, including extrusion of certain outlets and the inlet to promote physiologically relevant flow development. This refined model served as the geometric basis for the current study and simulations.

Catheter models were designed using ANSYS Discovery (ANSYS Inc., USA). Three distinct catheter designs were created: a standard end-hole microcatheter (SMC) and two side-hole catheters (SHCs) featuring radially positioned outlets with diameters of 0.2 mm (SHC 0.2) and 0.4 mm (SHC 0.4) (Figure 1). Each catheter had an internal diameter of 0.7 mm, an outer diameter of 0.9 mm, and a total length of 85 mm, slightly exceeding the extruded arterial inlet. This setup ensured that particle injection occurred entirely within the physiologically accurate arterial geometry, preventing boundary effects near the inlet. The SHCs were designed with a closed frontal tip and four evenly spaced outlets oriented



(a) Side-hole catheter with $\varnothing$ 0.2 mm. (b) Side-hole catheter with $\varnothing$ 0.4 mm.

Fig. 1: Two side-hole catheters with different side-hole diameters.

perpendicular to the catheter axis. This design was based on that of Zeebroek [11]. Variants of SHCs were created by rotating the catheters 30° and 60° anti-clockwise around the catheter axis, as viewed from the catheter tip. Together with the SMC, these seven catheter variants (SMC and 2 SHC types x 3 radial orientations) allowed for an assessment of how catheter type, outlet diameter, and radial orientation affected particle distribution in steady-state. However, in transient simulations only the baseline catheter orientation is studied.

Mesh generation was subsequently carried out using Fluent Meshing 2024 R2 (ANSYS Inc., USA). A structured meshing method was employed via the Fluent 'Watertight Geometry Workflow', with surface cell length ranging from 0.17 mm to 4.47 mm and a growth rate of 1.2. Local mesh refinements were applied at the catheter inlet and catheter volume. Finally, 17 different meshes with tetrahedral cells (2 025 982 - 9 840 605 cells for the hepatic arteries and 8 853 022 - 15 683 983 cells for the geometry with the catheter) and three prism boundary layers were constructed. All meshes adhered to quality thresholds: orthogonal quality exceeding 0.05 and skewness below 0.9.

A comprehensive mesh sensitivity analysis was performed to validate mesh density. Meshes with varying numbers of cells were evaluated based on the convergence of key hemodynamic and particle metrics, including particle distribution, wall shear stress, velocities after injections, and wall pressure. The final selected mesh configurations consisted of approximately eight million elements for the arterial domain and about 500 000 for the catheter models. These mesh densities yielded consistent results within a 1% tolerance.

B. Governing Equations and Boundary Conditions

The simulations employed the continuity and Navier-Stokes equations under assumptions of laminar, incompressible, and

non-Newtonian flow conditions [15]. Blood's viscosity was modelled using a simplified Quemada viscosity model [16] to represent its shear-thinning behaviour accurately. The discrete phase (particles) was simulated using the discrete phase model (DPM), governed by Newton's second law of motion, which incorporates forces such as gravity, drag, pressure gradient, and virtual mass. The multiple phases are connected with one-way coupling, ensuring that only the blood affects the particles [15].

Boundary conditions reflected physiological requirements: a pulsatile blood flow waveform derived from literature [17] was implemented at the arterial inlet, with a period of 0.8s and a mean velocity of 0.12 m/s. This mean velocity will be used for steady-state simulations. The particles and catheter fluid were uniformly injected at the catheter inlet with a velocity of 0.12 m/s. Outlet conditions employed predefined flow fractions based on the volumetric perfusion of tumour and healthy tissue calculations. These outflow fractions correspond to those used by Bomberna et al. [14] since the same geometry was utilised. Walls were modelled as rigid, no-slip surfaces with elastic particle interactions [15].

Solver settings utilised in Fluent Solution R2 2024 (ANSYS Inc., USA) employed the SIMPLE algorithm for pressure-velocity coupling, second-order spatial discretisation schemes, and convergence criteria (normalised residual thresholds set at $1 \cdot 10^{-6}$ absolute and $1 \cdot 10^{-3}$ relative).

C. Post-processing

The effectiveness of the catheter designs was assessed using several quantitative metrics: the Matching Deviation Index (MDI), the Targeting Deviation Index (TDI), and the Index of Particle Spread (IPS). The MDI quantified the alignment between particle distribution and blood flow, as outlined by Ortega et al. (2022) [9] and in Equation 1. The average difference between the percental blood flow and the percental particle flow over each outlet is calculated.

$$\text{MDI} [\%] = \frac{1}{N} \sum_{s=1}^N \left| \frac{N_{p,s}}{\sum_{s=1}^N N_{p,s}} - \frac{q_s}{\sum_{s=1}^N q_s} \right| \cdot 100 \quad (1)$$

Where s $[-]$ represents the number of the outlet, ranging from 1 to N . The variable $N_{p,s}$ $[-]$ denotes the number of particles in outlet s $[-]$, and q_s $[ml/min]$ represents the blood flow rate in outlet s $[-]$. The lower the MDI value, the better. TDI calculates a similar metric, but instead of the deviation from blood flow distribution, it assesses how effectively particle delivery matches tumour perfusion patterns by calculating the average difference between the percental perfused tumour volume and the percental particle flow over each outlet.

Particle spread analyses were conducted at critical cross-sectional planes downstream of catheter injection, evaluating spatial and temporal dispersion characteristics in detail. The Index of Particle Spread (IPS) (Equation 2) quantifies the extent to which particles are distributed across a cross-sectional area, expressed as the percentage of activated regions in a grid overlay [13].

$$\text{IPS} [\%] = \frac{N_{particle}}{N_{plane}} \cdot 100 \quad (2)$$

Where $N_{plane}[-]$ denotes the total number of reference squares in the cross-section and $N_{particle}[-]$ the number of reference squares where at least one particle passed through. An IPS value of 100 % indicates that particles are spread across the entire plane.

III. RESULTS AND DISCUSSION

A. Workflow Ansys Discovery

The computational workflow for this study leveraged Ansys Discovery to streamline the creation and insertion of catheters into patient-specific hepatic artery geometries. Previously, geometry reconstruction with SpaceClaim involved reverse engineering, where arterial geometries were manually approximated using circles and ellipses to enable catheter insertion. This approach was not only highly time-consuming (estimated time spent of two weeks) but also introduced deviations from true anatomy: the reconstructed model produced by the SpaceClaim workflow exhibited a total surface area of 9533.1846 mm^2 , compared to the original segmented geometry's 9466.0648 mm^2 . By contrast, the Discovery-based workflow automatically converts the original geometry while preserving its anatomical detail. Quantitatively, the model generated with Ansys Discovery has a surface area of 9466.0327 mm^2 , deviating by only 0.0003% from the native geometry. This new workflow eliminated the need for reverse engineering steps, preserving the original anatomical geometry and making the catheter insertion process easier and faster.

B. Particle Trajectories

Simulated particle trajectories revealed distinct dispersion patterns influenced by catheter designs. The SMC produced a single concentrated injection stream primarily targeting tumour-specific outlets. Conversely, the SHCs exhibited four distinct injection streams, especially prominent in the SHC with smaller side holes (0.2 mm) as shown in Figure 2. This design resulted in increased radial dispersion due to enhanced crossflow effects. Ortega et al. (2022) [9] previously concluded that smaller side holes, by generating higher outlet velocities, would enhance crossflow and facilitate lumen filling. The current results partially align with Ortega's findings, demonstrating increased crossflow with smaller side-holes; however, lumen filling was not achieved, and distinct injection streams persisted.

Across the entire arterial geometry, the catheter with smaller side-holes (0.2 mm) notably increased distribution over the outlets in steady-state, reaching more than 11 outlets, compared to only four outlets reached by the catheter with larger side-hole diameters (0.4 mm). Furthermore, variations in side-hole orientation introduced variability in the number of outlets reached (11-14 outlets) with the 0.2 mm side-hole catheter. This variability can be attributed to the proximity of injection streams to the arterial wall, resulting in increased particle-wall interactions. Under the elastic collision assumption of the simulation, these interactions scatter particles across the lumen.

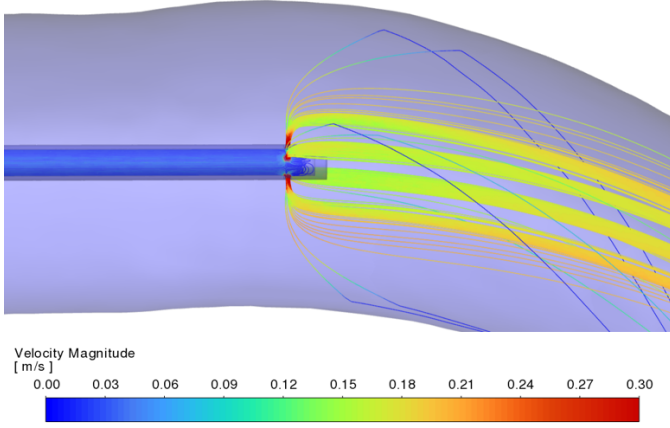


Fig. 2: Visualisation of the particle trajectories, indicated by velocity magnitude [m/s], at the catheter tip of the SHC ($\varnothing$ 0.2 mm) in steady-state conditions.

Conversely, the catheter with 0.4 mm side-holes consistently reached only four outlets, reflecting fewer interactions due to injection streams being further from the arterial wall.

These steady-state results were expanded upon with instantaneous catheter fluid velocity pathlines analysed at peak systole and mid-diastolic plateau (0.22s and 0.65s of the 0.8s cardiac cycle) from transient simulations. These results demonstrated that the radial extent of fluid streams varied over time depending on the ratio between catheter outlet velocity and blood flow velocity. The maximum velocity ratio was observed for the SHC with smaller side-holes, showing a radial extent of 1.79 mm in diastole (Table I). In comparison, the minimum ratio was noted for the SHC with larger holes, exhibiting a radial extent of 0.56 mm in systole. Moreover, the largest difference between the ratios at systole and diastole, and consequently the radial extent, was found for the SHC with smaller holes, specifically 0.84 mm, thereby enhancing lumen filling potential under transient conditions. No continuous particle tracks were generated, as transient simulations provide only discrete particle locations rather than continuous trajectories.

TABLE I: Overview of the radial extent of the injection streams for the SHC designs at orientation 1.

Catheter type	Steady-state	Systole	Diastole
SHC 0.2	1.29 mm	0.95 mm	1.79 mm
SHC 0.4	0.66 mm	0.56 mm	0.87 mm

C. Particle Spread

The quantitative assessment of particle spread, measured by IPS, revealed that all catheter designs and orientations displayed minimal dispersion 2 mm downstream of injection, with IPS values consistently below 5% in steady-state, clearly indicating distinct injection streams (Figure 3). The IPS values were also low across other planes, ranging from 2.1% to 18%, in contrast to the 19-88% reported by Bomberna et al. (2024) [13] for the non-truncated geometry using the SMC.

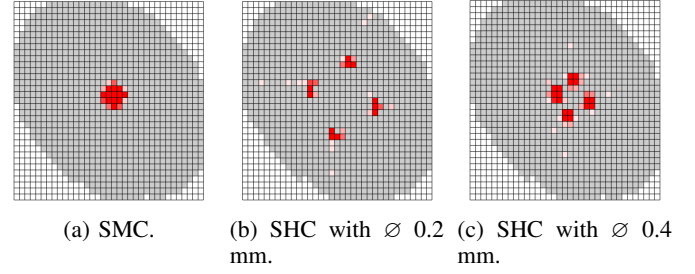


Fig. 3: Visualisation of the particle spread for the different catheter types in steady-state, 2 mm downstream of the catheter tip.

The lower IPS values observed in this section can be attributed to the steady-state nature of the simulations. Notably, the SMC consistently showed lower IPS values than the SHC across all evaluated cross-sections and orientations, which corresponds with the findings of Ortega et al. (2025) [10]. Additionally, in 75% of the examined cases, the SHC with smaller side-holes demonstrated greater particle spread than those with larger holes, aligning with Ortega et al. (2022) [9], who found that increased crossflow enhances particle dispersion.

Notably, the SHC with smaller holes showed a higher dependency on the orientation of side-holes, revealing IPS differences of 8.8% and 5% at cross-sectional planes located 20 mm downstream of the first (Table II) and 10 mm of the second bifurcation that led to the highest outflow outlet, respectively. In contrast, the SHC with larger side-holes demonstrated variability of merely 4.5% and 0.8% at the same planes. The increased variation seen with smaller holes is linked to injection characteristics and the closeness of particle streams to the arterial wall, which raises the chances of wall interactions and enhances particle dispersion. Those wall interactions and dispersion patterns are dependent on injection orientation. Generally, in 85% of the instances, IPS rose as particles moved deeper into the arterial geometry due to wall interactions and bifurcations. Nonetheless, the overall IPS values remained relatively low in steady-state, peaking at 18% with a maximum variability of 9.6% across different planes within a single simulation.

TABLE II: Overview of the IPS values at the cross-sectional plane located 20 mm downstream of the first bifurcation, leading to the highest outflow outlet. Values for all catheter types and orientations in steady-state conditions are shown.

Catheter type	SMC	SHC 0.2	SHC 0.4
Orientation 1	2.1	10.0	12.0
Orientation 2	/	18.0	8.8
Orientation 3	/	9.2	7.5

In transient simulations, the IPS values were, on average, 12-fold higher than the steady-state results, which was attributed to the dynamic crossflows at injection and the fluctuation in arterial flow. Despite these higher IPS values, the particle spread remained higher for SHC designs compared to the SMC. The SHC with the smallest holes exhibited the most uniform particle distribution across the arterial lumen

due to its four injection points and the greatest radial extent variation of the injection streams. Conversely, the SMC consistently produced the least uniform particle distribution (Table III). Additionally, IPS values showed temporal dependency, with higher values observed during systole due to elevated velocities compared to those during diastole.

TABLE III: Overview of the Uniform IPS values at the cross-sectional plane located 20 mm downstream of the first bifurcation, leading to the highest outflow outlet. Values for all catheter types in transient conditions are shown.

Catheter type	SMC	SHC 0.2	SHC 0.4
UIPS [%]	36	61	50

From a clinical perspective, analysing particle dispersion is essential since greater particle spread promotes better distribution within the arterial lumen, allowing particles to follow all blood flow paths and reach every outlet. Moreover, a more uniform particle distribution aligns more closely with blood flow distribution, minimising the impact of clinical parameters.

D. Particle Distribution and Tumour Dose

Analysis of particle distribution across arterial outlets underscored a critical trade-off between dispersion and targeting accuracy. The SMC provided the most focused distribution in steady-state, exclusively delivering particles to only three tumour-specific outlets, covering 68.86% of the tumour. In the current radial and axial catheter positions, it achieved a perfect tumour dose of 100% (Table IV). However, such outcomes may not readily apply in clinical scenarios, where accurate catheter placement is notoriously difficult. In contrast, the SHC design facilitated greater dispersion, reducing its reliance on precise catheter positioning.

TABLE IV: Overview of the tumour dose (TD) and tumour coverage (TC), represented in percentage points, for all catheter types and orientations in steady-state conditions.

Catheter type	Orientation	TD [%]	TC [%]
SMC	/	100.00	68.86
SHC 0.2	1	44.81	79.41
SHC 0.2	2	91.53	91.49
SHC 0.2	3	81.28	76.41
SHC 0.4	1	95.73	68.86
SHC 0.4	2	99.82	68.86
SHC 0.4	3	99.91	68.86

The particle distribution analysis for SHC configurations confirmed earlier expectations that smaller side holes, associated with higher crossflow, target more outlets. The SHC with larger side holes (0.4 mm) consistently targeted only four outlets, three of which were tumour feeders, all within a single arterial branch, resulting in limited tumour dose variability of 4.18%. In contrast, the SHC with smaller side holes (0.2 mm) distributed particles across 11 to 14 outlets, including 4 to 7 tumour tissue outlets, demonstrating substantial variability in tumour targeting accuracy (ranging from 44.81% to 91.53%).

Based on tumour dose, the SHC with larger side holes, averaging 98.49%, consistently outperformed the smaller side-hole design, displaying less dependency on catheter orientation. However, this performance came at the expense of lower overall tumour coverage (68.86%) compared to the broader coverage (76.41% to 91.49%) achieved by the SHC with smaller side holes.

Transient simulations enhanced the distribution of particles to 13 outlets, including 8 tumour-feeding ones, across all configurations, due to consistently high IPS values (89%-97%) that varied only slightly, by approximately 8%, except at the plane located 2 mm after injection. In terms of tumour and healthy doses, the SMC and SHC with larger holes (0.4 mm) yielded comparable results, with differences in the number of particles exiting the geometry complicating distinctions further (Table V). Both maintained the highest tumour doses and the lowest healthy doses, like in steady-state. Conversely, the SHC with the smallest side holes (0.2 mm) displayed the lowest tumour dose and the highest healthy dose due to its enhanced uniform particle spread, aligning the particle distribution better with the blood flow distribution at the expense of targeting less tumour tissue.

TABLE V: Overview of the tumour dose (TD), healthy dose (HD) and particles left in the geometry (Left particles), represented in percentage points, for all catheter types in transient conditions.

Catheter type	TD [%]	HD [%]	Left particles [%]
SMC	78.32	8.26	13.42
SHC 0.2	74.36	11.36	14.27
SHC 0.4	78.96	8.74	12.29

E. Matching and Targeting Deviation Index

The Matching Deviation Index (MDI), reflecting alignment with blood flow (lower values indicate better alignment), remained below 10% across all catheters (Table VI). Consistent with Ortega et al. (2025) [10], SHCs showed lower MDI than the SMC. SHC 0.2 generally outperformed in two orientations, supporting Ortega et al. (2022) [9] findings that enhanced crossflow from smaller side holes tends to lower MDI. MDI values correlated strongly with particle spread (IPS), especially with the IPS values shown in Table II, highlighting the importance of dispersion at bifurcations. SHC 0.2 exhibited greater orientation sensitivity (2.53% variability) compared to SHC 0.4 (1.11%).

The Targeting Deviation Index (TDI), which measures alignment with tumour perfusion, favoured SHCs over SMC, except for SHC 0.2 in one of the three orientations, aligning with the findings of Ortega et al. (2025) [10]. SHC 0.2 displayed notable orientation sensitivity, achieving both the highest (6.61%) and second-lowest (3.77%) TDI. Overall, SHC 0.4 consistently performed best clinically in steady-state due to its lower orientation sensitivity, optimal TDI, and improved alignment with tumour perfusion. However, SHC 0.4's superior TDI performance was not due primarily to an inherently better catheter design but rather because its injection

TABLE VI: Overview of the MDI and TDI, represented in percentage points, for all catheter types and orientations in steady-state conditions.

Catheter type	Orientation	MDI [%]	TDI [%]
SMC	/	6.06	5.15
SHC 0.2	1	5.81	6.61
SHC 0.2	2	3.28	3.77
SHC 0.2	3	4.61	4.87
SHC 0.4	1	4.28	3.77
SHC 0.4	2	4.49	3.57
SHC 0.4	3	5.39	4.46

streams were positioned closer to those of the SMC, achieving a perfect tumour dose. By enhancing dispersion with four injection streams, SHC 0.4 achieved improved alignment with tumour perfusion.

In the transient regime, the SHC with smaller side holes (0.2 mm) achieved the best MDI, consistent with steady-state findings. This performance stemmed from its highly uniform particle spread, which facilitated superior alignment with blood flow and aligned with the observations of Zeebroek (2024) [11] and Ortega et al. (2025) [10]. However, this same uniformity adversely affected targeting specificity, resulting in the highest TDI among all configurations. The broader spread led to increased particle deposition in healthy tissue and reduced tumour targeting, thereby elevating the TDI and diminishing clinical effectiveness in terms of tumour specificity.

IV. CONCLUSION

The integration of Ansys Discovery into the catheter insertion workflow markedly enhanced anatomical accuracy, streamlined the modelling process, and eliminated the time-intensive reverse-engineering steps inherent in previous methods involving SpaceClaim and Design Modeller. Comparative steady-state CFD simulations indicated substantial differences between SMC and novel SHC designs. Smaller side-hole catheters demonstrated increased crossflow and greater particle-wall interactions due to the proximity of the injection streams to arterial walls, resulting in substantial variability in tumour dose (up to 46.72%) dependent on radial orientation. Conversely, SHC 0.4 achieved higher and more consistent tumour doses across orientations but exhibited narrower dispersion, limiting overall tumour coverage.

Clinically relevant indices such as MDI consistently favoured SHC designs, indicating superior alignment with physiological blood flow patterns. Specifically, SHC 0.4 excelled in TDI, reflecting optimal alignment with tumour perfusion across orientations. Transient simulations underscored the necessity of considering pulsatile physiological conditions, revealing substantial temporal variability that affected particle distribution and dispersion, with IPS values on average being 12-fold higher. SHC 0.2 achieved the most favourable MDI in this regime due to its uniform particle spread, but this also led to diminished targeting specificity, resulting in the highest TDI.

Overall, this study highlights the critical role of patient-specific transient CFD modelling in optimising catheter design and treatment predictability. It advocates for further investigation through extended transient simulations, diversified patient anatomies, and experimental validation to enhance transarterial liver cancer therapies.

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Nomenclature

Roman Symbols

^{90}Y	Yttrium-90
BF_b	Branching factor (-)
C_D	Drag coefficient (-)
C_V	Virtual mass coefficient (-)
d_p	Particle diameter (m)
$\frac{d\vec{u}_p}{dt}$	Particle acceleration (m/s ²)
$\vec{f}$	Forces acting on the fluid (N/m)
$\vec{F}_D$	Drag force (N)
$\vec{F}_G$	Gravitational force (N)
$\vec{F}_P$	Pressure gradient force (N)
$\vec{F}_V$	Virtual mass force (N)
$\vec{g}$	Gravitational acceleration (m/s ²)
k_c	Tumour perfusion rate (min ⁻¹)
k_h	Healthy perfusion rate (min ⁻¹)
m_p	Particle mass (kg)
N_{burst}	Number of reference squares where at least one particle passed through in a certain time interval (-)
$N_{particle}$	Number of reference squares where at least one particle passed through (-)
N_{plane}	Total number of reference squares in the cross-section (-)
$N_{p,s}$	Number of particles in outlet s (-)

p	Pressure of the fluid (Pa)
P_b	Absolute number of particles in burst b (-)
p_{ij}	Percentage of particles passing through the reference square at row i and column j (-)
Q_b	Total outflow from an outlet b (ml/min)
$Q_{c,b}$	Outflow contribution from cancerous tissue at outlet b (ml/min)
$Q_{h,b}$	Outflow contribution from healthy tissue at outlet b (ml/min)
Q_s	Outflow for segment s (ml/min)
Q_t	Total tumour flow (ml/min)
Re_p	Particle Reynolds number (-)
t	Time (s)
$\vec{u}$	Velocity vector of the fluid (m/s)
U	Uniform particle distribution (-)
$\vec{u}_p$	Particle velocity vector (m/s)
$V_{c,s}$	Tumoral volume of outlet s (ml)
V_s	Volume of segment s (ml)
V_t	Total tumour volume (ml)

Greek Symbols

$\dot{\gamma}$	Shear rate (s^{-1})
λ	Shear stress modifier (s^{-1})
$\mu(\dot{\gamma})$	Apparent viscosity (Pa·s)
μ_0	Minimum viscosity (Pa·s)
μ_∞	Asymptotic viscosity (Pa·s)
ρ	Density of the fluid (kg/m^3)
ρ_p	Particle density (kg/m^3)
$\bar{\tau}$	Shear stress tensor (Pa)

τ_0 Apparent yield shear stress (Pa)

Other Symbols

∇ Nabla operator, representing spatial derivatives

Acronyms / Abbreviations

ASR Age Standardized incidence Rate

BCLC Barcelona Clinic Liver Cancer

CP Child-Pugh Score

CT Computed Tomography

cTACE Conventional Transarterial Chemoembolisation

DEB – TACE Drug-Eluting Bead Transarterial Chemoembolisation

DPM Discrete Phase Model

DSM – TACE Degradable Starch Microspheres Transarterial Chemoembolisation

ECOG Eastern Cooperative Oncology Group

EPR Enhanced Permeability and Retention

HBV Hepatitis B Virus

HCC Hepatocellular Carcinoma

HCV Hepatitis C Virus

IPS Index of Particle Spread

LSF Lung Shunt Fraction

MDI Matching Deviation Index

MRI Magnetic Resonance Imaging

MSA Mesh Sensitivity Analysis

NAFLD Non-Alcoholic Fatty Liver Disease

NPs Nanoparticles

PEG Polyethylene Glycol

PRM Particle Release Map

<i>PS</i>	Performance Status
<i>SHC</i>	Side-hole Catheter
<i>SIMPLE</i>	Semi-Implicit Method for Pressure-Linked Equations
<i>SMC</i>	Standard end-hole Microcatheter
<i>SPECT</i>	Single-photon Emission Computed Tomography
<i>TACE</i>	Transarterial Chemoembolisation
<i>TARE</i>	Transarterial Radioembolisation
<i>TDI</i>	Targeting Deviation Index
<i>tIPS</i>	Temporal Index of Particle Spread
<i>TPP</i>	Tumor Perfusion Percentage
<i>UIPS</i>	Uniform Index of Particle Spread
<i>VOI</i>	Volume Of Interest
<i>WIPS</i>	Weighted Index of Particle Spread

Part I

Literature Study

Chapter 1

Clinical Context of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) ranked as the third leading cause of cancer-related deaths worldwide, as well as the sixth leading cause in both the European Union and North America in 2022, according to the WHO [1]. As the most common primary liver cancer, HCC presents unique challenges in treatment due to the liver's intricate structure and its frequent development in patients with underlying cirrhosis, a key risk factor and precursor to HCC. This clinical chapter begins with section 1.1, which explores the liver anatomy and physiology, as well as the segmental organisation and vascular architecture that impact clinical interventions.

After the liver section, the clinical context of HCC is discussed. This part examines the epidemiology in section 1.2.1, staging in section 1.2.2, and treatment modalities of HCC in section 1.2.3, providing a clinical understanding of the disease's progression and the therapeutic strategies available to improve patient outcomes.

1.1 Liver Anatomy and Physiology

The liver, the largest internal human organ, accounts for approximately 2.5% of total body weight. Its primary roles include detoxifying the blood through the metabolism of toxins, drugs, and waste products. Another function of the liver is to produce critical proteins such as albumin and clotting factors, which regulate plasma volume and maintain hemostasis. Additionally, the liver produces bile, which is vital for lipid digestion and absorption in the intestines [2–4].

The liver is functionally divided into eight segments defined by Couinaud's segmentation system. This system can be seen in Figure 1.1. The bifurcations of the portal vein, hepatic arteries, and hepatic veins organise those segments. They have an independent vascular inflow,

outflow, and biliary drainage, making the system valuable in clinical and surgical planning. Segment I, or the caudate lobe, is notable for its dual blood supply from the right and left portal veins and hepatic arterial branches, conferring resilience to vascular occlusions. The left lobe comprises segments II to IV, with segment IV further subdivided into superior (IVa) and inferior (IVb) subsegments. The right lobe contains segments V to VIII, organised into anterior (V and VI) and posterior (VII and VIII) sectors [5].

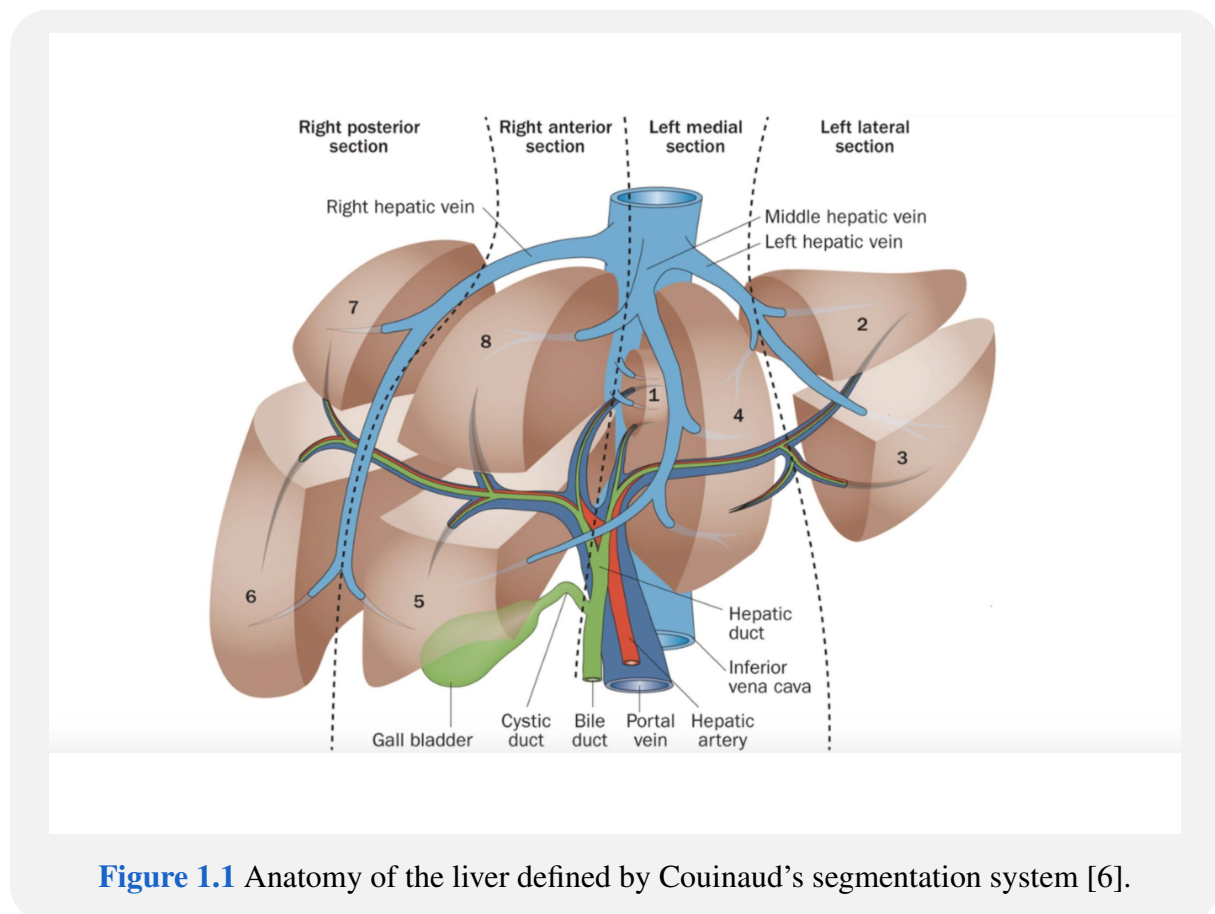


Figure 1.1 Anatomy of the liver defined by Couinaud's segmentation system [6].

The liver's blood supply is dual, with the hepatic artery and portal vein each contributing uniquely. The hepatic artery, originating from the celiac trunk, supplies 25–30% of blood flow but provides most of the liver's oxygen. The portal vein supplies 70–75% of blood flow, bringing nutrient-rich blood. This flow is essential for metabolic activities. However, there is no standard hepatic artery anatomy, affecting interventional and surgical procedures [5]. Typically, the common hepatic artery arises from the celiac artery, dividing into right and left hepatic arteries that supply respective lobes as per Couinaud's segmentation (Figure 1.2).

Variations in the hepatic artery are clinically important. In 10–30% of cases, the right hepatic artery originates from the superior mesenteric artery, while the left hepatic artery may arise from the left gastric artery in 12–21% of cases. Such variations complicate access during procedures like selective arterial catheterisation for chemoembolisation. Michel's classification organises these variations from Type I (standard anatomy) to Type X, covering rare instances like the

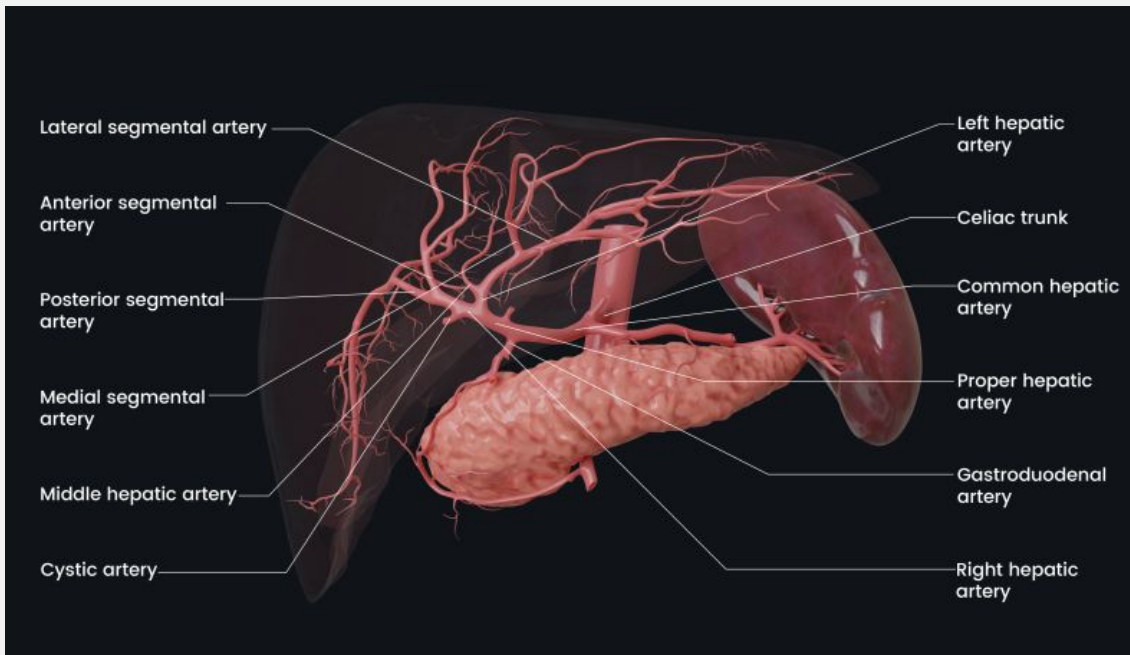


Figure 1.2 Arterial blood supply of the liver [7].

common hepatic artery originating from the left gastric artery. An awareness of these variations is crucial to ensure accurate targeting [5].

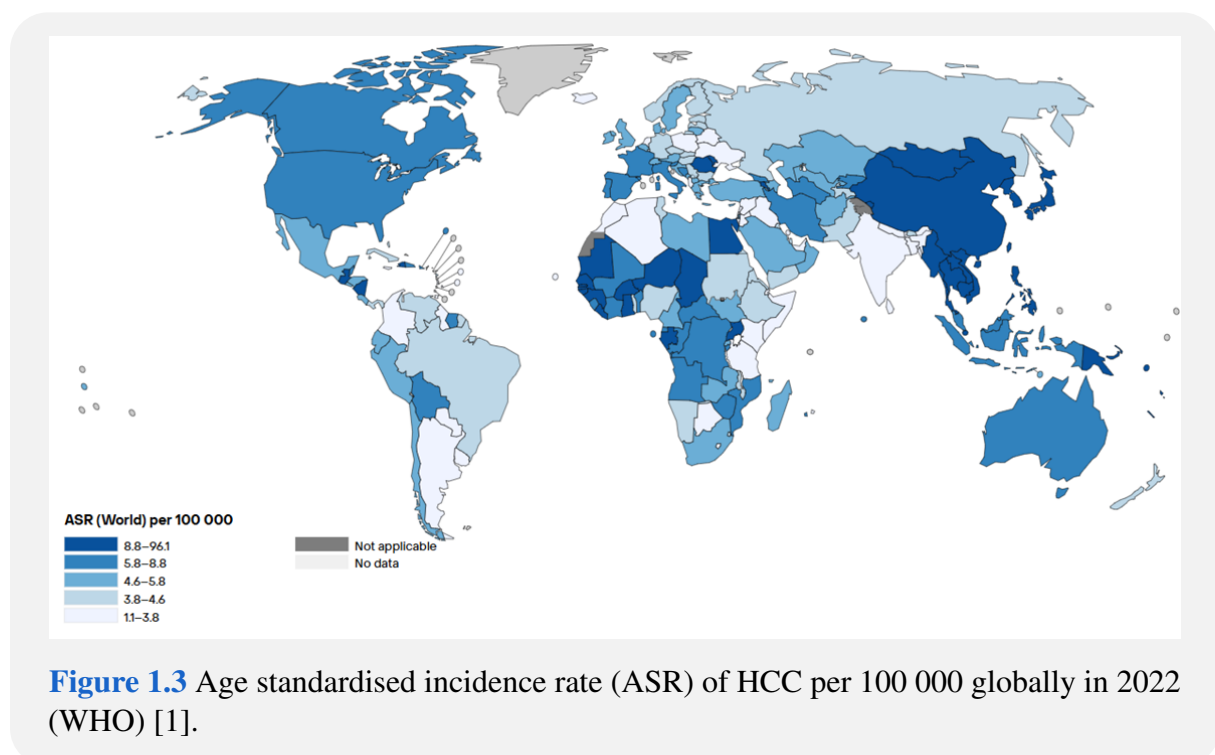
1.2 Hepatocellular Carcinoma and Treatment Challenges

HCC is the most common form of primary liver cancer, with an average five-year survival rate in the USA of 19.6% in 2020 [8]. Other liver malignancies, such as intrahepatic cholangiocarcinoma (ICC), exist but are less common than HCC [9]. Ranking as the third leading cause of cancer-related deaths worldwide, HCC poses a severe global health challenge, with high incidence and mortality rates concentrated in regions with endemic hepatitis infections, such as Asia and sub-Saharan Africa [10]. The rising rates of metabolic diseases, including non-alcoholic fatty liver disease, have also contributed to HCC cases in Western countries [11].

This section provides essential clinical context on HCC through three focused areas: 1.2.1 epidemiology and risk factors, which detail the environmental and genetic contributors to HCC; 1.2.2 staging and progression, describing how HCC is classified and its relevance to treatment planning; and 1.2.3 treatment modalities, outlining current therapeutic approaches and their limitations.

1.2.1 Epidemiology and Risk Factors

HCC shows considerable geographical variations, with the highest incidence rates in Eastern Asia, Northern Africa, and Southeast Asia, see Figure 1.3. Mongolia, Egypt, and Cambodia are among the countries with the most number of cases [12]. Over 80% of new HCC cases occur in developing regions, where hepatitis B virus (HBV) is highly prevalent. Chronic infections with HBV and hepatitis C virus (HCV) together account for over 70% of HCC cases worldwide [12, 13].



The progression of HCC typically follows a sequence that begins with liver injury, leading to chronic inflammation, fibrosis (scarring), cirrhosis, and eventually cancer [8]. In cases of HBV and HCV infections, the liver experiences repeated cycles of damage and repair, contributing to this pathway from fibrosis to HCC. HCV transmission, often through drug injection, remains an important factor in Western countries. Additionally, alcohol is linked to approximately 30% of HCC cases in the United States. It can cause liver damage directly and indirectly, the latter through its association with liver cirrhosis [13].

Non-alcoholic fatty liver disease (NAFLD) is now emerging as a leading cause of HCC, especially in Western countries. Rising obesity and diabetes rates have intensified its impact. The prevalence of NAFLD has led to a shift in HCC demographics, with an expected 122% increase in HCC incidence in the United States between 2016 and 2030 due to these risk factors [13, 14].

In addition to those geographic variations, there are also genetic variations. Males are 1.2 to 3.6 times more likely to develop HCC than females [13].

1.2.2 Staging and Progression of HCC

The diagnosis and staging of HCC are essential for determining the most effective treatment options and assessing patient prognosis. Staging is typically based on imaging techniques, such as dynamic contrast-enhanced MRI and multidetector CT scans, alongside blood tests and biopsies to confirm the cancer's presence, size, and extent [15].

A widely used classification system for HCC is the Barcelona Clinic Liver Cancer (BCLC) staging system. The BCLC evaluates the tumour characteristics, liver function, and overall patient health to identify appropriate treatment options. There are three main factors considered in BCLC staging: liver function, performance status, and the extent of liver cirrhosis [16].

The liver function in BCLC staging is typically assessed through the Child-Pugh score, which evaluates five clinical factors: levels of bilirubin and albumin (proteins produced by the liver), blood clotting ability (prothrombin time), fluid retention, and brain function impairment (hepatic encephalopathy). Based on these factors, the Child-Pugh score classifies liver function into three classes: Class A (good function), Class B (moderate impairment), and Class C (severe impairment). Patients with lower Child-Pugh scores have more treatment options and a better prognosis [8].

The Performance Status (PS) score, often evaluated using the Eastern Cooperative Oncology Group (ECOG) scale, measures a patient's physical abilities and general well-being. The PS score ranges from 0 (fully active) to 4 (completely disabled), indicating how the disease affects a patient's daily activities. A lower PS score means the patient has better overall health, which can broaden treatment options and improve outcomes. The PS score is a critical factor in the BCLC system, as it helps assess whether a patient can tolerate aggressive treatments or should be directed toward more supportive care [8].

Liver cirrhosis is a severe condition characterised by both extensive fibrosis and regenerative nodules. It is the result of chronic liver damage (e.g., hepatitis infections, alcohol misuse, or non-alcoholic fatty liver disease). Liver cirrhosis complicates HCC progression and treatment. Cirrhosis is not only a common precursor for HCC but also limits treatment options because the scarred liver has a reduced capacity for regeneration and recovery [16–18].

The BCLC system integrates these three factors to classify HCC into five stages, see Figure 1.4, each associated with specific survival rates and treatment options [19, 20]. This system is recommended by the American Association for the Study of Liver Diseases to classify the stage [17].

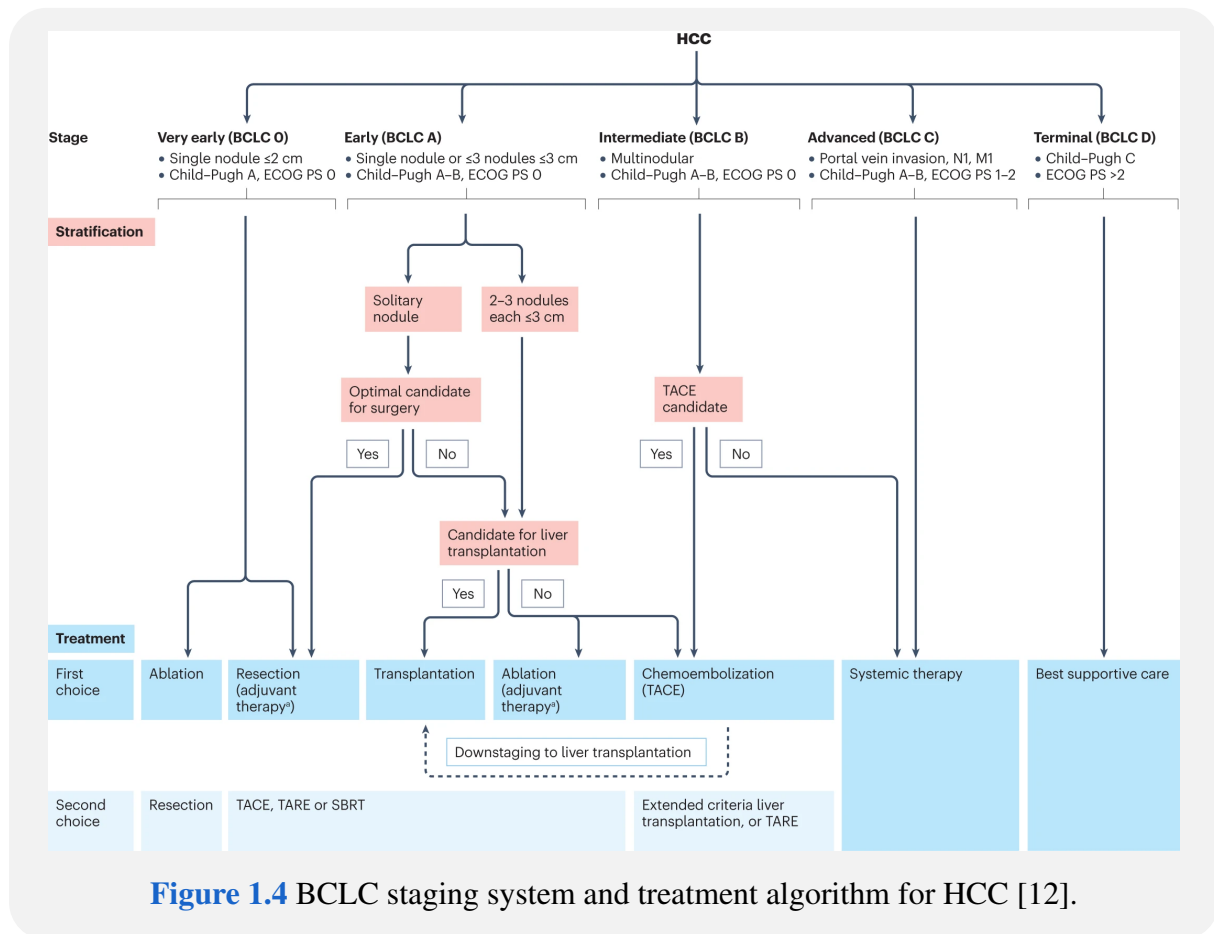


Figure 1.4 BCLC staging system and treatment algorithm for HCC [12].

Stage 0 (very early stage): In this initial stage, the tumour is small (less than 2 cm) and confined to the liver, with good liver function (typically Child-Pugh Class A). Treatment options like surgery or ablation are often possible, and survival rates are high, with many patients living over five years post-treatment.

Stage A (early stage): This stage includes a single tumour up to 5 cm or up to three tumours, each smaller than 3 cm. Patients often have good liver function (Child-Pugh Class A or B), making surgery, liver transplantation, or localised therapies feasible. Survival rates are favourable, with many patients achieving long-term survival.

Stage B (intermediate stage): By this stage, the cancer has multiple tumours confined to the liver, but curative treatments like surgery are no longer effective. Instead, transarterial chemoembolisation (TACE) is used to block blood flow to the tumours and deliver chemotherapy. Patients may live several years with proper treatment, though survival rates decline compared to earlier stages.

Stage C (advanced stage): Cancer has spread beyond the liver, affecting nearby blood vessels or distant organs. Systemic therapies, such as targeted or immunotherapy, are

recommended to manage symptoms and slow progression. Survival rates are lower, generally under two years.

Stage D (end stage): At this point, liver function is severely compromised, often classified as Child-Pugh Class C. Palliative care is the primary focus, aiming to improve quality of life and manage symptoms. Survival at this stage is typically limited to a few months.

This staging framework, incorporating tumour characteristics and liver function, enables a tailored treatment approach to address the complex progression of HCC [17].

1.2.3 Treatment Modalities

The treatment of HCC is complex. It is chosen by considering the cancer stage, liver function, and the patient's overall health [17]. A summary of the treatments linked to the stage of the cancer can be seen in Figure 1.4. Liver cirrhosis, as already said, could impact treatment options. Cirrhosis affects the liver's ability to process medications, regenerate tissue, and recover from invasive procedures. For many HCC patients, managing cirrhosis is integral to treatment, as it reduces the liver's capacity to withstand certain therapies and limits options to those with less risk of liver failure [18].

For patients with early-stage HCC and relatively well-compensated liver function, surgical removal of the tumour, or partial hepatectomy, can be a curative option. Surgery involves removing the cancerous portion of the liver, which is feasible when the liver is otherwise healthy and has enough functional reserve to regenerate. However, cirrhosis restricts eligibility for surgery because the damaged liver tissue may be unable to compensate for the loss of liver mass, potentially leading to liver failure. Patients with substantial cirrhosis are, therefore, rarely eligible for partial hepatectomy, limiting this option to a small percentage of HCC patients with very localised cancer and limited scarring.

Liver transplantation represents another potential curative treatment and is especially beneficial for patients with both HCC and advanced cirrhosis. Transplantation replaces the diseased liver entirely, removing both the cancer and the damaged tissue, thus addressing the dual challenge of HCC and cirrhosis. However, liver transplants are limited by the availability of donor organs and strict eligibility criteria, including the need for the cancer to be small and localised. Due to these restrictions, only select patients with early-stage HCC and severe cirrhosis qualify for transplantation. While transplantation is ideal for patients who meet these criteria, it is not a broadly available solution due to organ shortages and specific requirements.

For those ineligible for surgery or transplant, locoregional therapies offer alternative ways to target HCC. However, cirrhosis complicates the use of these therapies as well, given that reduced liver function affects the liver's ability to heal and withstand treatment. Among the locoregional

options, ablation is one method that uses heat (radiofrequency ablation) or cold (cryoablation) to destroy cancer cells within the liver. This approach is suitable for small tumours, typically less than 3 cm, and can be applied in cases of moderate cirrhosis where the liver can still tolerate some localised cell damage. In cases of severe cirrhosis, however, ablation may pose risks of liver decompensation (the worsening of liver function), limiting its use.

Another locoregional method is transarterial chemoembolisation (TACE), typically used for multiple liver-confined tumours. In patients with advanced cirrhosis, however, the procedure may worsen liver function since the tissue around the tumour is already damaged and may not tolerate reduced blood flow. Transarterial radioembolisation (TARE) is similar as it focuses on localised cancer treatment but is often viewed as less harmful to surrounding liver tissue compared to TACE. Further information on TACE and TARE will be provided in section 2.3.

When HCC has advanced beyond the liver, or other treatments are not feasible, systemic therapies are considered. Systemic therapies work throughout the body and are particularly useful for patients in advanced stages of HCC. Targeted therapies, such as sorafenib and lenvatinib, interfere with specific molecules critical for cancer cell growth and survival. Another systemic option, immunotherapy, involves using drugs that boost the immune system's capacity to identify and target cancer cells. Immunotherapy has shown promise in extending survival for patients with advanced HCC, yet cirrhotic patients may be at higher risk for adverse effects, and their response to treatment can be less predictable [16].

For patients with end-stage HCC, palliative care becomes inevitable. This approach focuses on managing pain, providing nutritional support, and offering psychological and emotional care to patients and their families. At this stage, treatment is centred on improving patient comfort, as the liver's advanced damage limits any possible interventions.

In summary, HCC treatment is heavily influenced by the presence and severity of cirrhosis. Early-stage patients with minimal cirrhosis may have surgical options, while advanced cirrhosis necessitates non-surgical approaches like transplantation or carefully selected locoregional therapies. For those with severe liver damage, systemic therapies and palliative care are often the most appropriate options [15–18].

Chapter 2

Targeted Drug Delivery Treatments

The first chapter, which delved into the clinical context of hepatocellular carcinoma (HCC), provided crucial insights. These insights not only underscore the necessity of precise and patient-specific therapeutic approaches but also lay the foundation for addressing the limitations of current treatment modalities.

Chapter 2 transitions to exploring targeted drug delivery treatments, which aim to overcome these challenges by concentrating therapeutic agents directly on the tumour while minimising systemic toxicity. The chapter begins by discussing the principles of targeted drug delivery and its potential benefits for HCC in section 2.1. Next, it examines passive and active targeting mechanisms, including the enhanced permeability and retention effect, ligand-based targeting, and magnetic targeting in section 2.2. Transarterial therapies are then explored in section 2.3, covering chemoembolisation (TACE) and radioembolisation (TARE) alongside advancements like Holmium-166. This chapter concludes with the section 2.4 by presenting different types of catheters, such as the standard end-hole microcatheter, the side-hole catheter, and the multi-lumen catheter.

2.1 Principles

Targeted drug delivery focuses on specific targeting and local delivery, concentrating treatment on the tumour cells and minimising the drug's spread to other areas of the body. This approach typically involves carriers like nanoparticles or liposomes, which can be engineered to navigate to the liver tumour effectively. Once in the tumour's blood vessels, the drug particles are deposited directly in the tumour tissue [21].

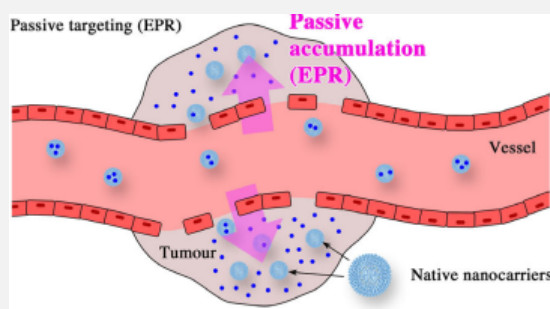
The primary objective of targeted delivery treatment is twofold: to maximise the effective dose at the tumour site while minimising exposure to healthy tissues. By delivering the drug

precisely to the tumour, a higher concentration of medication can act directly on the cancer cells, increasing the likelihood of destroying them without spreading the drug throughout the body. Consequently, only the tumour is exposed to a high drug concentration. At the same time, healthy liver cells and other organs receive minimal exposure, reducing potential side effects and limiting damage to non-cancerous tissues [21].

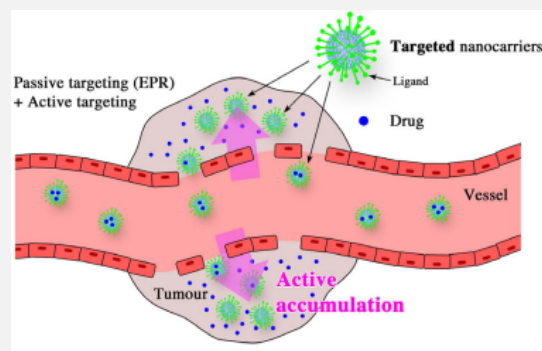
Targeted drug delivery offers advantages over traditional systemic therapies. It is minimally invasive, leading to shorter recovery times and reduced overall healthcare costs. By providing a localised treatment specifically focused on the liver tumour, it also minimises the systemic side effects typically associated with chemotherapy. This makes it more tolerable than both surgery and traditional systemic approaches.

2.2 Mechanisms

Targeted drug delivery leverages passive and active mechanisms to concentrate treatment directly on the tumour. Passive targeting relies on the Enhanced Permeability and Retention (EPR) effect. Tumour blood vessels are unusually “leaky” and poorly drained, allowing drug particles to pass through their walls and accumulate within the tumour tissue. This characteristic enables higher drug concentrations to remain within the tumour for extended periods, increasing drug effectiveness without modifying the particles [21]. This effect can be seen in Figure 2.1a.



(a) Passive targeting with Enhanced Permeability and Retention effect.



(b) Ligand-based active targeting mechanism.

Figure 2.1 Figure illustrating the passive targeting and the ligand-based active targeting into a tumour. Adapted from Mohamed et al. [22].

Active targeting goes further, employing methods like ligand-based and magnetic targeting to direct drugs more precisely. In ligand-based targeting, drug particles are engineered with ligands that bind specifically to overexpressed antigens on cancer cells [23]. This approach works on a “lock-and-key” basis, helping direct the drug particles precisely to the tumour cells. However, ligand-based targeting requires proximity between the drug particles and tumour cells to be

effective, as binding efficiency decreases with distance. Those drug particles are often coated with polyethene glycol (PEG) to minimise immune responses and reduce the likelihood of the body's immune system attacking the particles before they reach the tumour [21]. This principle can be seen in Figure 2.1b.

In magnetic targeting, drug particles contain magnetic materials, allowing them to be directed to the tumour using an external magnetic field [24]. This approach requires specific conditions for optimal effectiveness: low blood flow rates, as the high flow can push particles away from the tumor; high magnetic field strength to keep the particles in place; larger nanoparticles (NPs) that are more responsive to the magnetic field; and tumor sites close to the body's surface, where the magnetic field can effectively penetrate. Together, these requirements allow magnetic targeting to precisely concentrate the drug at the tumour site [21, 24].

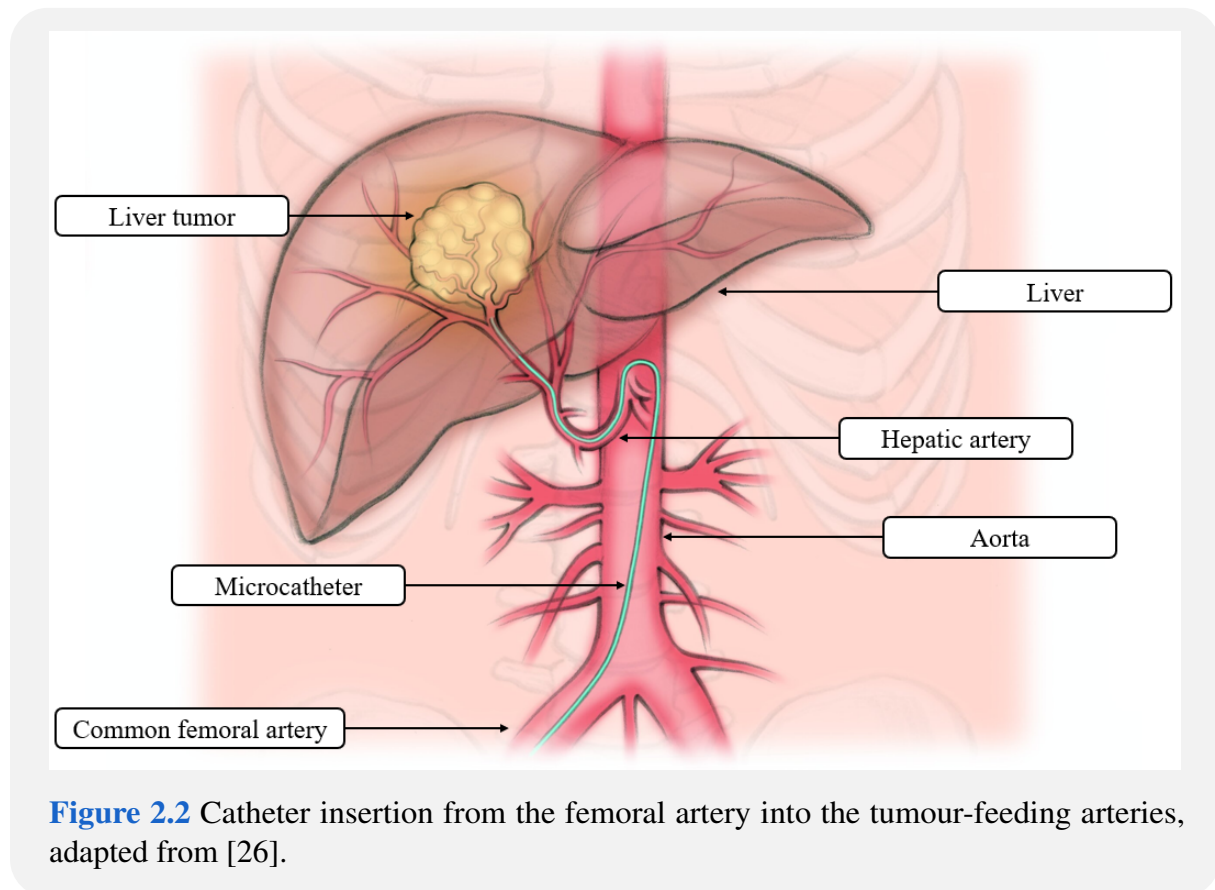
By combining passive targeting with active methods like ligand-based and magnetic targeting, these strategies create a focused and potent drug delivery system that maximises therapeutic impact within the tumour.

2.3 Transarterial Therapies

Transarterial treatments are specialised methods of targeted drug delivery systems that can be used for liver cancer. These treatments work by delivering therapeutic agents directly to the tumour through the hepatic artery, the main blood source for the tumour. This method takes advantage of the liver's unique blood supply system, where the hepatic artery primarily supplies the tumour. In contrast, healthy liver tissue relies mainly on the portal vein for blood, receiving approximately 70% of its blood supply from the portal vein and only 30% from the hepatic artery [5]. By targeting the hepatic artery, transarterial treatments concentrate therapy on the tumour while largely preserving healthy liver tissue [5, 21].

The procedure for transarterial treatments involves the insertion of a catheter through the patient's blood vessels, typically entering from the femoral artery. The catheter is then guided to the hepatic artery, as seen on Figure 2.2. Once positioned, the treatment includes not only delivering therapeutic agents but also embolising (blocking) these feeding arteries. This embolisation reduces blood flow to the tumour, which deprives it of nutrients and oxygen, thereby enhancing the effectiveness of the therapy by limiting the tumour's ability to grow and spread [21, 25].

Transarterial treatments are minimally invasive, often allowing for shorter recovery times and reduced side effects compared to traditional surgeries [5]. The main types are transarterial chemotherapy (TACE) and transarterial radioembolisation (TARE), each employing different methods to deliver treatment directly to the tumour in the liver.



2.3.1 Transarterial Chemoembolisation

Transarterial chemoembolisation (TACE) is a targeted treatment that combines the direct delivery of chemotherapy with the blockage of blood flow to the tumour. The most common types of TACE techniques are conventional TACE (cTACE) and Drug-Eluting Bead TACE (DEB-TACE) [27]. Other methods, such as Degradable Starch Microspheres TACE (DSM-TACE), also exist [28].

In cTACE, a chemotherapy drug (e.g. doxorubicin) is emulsified in Lipiodol® (Guerbet, France), an oily, radiopaque agent. This combination allows Lipiodol to act as both a carrier for the chemotherapy drug and a means to visualise the procedure under imaging. After this initial drug-lipiodol mixture is injected into the hepatic artery, an embolic agent such as polyvinyl alcohol particles is administered. These agents block the blood flow to the tumour, causing embolisation of the microcirculation within the tumour and enhancing the cytotoxic and ischemic effects. This procedure can be seen in Figure 2.3a. The lipiodol itself plays a dual role, delivering chemotherapy while also obstructing the small tumour vessels. Post-procedure imaging, typically a CT scan, often shows how well the lipiodol has been retained in the tumour, with better retention being associated with improved overall survival [27].

DEB-TACE was developed to further streamline and enhance this approach by combining both the chemotherapy and embolic components into a single system, as seen in Figure 2.3b. An example of a used microsphere is CalliSpheres® (Jiangsu Hengrui Medicine Co. Ltd., China).

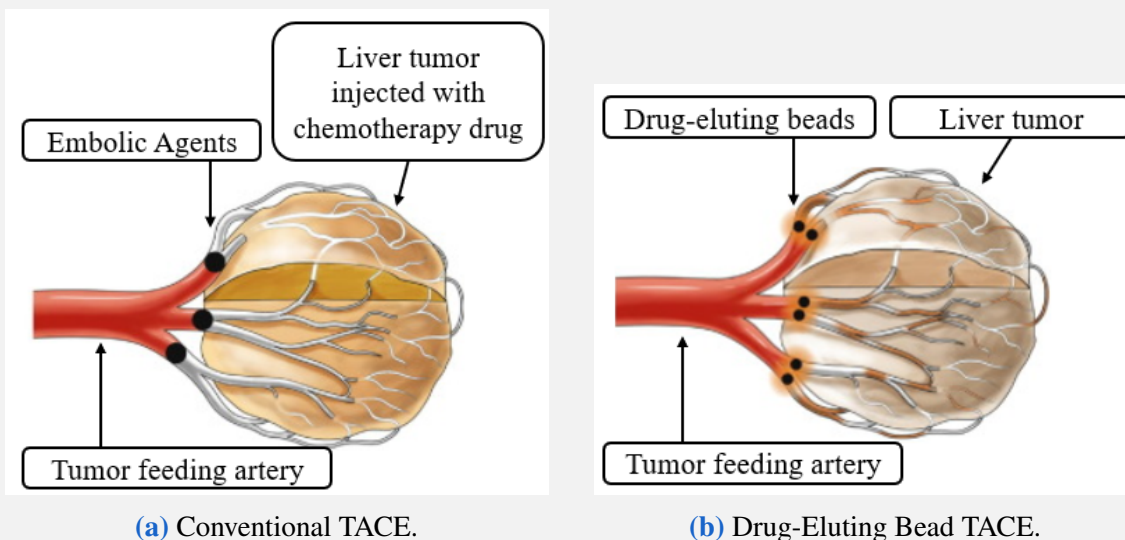


Figure 2.3 Transarterial chemoembolisation techniques, adapted from [29].

Drug-eluting beads (DEBs) are specialised, non-resorbable microspheres designed to deliver chemotherapy drugs with sustained release while simultaneously blocking the tumour's blood supply. DEBs consist of hydrophilic ionic polymers that bind with cytotoxic drugs like doxorubicin through ion exchange. The sustained release of doxorubicin from DEBs provides a gradual delivery of the drug over a prolonged period. In practice, DEB-TACE maintains a localised release within the tumour, with drug penetration detected up to 1.2 mm from the blocked vessel. Raoul et al. [27] concluded that DEB-TACE provides sustained drug delivery for 1 month. This controlled release makes DEB-TACE a viable approach for maintaining an effective drug concentration within the tumour over several weeks, enhancing localised treatment impact and minimising systemic side effects. Despite its innovative design, DEB-TACE has not shown a clear advantage over cTACE in terms of effectiveness or safety, with studies indicating similar outcomes in tumour response and side effects for both methods, according to Raoul et al. [27]. Thus, the choice between cTACE and DEB-TACE is often based on patient-specific factors and physician preference rather than a clear superiority of one technique over the other [27].

2.3.2 Transarterial Radioembolisation

In contrast to TACE, transarterial radioembolisation uses radiation instead of chemotherapy to destroy tumour cells. Radioactive microspheres will deliver a high dose of radiation further downstream within the tumour, while preserving blood flow, as shown in Figure 2.4. The most

commonly used radioactive material in TARE is Yttrium-90 (^{90}Y), a beta-emitting isotope. The half-life of ^{90}Y is 64.1 hours, which allows for sustained therapeutic radiation within the tumour over a few days. Its penetration is highly localised, with a maximum range in the tissue of 11 mm and an average range of 2.5 mm, concentrating radiation within the tumour and sparing nearby healthy cells [30].

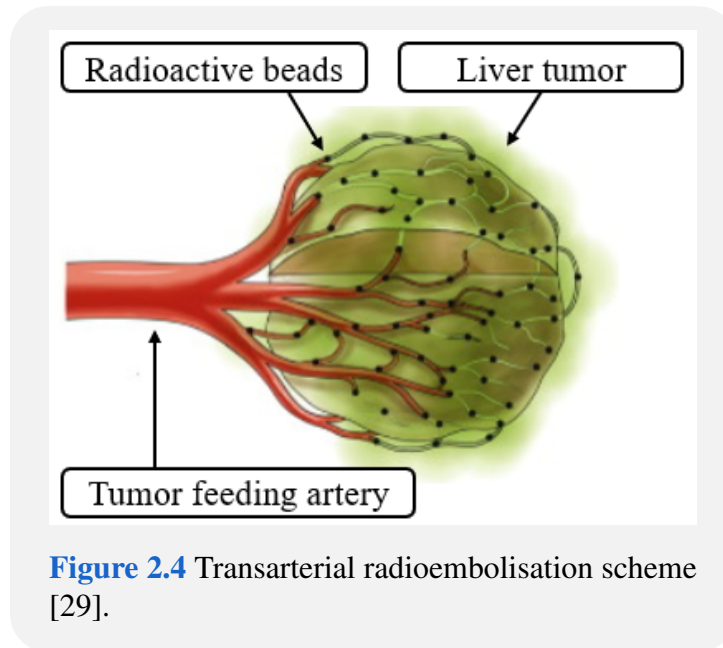


Figure 2.4 Transarterial radioembolisation scheme [29].

Recently, another radioactive agent, Holmium-166, has become available in Europe. Holmium-166 emits beta particles with slightly lower maximum energy (1.85 MeV), which means it has a slightly shorter tissue penetration [31]. However, it has unique imaging benefits, as it also emits gamma radiation at 81 keV. This benefit is ideal for SPECT/CT imaging and can be detected by magnetic resonance imaging (MRI). This dual imaging capability enables precise visualisation of Holmium-166 distribution within the liver during and after treatment, providing enhanced monitoring and planning capabilities [30, 31].

The TARE procedure begins with detailed imaging and mapping. Initial imaging, typically using contrast-enhanced CT or MRI, helps visualise the tumour's size, location, and any unique anatomical features or variant blood vessel structures that might influence treatment. This step is essential to identify any unusual arterial pathways or additional vessels supplying the tumour. Advanced techniques like two-dimensional angiography are employed to refine this mapping further. These methods allow the study of the tumour's blood supply, confirm blood flow in target areas, and, if necessary, block blood vessels outside the liver to prevent radiation from reaching unintended areas [30].

An important part of this mapping procedure is the Lung Shunt Fraction (LSF) assessment, which calculates the potential radiation dose that might inadvertently reach the lungs. After mapping, the radiologist injects a traceable compound ($^{99\text{m}}\text{Tc}$ macroaggregated albumin) and

imagines its distribution with a gamma camera. By measuring the distribution of the ^{99m}Tc macroaggregated albumin between the liver and lungs, the LSF is calculated as the ratio of radioactivity in the lungs compared to the combined liver and lung areas. This calculation, following guidelines on MIRD (Medical Internal Radiation Dose) dosimetry, helps ensure the planned dose remains safe for lung tissue. High lung shunting is a contraindication for TARE, as it increases the risk of radiation-induced pneumonitis. Standard guidelines recommend limiting lung doses to 30 Gy for a single treatment and 50 Gy cumulatively when using glass microspheres, with slightly lower limits for resin microspheres [30].

Following this, the Organ-Level MIRD dosimetry approach is used to customise the radiation dose specific to the tumour and the surrounding liver tissue [32]. The MIRD model is a foundational approach that calculates absorbed radiation dose based on the assumption that radioactive microspheres are evenly distributed throughout a target area, such as a tumour, lung, or entire liver. The absorbed dose for a volume of interest can be calculated with equation 2.1.

Equation 2.1 : The absorbed dose of a volume of interest (VOI)

$$\text{Absorbed Dose}_{\text{VOI}} (\text{Gy}) = \frac{50 \left(\frac{\text{J}}{\text{GBq}} \right) \times \text{Activity}_{\text{VOI}} (\text{GBq})}{\text{Mass}_{\text{VOI}} (\text{kg})} \quad (2.1)$$

This formula relies on a constant unique to ^{90}Y , the activity of the microspheres within the volume, and the mass of that volume.

Equation 2.1 assumes permanent trapping of the microspheres, with their radiation dose focused solely on the target region. While this model offers a straightforward approach to calculating doses, it does not account for the actual nonuniform distribution of microspheres within the liver's microvasculature, where the spheres often cluster. The MIRD model, therefore, provides an average dose across the volume, suitable for calculating an overall radiation safety profile for organs [30, 32].

The TARE treatment itself involves the selective delivery of microspheres loaded with ^{90}Y into the hepatic artery. These radioactive beads are tiny, allowing them to lodge within the tumour's small blood vessels. As they emit radiation, they damage the DNA within the tumour cells, impairing their ability to survive and multiply. The radiation is localised to the tumour and has a limited range of penetration, which helps spare nearby healthy liver cells [30, 33].

Two commonly used types of microspheres in TARE are SIR-Spheres® (Sirtex Medical, Australia) and TheraSphere® (MDS Nordion, Canada). Each type of microsphere has distinct characteristics suited for different clinical scenarios. SIR-Spheres® are resin-based microspheres that are relatively larger and designed for treating liver tumours with broader margins. TheraSphere® microspheres, on the other hand, are made of glass and are generally smaller. They

deliver a more intense radiation dose over a concentrated area, which can be beneficial for targeting smaller or more densely vascularised tumours [30, 33].

After the microspheres are delivered, post-treatment imaging plays an essential role in assessing the effectiveness and distribution of the treatment. ^{90}Y PET/CT or SPECT/CT scans are often used to confirm where the radioactive beads are located within the liver. This imaging ensures that the microspheres have reached the tumour and that radiation is concentrated where needed [30].

2.3.3 Importance of Patient-specificity

In transarterial treatments, patient-specific geometry is crucial for achieving optimal results. Each patient has a unique liver structure and blood vessel layout, as discussed in section 1.1, which affects how blood and therapeutic agents flow to the tumour. By including patient-specific geometries, the treatment can be tailored to the individual's unique anatomy, improving accuracy in targeting the tumour and minimising exposure to healthy tissues. Without accounting for these unique characteristics, there is a risk that the treatment may be less effective, as a standardised approach might not match the precise vascular pathways that lead to the tumour. Incorporating these personalised geometries allows for the optimisation of the delivery of therapeutic agents, enhances drug retention in the tumour, and reduces side effects, leading to a more effective and safe treatment approach [21, 25].

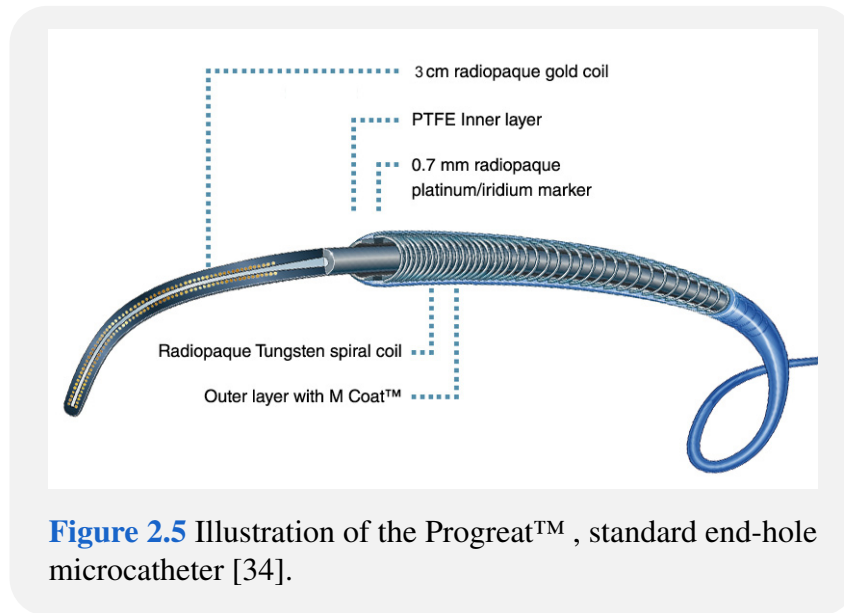
2.4 Catheters for Transarterial Treatments

Different catheters are available for transarterial therapies, including the standard end-hole microcatheter, the side-hole catheter, and the multi-lumen catheter. This section will discuss these three types of catheters.

2.4.1 Standard End-hole Microcatheter

The standard end-hole microcatheter (SMC) is a catheter that consists of a single lumen that delivers embolic agents or therapeutic particles exclusively through its distal end. An example of this catheter is the ProgreatTM microcatheter (Terumo Interventional Systems, Japan), illustrated in Figure 2.5. Other examples of SMCs include the DrakonTM microcatheter (Guerbet, France) and the DirexionTM microcatheter (Boston Scientific, United States).

One of the main advantages of the SMC is its capability for precise targeting of embolic particles. The unidirectional flow enables the delivery to specific arterial branches, ensuring

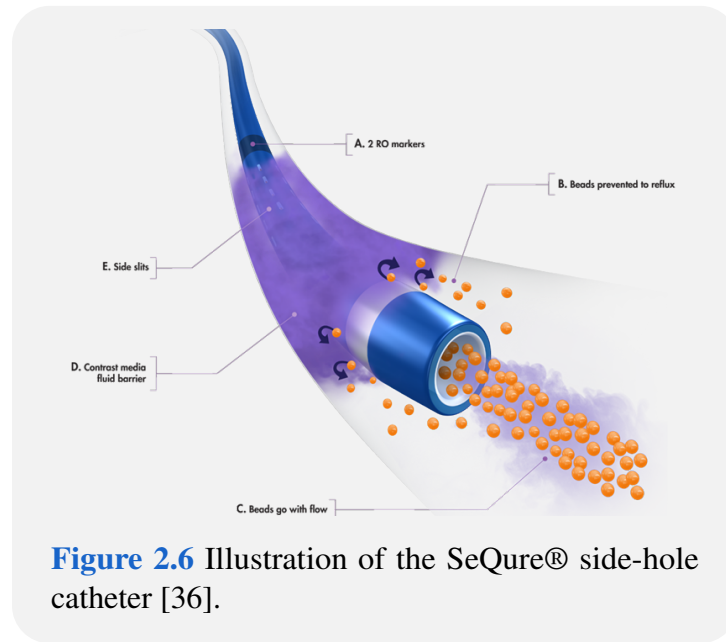


a high degree of control over the distribution of therapeutic agents. This characteristic is particularly beneficial when targeting smaller or distal arteries that supply tumour tissues, as it reduces the risk of non-target embolisation and maximises tumour dose while minimising adverse effects on healthy liver tissue [35].

Despite its benefits, the SMC has notable limitations that affect its performance in clinical practice. An important drawback is its sensitivity to various parameters influencing particle distribution, as will be discussed in 3.2 [25, 35]. These factors introduce variability in treatment outcomes, making it challenging to achieve consistent and predictable results [35]. Moreover, this catheter introduced an increased likelihood of particle reflux into non-target regions, which may cause unintended damage to healthy tissues [25].

2.4.2 Side-hole Catheter

The SeQuire® (Guerbet, France) is a representative example of a modern side-hole catheter (SHC). It features a frontal tip combined with multiple side holes along its distal segment, which facilitate the outflow of contrast media. This is visualised in Figure 2.6. This design aims to minimise the reflux of microspheres, enhancing safety by reducing the risk of non-target embolisation [36].



2.4.3 Multi-lumen Catheter

Another possible catheter design is the multi-lumen catheter. This catheter incorporates multiple lumens, enabling the simultaneous or sequential injection of therapeutic agents, which could improve control over particle dispersion. This design facilitates targeted drug delivery by allowing operators to modulate flow characteristics more precisely than standard end-hole or side-hole catheters.

Filed patents [37, 38] detail various multi-lumen catheter configurations tailored for embolisation and other interventional therapies. For instance, designs include adjustable flow paths and lumens dedicated to delivering agents at varying pressures or velocities, enhancing the precision of therapeutic particle deposition. Additionally, multi-lumen catheters can be utilised to administer multiple agents simultaneously, providing a more integrated therapeutic approach in transarterial procedures.

Chapter 3

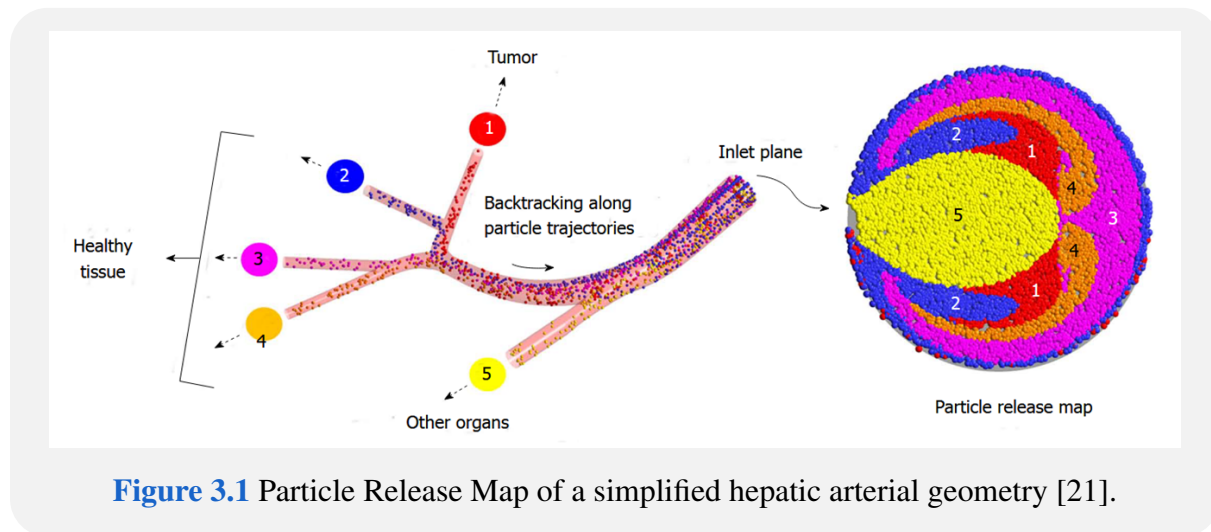
Computational Fluid Dynamics

Computational Fluid Dynamics (CFD) is a computational methodology that has greatly advanced the study of fluid mechanics. CFD can provide insights into fluid flows within complex systems by solving the governing equations of fluid dynamics through numerical methods. One of the key advantages of this approach is its ability to investigate phenomena that are often challenging to observe or measure through experimental means. Its precision and adaptability have established it as a great tool across a wide range of disciplines, including aerodynamics, energy systems, and, increasingly, the biomedical field [39].

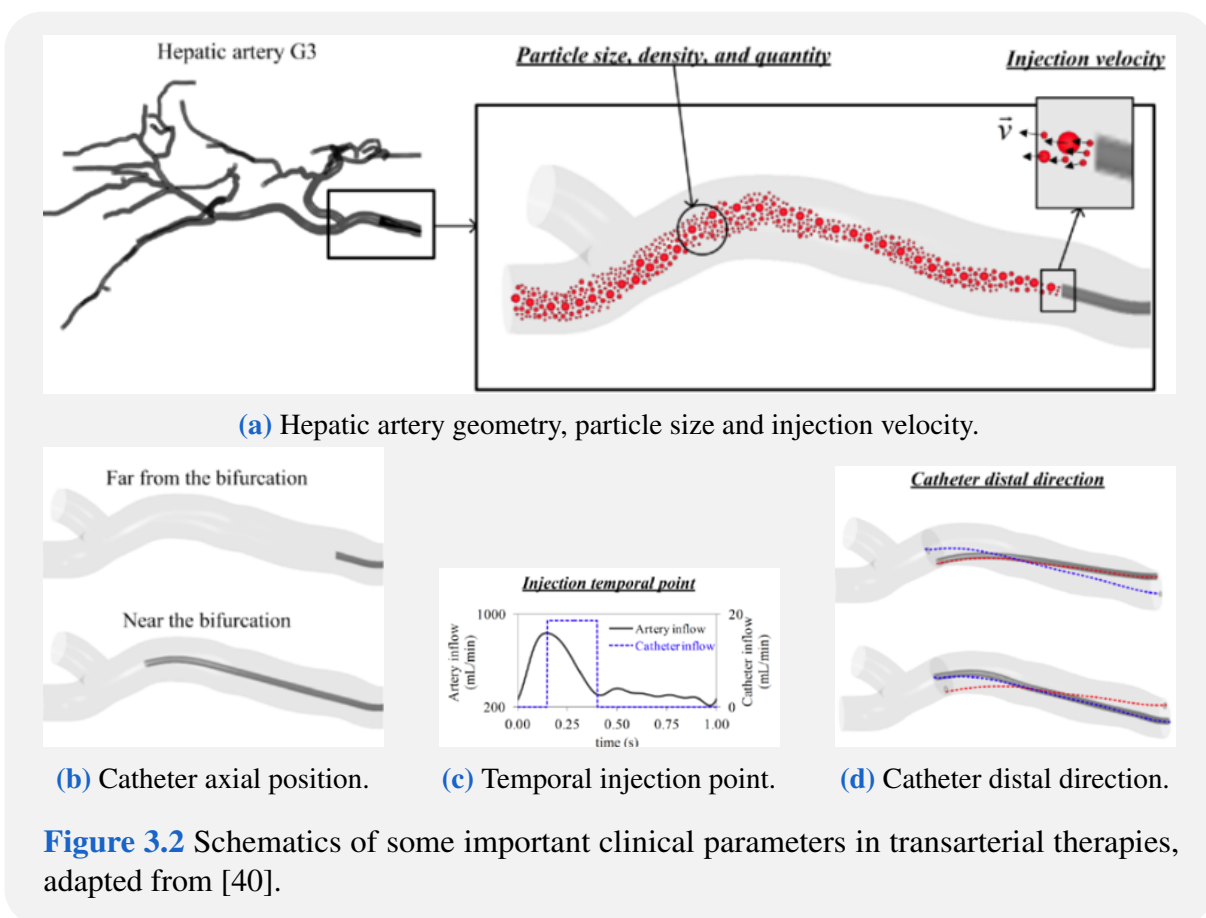
This chapter explores the applications of CFD in targeted drug delivery treatments such as TARE and TACE (section 3.1). Key parameters (section 3.2) influencing particle distribution, including particle properties, catheter position, and injection velocity, are analysed with CFD to highlight their impact on treatment outcomes. This chapter concludes with strategies to mitigate the sensitivity of those key parameters (section 3.3).

3.1 Role in Targeted Drug Delivery Treatments

In targeted drug delivery treatments, the placement of a catheter within the hepatic arterial system is important for the effective delivery of therapeutic agents. The injected particles rely on blood flow to transport them from the injection site to the tumour region. CFD enables the mapping of blood flow paths from the injection site to the tumour outlet by simulating the hemodynamic environment within the hepatic arteries. By tracking these trajectories backwards to the injection site, CFD generates a Particle Release Map (PRM), as seen in Figure 3.1. The PRM determines the ideal injection location within the injection plane to maximise particle delivery to the tumour [40].



The PRM depends on several parameters. These parameters influence the particle trajectories and their likelihood of reaching the tumour region. Those parameters are visually represented in Figure 3.2.



Parameters with high importance include the axial catheter position and arterial geometry, as they have the most substantial impact on optimising particle delivery. Parameters with moderate

importance, such as injection velocity and injection temporal point, also contribute meaningfully to the PRM but to a lesser extent. Finally, parameters with lower importance, including particle size and catheter distal direction, play a minor role in shaping the PRM and its effectiveness in targeting the tumour region [40].

Fine-tuning these parameters maximises the area in the PRM that aligns with pathways leading to the tumour outlet, achieving an optimal PRM. This optimal PMR is a tool to maximise the amount of therapeutic particles that are delivered to the target site, by determining the best catheter tip location. However, achieving that catheter tip position in clinical practice is almost impossible.

The parameter selection process is a critical step in the broader CFD workflow for targeted drug delivery. The CFD workflow for targeted drug delivery begins with reconstructing patient-specific arterial geometries using imaging data like CT or MRI. These geometries are converted into computational meshes. Afterwards, boundary conditions, such as blood flow rates and injection properties, are defined. Simulations are then performed to model blood flow and particle transport, generating a PRM. The optimised results are validated and integrated into clinical treatment plans, ensuring precise and effective drug delivery [25].

3.2 Clinical Parameters

The effectiveness of transarterial treatments relies heavily on the careful selection and optimisation of the earlier-mentioned parameters. These parameters, such as particle properties, catheter position, and injection velocity, directly influence flow dynamics and particle distribution. These parameters can be seen in Figure 3.3.

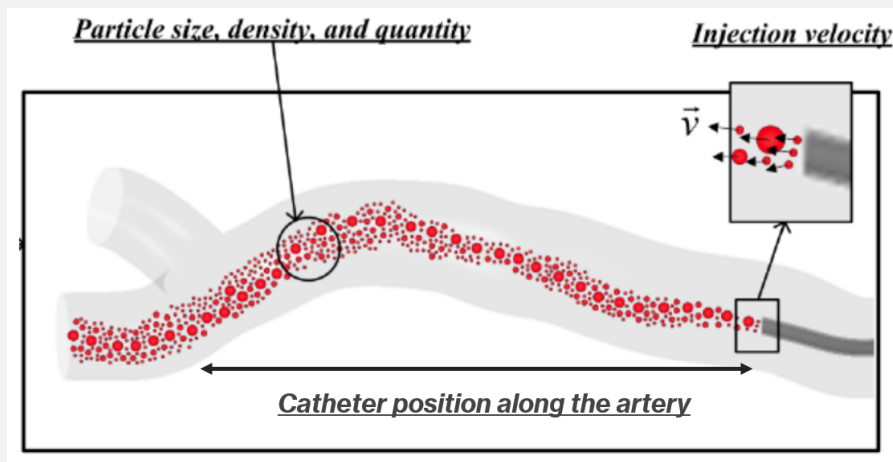


Figure 3.3 Schematic of important clinical parameters, like particle properties, position along the artery and injection velocity, in transarterial therapies, adapted from [21].

3.2.1 Particle Properties

Particle size, density, and quantity exhibit limited influence on the downstream distribution of particles in CFD simulations for transarterial therapies, as demonstrated by Aramburu et al. (2018) [40]. Although particle density generally has a minimal effect on overall distribution patterns, particles remain vulnerable to the "skimming effect," wherein smaller particles are preferentially diverted into side branches, potentially altering their localised distribution. Gravitational forces, particularly for denser particles such as SIR-spheres, can exacerbate these effects by causing particles to become stuck within complex arterial geometries, thereby compromising targeted delivery [41]. While particle quantity has a negligible direct impact on outlet distribution, excessive amounts may induce clustering and increased flow resistance. The particle size, density, and quantity are visually represented in Figure 3.3.

3.2.2 Axial Catheter Position

According to Aramburu et al. (2018) [40], the position of the catheter within the artery is a critical parameter influencing the effectiveness of transarterial therapies. When the catheter is placed near arterial bifurcations, small positional deviations can result in substantial variations in particle distribution due to localised alterations in flow dynamics. This parameter is illustrated in Figure 3.3.

Matching catheter placement between the pretreatment phase and the actual treatment is essential for maintaining consistency and maximising therapeutic outcomes [40]. Variations in positioning between these stages can lead to discrepancies in particle delivery patterns, reducing the accuracy of pretreatment simulations in predicting actual outcomes. Ensuring alignment between these phases simplifies the planning process and improves reliability.

On the other hand, controllability is a key advantage of axial catheter positioning as a parameter [25]. Catheter placement can be adjusted with precision during the procedure, offering clinicians a practical means of optimising particle delivery to tumour-feeding vessels.

3.2.3 Injection Velocity

Injection velocity is an important parameter, directly influencing particle trajectories and their eventual distribution within the arterial network. Figure 3.3 shows this parameter visually. In controlled experiments with simplified geometries [42], five different volumetric flow rates demonstrated the impact of injection velocity. At the lowest velocities, particles tended to follow the natural flow patterns of the bloodstream. Conversely, at the highest velocities, a greater proportion of particles exited through side branches, such as the gastroduodenal artery (GDA).

The ratio between the average bloodstream velocity and the velocity of injected particles is a decisive factor. When the injection speed matches the velocity of the surrounding blood flow, as suggested by Kleinstreuer [21], the particles integrate seamlessly into the bloodstream, minimising disruption and ensuring precise targeting. However, deviations from this equilibrium can result in remarkably different outcomes. For example, at higher injection velocities (where the ratio exceeds 2 [25]), particles cross fluid flow streamlines, leading to less predictable distributions.

When injecting the particles, the S-curve (injection velocity as a function of time) approach has been identified as one of the safest strategies for managing injection velocity. This method ensures the smooth integration of particles into the flow, reducing the likelihood of abrupt transitions or disruptions. However, in clinical practice, injections are typically performed at a constant velocity [40].

3.3 Mitigating Parameter Sensitivity

To address the sensitivity of the particle distribution related to the catheter parameters, the study by Ortega et al. [43] proposed a modified design of the side-hole catheter. This catheter emphasises particle dispersion rather than merely focusing on the delivery of contrast agents near the injection point, as seen with the SeQure catheter discussed in 2.4.2. The revised version aims to achieve an outlet-to-outlet particle distribution that replicates the natural flow of blood within the vasculature. This feature is particularly beneficial due to the preferential increase in arterial blood flow to tumours compared to normal tissue. Additionally, it seeks to reduce the impact of clinical parameters on the resultant particle distribution.

This catheter design's optimal efficacy is attained when it includes side holes along the wall with a closed frontal tip. The closed frontal tip leads to a lumen-filling phenomenon. Performance greatly improves with increased injection flow [43]. Higher injection flow enhances crossflow, enabling more particle dispersion and a better alignment of particle distribution with targeted blood flow. This configuration is especially beneficial because it mitigates the influence of other uncontrolled variables, such as the catheter's radial positioning.

The study further investigated multiple parameters affecting catheter performance, as illustrated in Figure 3.4. The findings of Ortega et al. suggest that a smaller area ratio between the outlet and inlet enhances the velocity ratio of the catheter outlet relative to the blood flow. This, in turn, enhances the Matching Deviation Index (MDI) and the catheter's overall effectiveness. The Matching Deviation Index measures the degree to which the particle distribution aligns with the blood flow distribution, with lower values indicating a better match. This is illustrated in Equation 3.1.

Equation 3.1: Matching Deviation Index [43]

$$\text{MDI} [\%] = \frac{1}{N} \sum_{s=1}^N \left| \frac{N_{p,s}}{\sum_{s=1}^N N_{p,s}} - \frac{q_s}{\sum_{s=1}^N q_s} \right| \cdot 100 \quad (3.1)$$

Where s [-] represents the number of outlets, ranging from 1 to N . The variable $N_{p,s}$ [-] denotes the number of targeted particles in outlet s , and q_s [ml/min] represents the blood flow rate in outlet s .

It was also observed that the area ratio has a threshold; below this threshold, its influence on MDI diminishes, indicating a negligible effect on performance at extremely low values.

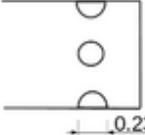
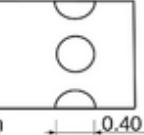
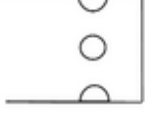
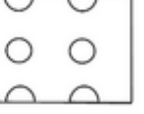
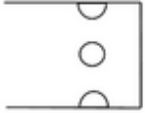
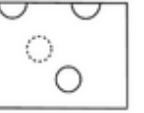
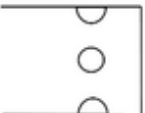
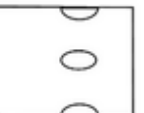
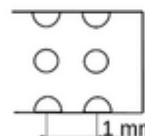
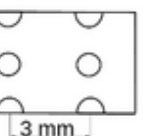
Fractional Design				
Main Factors	Low	High		
Side-hole diameter (mm)	0.23	0.40		
Number of rows	1	2		
Angle between holes	0°	120°		
Side-hole shape	Circular	Elliptical		
Distance between rows (mm)	1	3		
Front opening	Closed	Open		

Figure 3.4 Different parameters for side-hole catheters [43].

De Smet [44] conducted a comparative analysis between the side-hole catheter and the standard end-hole microcatheter using a patient-specific case. The study investigated the effects of different radial injection locations and varying injection velocities on particle distribution. The SHC demonstrated a slightly superior Matching Deviation Index (MDI) compared to the

SMC, with performance improving further under conditions of higher injection velocities. The observed differences in particle dispersion effectiveness between the SHC and SMC were, however, relatively minor, with differences below three percentage points for matching across the entire vascular geometry.

Zeebroek [35] investigate the SHC as well. A comparison between two different side-hole catheters was made, each featuring distinct side-hole diameters (0.2 mm and 0.4 mm) and a standard end-hole microcatheter. Three different particle injection velocities were analysed: 0.12 m/s, 0.30 m/s, and 0.50 m/s. The results indicated that smaller side-hole diameters led to a higher crossflow effect, which correlated with a lower Matching Deviation Index (MDI). Moreover, an intermediate injection velocity (0.3 m/s) provided a more optimal match between blood flow and particle distribution compared to the lower and higher velocities.

Despite these benefits, the SHC also introduces certain challenges. One limitation is its reduced ability to achieve the same level of precision targeting as the SMC, as the presence of side holes leads to a more diffuse dispersion pattern. This could be suboptimal in scenarios requiring highly localised embolisation, such as treating small, isolated arterial branches.

Chapter 4

Research Aim and Scope

This thesis aims to enhance the precision and efficacy of targeted drug delivery in transarterial liver cancer treatments by examining the impact of SHC design parameters on particle distribution using computational fluid dynamics (CFD) in a patient-specific arterial model.

This thesis is structured around three primary objectives:

- 1. Developing a new workflow for catheter modelling and insertion**

The primary objective is to develop a new catheter modelling and insertion workflow in Ansys Discovery (Ansys Inc., Canonsburg (PA), USA). Its impact on simulation results will be assessed by replicating key simulations from Zeebroek [35] using three catheter types (SMC, SHC with a side-hole diameter of 0.2 mm, and SHC with a side-hole diameter of 0.4 mm) at an injection velocity of 0.12 m/s. Alongside the development of the new workflow, this goal encompasses a comparative analysis of catheter performance within the new framework based on particle distribution metrics, such as the matching deviation index. This analysis offers insight into how catheter design influences the alignment between blood flow and particle transport.

- 2. Assessment of radial orientation effects on particle distribution**

This objective investigates how varying the radial orientation of the SHC's side holes influences particle dispersion. Additionally, the study quantifies the magnitude of this effect using metrics such as the MDI and spatial spread indices. The aim is to identify configurations that enhance tumour targeting and limit variability in outcomes based on radial orientation.

- 3. Extending side-hole catheter research in transient flow regimes**

Building on the first objective and Zeebroek's steady-state findings, this thesis aims to validate these findings under transient flow conditions. Transient modelling captures the temporal variations of blood flow, providing a more realistic and dynamic estimate of

catheter behaviour. This objective ensures that the proposed designs perform consistently under physiological conditions. The aim is to determine whether the conclusions drawn from steady-state simulations hold true under transient conditions.

By addressing these objectives, this thesis aims to advance the understanding of side-hole catheter design parameters and their influence on targeted drug delivery.

Part II

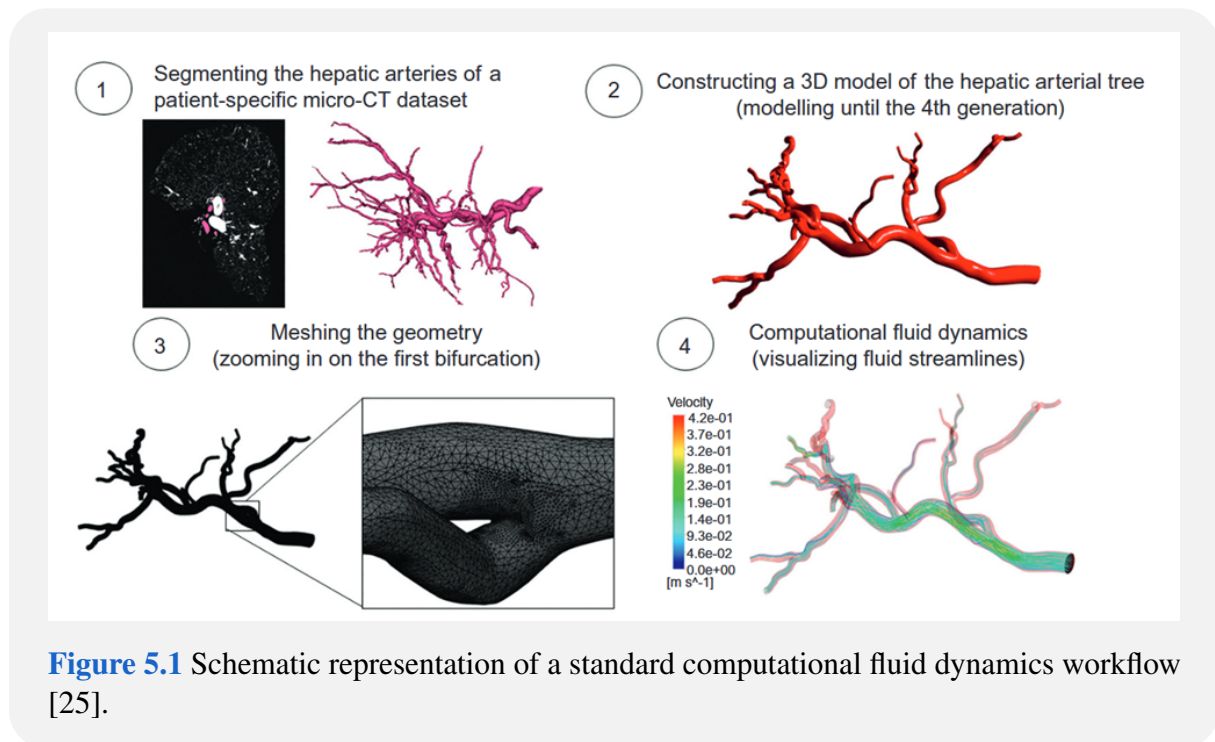
Materials and Methods

Chapter 5

Geometry and Mesh Generation

The methodological approach follows a standard CFD workflow, initiating with CT images. These images are segmented by slices to construct a three-dimensional model of the hepatic arteries. Subsequently, surface and volume meshes are created by dividing the 3D model into finite elements. The final stage involves setting up and executing a computer simulation, which will be discussed in Chapter 6. The post-processing is discussed in Chapter 7.

The whole workflow is visualised in Figure 5.1.

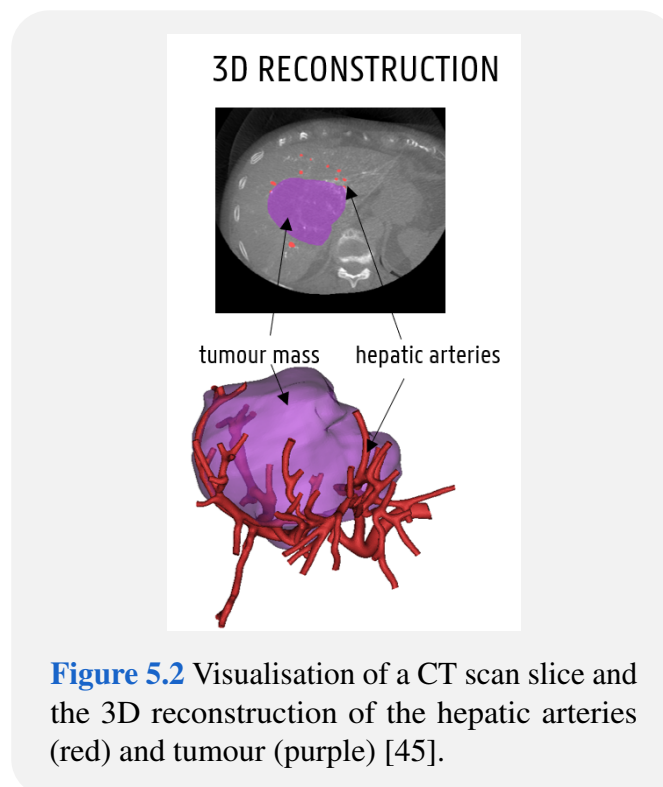


5.1 Medical Images

The geometry of the hepatic arteries in a patient diagnosed with HCC is derived from micro-computed tomography (micro-CT) images with a pixel size of 0.655 mm and a slice thickness and increment of 0.655 mm. These images were produced with a cone-beam CT scanner (Philips Medical Systems, Netherlands). During image acquisition, a contrast agent was injected intra-arterially into the right and left branches of the proper hepatic artery [45]. This patient-specific data serves as the input for subsequent segmentation and modelling processes.

5.2 3D Reconstruction of the Liver Arterial Anatomy

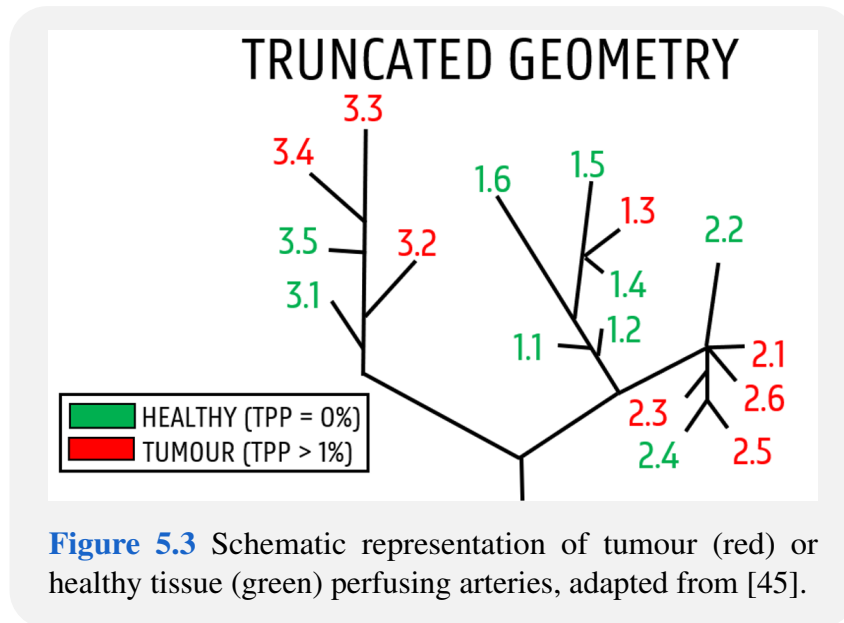
CT images were utilised to create three-dimensional models using the Mimics 26.0 software (Materialise NV, Leuven, Belgium). This process was previously conducted by Bomberna et al. (2022) [45], described in the next two paragraphs, and the results serve as a starting point for this study. Figure 5.2 displays a CT scan slice alongside the corresponding three-dimensional reconstruction of the arterial network and tumour mass.



The study began by segmenting the hepatic arteries based on the contrast difference between arterial and venous trees. This resulted in a 3D representation of the liver's arteries with one inlet at the proper hepatic artery and 48 outlets. To simplify the arterial model, the study introduced a

novel truncation algorithm [45]. To truncate the model, the tumour perfusion percentage (TPP) for each outlet was calculated. The TPP represent the volume fraction of the tumour that each outlet perfuses. In the first step, distal bifurcations containing outlets with $0\% < TPPs \leq 1\%$ were pruned. In the second step, outlets that perfused the same tissue type were pruned as well. These pruning operations reduced the number of outlets from 48 to 17. Some outlets were located close to the preceding bifurcation (< 5 mm distance along the centerline) and were extruded to a total length of 20 mm to ensure that fluid flow reaching the outlets developed properly after the bifurcation. The inlet was also extruded by 80 mm. This modification enabled a uniform velocity to be applied at the extruded inlet, allowing a physiological parabolic-like velocity profile to develop before the original inlet of the model. After those operations, the outlets that experienced recirculation during the simulations were extruded an additional 20 mm.

In the final model, 8 out of 17 branches are identified as "tumour feeding branches," which account for 98% of the tumour's blood supply. The other 2% came from non-segmented or pruned hepatic arteries. Figure 5.3 illustrates which arteries supply the tumour and which supply healthy tissue. In the three 2D visualisations shown in Figure 5.4, the tumour feeding arteries are seen pointing toward or into the tumour mass. In both figures, the outlets are divided into three branches, denoted by the first number in the outlet numbering.



Finally, a centerline was added to assist with measurement and catheter placement. The segmented model was exported to 3-matic 26.0 software (Materialise NV, Leuven, Belgium), where geometry issues such as intersecting and overlapping triangles were addressed. The surface mesh was also optimised using adaptive remesh to ensure a skewness threshold of 0.4.

A detailed workflow of the steps performed in this study can be found in Appendix D.1.

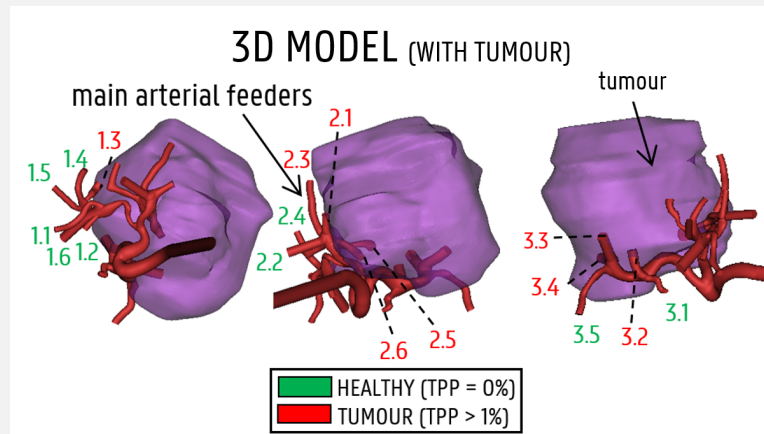


Figure 5.4 Visualisation of the 3D reconstruction of the hepatic arteries (red) and tumour (purple) alongside with tumor (red numbers) or healthy tissue (green numbers) perfusing arteries, adapted from [45].

5.3 Catheter Modeling

The catheter was designed and inserted using Ansys Discovery (Ansys Inc., Canonsburg (PA), USA). The 3D model of the hepatic arteries was transformed into a solid body to facilitate manipulation and compatibility with the catheter. Three distinct catheter types were developed, all based on the design of Zeebroek (2024) [35]. Each catheter measures 85 mm in length, slightly exceeding the length of the hepatic arteries' extruded inlet, which allows for particle injection within the original arterial structure, as shown in Figure 5.5.

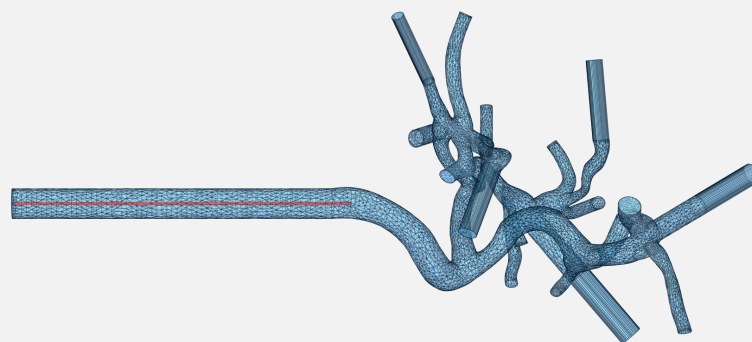


Figure 5.5 Visualisation of the hepatic arteries (blue) model with a catheter (red) inserted.

The standard end-hole microcatheter (SMC) has an inner diameter of 0.7 mm and an outer diameter of 0.9 mm, featuring a frontal opening. The side-hole catheters (SHCs) maintain the

same dimensions as the SMC but are modified to include side holes. The frontal outlet is sealed with a wall thickness of 0.3 mm, and four evenly distributed side holes are positioned around the catheter radius, oriented perpendicular to the flow. This study investigates two SHCs: one with 0.2 mm diameter side holes (SHC 0.2, Figure 5.6a) and another with 0.4 mm side holes (SHC 0.4, Figure 5.6b). The two side-hole catheter types are depicted in Figure 5.6.

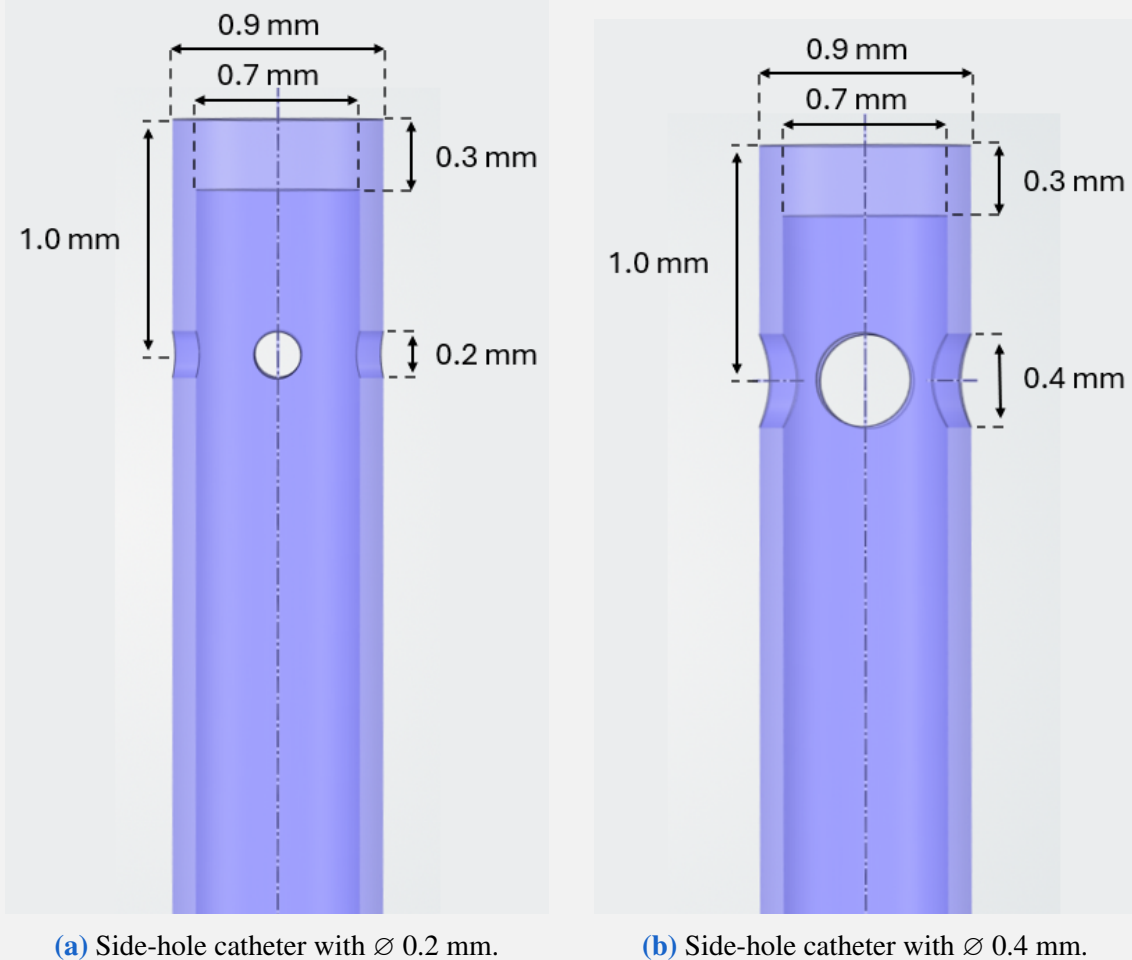


Figure 5.6 Two side-hole catheters with different side-hole diameters.

For the second objective, the three catheter designs (SMC, SHC 0.2, and SHC 0.4) were rotated around the catheter axis. The first orientation (o1) is identical to the one already constructed. The second and third orientations (o2 and o3) are achieved by turning the catheter 30° and 60°, respectively, in an anticlockwise direction as viewed from the tip of the catheter. These orientations are illustrated for the SHC 0.2 in Figure 5.7 with each colour representing a different orientation. The catheters are overlaid, with only one colour of side-holes present per orientation.

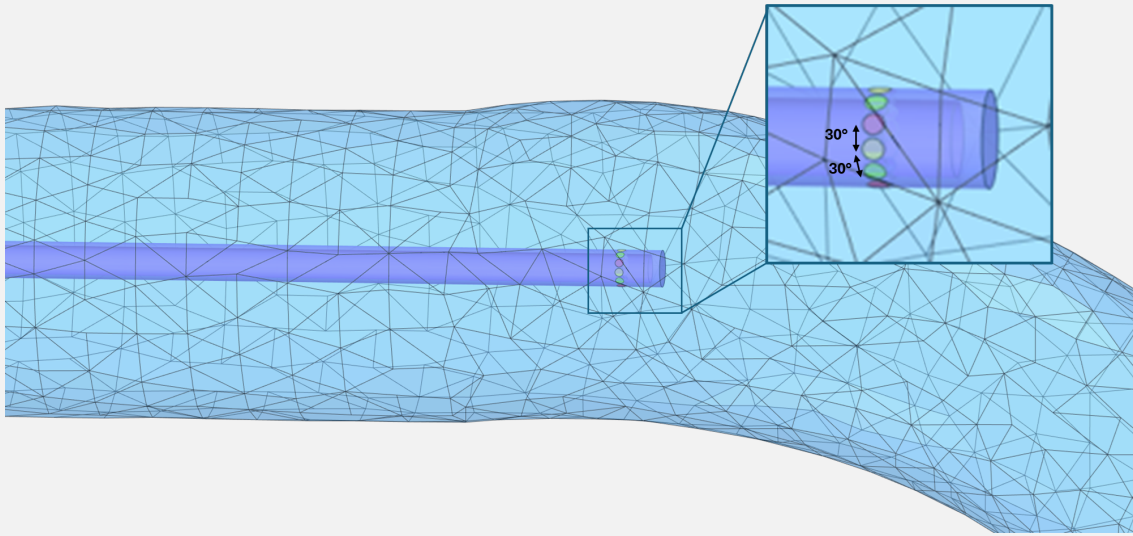


Figure 5.7 Visualisation of the different catheter orientations for SHC 0.2 inside the hepatic arteries. All catheter orientations are shown over each other. Only one colour of side-holes is present per orientation. The red side-holes correspond with orientation 1, yellow with orientation 2 and green with orientation 3.

5.4 Discretization of the 3D Model

Four geometries, the geometry without catheter (GEO), SMC, SHC 0.2, and SHC 0.4, were exported to Fluent Meshing 2024 R2 (Ansys Inc., Canonsburg, PA, USA). This tool facilitated the generation of surface and volume meshes. The Fluent 'Watertight Workflow' was utilised to create a surface mesh using default values of 0.17 mm as the minimum, 4.47 mm as the maximum surface cell length, and a growth rate of 1.2. 17 volume meshes with varying cell counts (2 025 982 - 15 683 983) and three boundary layers with a growth rate of 1.2 were produced. The number of cells for all geometries is provided in Table 5.1. These meshes all meet the requirements for minimum orthogonal quality values of 0.05 and a maximum (Fluent) skewness of 0.9. The orthogonal quality measures the angle between the cell faces and edges; the higher the orthogonal quality, the better the alignment. Skewness assesses the deviation of a cell from a perfect shape; lower skewness indicates a more regular and higher-quality mesh.

Two local target meshes are introduced for geometries involving a catheter. A local face size at the catheter inlet of $3 \cdot 10^{-2}$ mm, based on the value used in the study by Bomberna et al. (2022) [45], which utilised a comparable mesh. This value is used to ensure accurate particle injection. A local body size is required for the catheter as well.

A mesh sensitivity analysis (MSA) was performed to determine the optimal mesh for the geometries with a catheter. First, an MSA of GEO was carried out to identify the ideal 'max cell length' of the volume mesh. Subsequently, the local body size of the catheter was assessed

using the same 'max cell length' as in the geometry GEO. These analyses focused on critical parameters such as particle distribution across the outlets, static pressure on the wall, wall shear stress on the wall and the velocity profile downstream of the injection. These metrics are essential for ensuring stable particle distribution. The selection criterion for the optimal mesh was based on maintaining parameter stability within a 1% convergence tolerance.

5.4.1 Mesh Sensitivity Analysis Planning

For each of the volume meshes mentioned in Table 5.1, a steady-state simulation has been carried out to assess the most optimal volume mesh, balancing accuracy and computational time. The MSA concluded that simulation 6 for SMC, simulation 10 for SHC 0.2, and simulation 14 for SHC 0.4 provide the best mesh in terms of parameter stability and computational resources. This conclusion is supported by Figure 5.8, which shows that 8 million volume elements in the arterial lumen were chosen due to their convergence stability within 1%. Figure 5.9 indicates that 500 000 volume elements for the catheter are sufficient to ensure stability for various metrics.

Table 5.1 Overview simulations (Sim 1-17) for the mesh sensitivity analysis, along with the corresponding catheter type, arteries, and catheter cell counts. The final mesh for that catheter type is indicated in bold.

Simulation	Catheter Type	Arteries	Catheter	Total
1	No catheter	2025982	x	2025982
2	No catheter	3979898	x	3979898
3	No catheter	6165007	x	6165007
4	No catheter	8144288	x	8144288
5	No catheter	9840605	x	9840605
6	SMC	9281780	498012	9779792
7	SMC	10334337	987200	11321537
8	SMC	11332376	1515062	12847438
9	SMC	12283504	1928941	14212445
10	SHC 0.2	9290444	504360	9794804
11	SHC 0.2	10317639	972362	11290001
12	SHC 0.2	11299949	1476080	12776029
13	SHC 0.2	13189651	2494332	15683983
14	SHC 0.4	8363231	489791	8853022
15	SHC 0.4	9387031	959496	10346527
16	SHC 0.4	10378545	1463944	11842489
17	SHC 0.4	12257911	2483971	14741882

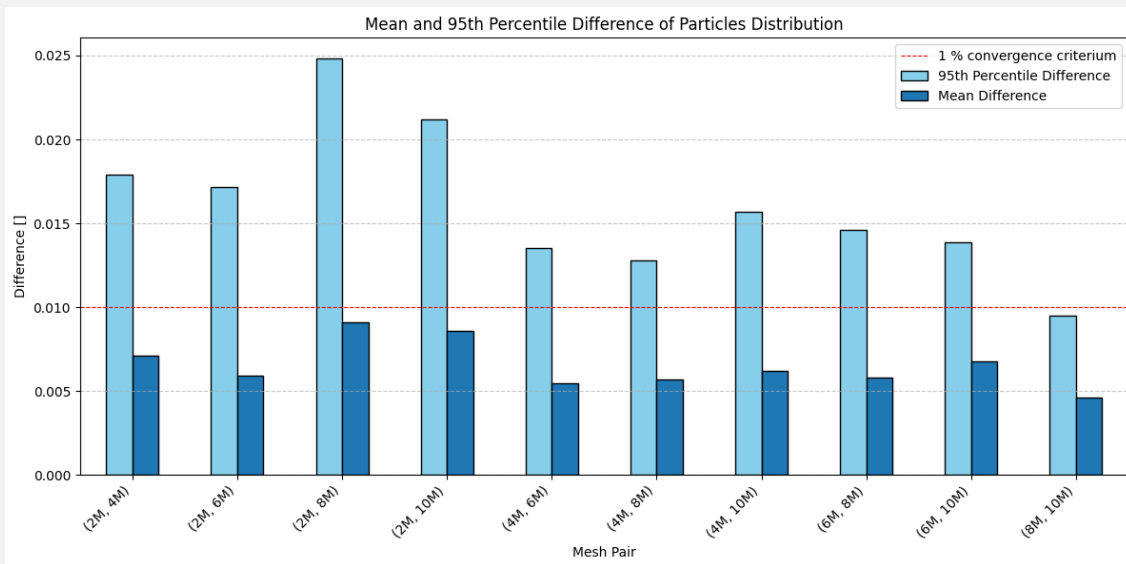
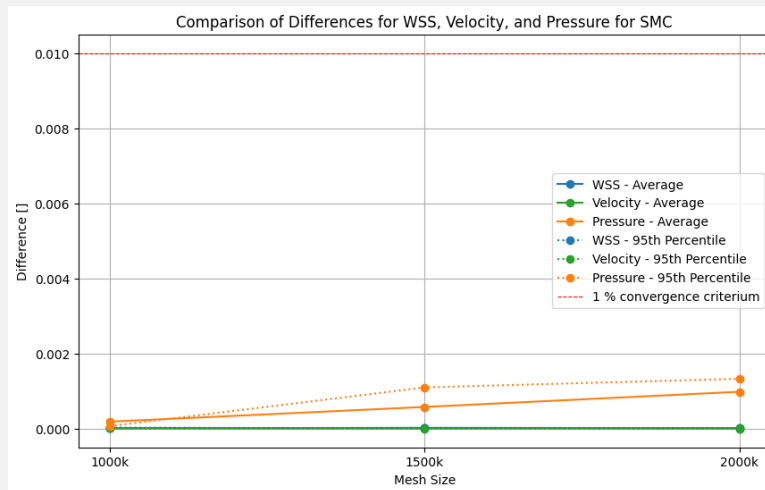
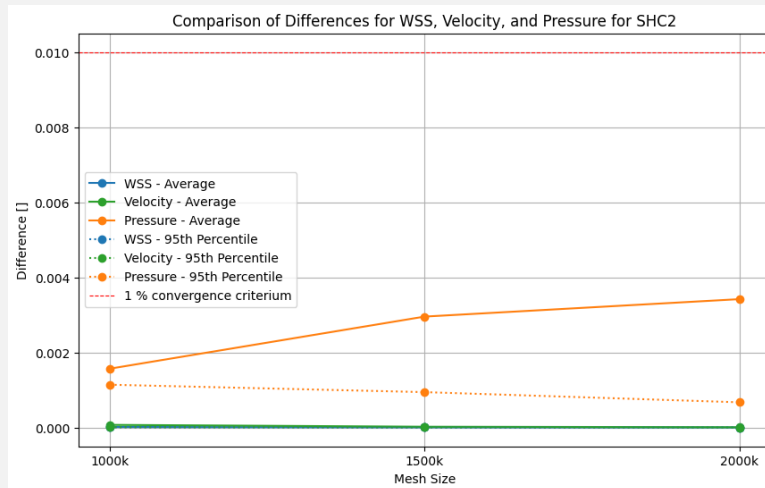


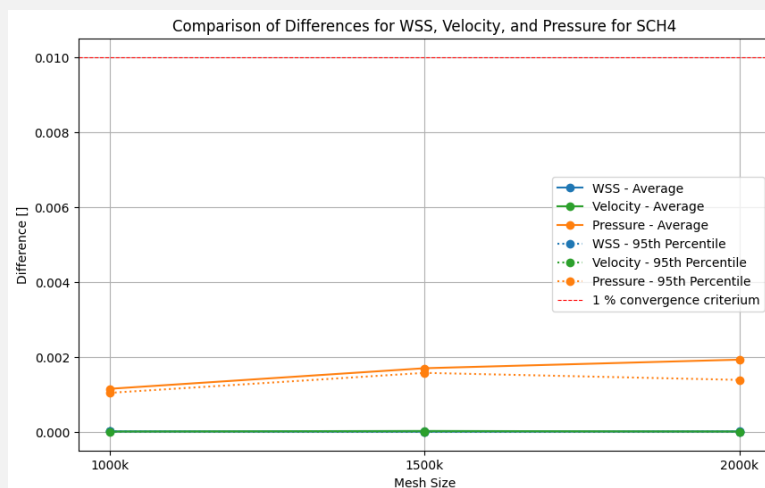
Figure 5.8 Mesh sensitivity analysis of the hepatic arteries without a catheter. The percentage difference of the mean and 95th percentile of the particle distribution at the outlets between all meshes is plotted. The x-axis shows the mesh pairs, denoted in million (M) volume cells.



(a) Mesh sensitivity analysis of SMC.



(b) Mesh sensitivity analysis of SHC with side-holes of diameter 0.2 mm.



(c) Mesh sensitivity analysis of SHC with side-holes of diameter 0.4 mm.

Figure 5.9 Mesh sensitivity analysis of the different catheters shows the percentage difference in the mean and 95th percentile of the wall shear stress (WSS), the static pressure on the wall, and the velocity profile downstream of the injection between all meshes. Some plotlines are not visible because they have comparable values as velocity-average.

Chapter 6

Computer Simulations

This chapter presents the computational approach used to model blood flow and embolic particle transport in transarterial liver cancer treatments. The governing equations of the continuous phase (Section 6.1) describe blood as an incompressible, non-Newtonian fluid, solved using the Navier-Stokes equations with a simplified Quemada viscosity model. The discrete phase (Section 6.2) is modelled using the Discrete Phase Model (DPM), where embolic particles follow Newton's second law under one-way coupling assumptions.

Key boundary conditions (Section 6.3) include a pulsatile blood inlet, particle injection settings, and flow-based outlet constraints. Numerical methods and solver settings (Section 6.4) ensure stability and accuracy. The simulation plan (Section 6.5) investigates the effects of catheter design and side-hole orientation on particle distribution.

6.1 Governing Equations of the Continuous Phase

The governing equations for blood will be analysed in a laminar flow regime. Blood is treated as a non-Newtonian and incompressible fluid. The equations that describe the continuous phase are based on conservation laws. The initial law is mass conservation, which simplifies to the continuity equation given the assumption of incompressibility. This continuity equation is defined in Equation 6.1.

Equation 6.1: Continuity equation

$$\nabla \cdot \vec{u} = 0 \quad (6.1)$$

Where $\vec{u}$ [m/s] is the velocity vector of the fluid.

The second law describes the conservation of momentum. Assuming incompressibility allows this equation to be simplified to the Navier-Stokes equation. The Navier-Stokes equation is shown in Equation 6.2.

Equation 6.2: Navier-Stokes equation

$$\rho \left(\frac{\partial \vec{u}}{\partial t} + (\vec{u} \cdot \vec{\nabla}) \vec{u} \right) = -\nabla p + \nabla \cdot \bar{\tau} + \vec{f} \quad (6.2)$$

Where ρ [kg/m³] is the density of the fluid, $\vec{u}$ [m/s] is the fluid velocity vector, t [s] is the time, p [Pa] is the fluid pressure, $\bar{\tau}$ [Pa] is the shear stress tensor and $\vec{f}$ [N/m] are the forces acting on the fluid [25].

The density of blood (ρ) is set at 1060 kg/m³ as Bomberna et al. (2022) [45] used. To capture the non-Newtonian, shear-thinning behaviour of blood, a simplified quemada model [46] is used to model the viscosity of blood. The shear stress tensor $\bar{\tau}$ is in this case dependent on the apparent viscosity (Equation 6.3), which itself is dependent on the shear rate (Equation 6.4). The equation of the shear rate itself in function of $\vec{u}$ is given by Equation 6.5 [25, 45, 47].

Equations 6.3 - 6.5: Simplified quemada model [25, 45, 47]

$$\bar{\tau} = \mu(\dot{\gamma}) \left[\nabla \vec{u} + (\nabla \vec{u})^T \right] \quad (6.3)$$

$$\mu(\dot{\gamma}) = \max \left\{ \mu_0, \left(\sqrt{\mu_\infty} + \frac{\sqrt{\tau_0}}{\sqrt{\lambda} + \sqrt{\dot{\gamma}}} \right)^2 \right\} \quad (6.4)$$

$$\dot{\gamma} = \sqrt{\nabla \vec{u} \left[\nabla \vec{u} + (\nabla \vec{u})^T \right]} \quad (6.5)$$

Where $\bar{\tau}$ [Pa] is the shear stress tensor of the fluid, $\mu(\dot{\gamma})$ [Pa · s] the apparent viscosity with $\dot{\gamma}$ [s⁻¹] the shear rate, $\vec{u}$ [m/s] is the fluid velocity vector, μ_0 and μ_∞ [Pa · s] the minimum and asymptotic viscosity, τ_0 [Pa] is the apparent yield shear stress and λ [s⁻¹] is the shear stress modifier [25].

The parameters of the quemada model are defined as follows: $\mu_0 = 0.00309$ Pa · s, $\mu_\infty = 0.002654$ Pa · s, $\tau_0 = 0.00436$ Pa, and $\lambda = 0.02181$ s⁻¹ [25, 48]. The implementation in C code is given in Appendix E.

6.2 Governing Equations of the Discrete Phase

The particle trajectories were modelled using the Discrete Phase Model (DPM) in Fluent Solution R2 2024 (Ansys Inc., Canonsburg, PA, USA). This model employs a Lagrangian framework to track each particle. The governing equation for the particles is Newton's second law of motion, or conservation of linear momentum, as expressed in Equation 6.6. The total force acting on a particle is the sum of the gravitational force (Equation 6.7), drag force (Equation 6.8), pressure gradient force (Equation 6.10), and virtual mass force (Equation 6.11). This equation can be utilised to derive the particle trajectories by integrating Equation 6.6 twice [25, 45, 47].

Equation 6.6: Newton's second law [25, 45, 47]

$$m_p \frac{d\vec{u}_p}{dt} = \vec{F}_G + \vec{F}_D + \vec{F}_P + \vec{F}_V \quad (6.6)$$

Where m_p [kg] is the particle mass, $\vec{u}_p$ [m/s] is the particle velocity vector, t [s] is the time, $\vec{F}_G$ [N] is the gravitational force, $\vec{F}_D$ [N] is the drag force, $\vec{F}_P$ [N] is the pressure gradient force and $\vec{F}_V$ [N] is the virtual mass force [25].

The microspheres are represented as inert spheres with a diameter (d_p) of $40 \cdot 10^{-6}$ m and a density (ρ_p) of 1600 kg/m^3 , comparable to SIR-spheres [45]. For a perfect sphere, this would result in a mass (m_p) of $5.36 \cdot 10^{-11}$ kg. These forces in Equation 6.6 are given by Equations 6.7 - 6.11.

Equations 6.7 - 6.11: Forces acting on the particles [49]

$$\vec{F}_G = m_p \vec{g} \frac{(\rho_p - \rho)}{\rho_p} \quad (6.7)$$

$$\vec{F}_D = m_p \frac{18\mu}{\rho_p d_p^2} \frac{C_D Re_p}{24} (\vec{u} - \vec{u}_p) \quad (6.8)$$

$$Re_p = \frac{\rho d_p |\vec{u} - \vec{u}_p|}{\mu} \quad (6.9)$$

$$\vec{F}_P = m_p \frac{\rho}{\rho_p} \vec{u}_p (\nabla \vec{u}) \quad (6.10)$$

$$\vec{F}_V = C_V m_p \frac{\rho}{\rho_p} \left[\vec{u}_p (\nabla \vec{u}) - \frac{d\vec{u}_p}{dt} \right] \quad (6.11)$$

Where $\vec{F}_G$ [N] is the gravitational force acting on the particle, m_p [kg] is the particle mass, $\vec{g}$ [9.81 m/s²] is the gravitational acceleration, ρ [kg/m³] and ρ_p [kg/m³] are the fluid and particle densities, respectively.

$\vec{F}_D$ [N] is the drag force, with μ [Pa · s] representing the dynamic viscosity of the fluid, d_p [m] the particle diameter, C_D [–] the drag coefficient, and Re_p [–] is the particle Reynolds number. The term $\vec{u} - \vec{u}_p$ [m/s] represents the relative velocity between the fluid and the particle.

The particle Reynolds number Re_p [–] is defined as the ratio of inertial to viscous forces acting on the particle, where ρ [kg/m³] is the fluid density and μ [Pa · s] is the dynamic fluid viscosity.

$\vec{F}_P$ [N] is the pressure gradient force with $\nabla \vec{u}$ [1/s] representing the velocity gradient tensor.

$\vec{F}_V$ [N] is the virtual mass force. Here, C_V [–] is the virtual mass coefficient, and $\frac{d\vec{u}_p}{dt}$ [m/s²] represents the acceleration of the particle.

The virtual mass coefficient C_V was set to 0.5 [25].

One-way coupling was utilised to couple the discrete phase of microparticles with the continuous phase of blood. This method is essential for enabling mass and momentum exchange between the two phases. In this approach, the effects of the fluid on the particles are considered while ignoring any influence the microparticles might exert on the fluid itself. One-way coupling is sufficient for diluted suspensions, where interactions between particles are minimal. Numerous studies have adopted this assumption of implementing one-way coupling [25]. In instances

where two-way coupling was applied, findings indicated that the particles did not significantly affect the fluid [48].

6.3 Boundary Conditions

In computational simulations, appropriate boundary conditions are crucial for accurately modelling physical phenomena. These conditions define fluid and particle interactions at the simulation's limits, impacting overall flow dynamics and model performance. This section will discuss the specific boundary conditions applied to the inlets, outlets and walls.

6.3.1 Inlet Boundary Conditions

In the geometries employed for this study, two inlets are defined: the arterial blood inlet and the catheter inlet. A pulsatile mass flow profile is implemented for the arterial blood inlet. In an ideal case, the inlet waveform is determined based on patient-specific measurements. However, the personalised measurements are currently not available due to technical complexities [25]. Therefore, a waveform is constructed following the methodology of Bomberna et al. (2022) [45], which is derived from a one-dimensional arterial circulation model by Campos et al. (2017) [50]. The velocity waveform has a period of 0.8 seconds and a mean velocity of 0.1254 m/s, as illustrated in Figure 6.1. The mean velocity is applied in place of the pulsatile profile in steady-state simulations.

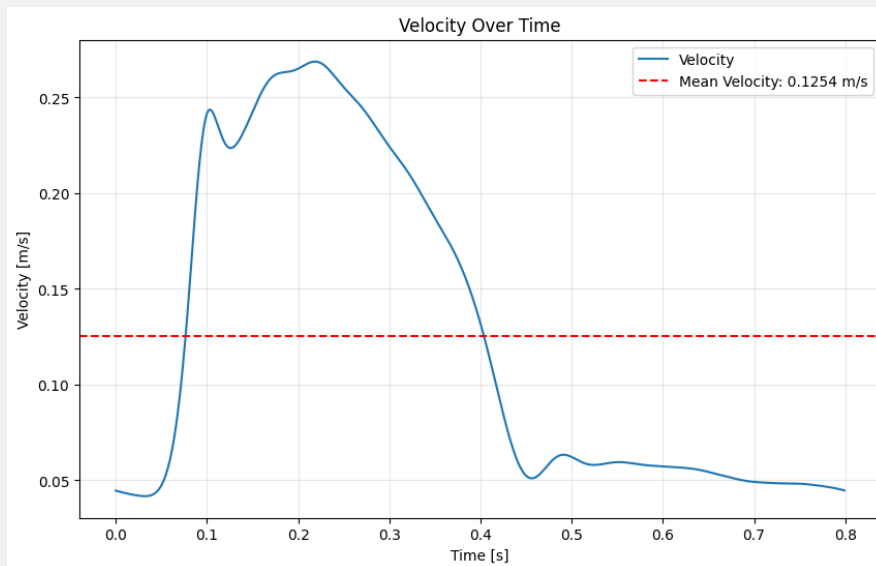


Figure 6.1 Velocity of blood during a single cardiac cycle at the hepatic artery inlet, with a mean velocity of 0.1254 m/s .

At the catheter inlet, boundary conditions are specified for both the continuous phase (blood) and the discrete phase (particles), with both having the same velocity magnitude. The particles are uniformly injected across the catheter injection plane with an inlet velocity of 0.1254 m/s, matching the mean blood inlet velocity of 0.1254 m/s. Additionally, a total particle mass flow rate is prescribed, with particle injection occurring at intervals of 0.01 seconds.

6.3.2 Outlet Boundary Conditions

The outlet boundary conditions are defined as outflow fractions. These fractions were previously calculated in the study by Bomberna et al. (2022) [45]. The final flow fractions are outlined in Table 6.1 for each outlet. The flow fractions were determined based on the volume of perfused healthy tissue and the volume of perfused tumour tissue for each outlet. The total flow for each outlet is the sum of both flow terms, as detailed in Equation 6.12.

Equation 6.12: Blood flow to each outlet [45]

$$Q_b = Q_{h,b} + Q_{c,b} \quad (6.12)$$

Where Q_b [ml/min] denotes the total outflow from an outlet b , $Q_{h,b}$ [ml/min] represents the outflow contribution from healthy tissue, and $Q_{c,b}$ [ml/min] indicates the outflow contribution from cancerous tissue [45].

The flow contribution for the healthy tissue at outlet b can be calculated using Equations 6.13 and 6.14.

Equation 6.13 - 6.14: Blood flow of each outlet to healthy tissue [45]

$$Q_s = V_s \cdot k_h \quad (6.13)$$

$$Q_{h,b} = Q_s \cdot BF_b \quad (6.14)$$

Where outflow Q_s [ml/min] is defined for each segment s , V_s [ml] is the volume of each segment s and k_h [min^{-1}] the healthy perfusion parameter.

The healthy flow contribution $Q_{h,b}$ [ml/min] to each outlet b is determined from Q_s and the branching factor BF_b [–] [45].

The liver is divided into segments according to the Couinaud classification, as explained in section 1.1. The volume of these segments can be found in the literature and is scaled to the patient-specific case. The healthy perfusion parameter k_h is set to 0.100 min^{-1} [51]. After

calculating the flow to each segment, the flow to each outlet is estimated based on the branching factor, assuming that in one segment, the flow split is equal between the branching arteries.

The flow contribution of the tumorous tissue at outlet b can be calculated using Equations 6.15 and 6.16.

Equation 6.15 - 6.16: Blood flow of each outlet to cancerous tissue [45]

$$Q_t = V_t \cdot k_c \quad (6.15)$$

$$Q_{c,b} = Q_t \cdot TPP \quad (6.16)$$

Where Q_t [ml/min] represents the total tumour flow, V_t [ml] denotes the total tumour volume, and k_c [min^{-1}] indicates the perfusion rate in tumour tissue.

The contribution of cancerous flow $Q_{c,b}$ [ml/min] at each outlet b is derived from Q_t and the Tumour Perfusion Percentage TPP [–] [45].

The total tumour flow is calculated based on the tumour volume, which can be derived from the CT scans, registering at 310 ml for this patient, and the tumour perfusion rate k_h , which is 0.415 min^{-1} [51]. The tumour flow to each outlet is determined based on the TPP. The TPP represents the percentage of the tumour that the outlet perfuses, calculated using the region growing model of De Backer et al. (2023) [52]. The TPP for each outlet is presented in Table 6.1 along with the flow fractions of each outlet. The outlets segmented in the hepatic geometry feed 98% of the tumour tissue. This brings the total TPP to 98 %.

Table 6.1 Outflow fractions and tumour perfusion percentage (TPP) of each outlet.

Outlet	Flow fraction [%]	TPP [%]
Outlet 1.1	3.657	0
Outlet 1.2	1.799	0
Outlet 1.3	3.894	7.548
Outlet 1.4	0.326	0
Outlet 1.5	0.461	0
Outlet 1.6	0.948	0
Outlet 2.1	2.985	3.311
Outlet 2.2	6.333	0
Outlet 2.3	4.069	6.953
Outlet 2.4	0.788	0
Outlet 2.5	4.368	6.834
Outlet 2.6	3.446	4.938
Outlet 3.1	3.630	0
Outlet 3.2	15.009	16.855
Outlet 3.3	14.911	20.275
Outlet 3.4	31.732	31.731
Outlet 3.5	1.644	0
Total	100	98.447

6.3.3 Wall Boundary Conditions

The wall of the hepatic arteries is considered to be a rigid and non-slip surface. This is a simplification, as the arteries are, in reality, non-rigid, and their diameter varies during the cardiac cycle. The non-slip boundary condition, which assumes zero velocity at the walls, simplifies calculations [53].

The interaction between the particles and the hepatic artery walls is regarded as elastic. This behaviour is implemented by setting the tangent and normal wall restitution coefficients to one.

6.4 Solver Settings

The simulations were conducted using the SIMPLE (Semi-Implicit Method for Pressure-Linked Equations) algorithm in Fluent Solution R2 2024 (Ansys Inc., Canonsburg, PA, USA) for pressure-velocity coupling. To prevent pressure-velocity decoupling, the Rhie-Chow interpolation method with momentum-based correction was employed. Spatial discretisation was

implemented using a Least Squares cell-based approach, a second-order scheme for pressure, and a second-order upwind scheme for momentum.

Under-relaxation factors were set at 0.3 for pressure, 1.0 for density and body force, and 0.7 for momentum to ensure numerical stability. The convergence criteria were defined by an absolute normalised residual threshold of $1 \cdot 10^{-6}$ and a relative residual threshold of $1 \cdot 10^{-3}$ for continuity and velocity components. The solution reached convergence once either of the thresholds was reached.

The initial solution was achieved using the hybrid initialisation method over 10 iterations, ensuring a stable starting condition for the iterative solver.

6.5 Simulation Planning

For the first objective, three steady-state simulations are performed with three different types of catheter: SMC, SHC 0.2, and SHC 0.4. The catheter injection speed is set at 0.1254 m/s. These simulations allow for the evaluation of the new workflow using Ansys Discovery (Ansys Inc., Canonsburg, PA, USA) and the impact of catheter design on particle distribution. The different simulations (Sim. 6, 10, and 14) are shown in Table 6.2. These simulations were part of the MSA, where the other simulations between 1 and 17 were performed.

Table 6.2 Overview steady-state simulations (Sim 6,10, and 14) with different catheter geometries.

Simulation	Catheter Type	Injection Velocity Particles [m/s]
6	SMC	0.12
10	SHC 0.2	0.12
14	SHC 0.4	0.12

The second objective investigates how the radial position of the side-holes affects outcomes within individual patient contexts, including geometry and outlet flows. These simulations (Sim. 18-21, Table 6.3) are performed in steady-state conditions. The results of the previous objective are considered the catheters with orientation 1.

Table 6.3 Overview steady-state simulations (Sim. 18-21) with different catheter types and radial orientation.

Simulation	Catheter type	Side-hole orientation
18	SHC 0.2	orientation 2
19	SHC 0.2	orientation 3
20	SHC 0.4	orientation 2
21	SHC 0.4	orientation 3

To achieve the third objective, transient simulations are conducted for the three catheter types: SMC, SHC 0.2, and SHC 0.4. Each catheter type is tested with one particle injection velocity. These catheter types align with the research of Zeebroek (2024) [35]. This approach allows for a comparison between the steady-state simulation from that study, the results of objective 1 and the simulations performed here (Sim. 22-24, Table 6.4).

Table 6.4 Overview transient simulations (Sim. 22-24) with different catheter geometries.

Simulation	Catheter Type	Injection Velocity Particles [m/s]
22	SMC	0.12
23	SHC 0.2	0.12
24	SHC 0.4	0.12

Chapter 7

Post-Processing

Upon completing the steady-state and transient simulations, figures can be created in Ansys Fluent to facilitate comparisons among the simulations. These visuals help examine the behaviour of particles in the hepatic arteries for different catheters. Each simulation can also undergo numerical comparisons using specific indices like the matching deviation index, the targeting deviation index, and the particle spread index. These metrics relate to particle behaviour and can be visually analysed to enhance understanding of their impact on the numerical parameters. Using these numerical metrics, the design of the SHC can be optimised further.

7.1 Matching Deviation Index

The matching deviation index (MDI) serves as a quantitative measure demonstrating the extent to which the particle distribution aligns with the blood flow distribution. The primary objective of the SHC is to enhance this alignment, effectively reducing the influence of other parameters as elaborated in 3.3 [43]. The mathematical representation for calculating the MDI is provided in Equation 3.1. Upon completion of the simulation, the total number of particles that exit through each outlet was exported and subsequently analysed. The total particles exiting through outlet s are represented by the variable $N_{p,s}$. Additionally, the variable q_s denotes the blood flow that exits through outlet s . For this study, the outflow boundary conditions were selected as mentioned in 6.3.2. The outflow fractions were established prior to the simulations and are presented in Table 6.1. The outflow fraction [%] of outlet s is equal to $\frac{q_s}{\sum_{s=1}^N q_s}$ in the MDI equation. Furthermore, the average of the difference in blood flow and particle distribution across all outlets is calculated. The total number of outlets, denoted as N , is 17 for this hepatic artery geometry. The MDI results will be expressed in percentage points, with a value of 0% representing perfect alignment between the blood flow and particle distributions.

7.2 Targeting Deviation Index

Another metric was needed to quantify the performance of the catheter in terms of medical outcomes. The MDI assesses how well the distributions align to enhance outcome stability. This metric, however, does not provide insight into catheter performance regarding medical outcomes. MDI is a metric focusing purely on fluid mechanics. To further quantify the medical performance, the targeting deviation index (TDI) is calculated [47]. TDI describes how well the particle distribution aligns with the perfused tumour fraction of each outlet. The formula is detailed in Equation 7.1.

Equation 7.1: Targeting Deviation Index [47]

$$\text{TDI} [\%] = \frac{1}{N} \sum_{s=1}^N \left| \frac{N_{p,s}}{\sum_{s=1}^N N_{p,s}} - \frac{V_{c,s}}{\sum_{s=1}^N V_{c,s}} \right| \cdot 100 \quad (7.1)$$

Where s represents the number of outlets, ranging from 1 to N . The variable $N_{p,s} [-]$ denotes the number of particles in outlet s , and $V_{p,s} [ml]$ represents the tumoral volume of outlet s .

$\frac{V_{c,s}}{\sum_{s=1}^N V_{c,s}}$ can be replaced by TPP, which is given in Table 6.1. The TDI results will be represented in percentage points, with a value of 0% indicating the ideal particle transport scenario, leading to the optimal medical outcome.

7.3 Particle Spread

In the previous indices, Ortega et al. (2025) [47] examined only the particle distribution across different outlets, treating these outlets merely as points of investigation. To quantify how particles spread within the arterial lumen and ultimately affect other indices, the particle spread in various cross-sections is analysed. Cross-sections post-bifurcation are examined along the pathway from the catheter tip to the outlet that receives the most blood flow and has the highest TPP. To quantify particle dispersion in these cross-sections, indices from Bomberna et al. (2024) [54] are utilised.

7.3.1 Global Spread Indices

To quantify the maximal dispersion of particles, the Index of Particle Spread (IPS) is employed. The mathematical expression for IPS is given in Equation 7.2. The cross-section is discretised into squares to determine if at least one particle has crossed the plane within that square.

Equation 7.2: Index of Particle Spread [54]

$$\text{IPS} [\%] = \frac{N_{\text{particle}}}{N_{\text{plane}}} \cdot 100 \quad (7.2)$$

Where $N_{\text{particle}} [-]$ denotes the number of reference squares where at least one particle passed through and $N_{\text{plane}} [-]$ the total number of reference squares in the cross-section.

The IPS results will be represented in percentage points, with a value of 100% indicating that particles are spread across the entire plane. However, the IPS does not quantify how the particles are distributed over the cross-section. The Uniform IPS measures the uniformity of the particle distribution over N_{particle} . The equation is given by Equation 7.3. This metric quantifies the dissimilarity between the actual particle distribution and the hypothetical uniform distribution.

Equation 7.3: Uniform Index of Particle Spread [54]

$$\text{UIPS} [\%] = 100 - \left[\frac{\sum_i \sum_j |p_{ij} - U|}{(N_{\text{particle}} - 2)U + 100} \right] \cdot 100 \quad (7.3)$$

Where $p_{ij} [-]$ is the percentage of particles passing through the square at row i and column j , $U [-]$ represents the uniform distribution as $U = \frac{100}{N_{\text{particle}}}$ and N_{particle} is the number of reference squares where at least one particle passed through.

The UIPS is normalised by dividing by the maximal dissimilarity between the actual and theoretical uniform distribution. This maximal value is given by $(N_{\text{particle}} - 1)U + (100 - U)$, which can also be rewritten as $(N_{\text{particle}} - 2)U + 100$. The UIPS results will be represented in percentage points, with a value of 100% indicating a perfectly uniform particle distribution.

7.3.2 Temporal Spread Indices

Previous indices did not consider time as a variable. To account for time-dependent phenomena, Bomberna et al. (2024) [54] introduced the temporal IPS (tIPS). The N_{particle} value from Equation 7.2 is now considered in separate time intervals of 0.2 s and is denoted as N_{burst} . The mathematical formula of tIPS is provided by Equation 7.4.

Equation 7.4: temporal Index of Particle Spread [54]

$$tIPS [\%] = \frac{N_{burst}}{N_{plane}} \cdot 100 \quad (7.4)$$

Where $N_{burst} [-]$ denotes the number of reference squares where at least one particle passed through in a certain time interval, and $N_{plane} [-]$ the total number of reference squares in the cross-section.

tIPS is expressed in percentage points, with high variations indicating a strong time-dependent character. The weighted average (WIPS) is determined to calculate a single time-dependent value for one cross-section. The weighted IPS is given by Equation 7.5.

Equation 7.5: Weigthed Index of Particle Spread [54]

$$WIPS [\%] = \frac{\sum_b tIPS_b \cdot P_b}{\sum_b P_b} \quad (7.5)$$

Where $P_b [-]$ denotes the absolute number of particles in burst b.

The WIPS is expressed in percentage points, with a high value indicating high dispersion for a large number of particles.

Part III

Results and Discussion

Chapter 8

Evaluation Steady State Simulations

This chapter presents the results of steady-state CFD simulations used to validate a new catheter modelling and insertion workflow. Simulations replicated the study by Zeebroek (2024) [35] using three catheter types (SMC, SHC 0.2, and SHC 0.4) with an injection velocity of 0.1254 m/s. Results include analysis of the workflow in Ansys Discovery (section 8.1), particle trajectories (section 8.2), cross-sectional spread (section 8.3), outlet distributions (section 8.4), and performance metrics (MDI and TDI) (section 8.5), allowing both validation of the workflow and comparison of catheter designs in terms of particle transport and targeting. This chapter ends with a comparison of the results with those of previous studies (section 8.6).

8.1 Workflow Ansys Discovery

The integration of Ansys Discovery into the workflow streamlined the process of catheter creation and insertion into the segmented hepatic artery geometries. Previously, SpaceClaim was employed for this task, necessitating a preliminary reverse engineering step due to the inherent limitations in directly manipulating segmented geometries. Specifically, this process involved reconstructing arterial geometries using elliptical and circular cross-sections, which introduced notable limitations which will be covered below.

The primary concern associated with the SpaceClaim-based workflow was the inevitable loss of anatomical detail resulting from the geometric simplification. While previous arguments suggested that this loss was negligible compared to segmentation errors, several critical factors challenged this assumption. First, the cumulative errors stemming from segmentation inaccuracies combined with simplifications made during reverse engineering could become relevant, especially given the small-scale nature of hepatic artery geometries. Second, the simplification using ellipses and circles could only approximate complex arterial contours, inherently ignoring subtle yet potentially impactful anatomical features. Although the approximation error could

be mitigated by increasing the number of fitted contours, this approach prolonged the process without entirely overcoming the limitations of geometric approximation. Consequently, the resultant geometry, while usable, represented a smoother and less anatomically accurate version of the original segmentation.

The adoption of Ansys Discovery effectively addressed these concerns, preserving the original segmentation details and enabling more accurate and realistic simulations. By directly converting segmented geometries into solid bodies, Ansys Discovery eliminated the need for reverse engineering. Figure 8.1 illustrates the three distinct geometries: the original segmentation, the geometry created with Spaceclaim, and the geometry generated with Discovery. In areas where the original geometry (purple) appears, numerous black edges (representing Discovery geometry) can also be observed. In contrast, regions marked by green (indicating Spaceclaim geometry) show no signs of purple or black edges, implying that the Discovery workflow better preserved the original geometry. This statement is supported by the total surface area (Table 8.1), which reveals that Discovery geometry deviated only by 0.03 mm^2 from the original geometry, compared to a difference of 67.12 mm^2 with Spaceclaim. Thus, the discrepancy with Discovery is 2 090 times smaller than that with Spaceclaim.

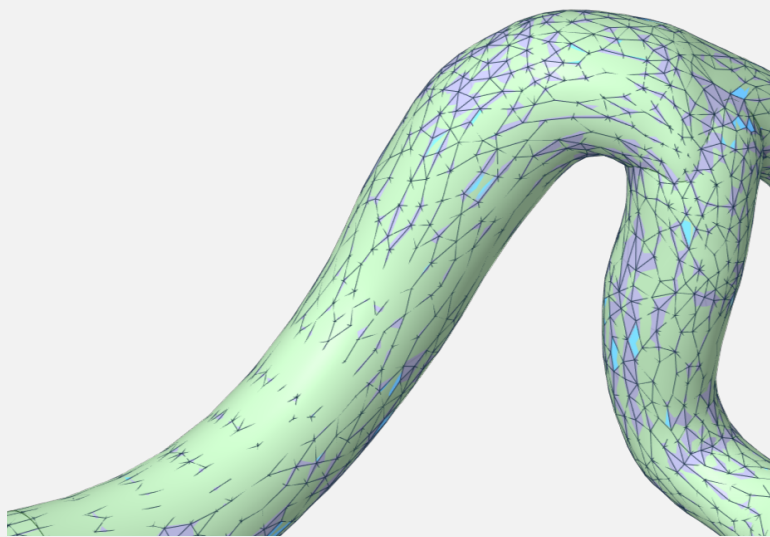


Figure 8.1 Visualisation of the two different workflow geometries with the original segmentation (purple). The geometry with Spaceclaim is shown in green and with Discovery in blue with black edges.

Moreover, Ansys Discovery markedly improved workflow efficiency. Previously, catheter creation and insertion processes consumed approximately two weeks, primarily due to the time-intensive reverse engineering tasks. In contrast, employing Ansys Discovery reduced this duration substantially, achieving the same tasks in several days. This acceleration resulted from

Table 8.1 Total surface area of the two geometries with different workflows, alongside the original segmented geometry.

	Original	Discovery	Spaceclaim
Surface Area [mm^2]	9466.0648	9466.0327	9533.1846

the software's capability to replace the reverse engineering task with an automated solid-body conversion, a considerable advantage detailed in the workflow provided in the appendix D.2.

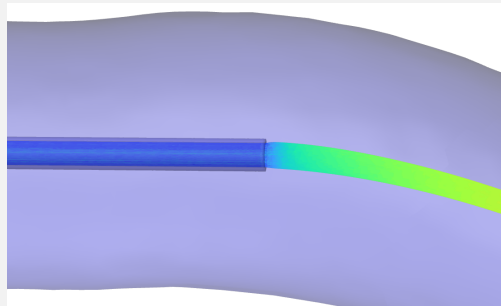
Finally, integrating Ansys Discovery streamlined the broader workflow by reducing the reliance on multiple software programs. Both SpaceClaim and Design Modeller could be effectively replaced, simplifying the entire workflow pipeline. Segmented geometries were directly loaded into Discovery, and following catheter insertion, seamless integration with the meshing processes in Ansys Fluent was established.

8.2 Particle Tracks

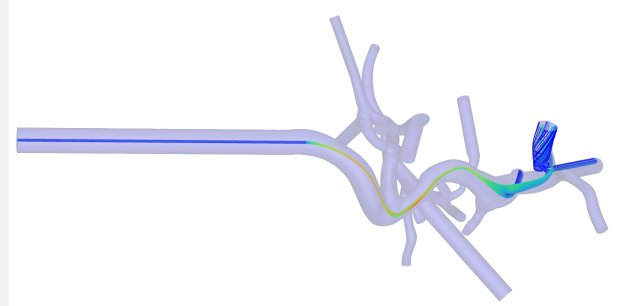
Figure 8.2 presents visualisations of particle trajectories resulting from simulations (sim. 6, 10, 14) conducted in steady-state with three different catheter configurations. The shown particle tracks are coloured based on their velocity magnitudes (m/s), with a maximum of 0.30 m/s for the visual representation. Those trajectories emphasise the different dispersion patterns generated by each catheter type. The Subfigures 8.2a, 8.2c, and 8.2e provide detailed close-up views of the catheter injection tips, illustrating the immediate influence of catheter design on particle exit velocities and initial trajectories. Subfigures 8.2b, 8.2d, and 8.2f extend this visualisation to the broader hepatic artery geometry, capturing how each catheter design affects downstream particle distribution within the arterial network.

Analysing the particle tracks at the catheter inlet (Figure 8.2a, 8.2c, and 8.2e), it is observed that all catheters exhibit identical injection speeds and flow rates. Consequently, the outlet velocities differ inversely to outlet area, which is a direct result of mass conservation (Equation 6.1). This phenomenon is explicitly highlighted by comparing the SHCs, where the SHC 0.2 yields an average outlet velocity of 0.26 m/s (maximum of 0.66 m/s), compared to 0.06 m/s (maximum of 0.18 m/s) for the SHC 0.4 .

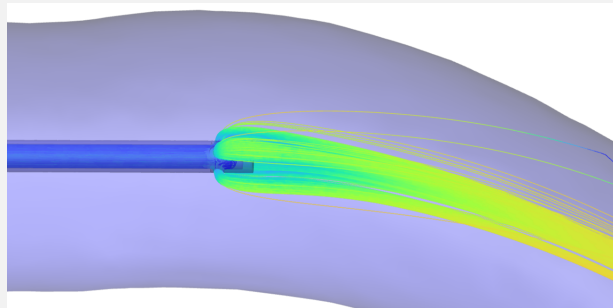
Furthermore, for SHC configurations (Figure 8.2c and 8.2e), the correlation between increased velocities and greater crossflow becomes apparent. Higher velocities induce trajectories that deviate radially from the lumen's centerline and remain within the bloodstream longer before aligning with the primary blood flow direction. This can be seen in Figure 8.2c where the trajectories of SHC 0.4 are more centralised within the lumen (radial extend of 0.66 mm), while those of SHC 0.2 (Figure 8.2e) are positioned nearer to the arterial lumen walls (radial extend of 1.29 mm). This finding partially aligns with Ortega et al.'s observations (2022) [43],



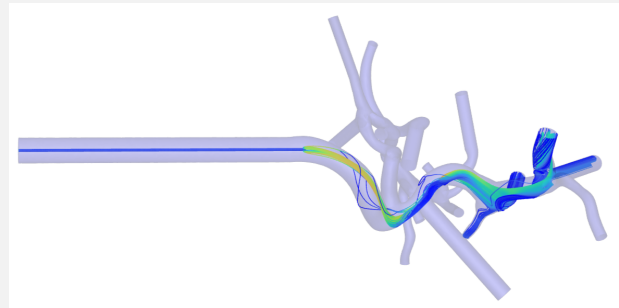
(a) SMC catheter injection tip.



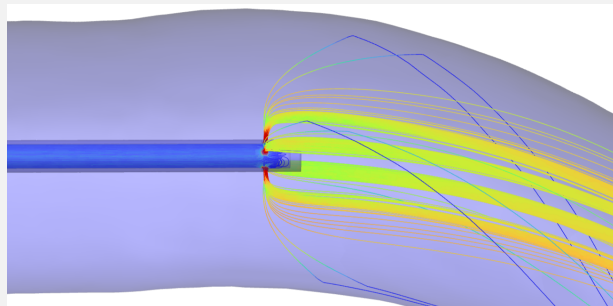
(b) Hepatic arteries geometry with SMC.



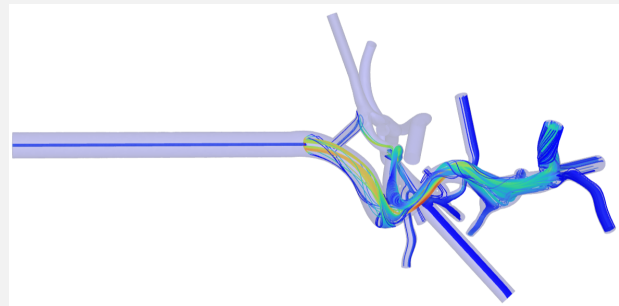
(c) SHC 0.4 catheter injection tip.



(d) Hepatic arteries geometry with SHC 0.4.



(e) SHC 0.2 catheter injection tip.



(f) Hepatic arteries geometry with SHC 0.2.

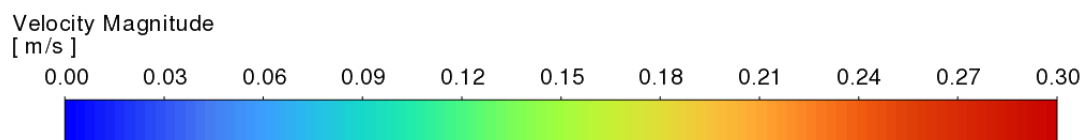


Figure 8.2 Visualisation of the particle tracks, indicated by velocity magnitude [m/s], from the three steady-state simulations (sim. 6, 10, 14) with a catheter.

which suggested that increased injection velocity would enhance crossflow velocities and lumen filling. However, the present simulations diverge from this study's predictions, showing distinct and localised injection streams instead of dispersed lumen filling. The side holes produce four clearly delineated streams, countering expectations of broad dispersion within the lumen.

When examining particle dispersion within the geometry of the hepatic artery (Figure 8.2b, 8.2d, and 8.2f), distinct flow behaviours emerge between the SMC and SHCs. The SMC demonstrates centralised particle injection, causing all particles to preferentially follow the primary blood flow pathways toward the most perfused arterial outlets (62 %). In contrast, SHCs enhance particle distribution, with smaller hole diameters markedly improving the extent of dispersion.

Because of the no-slip boundary condition, particles drifting toward the arterial wall reduce their speed to nearly zero upon contact with the vessel surface, as illustrated for SHC 0.2 in Figure 8.3. These wall-induced reductions in speed occur in every catheter design and are followed by short bursts of re-acceleration as particles rejoin the faster central flow. Additionally, when the jet exits the catheter, it quickly mixes with the slower bloodstream ($\approx 0.12\text{m/s}$), resulting in a sudden velocity drop from the injection plateau. Additionally, particle streams that encounter arterial walls tend to disperse radially along the vessel wall, further contributing to a more extensive particle distribution downstream.

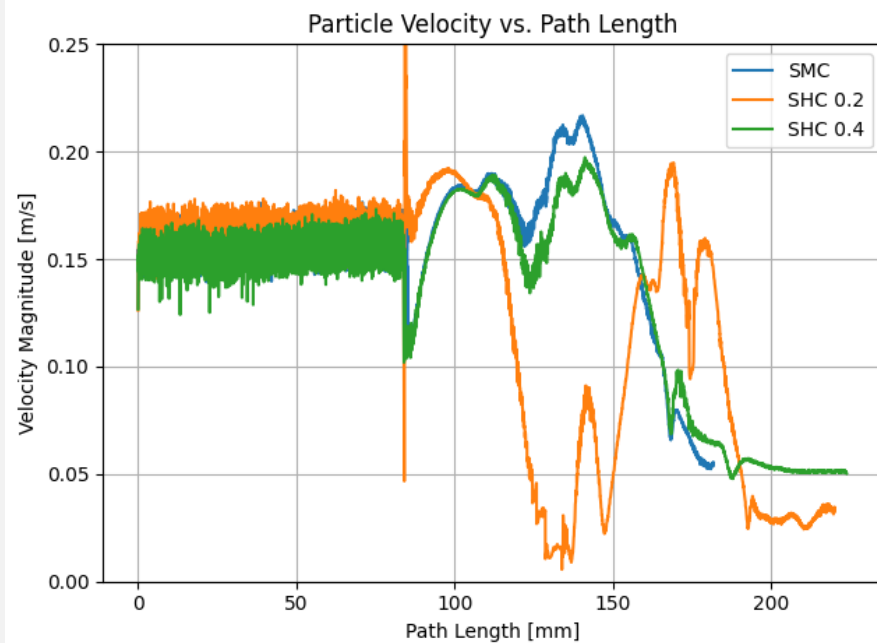


Figure 8.3 Visualisation of three particle tracks, each per design. The velocity magnitude [m/s] is shown as a function of path length [mm].

8.3 Particle Spread

Figure 8.4 illustrates the spatial locations of four cross-sectional planes used to analyse particle spread. Plane 1 is positioned 2 mm downstream of the catheter tip, immediately after the injection point. In contrast, plane 2 is located further downstream, 20 mm after the first bifurcation, leading to the highest outflow outlet. Planes 3 and 4 are situated closer to the outlets, with plane 3 located 10 mm downstream of the second bifurcation and plane 4 2 mm before the arterial outlet 3.4, capturing the particle distribution near the exit with the highest outflow.

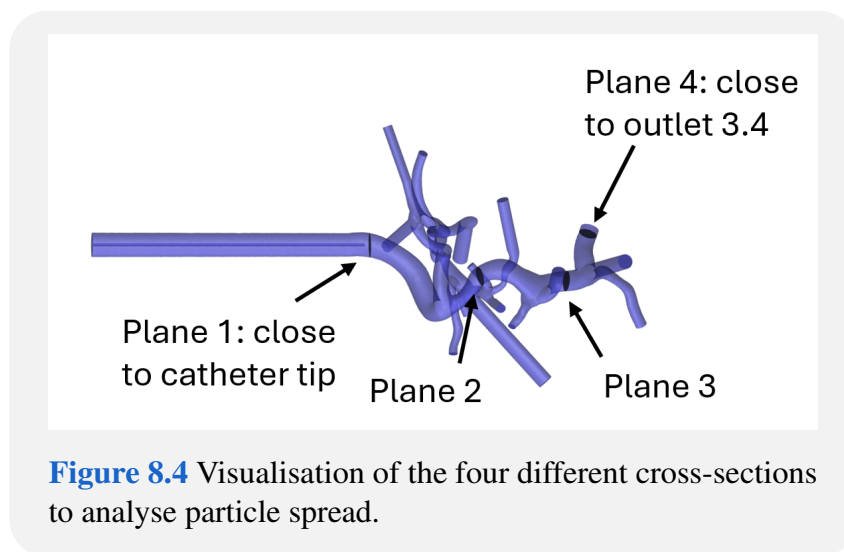


Figure 8.5 provides detailed visualisations of particles distributed across these four cross-sections for the SMC. Each subfigure represents a cross-sectional plane and displays particle distribution patterns as red areas within a structured grid, indicating local concentrations and dispersion of particles. The visualisation clearly highlights minimal particle dispersion at planes 1 and 2, demonstrating a highly focused particle stream shortly after injection. Increased dispersion is observed downstream at planes 3 and 4, due to the complex arterial geometries and bifurcations, which lead to more dispersed particle distributions.

Table 8.2 quantifies the particle dispersion using the Index of Particle Spread (IPS), at each cross-sectional plane for the SMC under steady-state conditions with an injection speed of 0.1254 m/s. The IPS values suggest limited particle dispersion at planes 1 (2.1%) and 2 (2.1%), with slightly increased dispersion at plane 3 (3%) and greater dispersion at plane 4 (5.8%). These data collectively illustrate how particle dispersion change as particles process through the arterial network.

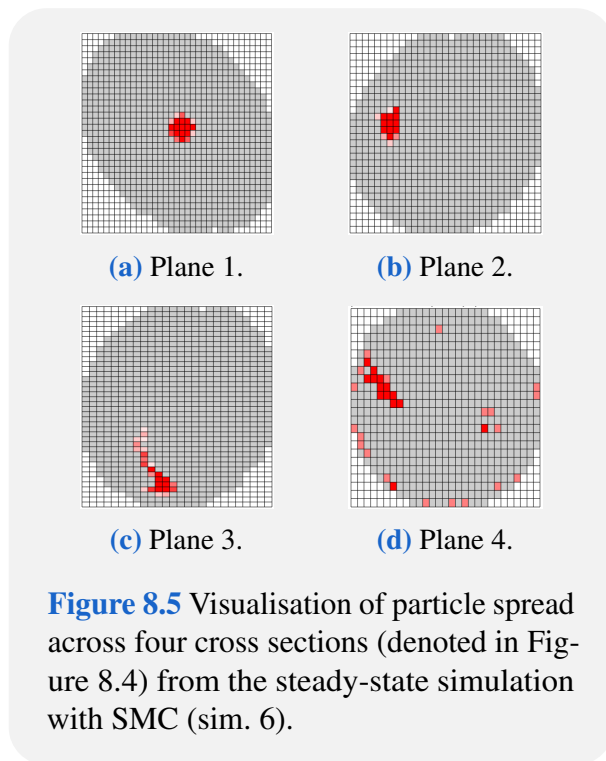


Table 8.2 Overview of the IPS values for SMC at an injection speed of 0.1254 m/s in steady-state conditions.

Spread Index	IPS [%]
Plane 1	2.1
Plane 2	2.1
Plane 3	3.0
Plane 4	5.8

Figure 8.6 extends this analysis to the SHC 0.4. Visualisations for this catheter show noticeably greater particle dispersion already at plane 1 (Figure 8.6a versus Figure 8.5a), characterised by distinct injection streams emerging from multiple side holes ranging in a wider initial distribution. At plane 2, the dispersion becomes more pronounced with particle trajectories spreading radially outward, skewed to one side (Figure 8.6b). As particles move downstream to planes 3 and 4, different distribution pattern emerges, illustrating considerable spread along the arterial lumen and reaching multiple areas across the arterial cross-section.

Table 8.3 provides quantitative insight into particle dispersion for the SHC 0.4 configuration. IPS values reflect an increase in dispersion compared to the SMC, particularly noticeable at planes 2 and 4, with IPS values reaching 12%.

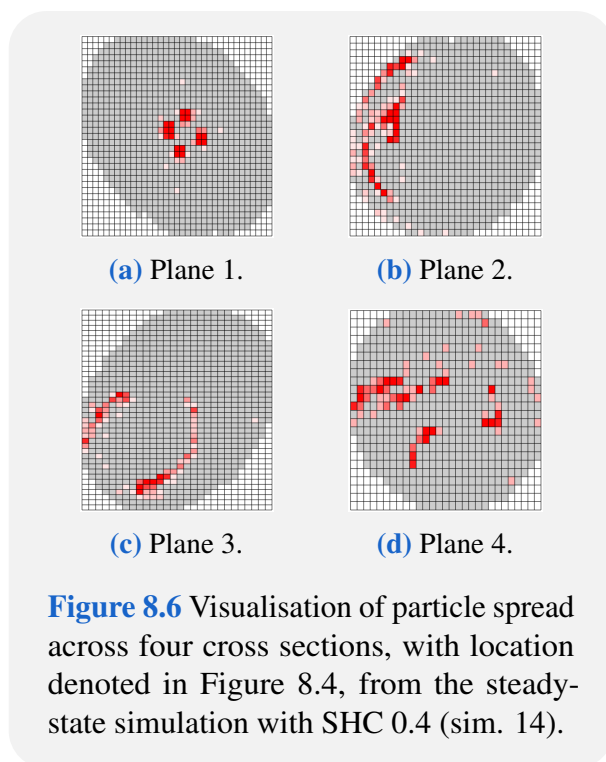


Table 8.3 Overview of the IPS values for the SHC with 0.4 mm side-holes and an injection speed of 0.1254 m/s in steady-state conditions.

Spread Index	IPS [%]
Plane 1	4.3
Plane 2	12.0
Plane 3	8.7
Plane 4	12.0

Figure 8.7 expands the visualisation and analysis for the SHC configuration with a SHC featuring smaller side-holes (SHC 0.2). At plane 1, multiple distinct injection streams are visible as well, though slightly less extensive compared to SHC 0.4 (Figure 8.7a versus 8.6a), but more to the arterial wall. Further downstream particles exhibit visually broader and more dispersed radial distribution.

Quantitative analysis from Table 8.4 highlights the IPS values for SHC 0.2, which, despite slight numerical differences, do not quite differ from those of SHC 0.4 due to inherent variability in IPS values resulting from plane rotation before calculating IPS values.

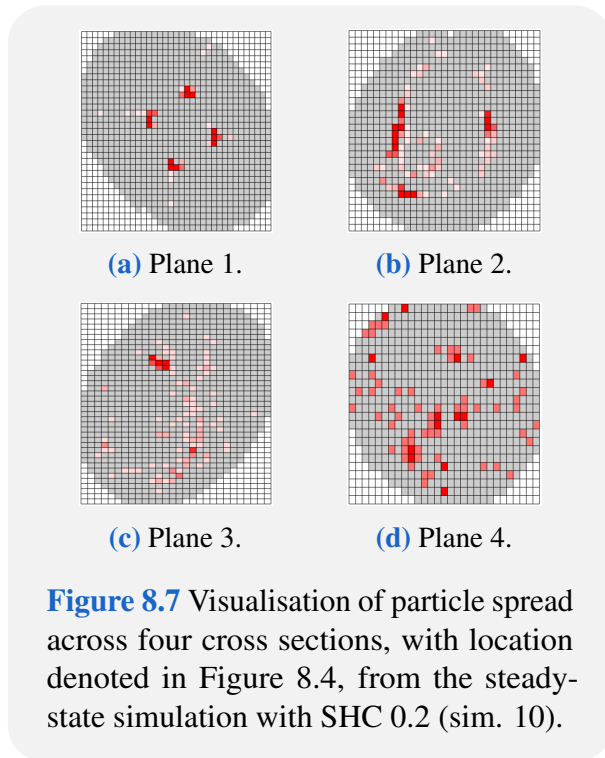


Table 8.4 Overview of the IPS values for the SHC with 0.2 mm side-holes and an injection speed of 0.1254 m/s in steady-state conditions.

Spread Index	IPS [%]
Plane 1	3.4
Plane 2	10.0
Plane 3	11.0
Plane 4	13.0

The particle spread analysis demonstrates notably localised dispersion across all evaluated catheter configurations under steady-state conditions. All IPS values were relatively low, with the highest recorded value of only 13% occurring just before the arterial outlet of SHC 0.2. This suggests that particle dispersion remains highly localised, a finding further supported by the visual evidence provided in the cross-sectional figures. Specifically, the IPS values at the first plane, immediately downstream from the injection point, remain under 5% for all catheter types. These visualisations clearly indicate concentrated injection streams, marked by red cells occupying a minimal area within each cross-section. This behaviour was also seen in the particle tracks.

The minimal particle spread observed can be largely attributed to the steady-state condition of the simulations, with the injection speed closely matching the blood flow velocity. As demonstrated by Bomberna et al. (2024) [54], particle dispersion behaviour is inherently time-

dependent. A transient scenario, characterised by fluctuations in blood flow during the injection process, would likely result in variable fluid forces on the particles, potentially increasing particle dispersion and subsequently elevating IPS values.

The IPS values confirmed the expectation of an increase in spread from proximal to distal cross-sections. In most cases, particles dispersed more extensively as they navigated through complex arterial geometry, particularly due to wall interactions and arterial bifurcations. Consequently, the particle spread at the cross-section nearest to the outlet consistently displayed the highest IPS.

As already mentioned, Ortega et al. (2022) [43] highlighted that higher crossflow conditions promote greater particle spread. However, in the current analysis, the differences in dispersion between the SHC 0.2 and SHC 0.4 configurations were not coherent, with both SHC designs having a higher IPS value at half of the cross-sectional locations. Instead, the apparent increase in dispersion from the SMC to the SHC configurations can predominantly be ascribed to the presence of multiple injection streams, rather than intrinsic differences in lumen filling characteristics.

Notably, the SHC 0.2 configuration facilitated injection streams positioned closer to the arterial walls compared to the SHC 0.4. This proximity to the arterial walls generally predisposes particles towards a wider range of outlets, contributing to increased dispersion over the outlets. PRMs support this statement in the article of Bomberna et al. (2021) [55], with injection regions close to the wall being more variable in targeted outlet. Hence, the higher dispersion observed in the SHC configurations relative to the SMC arises mainly from the injection stream dynamics rather than from a fundamental difference in particle spread.

The analysis of the particle dispersion is clinically relevant, as a greater particle spread improves particle distribution throughout the arterial lumen, allowing them to follow all bloodflow paths and reach every outlet. Moreover, if the particles are distributed more uniformly, this results in a better alignment with blood flow distribution, which helps reduce the influence of clinical parameters. However, the uniformity of particle spread becomes unimportant when the IPS is low. For instance, if the particle distribution is unevenly concentrated on one side of the lumen, resulting in all particles being directed into a single outlet, uniformity in their spread becomes irrelevant.

8.4 Particle Distribution and Tumour Dose

Figures 8.8, 8.9, and 8.10 illustrate the particle distribution across 17 arterial outlets for the three distinct catheter configurations. The visualisations distinguish between tumour outlets (marked in red) and healthy tissue outlets (marked in green).

For the SMC (Figure 8.8), particles demonstrate a highly targeted distribution, exclusively accumulating in tumour-specific outlets. Quantitative analysis (Table 8.5) confirms that the SMC reaches only three tumour outlets. Those three outlets account for 62 % of the total blood outflow and perfuse 68.86% of the tumour, denoted by tumour coverage in Table 8.6. The tumour coverage was calculated by summing all TPPs of the perfused outlets. The same table underscores the precision of SMC, delivering 100% of particles to tumour tissue while effectively avoiding healthy tissue altogether.

Table 8.5 The total number of (tumour) outlets accessed by the particles in the three steady-state simulations (sim. 6, 10, 14): eight out of 17 outlets are related to tumour perfusion outlets.

Catheter type	Number of outlets reached	Number of tumour outlets reached
SMC	3	3
SHC 0.4	4	3
SHC 0.2	12	4

Table 8.6 Overview of the tumour dose and healthy dose, represented in percentage points, for the three steady-state simulations (sim. 6, 10, 14).

Catheter type	Tumour dose [%]	Healthy dose [%]	Tumour coverage [%]
SMC	100.00	0.00	68.86
SHC 0.4	95.73	4.27	68.86
SHC 0.2	44.81	55.19	79.41

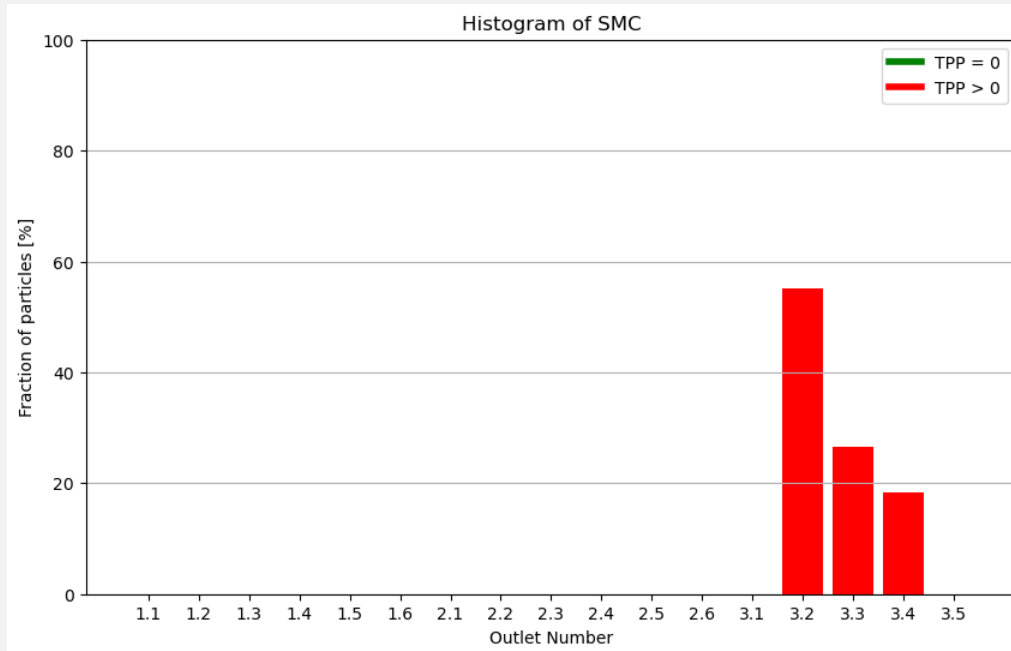


Figure 8.8 Particle distribution over the 17 outlets for the SMC. The tumour outlets are denoted in red and the healthy tissue in green.

The SHC 0.4 configuration (Figure 8.9) slightly broadens particle dispersion, distributing particles across four arterial outlets, primarily tumour-related. Outlet 3.2 receives the highest amount of particles (36.39 %) but has a moderate blood outflow of 15.00 %. In contrast, the outlet with the highest outflow, 3.4 (31.73 %), received only 30.07 %. A minimal particle fraction reaches a healthy tissue outlet, evident by a modest increase in the healthy tissue dose to 4.27% (Table 8.6), slightly reducing tumour targeting precision to 95.73%. Nonetheless, the distribution remains predominantly tumour-focused.

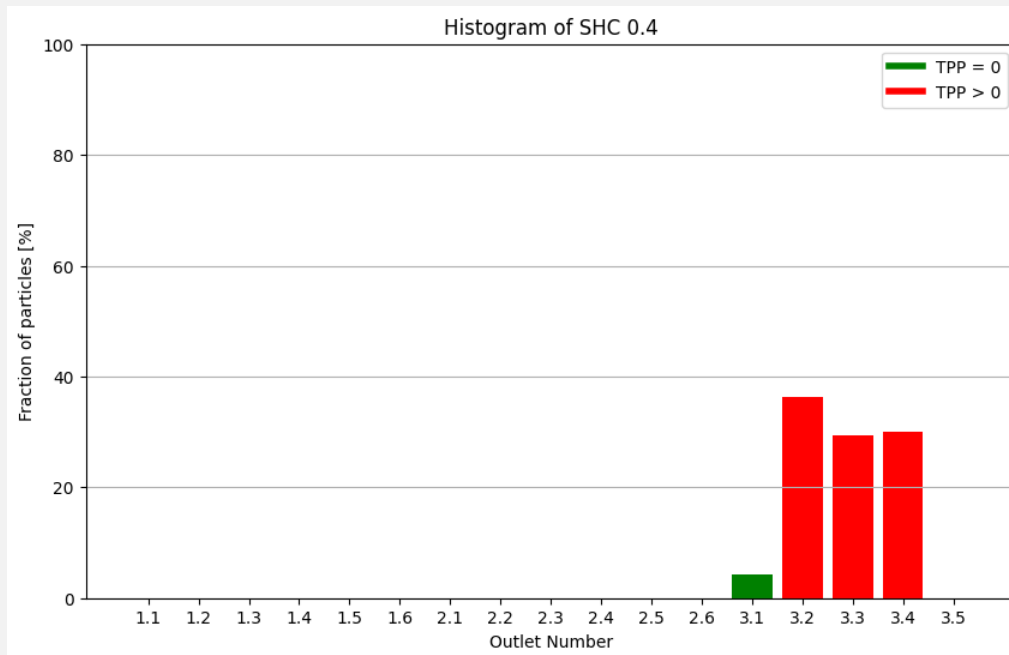


Figure 8.9 Particle distribution over the 17 outlets for the SHC 0.4. The tumour outlets are denoted in red and the healthy tissue in green.

Changes occur with the SHC 0.2 configuration (Figure 8.10), where extensive dispersion is observed. Those results confirm earlier expectations regarding the effect of side-hole size on particle dispersion over the outlets. Specifically, the smaller the side-holes, the greater the crossflow, resulting in increased dispersion across arterial outlets. This is evidenced by the rise in outlet targeting from 4 outlets in the SHC 0.4 to 12 outlets in the SHC 0.2. However, this broader dispersion predominantly involves healthy tissue outlets (8 out of 12) rather than tumour-specific outlets, markedly reducing targeting accuracy. For instance, the SHC 0.2 delivered only 44.81% of particles to tumour tissue, compared to 95.73% for the SHC 0.4 (Table 8.6). Conversely, the SHC 0.2 configuration exposed 55.19 % of particles to healthy tissues.

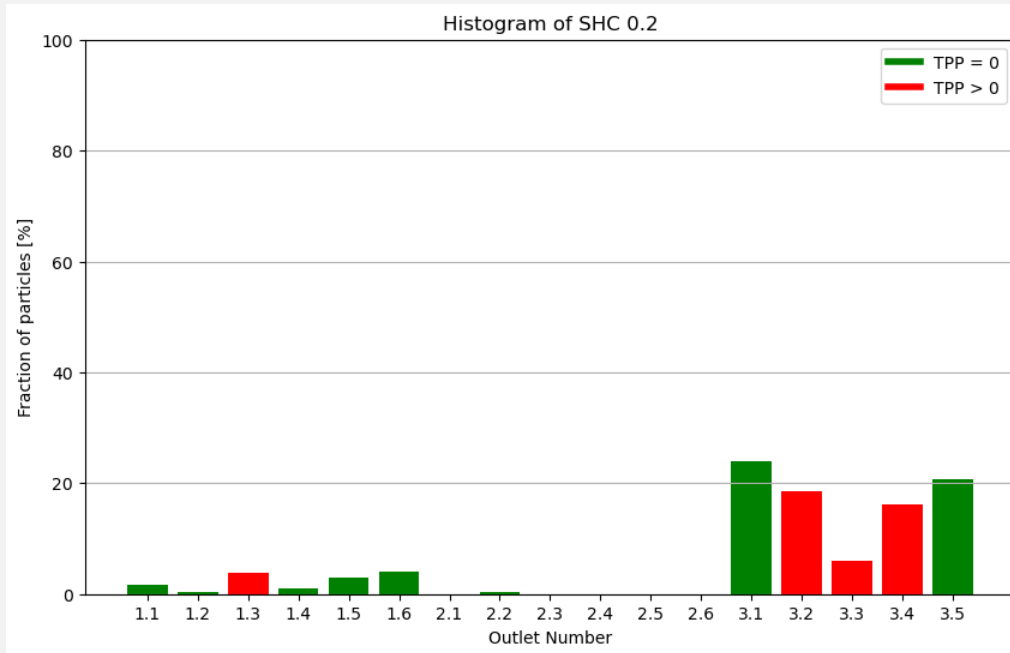


Figure 8.10 Particle distribution over the 17 outlets for the SHC 0.2. The tumour outlets are denoted in red and the healthy tissue in green.

Evaluating the catheters based on tumour dose alone, the SMC emerges as the optimal design under the tested conditions, as it exclusively reaches tumour outlets and thus achieves a perfect tumour dose of 100%. In contrast, the SHC 0.2, despite superior tumour coverage (79.41%) and accessing four tumour outlets compared to three for the other configurations (Table 8.5), compromises therapeutic precision due to extensive healthy tissue engagement.

In terms of tumour coverage, the SHC 0.2 indeed provides the highest coverage at 79.41%. However, this advantage comes with substantial dispersion into non-targeted areas. Interestingly, both the SMC and SHC 0.4 configurations reach three tumour outlets each, yet the SMC achieves a higher tumour dose. Thus, under these specific simulation parameters (radial tip position, axial tip position, and injection speed), the SMC performs the best overall, with exceptional targeting precision and a high tumour dose, albeit at a slightly lower coverage rate.

It must be emphasised that conclusions regarding catheter performance are currently limited by the small number of simulations, with only one simulation performed per catheter type. Factors such as axial tip position, radial tip position, and side-hole orientation were not varied in this analysis. The ideal performance observed for the SMC in these specific conditions might not be generalised effectively in clinical settings, where achieving precise catheter placement is notoriously challenging. As detailed in Section 3.2, variability in clinical parameters has a substantial impact on catheter performance. The concept behind the SHC design aims to mitigate such sensitivity by fostering particle dispersion within the arterial lumen. However, the four

distinct particle streams observed indicate that particle distribution remains somewhat dependent on these clinical parameters. Thus, despite their dispersion-enhancing design, SHCs also require parameter tuning similar to the SMC to optimise therapeutic outcomes.

8.5 Matching and Targeting Deviation Index

When assessing the performance of catheters, both the Matching Deviation Index (MDI) and the Targeting Deviation Index (TDI) offer essential insights. Both indices are presented in Table 8.7. Lower values of these indices signify better catheter performance. All evaluated catheters exhibited values below 10%, indicating generally effective designs.

Table 8.7 Overview of the matching deviation index (MDI) and targeting deviation index (TDI) for the three steady-state simulations (sim. 6, 10, 14).

Catheter type	Matching Deviation Index	Targeting Deviation Index
SMC	6.09	5.15
SHC 0.4	4.28	3.77
SHC 0.2	5.81	6.61

The SHC 0.4 demonstrated the best overall performance, based on both MDI and TDI, with an MDI of 4.28% and a TDI of 3.77%. This indicates that the SHC 0.4 achieved the best alignment of particle distribution with blood flow distribution, thereby reducing the possible impact of catheter parameters. Additionally, the low TDI reflects improved medical performance, suggesting that the particles delivered through this catheter closely matched the tumour perfusion percentages, ensuring optimal tumour coverage and effective dose distribution.

In comparison, the SMC recorded an MDI of 6.09% and a TDI of 5.15%. These slightly elevated values suggest that the particle distribution does not align as closely with the blood flow distribution. As previously mentioned, the SMC design exhibits limited spread and targets only three specific outlets, leading to increased deviation values. This finding correlates with those of Ortega et al. (2025) [47], which indicate that SHC designs typically outperform SMC. In these simulations, the lower MDI and TDI values for the SHC 0.4 are a result of the enhanced spreading within the arterial lumen facilitated by four injection streams.

Interestingly, Ortega et al. (2022) [43] previously found that increased crossflow typically results in lower MDI and TDI values. However, the SHC 0.2 deviated from this expectation, exhibiting a higher MDI of 5.81% and the highest TDI of 6.61%. It is essential to note that only three simulations were conducted for each catheter type, which limits the generalizability of the findings. The difference between SHC 0.2 and SHC 0.4 can be explained by the unique particle spread patterns of SHC 0.2, where particle trajectories are closer to the arterial wall,

preferentially targeting peripheral outlets with relatively lower outflow, resulting in a greater deviation from optimal distribution.

The SHC 0.4 effectively targeted the outlets with the highest outflow (62.28%). The remaining blood flow fraction (34.72%) is spread across the thirteen other outlets, resulting in low outflow fractions for those outlets. Thus, avoiding targeting these outlets is advantageous for the MDI.

The elevated TDI in the SHC 0.2 case primarily arises from increased particle dispersion toward healthy tissue, resulting in suboptimal targeting and greater deviation. In contrast, both SHC 0.4 and SMC targeted three tumour outlets. Although the tumour doses delivered by these two catheters were similar, SHC 0.4 achieved lower TDI values due to its more effective particle dispersion, ensuring improved alignment with the tumour perfusion fractions. At the same time, the four streams remained close to the SMC injection stream compared to SHC 0.2, reducing particles to the peripheral outlets.

8.6 Comparison with Previous Studies

Upon comparing the findings of this study with those of previous research, several points of agreement and divergence become clear.

Firstly, the current study can be directly compared with Jana Zeebroek's thesis. Zeebroek concluded that the MDI values were highest for SHC 0.4 and lowest for SHC 0.2 [35]. Interestingly, this outcome is precisely the opposite of the results obtained in this study. These differences in results could be attributed to the differences in geometric detailing. As previously emphasised, particle distribution is considerably influenced by arterial wall interactions and bifurcations, indicating that the enhanced geometric detail in this study might contribute to the altered dispersion patterns observed. Moreover, variations in catheter positioning and orientation within the arterial geometry affected the results as well. The SHCs aimed to reduce the sensitivity of those parameters but didn't eliminate them due to the persistent clear injection streams.

Another explanation for this discrepancy lies in the differences in viscosity values used in the respective simulations. The simplified Quemada viscosity model employed in this study, as detailed in Section 6.1 and Appendix E, notably affects the behaviour of blood flow and particle trajectories due to the one-way coupling mechanism used. Specifically, when applying the simplified Quemada model to Zeebroek's case, computed viscosity values averaged at 0.003766 Pa·s, with a 95th percentile of 0.006565 Pa·s, contrasting slightly with Zeebroek's noted average of 0.003985 Pa·s and a 95th percentile of 0.006916 Pa·s. Reproducing Zeebroek's scenario with the simplified Quemada model yielded particle distribution outcomes comparable to those in this study, strongly suggesting that the choice of the viscosity model impacts the simulation results.

Secondly, comparisons with Ortega et al. (2022) [43] revealed insightful differences. The article concluded that higher crossflow reduces MDI values. Still, their conclusions were drawn from an idealised, simplistic model of the hepatic artery, potentially overlooking the substantial influence of detailed hepatic geometry. The current study conclusively highlights hepatic geometry as a critical factor influencing MDI outcomes.

Lastly, the present study partially aligns with Ortega et al. (2025) [47], who performed simulations on personalised hepatic geometry. This article compared only one SHC configuration with an SMC, noting lower MDI values for SHC compared to SMC, which is consistent with this study's findings. However, the article also concluded that the TDI was typically lower for SHC than SMC. Contrarily, this study finds the highest TDI for SHC with 0.2 mm side holes, attributed to the unique injection and dispersion patterns already elaborated in section 8.5.

Chapter 9

Evaluation Side-hole Orientation

This chapter presents the results and discussion of objective 2, assessing the influence of radial orientation of side-hole catheters (SHCs) on particle distribution within hepatic arteries. Initially, the visualisation of particle trajectories (Section 9.1) demonstrates differences in dispersion patterns across catheter configurations. This visual analysis is complemented by a quantitative study, which evaluates particle spread indices and their dependency on radial orientation (Section 9.2). Finally, the impact of radial orientation on particle distribution and key metrics (MDI, TDI) is rigorously assessed (Section 9.3 and 9.4).

9.1 Particle Tracks

Figure 9.1 visualises particle trajectories from six steady-state simulations (sim. 10, 14, 18, 19, 20, 21). These simulations consist of two types of catheters: SHC 0.2 (subfigures 9.1a, 9.1c, 9.1e) and SHC 0.4 (subfigures 9.1b, 9.1d, 9.1f). Additionally, they include three distinct radial orientations of the catheter side-holes, each shifted radially by 30 degrees, as shown in Figure 5.7. Particle tracks are colored based on their velocity magnitudes, with the maximum set to 0.30 m/s. Visualisations of the pathlines at the catheter tip are excluded from this figure as they remain consistent with those presented in Figure 8.2, varying only in side-hole orientation.

The analysis of particle tracks confirms conclusions similar to those drawn in Section 8.2. Notably, SHC 0.2 consistently demonstrates greater dispersion of particles compared to SHC 0.4 across all examined orientation scenarios. This heightened dispersion can largely be attributed to the proximity of the injection streams to the arterial wall in the SHC 0.2 configuration, greatly increasing the likelihood of wall interactions.

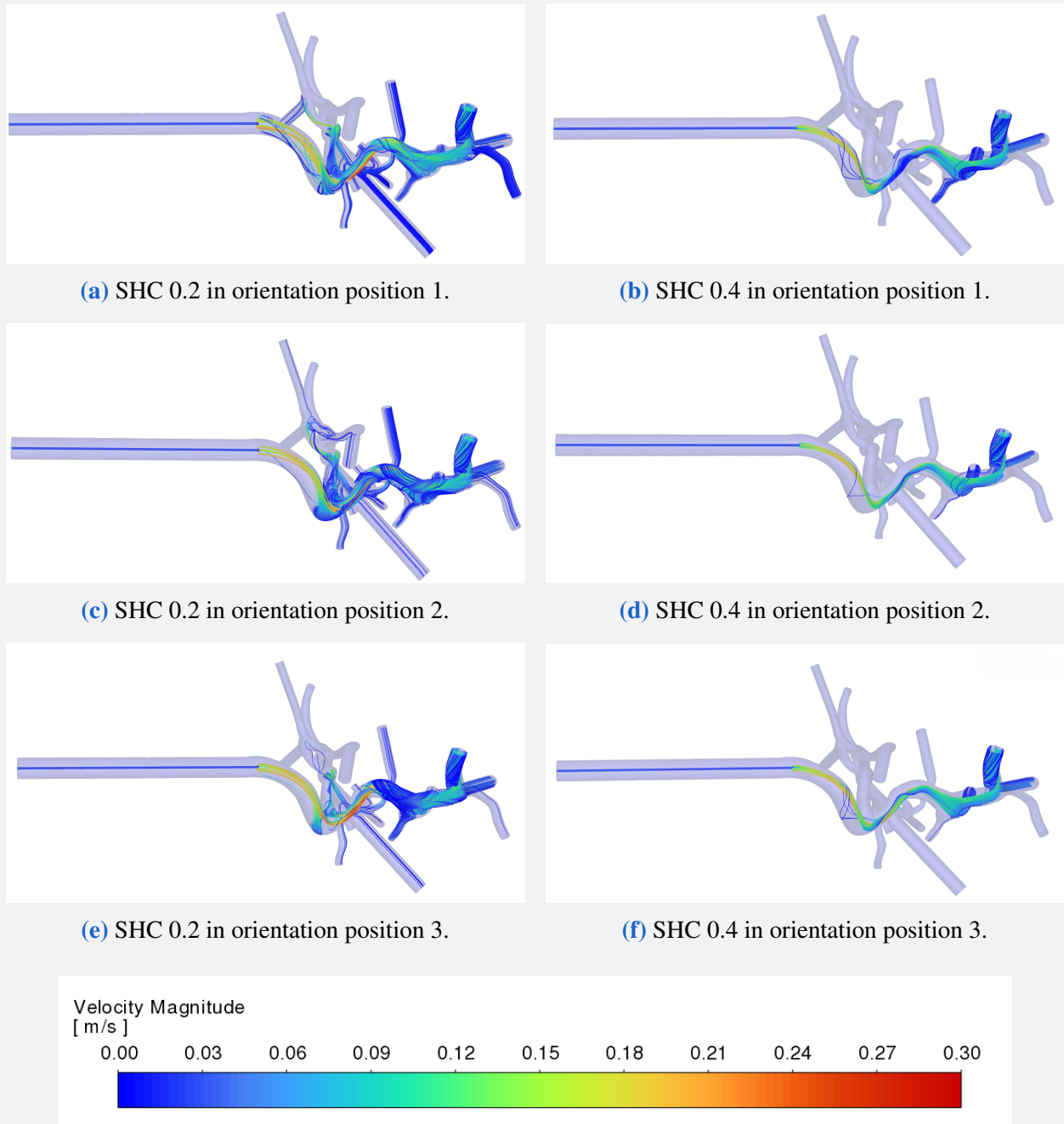


Figure 9.1 Visualisation of the particle tracks, indicated by velocity magnitude [m/s], from the six steady-state simulations with two types of catheter (SHC 0.2 and SHC 0.4) and three different radial orientations of the side-holes (Figure 5.7) (sim. 10, 14, 18, 19, 20, 21).

The particles interacting with the arterial walls experience a substantial reduction in velocity due to the no-slip boundary condition imposed on the arterial surface. Consequently, this interaction dramatically influences the particle trajectories. Specifically, the SHC 0.2 catheter consistently induces collisions with the arterial wall prior to the first bifurcation across all orientations. Given the simulation assumption of elastic interactions, with both tangent and

normal restitution coefficients set to 1, these wall collisions effectively scatter particles across the arterial lumen. Such scattering behaviour increases particle dispersion.

The interaction patterns observed with the SHC 0.2 align with the typical PRM of a patient-specific case. A typical PRM is presented by Bomberna et al. (2021) [55]. They illustrate that four evenly spaced injection points situated further from the lumen centre lead to a greater likelihood of dispersion into side-branches. Correspondingly, each different orientation of the SHC 0.2 catheter results in unique interaction patterns with the arterial wall, creating considerable variability and reduced predictability regarding which arterial outlets become targeted. This variability is also apparent in the outer circle of the PRM, where the outlet that will be targeted becomes less clear. This variability in particle trajectories can be seen in Figure 9.1.

Conversely, the SHC 0.4 shows fewer interactions with the arterial walls, especially preceding the first bifurcation. The injection points are located closer to the lumen centre, aligning with a PRM region that is more consistent and uniform. This configuration yields predictable and similar particle dispersion patterns across the examined orientations. Furthermore, the dispersion of particles predominantly occurs immediately before the arterial outlets rather than at earlier bifurcations, further enhancing the predictability and reproducibility of particle trajectories observed with the SHC 0.4.

9.2 Particle Spread

Figures 9.2 and 9.3 present detailed analyses of the Index of Particle Spread (IPS) at planes 2 and 3, respectively. These planes correspond to those previously defined in Figure 8.4, though only results for planes 2 and 3 are included here. Plane 1 is excluded because no difference in injection behaviour, compared to the results from Section 8.3, was observed, making further analysis redundant. Plane 4, positioned immediately before the arterial outlet, was considered less relevant for characterising the impact of side-hole orientation on particle spread.

The particle spread analysis was conducted at an injection speed of 0.1254 m/s for three catheter types and three side-hole orientations. Higher IPS values are visualised in red, indicating a greater particle spread across the arterial lumen.

At plane 2, only two configurations yielded IPS values above 10%: SHC 0.4 orientation 1 (12%) and SHC 0.2 orientation 2 (18%), with the latter clearly exhibiting the highest spread. The SMC consistently demonstrated the lowest dispersion at plane 2, with an IPS value of 2.1% across all orientations. Notably, SHC 0.2 had the highest spread for two of the three orientations, with orientation 2 standing out distinctly.

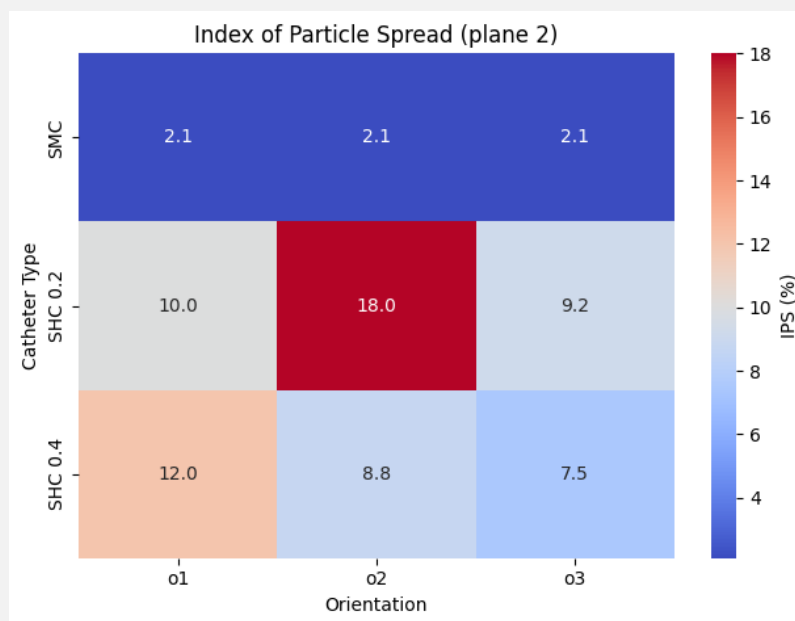


Figure 9.2 Visualisation of the Indices of Particle Spread at plane 2 for the different orientations and catheters, with red indicating a better result and blue indicating a poorer result.

At plane 3, located after the second bifurcation involving outlet 3.1, the SMC again consistently exhibited the least dispersion, with an IPS of 3.0% for all orientations. Conversely, SHC 0.2 consistently had the highest IPS, exceeding 10% across all orientations, with a particularly prominent spread at orientation 2 (16%). The differences in particle spread across orientations were most pronounced at orientation 2 and least noticeable at orientation 1.

Notably, IPS values across both planes are relatively low, ranging between 2.1% and 18%. These values are considerably lower than those reported by Bomberna et al. (2024) [54], who observed IPS values between 19% and 88% for the non-truncated geometry with 48 outlets instead of 17. This discrepancy is likely attributable to the steady-state condition used in the current objective, as previously discussed in Section 8.3.

The SMC maintains uniform IPS values across all orientations, a direct consequence of its symmetrical design around its axis, meaning rotation does not influence its spatial configuration. Moreover, the IPS values of the SMC are always lower than those of the SHC. This conclusion aligns with the conclusion by Ortega et al. (2025) [47] that SHCs disperse particles more than SMCs.

In comparing the SHCs, SHC 0.2 consistently demonstrates a higher particle spread than SHC 0.4 at both evaluated planes, except for orientation 1 at plane 2. This observation aligns with the findings of Ortega et al. (2022) [43], who reported that smaller side-hole diameters lead to greater crossflow and, consequently, increased particle dispersion. Orientation 2 exhibits the

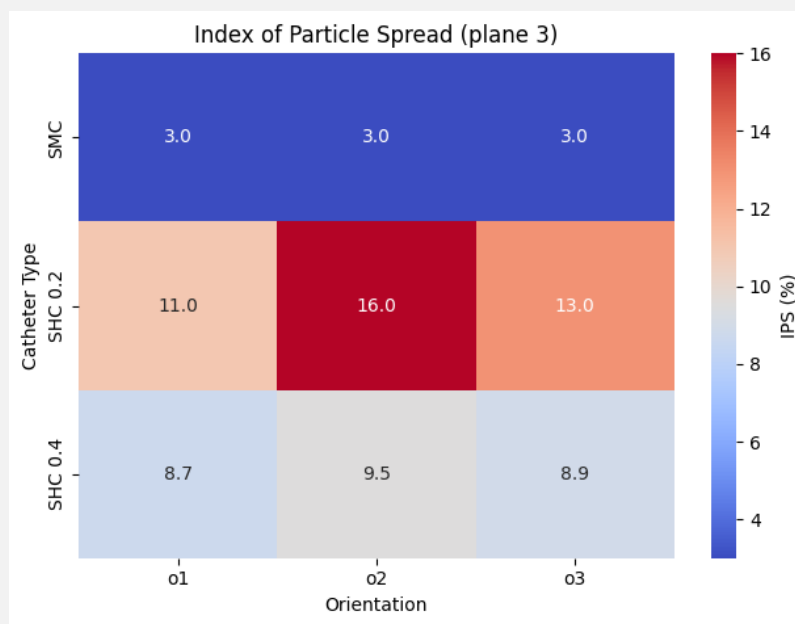


Figure 9.3 Visualisation of the Indices of Particle Spread at plane 3 for the different orientations and catheters, with red indicating a better result and blue indicating a poorer result.

highest spread difference between the SHCs, indicating an influence of catheter orientation on dispersion characteristics. Conversely, orientation 1 exhibits a reversed relationship or minimal difference in IPS between SHC types. This anomaly arises due to an unusually elevated IPS value (12%) for SHC 0.4 orientation 1 at plane 2, which remains relatively low in absolute terms but noticeably higher in comparison to other SHC 0.4 configurations. A supplemental calculation of IPS yielded a value of 9.3%, aligning more closely with the overarching trend, suggesting that even slight deviations can influence relative comparisons. The changing IPS value can be attributed to the manner in which it is calculated by rotating the cross-sectional plan to the xy-plane, which does not yield consistent results.

SHC 0.2 exhibits considerable variability in IPS across orientations, as evidenced by a spread difference of 8.8% at plane 2 and 5% at plane 3 between the minimum and maximum values. Such variability underscores a dependency on catheter orientation, contributing to reduced predictability. In contrast, SHC 0.4 exhibits substantially less variability, with IPS differences of only 4.5% at plane 2 and a minimal 0.8% at plane 3. This stability implies that particle spread patterns for SHC 0.4 are more predictable and orientation-independent.

Moreover, the IPS typically increases from plane 2 to plane 3. This is the case in seven out of the nine cases examined, where particles are dispersed more extensively as they navigate through complex arterial geometry, particularly due to wall interactions and arterial bifurcations.

Interestingly, the two exceptions, those configurations with initially high IPS (above 10%) at plane 2, show a decrease toward plane 3, deviating from the general expectation.

9.3 Particle Distribution and Tumour Dose

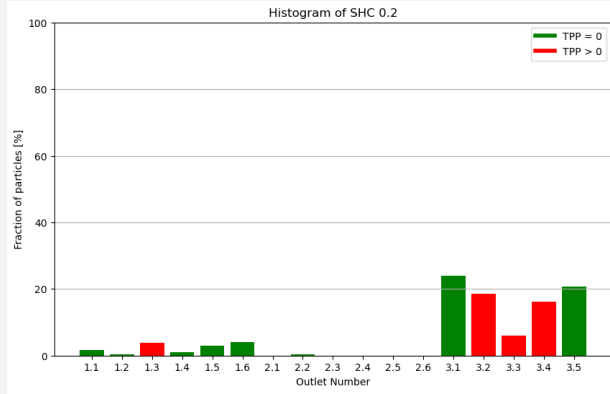
Figure 9.4 illustrates particle distributions across the 17 arterial outlets for the two catheter types in three radial orientations. Tumour outlets are indicated in red, while healthy tissue outlets are in green.

Catheter SHC 0.2 exhibits a broader distribution, spanning between 11 and 14 outlets (Table 9.1), confirming the observations in Figure 9.1. In contrast, SHC 0.4 exhibited a focused distribution, consistently concentrating particles in only four outlets regardless of orientation. Particles remained confined within branch 3 for SHC 0.4. This targeted behaviour stems from its injection characteristics, as particles are released closer to the lumen centre, reducing interactions with the arterial wall before reaching the first bifurcation. Consequently, particles predominantly follow the primary arterial flow, accounting for 66.93%, continuing straight rather than turning into side branches. In contrast, SHC 0.2 injects particles closer to the arterial walls, substantially increasing wall interactions and thus particle dispersion. Consequently, SHC 0.2 targets all three arterial branches, though it predominantly focuses on branch 3.

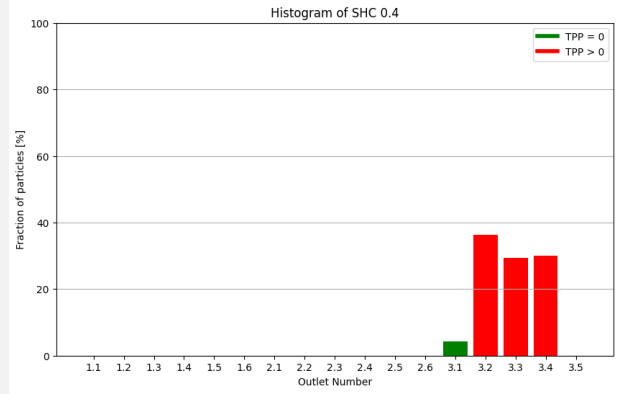
Table 9.1 The total number of (tumour) outlets accessed by the particles with the steady-state SMC (sim. 6) and in the six steady-state simulations with two types of catheter (SHC 0.2 and SHC 0.4) and three different radial orientations of the side-holes (sim. 10, 14, 18, 19, 20, 21): eight out of 17 outlets are related to tumour perfusion outlets.

Catheter type	Catheter orientation	Outlets reached	Tumour outlets reached
SMC	/	3	3
SHC 0.2	1	12	4
SHC 0.2	2	14	7
SHC 0.2	3	11	4
SHC 0.4	1	4	3
SHC 0.4	2	4	3
SHC 0.4	3	4	3

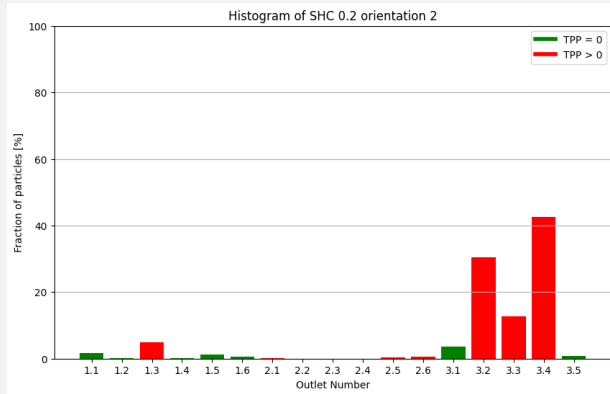
SHC 0.4's near-exclusive distribution to tumour outlets results in superior tumour dose performance compared to SHC 0.2 across all configurations, as shown in Table 9.2. The particle distribution further emphasises the greater predictability of SHC 0.4, which consistently targets four outlets, three of which feed tumour tissue, regardless of orientation. Conversely, SHC 0.2 demonstrates minimal variability in tumour dose, with only a 4.18% difference. SHC 0.2, however, exhibits substantial dependency on orientation, targeting between 11 and 14 outlets with tumour-feeding outlets between 4 and 7, resulting in a substantial variability in tumour dose



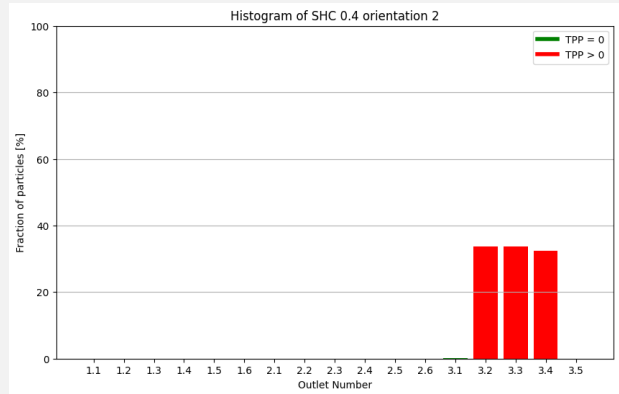
(a) SHC 0.2 in orientation position 1.



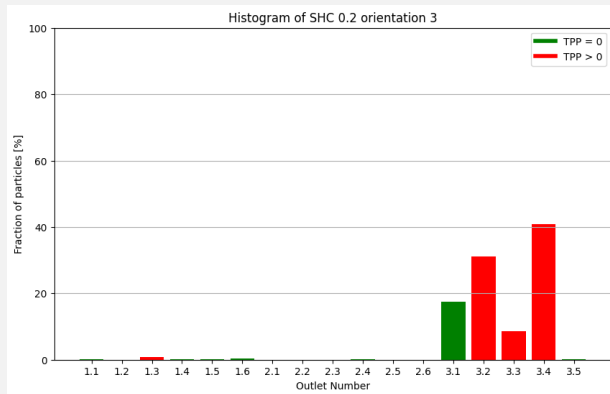
(b) SHC 0.4 in orientation position 1.



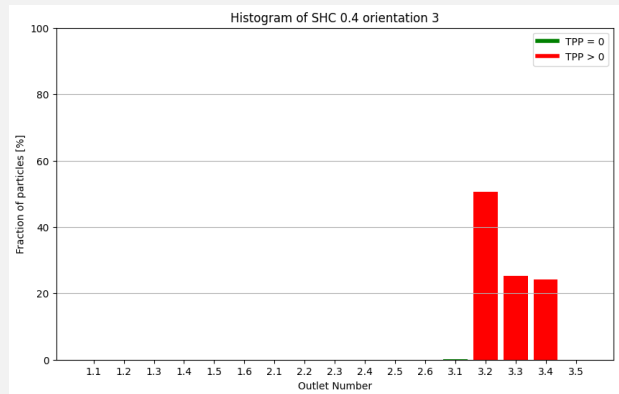
(c) SHC 0.2 in orientation position 2.



(d) SHC 0.4 in orientation position 2.



(e) SHC 0.2 in orientation position 3.



(f) SHC 0.4 in orientation position 3.

Figure 9.4 Visualisation of the particle distribution, red for tumour outlets and green for healthy tissue outlets, for the six steady-state simulations with two types of catheter (SHC 0.2 and SHC 0.4) and three different radial orientations of the side-holes (sim. 10, 14, 18, 19, 20, 21).

(44.81% to 91.53%). The broader distribution achieved by SHC 0.2 resulted in higher tumour coverage, but this also increased the dose to healthy tissue.

Table 9.2 Overview of the tumour dose (TD), healthy dose (HD) and tumour coverage (TC), represented in percentage points, for the steady-state SMC (sim. 6) and the six steady-state simulations (sim. 10, 14, 18, 19, 20, 21).

Catheter type	Orientation	TD [%]	HD [%]	TC [%]
SMC	/	100.00	0.00	68.86
SHC 0.2	1	44.81	55.19	79.41
SHC 0.2	2	91.53	8.47	91.49
SHC 0.2	3	81.28	18.72	76.41
SHC 0.4	1	95.73	4.27	68.86
SHC 0.4	2	99.82	0.18	68.86
SHC 0.4	3	99.91	0.09	68.86

Detailed dose analysis indicates that outlets 3.2, 3.3, and 3.4 are predominantly targeted by all configurations except SHC 0.2 orientation 1, which favours healthy tissue. Notably, despite outlet 3.4 having the highest outflow among these three outlets, this is inconsistently reflected in the dose distribution. Only SHC 0.2 orientations 2 and 3 allocate the highest particle dose to outlet 3.4. Outlet 3.2 consistently receives a relatively high dose despite its lower outflow, attributed to the low IPS at plane 2, causing particles to skew towards one side, as evident in Figures 8.5 and 8.6, thus diverting them from their intended outlets.

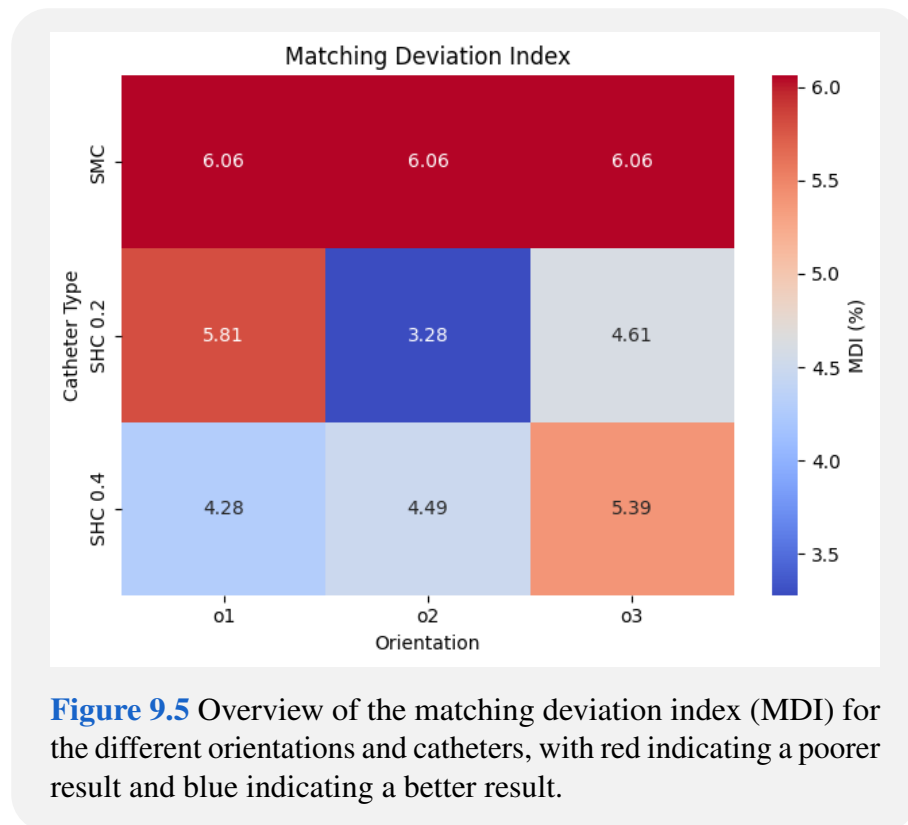
In the current radial position, the catheter positioning already achieves a tumour dose of 100% for SMC. As noted in Section 8.4, these results specifically pertain to the examined radial and axial tip positions and injection speeds, with limited parameter variations. Within these limited configurations, SHC 0.4 consistently outperforms SHC 0.2 in tumour dose, though at the expense of lower tumour coverage.

However, the SHC 0.2 orientation 2 configuration uniquely combines high tumour dose with extensive tumour coverage, potentially marking it as the optimal catheter configuration. A critical consideration is that a mere 30-degree shift in catheter orientation results in a drastically elevated healthy tissue dose (55.19%), thereby introducing additional sensitivity rather than achieving the intended goal of reducing parameter dependency with SHC designs.

9.4 Matching and Targeting Deviation Index

Figures 9.5 and 9.6 analyse the Matching Deviation Index (MDI) and the Targeting Deviation Index (TDI), respectively. The MDI, indicating alignment with blood flow (lower values are better, more blue), remains consistently below 10% for all configurations. Consistent with the

conclusions of Ortega et al. (2025) [47], SHCs demonstrate lower MDI values compared to SMC. This indicates better alignment for SHCs with the natural blood flow. SHC 0.2 exhibited superior performance in two of the three orientations (orientations 2 and 3) examined, aligning closely with Ortega et al.'s (2022) [43] conclusion that increased crossflow through smaller side holes tends to lower MDI.

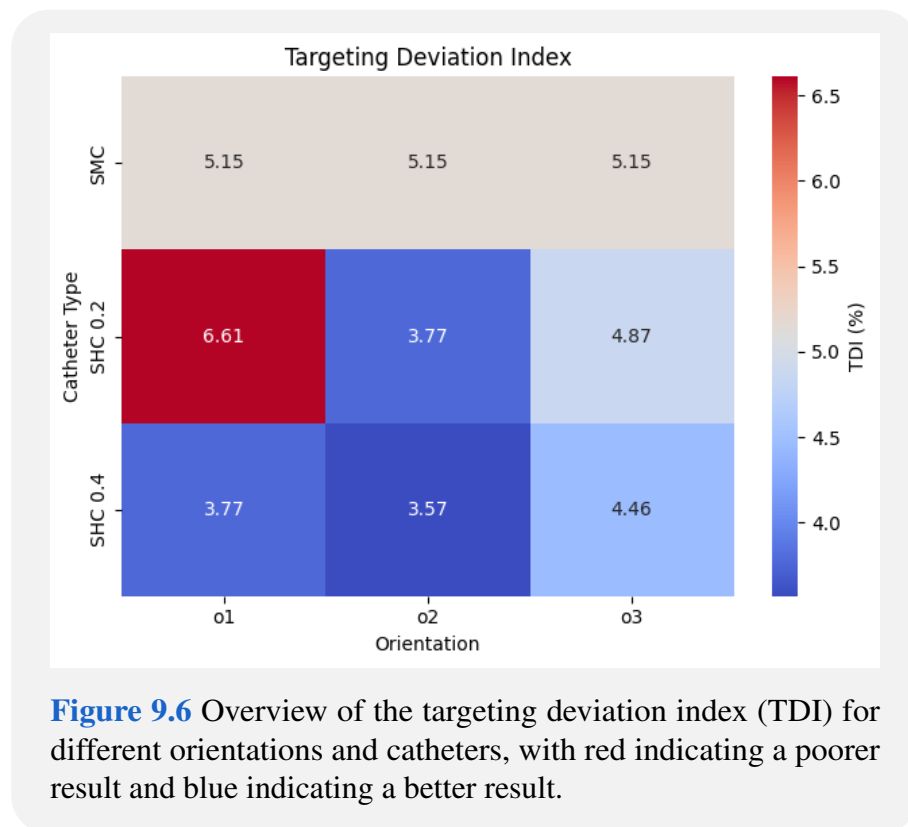


The observed MDI values exhibit a direct correlation with particle spread (IPS) at plane 2, suggesting that greater particle spread results in improved blood flow alignment, thereby lowering MDI. The dispersion of particles at the first bifurcation influences their distribution among arterial branches, aligning closely with the natural flow split between branches 1 & 2 and branch 3. Hence, increased dispersion at this bifurcation promotes a more natural and effective particle distribution. The variability in IPS observed between catheter orientations notably corresponds with variability in MDI, with SHC 0.2 displaying higher variability (2.53%) compared to SHC 0.4 (1.11%). This indicates a greater dependency on catheter orientation for SHC 0.2.

The TDI evaluates how effectively the particle distribution matches tumour perfusion requirements, with lower values denoting enhanced medical outcomes. Ortega et al. (2025) [47] similarly concluded that SHC catheters generally exhibit lower TDI values than the SMC. This aligns well with the presented findings, except in the case of SHC 0.2 orientation 1, which recorded an unusually high TDI value directly correlated with its notably low tumour dose.

Overall, SHC 0.4 consistently outperformed other configurations in terms of TDI, corresponding with consistently higher tumour dose efficiency.

Notably, SHC 0.2 demonstrates orientation dependency, exhibiting both the highest (6.61% at orientation 1) and the second-lowest TDI (3.77% at orientation 2).



From a medical performance perspective, SHC 0.4 emerges as the superior choice due to its lower orientation dependency, optimal TDI, and effective alignment of particle dose with TPP. However, SHC 0.4's superior TDI performance was not due primarily to an inherently better catheter design but rather because its injection streams were positioned closer to those of the SMC, achieving a perfect tumour dose. By enhancing dispersion with four injection streams, SHC 0.4 achieved improved alignment with tumour perfusion.

Chapter 10

Evaluation Transient Simulations

The third objective of this thesis extends previous steady-state studies by evaluating side-hole catheter performance under transient flow conditions. These simulations mimic physiological blood flow more realistically and aim to validate whether steady-state conclusions hold true dynamically.

This chapter investigates catheter behaviour during transient simulations by focusing on key factors affecting performance. It begins with fluid velocity analysis to understand how dynamic conditions impact particle trajectories (Section 10.1). Particle spread is then examined to assess whether transient flow alters dispersion patterns in the hepatic arterial network (Section 10.2). Next, the effect of particle distribution on tumour dose is evaluated to determine if transient conditions affect therapeutic delivery (Section 10.3). Lastly, the Matching and Targeting Deviation Index quantifies how well particle delivery aligns with blood flow and tumour perfusion (Section 10.4). Together, these analyses test the robustness of side-hole catheter designs in realistic, time-dependent scenarios.

10.1 Catheter Fluid Velocity

Figure 10.1 shows the catheter fluid velocity, represented by its magnitude (m/s). It displays instantaneous visualisations of the fluid instead of particle tracks. Due to the transient nature of the simulations, particles have discrete locations rather than continuous paths, which is less relevant for analysis. These visualisations offer an understanding of the behaviour of the catheter fluid, which influences particle dynamics. Furthermore, the fluid in the catheter is modelled as blood flow.

The visualisation includes three catheter types: SMC, SHC 0.2, and SHC 0.4 (sim. 22, 23, 24). Two critical cardiac cycle time points are considered: the peak systolic phase at 0.22 s and

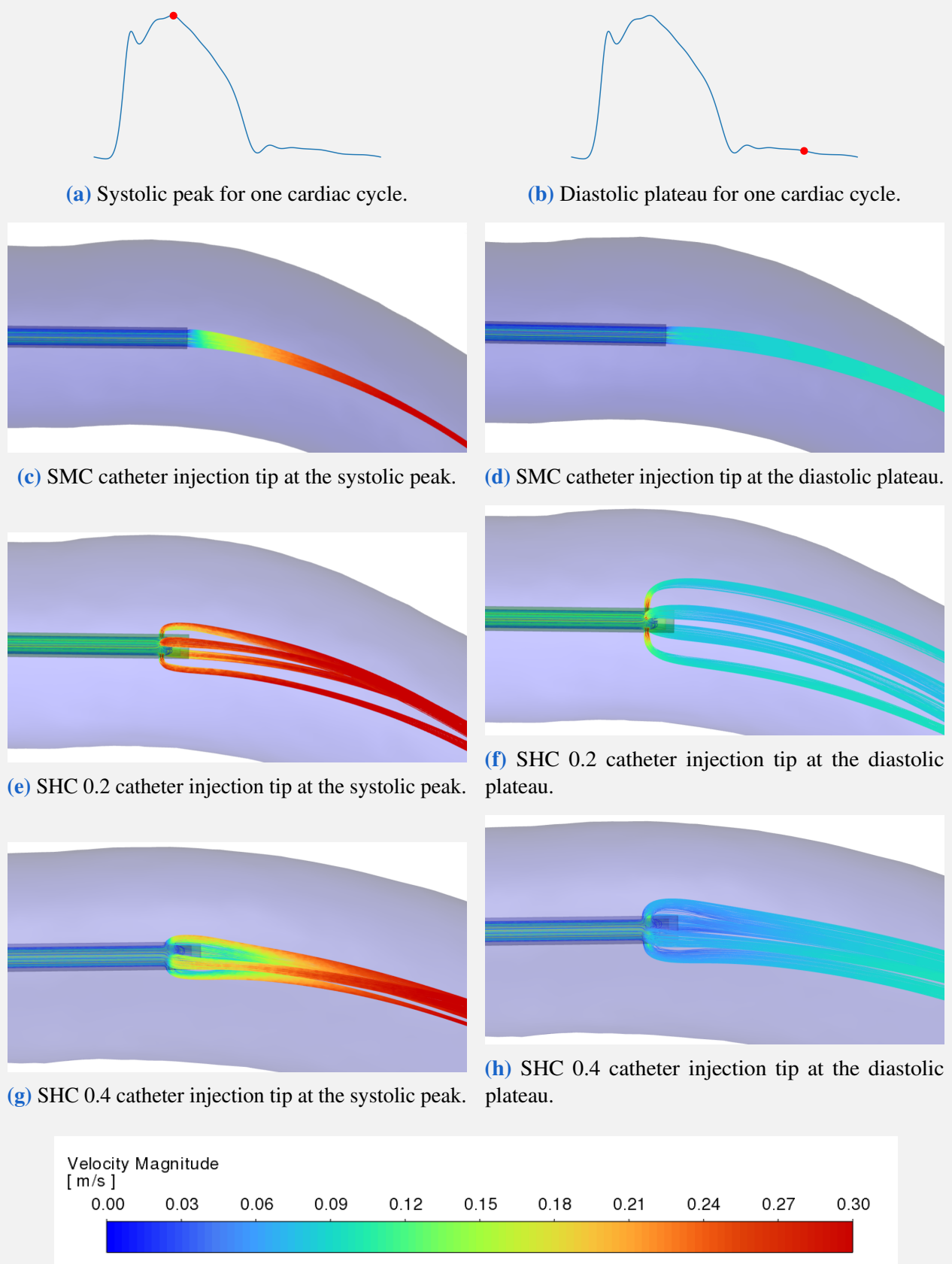


Figure 10.1 Visualisation of the catheter fluid, indicated by velocity magnitude [m/s], from the three transient simulations (sim. 22, 23, 24) with a catheter.

the middle of the diastolic plateau at 0.65 s, within a 0.8 s cardiac cycle. At peak systole, the arterial inlet exhibits the maximum flow velocity of 0.27 m/s, while at diastolic plateau, the flow reduces to 0.05 m/s. These timepoints are displayed on the velocity profiles at the arterial inlet in Figure 10.1a and 10.1b.

Despite identical injection velocities of 0.12 m/s across catheter types, catheter outlet velocities differ due to variations in outlet cross-sectional area, adhering to the continuity equation (Equation 6.1). The average and maximum velocities at catheter outlets are clearly distinguishable in the visualisation, with maximum velocities capped at 0.30 m/s for visualisation clarity. Specifically, average outlet velocities with respective maxima are as follows: SMC with 0.09 m/s (max 0.22 m/s), SHC 0.2 with 0.25 m/s (max 0.63 m/s), and SHC 0.4 with 0.06 m/s (max 0.17 m/s). These velocity differences notably influence the radial extension of the injection streams.

The temporal variations in injection stream velocities are also evident. At both phases, the catheter fluid velocity closely aligns with the arterial blood flow after injection. During peak systole, the catheter fluid velocity is notably higher due to the elevated arterial flow, approximately fivefold greater compared to the diastolic plateau. This alignment underscores the drag effect of arterial flow on the catheter fluid, demonstrating that fluid dynamics are highly responsive to cardiac-cycle-induced flow variations.

Furthermore, notable differences exist in the radial extent of injection streams across catheter types and cardiac phases. This radial extent directly correlates with the inertia of particles to cross fluid streamlines, termed crossflow, influenced by the velocity ratio between catheter outlet velocity and blood flow velocity. SHC 0.2 at diastole, with the highest ratio of 4.60, exhibits the greatest radial extent (1.79 mm). In contrast, SHC 0.4 during systole displays the lowest ratio (0.22), resulting in a minimal radial extent of 0.56 mm, knowing that the catheter radius is 0.45 mm. The SHC 0.2 shows the most difference in radial extent between the systolic and diastolic phases (0.84 mm), emphasising how temporal fluctuations affect the radial extent of the injection streams, resulting in lumen filling and particle spread. Nevertheless, four separate injection streams are still distinctly recognisable.

These results closely align with findings by Ortega et al. (2022) [43], confirming maximal blood flow and minimal crossflow during peak systole and, conversely, minimal blood flow with maximal crossflow at diastole. Specifically, SMC consistently presents ratios below 2 (0.34 at systole and 1.66 at diastole), aligning with Aramburu et al.'s [56] assertion that such ratios impede particles from effectively crossing flow streamlines.

10.2 Particle Spread

Figures 10.2, 10.3, and 10.4 distinctly visualise the particle distribution across four cross-sections over five post-injection cycles for transient simulations using the SMC, SHC 0.2, and SHC 0.4 (sim. 22, 23, and 24). In these figures, darker red regions indicate higher particle counts traversing grid cells. The cross-sectional planes employed for these analyses are positioned as shown in Figure 8.4. Quantitative analysis of those visualisations is provided by Table 10.1, 10.2, and 10.3.

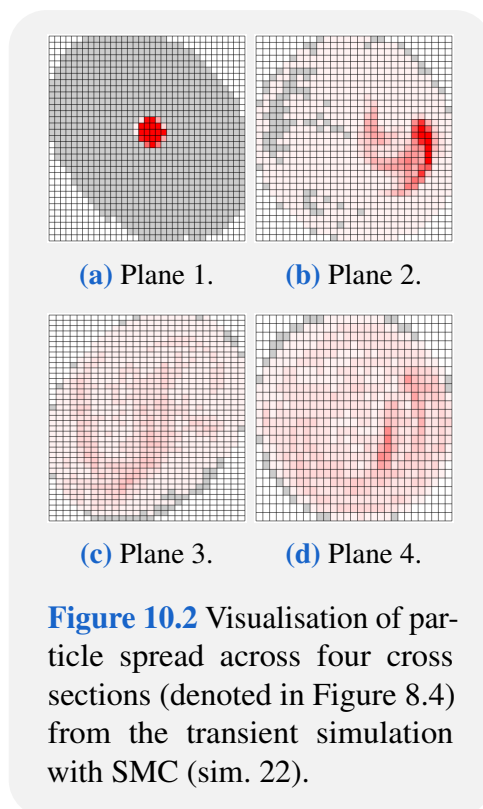


Table 10.1 Overview of the spread indices (IPS, UIPS and WIPS) for SMC at an injection speed of 0.1254 m/s in transient conditions.

Spread Index	IPS [%]	UIPS [%]	WIPS [%]
Plane 1	3	/	2
Plane 2	89	36	28
Plane 3	95	71	71
Plane 4	95	76	70

Figure 10.2 Visualisation of particle spread across four cross sections (denoted in Figure 8.4) from the transient simulation with SMC (sim. 22).

The first plane, located 2 mm post-injection, clearly still reveals the distinct injection streams for each catheter type. Notably, the SHC designs exhibit more elliptical particle streams compared to the SMC. These elliptical patterns result from a cumulative effect of streams that vary radially over time. This observation aligns with earlier conclusions indicating substantial temporal radial variability, particularly pronounced in SHC 0.2 (Figure 10.3a), characterised by a more prominent elongation along the major elliptical axis. Furthermore, all catheter designs display evident regions of high particle concentration or "hotspots," as represented by the darkest red areas. The IPS values corroborate this visual interpretation, with SMC showing a low IPS value of 3% (Table 10.1), whereas SHC 0.2 and SHC 0.4 register slightly higher values at 13% and 7%, respectively (Table 10.2 and 10.3).

As particles move downstream beyond the immediate vicinity of injection (planes 2, 3, and 4), a more spread-out distribution emerges, except notably for plane 2 in the SMC configuration

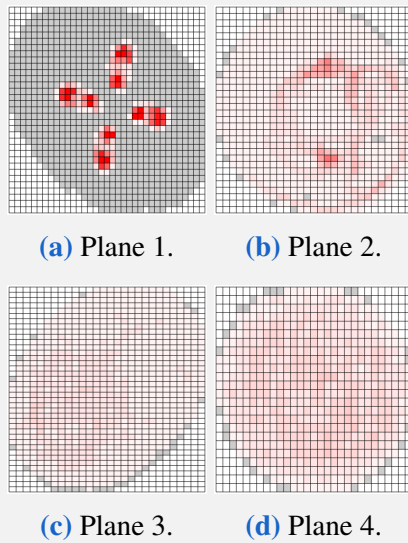


Figure 10.3 Visualisation of particle spread across four cross sections, with location denoted in Figure 8.4, from the transient simulation with SHC 0.2 (sim. 23).

Table 10.2 Overview of the spread indices (IPS, UIPS and WIPS) for the SHC with 0.2 mm side-holes and an injection speed of 0.1254 m/s in transient conditions.

Spread Index	IPS [%]	UIPS [%]	WIPS [%]
Plane 1	13	/	7
Plane 2	97	61	59
Plane 3	96	79	76
Plane 4	95	83	77

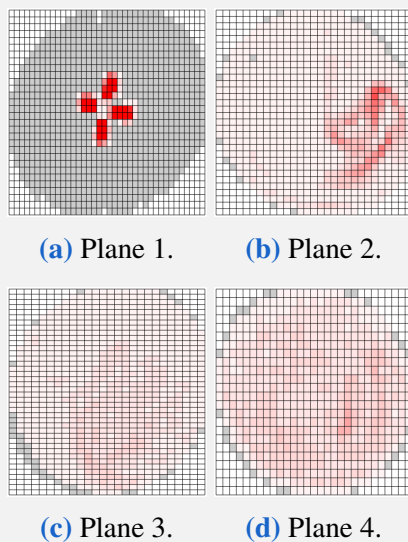


Figure 10.4 Visualisation of particle spread across four cross sections, with location denoted in Figure 8.4, from the transient simulation with SHC 0.4 (sim. 24).

Table 10.3 Overview of the spread indices (IPS, UIPS and WIPS) for the SHC with 0.4 mm side-holes and an injection speed of 0.1254 m/s in transient conditions.

Spread Index	IPS [%]	UIPS [%]	WIPS [%]
Plane 1	7	/	5
Plane 2	97	50	46
Plane 3	96	76	76
Plane 4	95	82	76

(Figure 10.2b), which shows an absence of particles in its upper-left quadrant. Quantitative analysis confirms this visual observation, with IPS values consistently surpassing 90% from plane 2 onwards, highlighting an extensive and stable particle dispersion, except for the slightly lower IPS noted at plane 2 of the SMC.

Interestingly, all catheter designs exhibit a marked increase in IPS values transitioning from plane 1 to plane 2, stabilising thereafter at a high plateau between approximately 80% and 100%. This observation is supported by the findings of Bomberna et al. (2024) [54], who reported similar behaviour in particle dispersion dynamics. Additionally, the IPS range reported in their study for the non-truncated geometry using the SMC (ranging from 2.5% to 88%) aligns closely with the results observed here.

Comparing transient to steady-state (section 8.3) simulations, IPS values demonstrate a considerable increase under transient conditions. Specifically, transient simulations yield an average IPS enhancement of approximately 12-fold, with the SMC configuration peaking at a 41-fold increase for plane 2. This substantial rise in dispersion is attributable to dynamic crossflows at the catheter tip and fluctuations in arterial flow velocities within the hepatic artery, inducing varied particle-wall and bifurcation interactions that enhance overall spread.

From a comparative design perspective, the SMC consistently exhibits lower IPS values compared to both SHCs, aligning well with findings from Ortega et al. (2025) [47], which highlighted the superior dispersion capabilities of SHC designs. Notably, however, the difference in IPS between catheter designs diminishes greatly at distal planes 3 and 4.

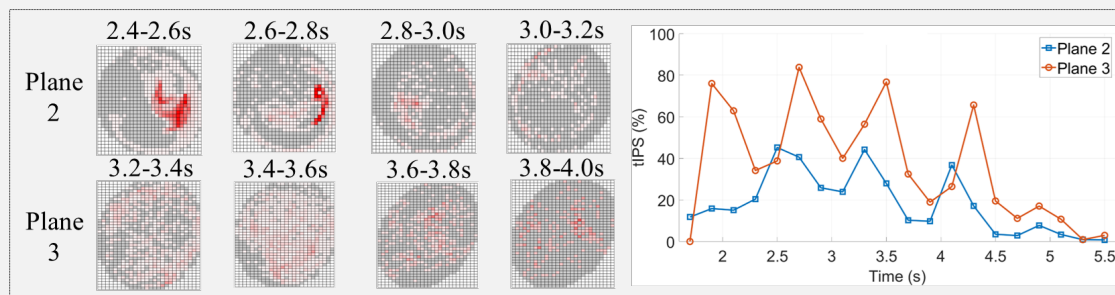
Beyond IPS, the uniformity of particle distribution, quantified by the Uniform Index of Particle Spread (UIPS), is essential for ensuring alignment with arterial blood flow. SMC records UIPS values ranging between 36% to 76%, closely matching findings reported by Bomberna et al. (2024) [54]. Furthermore, the observed trend of increasing UIPS values from proximal to distal planes across all three catheter types further aligns with Bomberna's results. Among the catheters, SHC 0.2 consistently achieves the highest UIPS values, whereas SMC exhibits the lowest. This trend is visually supported by the presence of fewer "red hotspots" in the SHC 0.2 planes compared to those of the SMC.

The observed differences in UIPS across catheter types can be attributed directly to their injection characteristics. The SMC, with its singular injection stream, inherently limits particle distribution uniformity compared to the SHCs, which benefit from initial distribution through four distinct injection points. Furthermore, SHC 0.2's more pronounced radial variability of injection streams enables particles to be uniformly distributed over a larger initial cross-sectional area, contributing to its higher overall uniformity in particle spread compared to SHC 0.4.

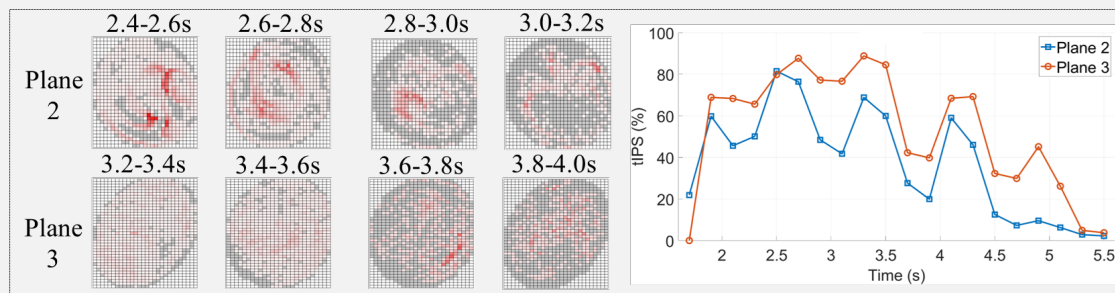
In addition to the global IPS values, Figure 10.5 provides a comprehensive representation of the temporal characteristics of particle spread, highlighting the dynamic, time-dependent

nature of dispersion across planes 2 and 3, downstream of two bifurcations. Plane 1, located immediately downstream of the catheter tip, and plane 4, situated just before the outlet, are less relevant for analysing the dynamics of temporal dispersion. Consequently, planes 2 and 3 are the primary focus of this temporal analysis.

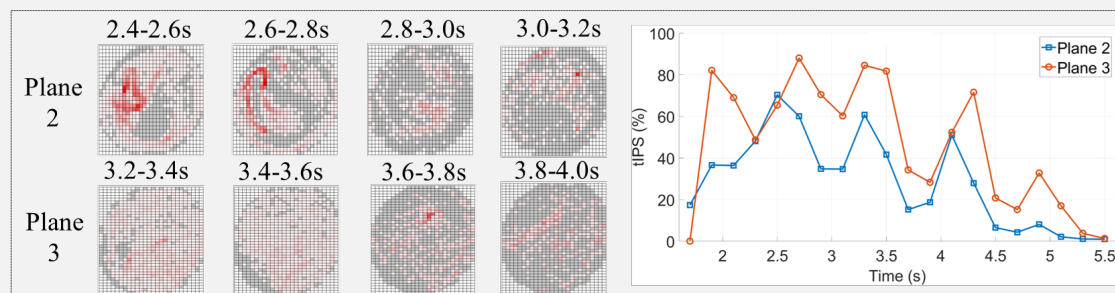
On the left side of Figure 10.5, particle dispersion is visually presented similarly to the IPS but analysed within 0.2-second intervals. For plane 2, the second post-injection cardiac cycle, spanning from 2.4 to 3.2 seconds, is depicted, whereas plane 3 illustrates the third cardiac cycle post-injection from 3.2 to 4.0 seconds. Correspondingly, on the right side, the temporal Index of Particle Spread (tIPS) is plotted against time, providing quantitative insight into dispersion at each interval.



(a) SMC



(b) SHC 0.2



(c) SHC 0.4

Figure 10.5 Visualisation of two different cross-sections (plane 2 and 3) along with tIPS values to analyse time-dependent particle spread for the three different catheters (sim. 22, 23, 24).

The temporal graphs explicitly illustrate the cyclical nature of particle dispersion, evidenced by approximately five distinct peaks corresponding directly to the five post-injection cardiac cycles. The cyclic behaviour recurs consistently every 0.8 seconds, with the peak dispersion invariably occurring in the initial interval of each cardiac cycle. These prominent peaks align with the onset of the systolic phase, characterised by rapidly accelerating blood flow that induces vortices and potential flow separation. This finding is consistent with observations reported by Bomberna et al. (2024) [54], who documented similar cyclical behaviour and tIPS values using the SMC.

When comparing catheter designs, notable distinctions emerge, particularly evident at plane 3. While the maximum IPS values or peaks are relatively comparable across all catheter configurations, noteworthy variation is observed in the minimum IPS values or troughs. Specifically, the SMC exhibits notably lower minimum IPS values compared to SHC 0.4 and substantially lower values relative to SHC 0.2. This discrepancy can be primarily attributed to the four-stream injection characteristics inherent in SHC designs, which inherently encourage greater particle spread during the diastolic phase.

Visual assessment of the particle dispersion in Figure 10.5 reinforces these quantitative findings. The greatest particle dispersion consistently occurs during the first two intervals (2.4-2.8 seconds for plane 2 and 3.2-3.6 seconds for plane 3), correlating closely with the systolic phase of the cardiac cycle. Increased blood flow velocities during systole likely contribute to enhanced flow separation and vortex formation, subsequently facilitating broader particle dispersion. However, it is also notable that concentrated particle "hotspots" persist during these intervals, most prominently for the SMC due to its focused injection stream.

Visual observations reflect the conclusions derived from the tIPS graphs: the SMC consistently yields the least particle dispersion, whereas SHC 0.2 demonstrates the greatest, particularly evident during the diastolic intervals (the last two intervals of each row). Further quantitative support for these observations is provided by the Weighted Index of Particle Spread (WIPS) values (Tables 10.1, 10.2, and 10.3), which provide an averaged IPS measure weighted by particle throughput within each interval. Thus, WIPS values underscore the conclusion that SHC 0.2 outperforms the SMC and SHC 0.4 in terms of achieving superior temporal dispersion.

10.3 Particle Distribution and Tumour Dose

Table 10.4 outlines the arterial outlets targeted with various catheter configurations (SMC, SHC 0.2, and SHC 0.4) under transient conditions (sim. 22, 23, and 24). These transient simulations have markedly enhanced particle dispersion, resulting in a greater number of targeted arterial outlets compared to steady-state simulations (section 8.4). This enhancement in dispersion, as indicated by elevated IPS values, was thoroughly detailed in the previous section. Notably, IPS

values across all transient configurations remained high and varied only slightly by approximately 8%, except for the first plane. Consequently, this led to identical numbers of targeted outlets (13 in total, including eight that specifically feed tumour tissue) across all catheter designs.

Table 10.4 The total number of (tumour) outlets accessed by the particles in the three transient simulations (sim. 22, 23, 24): eight out of 17 outlets are related to tumour perfusion outlets.

Catheter type	Number of outlets reached	Number of tumour outlets reached
SMC	13	8
SHC 0.2	13	8
SHC 0.4	13	8

Figures 10.6, 10.7, and 10.8 provide a comprehensive visualisation of particle distributions across the various arterial outlets under transient conditions, with tumour-perfusion outlets highlighted in red and healthy tissue outlets in green. The most notable difference is observed at outlet 3.2, where the particle fraction for both SHC configurations surpasses that of the SMC by approximately 8%. In the case of the SMC, despite outlet 3.3 having a slightly lower outflow than outlet 3.2, the particle fraction for outlet 3.3 exceeds that for outlet 3.2 by around 5%. This particle distribution alignment is more optimal for the SHC designs, where outlet 3.2 consistently receives more particles than outlet 3.3. Furthermore, notable differences in particle fractions are apparent at outlet 3.1, though to a lesser extent; the SMC design directs an almost negligible fraction (0.3%) compared to SHC 0.2 (2%) and SHC 0.4 (3%). With an outflow fraction of 3%, outlet 3.1 is notably undersupplied by the SMC configuration. The explanation for this variance lies in the particle spread characteristics leading to the second bifurcation (plane 2), where the SMC achieves an 8% lower particle spread than SHC designs. This reduced dispersion results in fewer particles being directed towards the side-branches (outlets 3.1 and 3.2) for the SMC.

Furthermore, distinct differences are observed in branch 2, particularly at outlet 2.2, which has an outflow of approximately 6%. SHC 0.2 exhibits the highest particle fraction directed towards outlet 2.2 (5.5%), compared to SMC (4%) and SHC 0.4 (2%), respectively.

Table 10.5 summarises the tumour dose, coverage, and the fraction of particles that have not yet exited through the outlets across the three catheter designs. Tumour coverage is consistent across all catheter configurations due to the identical outlets targeted. The tumour and healthy tissue doses for the SMC and SHC 0.4 catheter configurations are comparable, with differences in particle fractions exiting the geometry, complicating clear distinctions between them. Notably, the SMC catheter, positioned in this radial position, demonstrated focused tumour distribution in steady-state simulations, resulting in better targeting, a higher tumour dose, and a lower healthy tissue dose. The SHC 0.4 configuration, due to its small radial extent, achieves similar outcomes to the SMC but benefits from improved particle dispersion due to its four injection streams. Conversely, the SHC 0.2 configuration experiences the highest healthy tissue dose and lowest tumour dose. This adverse outcome is primarily attributed to its higher UIPS values, resulting

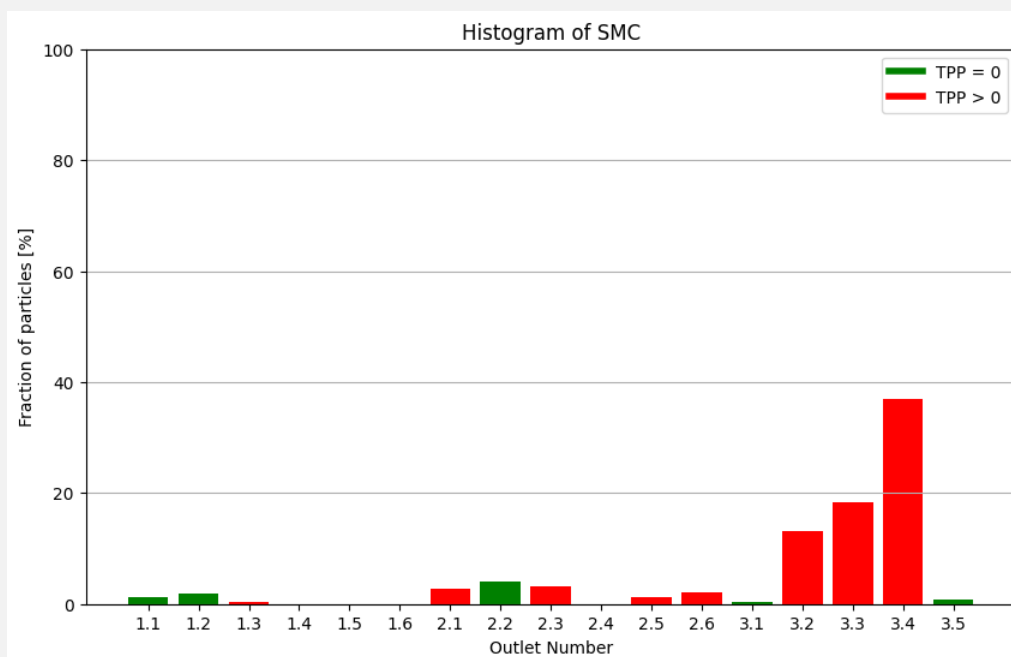


Figure 10.6 Particle distribution over the 17 outlets for the SMC in transient condition. The tumour outlets are denoted in red and the healthy tissue in green.

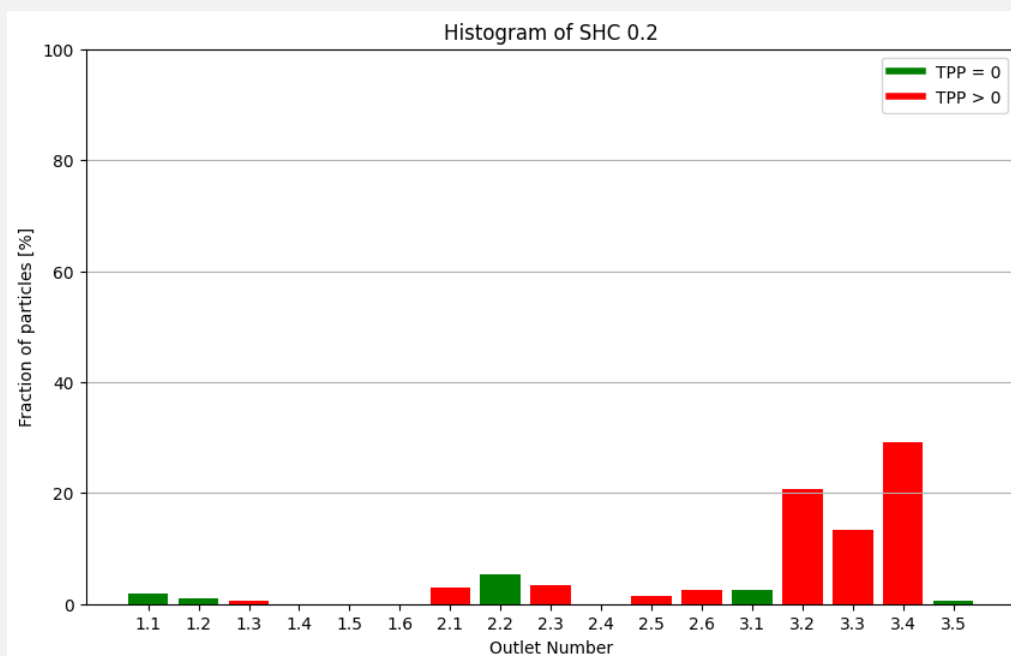


Figure 10.7 Particle distribution over the 17 outlets for the SHC 0.2 in transient condition. The tumour outlets are denoted in red and the healthy tissue in green.

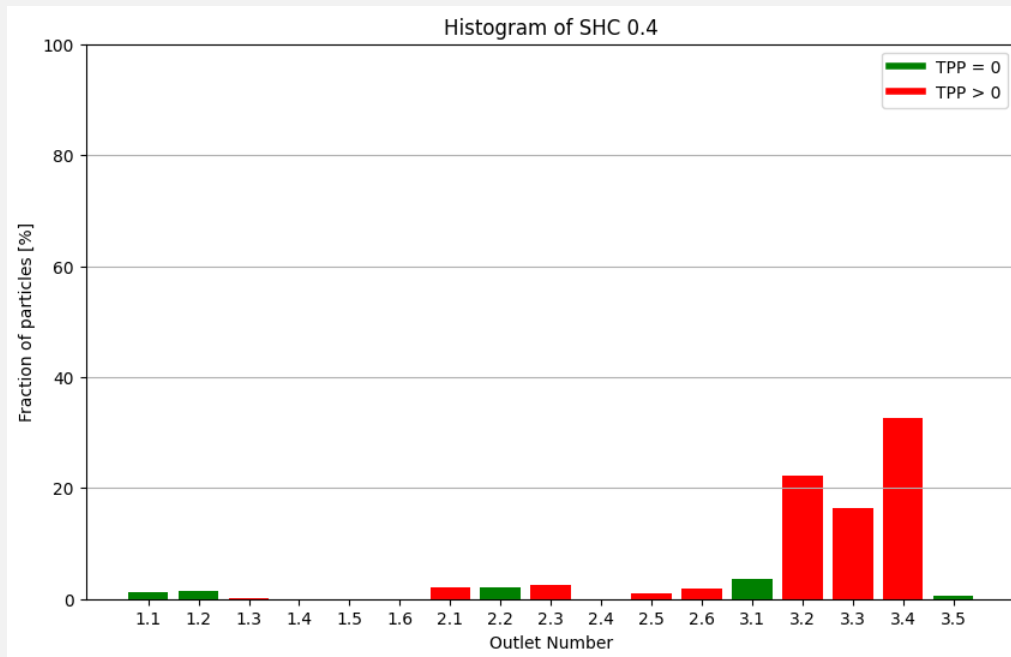


Figure 10.8 Particle distribution over the 17 outlets for the SHC 0.4 in transient condition. The tumour outlets are denoted in red and the healthy tissue in green.

in enhanced overall dispersion that unintentionally targets more healthy tissue and less tumour tissue.

Table 10.5 Overview of the tumour dose (TD), healthy dose (HD), tumour coverage, and particles left in the geometry, represented in percentage points, for the three transient simulations (sim. 22, 23, 24).

Catheter type	TD [%]	HD [%]	Tumour coverage [%]	Stuck particle [%]
SMC	78.32	8.26	98.44	13.42
SHC 0.2	74.36	11.36	98.44	14.27
SHC 0.4	78.96	8.74	98.44	12.29

Lastly, the "fraction of stuck particles" represents particles that have not yet crossed outlet boundaries, either because they are trapped within the geometry or because insufficient simulation time has elapsed. Since the number of particles exiting the geometry has not yet plateaued, no definitive conclusions can be drawn regarding this metric at the present stage.

10.4 Matching and Targeting Deviation Index

Table 10.6 provides a comprehensive overview of the Matching Deviation Index (MDI) and Targeting Deviation Index (TDI) for the three catheter configurations (SMC, SHC 0.2, and SHC

0.4) under transient simulation conditions. Remarkably, all values obtained were extremely low, with MDI remaining below 2% and TDI below 3%, denoting minimal deviation between the particle distributions and both the blood flow and tumour perfusion.

Table 10.6 Overview of the matching deviation index (MDI) and targeting deviation index (TDI) for the three transient simulations (sim. 22, 23, 24).

Catheter type	Matching Deviation Index	Targeting Deviation Index
SMC	1.80	2.28
SHC 0.2	1.51	2.53
SHC 0.4	1.83	2.38

The values observed in transient conditions were notably lower than those recorded during steady-state simulations (section 8.5). This improvement in alignment can primarily be attributed to the dynamic flow characteristics inherent to transient regimes, which facilitate enhanced particle dispersion as previously detailed. Given the complexity and realism of transient flow conditions, the relationships among catheter designs regarding MDI and TDI observed here are considered to be more representative of clinical realities.

Regarding the MDI, the SHC 0.2 demonstrated the most optimal alignment, whereas SHC 0.4 exhibited the least, though marginally by only 0.03% worse than the SMC. This finding aligns closely with previous research, specifically the works of Zeebroek (2024) [35] and Ortega et al. (2022) [43], highlighting that smaller side-hole diameters are associated with lower MDI values. It is also confirmed by the conclusions of Ortega et al. (2025) [47], who reported lower MDI values for side-hole catheters (with hole diameters around 0.2 mm) compared to standard end-hole microcatheters. Moreover, the improved MDI observed for SHC 0.2 is directly correlated with higher UIPS values, as a more uniform particle distribution intrinsically leads to better alignment with physiological flow patterns.

Concerning TDI, which measures alignment with tumour perfusion, the SMC exhibited superior clinical performance, whereas SHC 0.2 yielded the least favourable outcomes. This disparity can be primarily attributed to the lower tumour dose associated with the SHC 0.2 configuration. However, as visualised in Figure 10.9, the TDI values evolve across post-injection cardiac cycles, demonstrating dynamic fluctuations. Interestingly, the MDI of SHC 0.2 transitioned from the poorest to the best after an additional cardiac cycle. A similar trend might also apply to the TDI, particularly since a substantial fraction (14.27%) of particles had not yet traversed the outlet boundaries at the time of analysis. Notably, SHC 0.2 had the highest fraction of these 'stuck' or non-exited particles among all catheter designs. This observation suggests the potential for further improvements in TDI metrics for SHC 0.2 with additional cardiac cycles, thereby underscoring the necessity for longer simulation durations to capture fully stabilised outlet distributions.

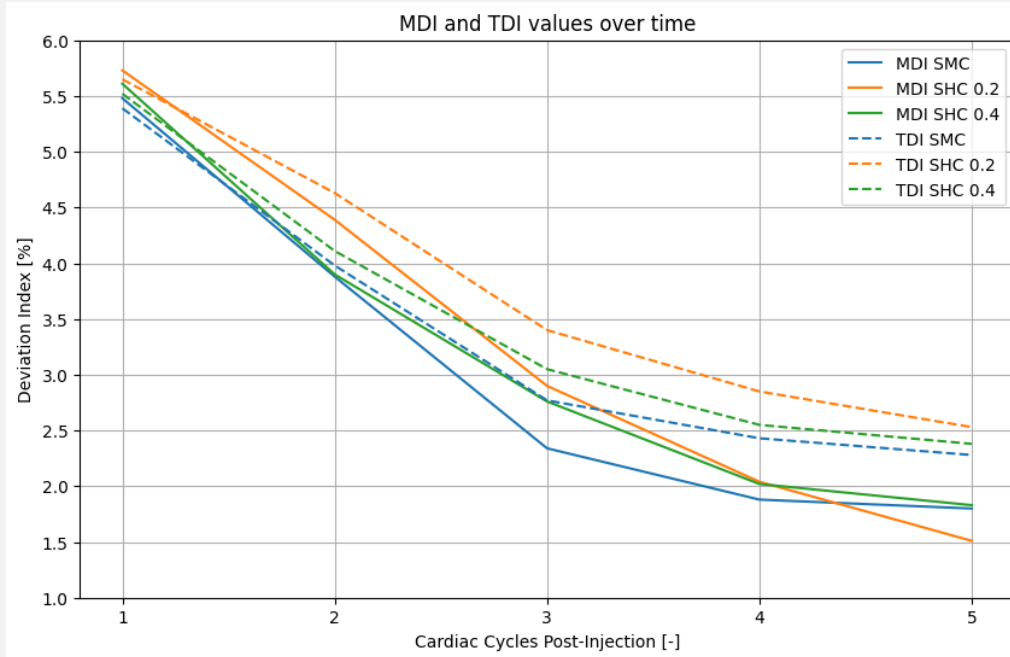


Figure 10.9 Visualisation of the MDI and TDI over the number of cardiac cycles to analyse time-dependent particle distribution for the three different catheters (sim. 22, 23, 24).

10.5 Residuals

The convergence characteristics of residuals during transient simulations provide essential insights into the accuracy and reliability of numerical results. Throughout the three simulations conducted (SMC, SHC 0.2, and SHC 0.4), over 90% of the timesteps successfully met the convergence criteria, defined by achieving normalised residuals below 10^{-6} or a three-order magnitude reduction in residuals for all equations at each timestep. Specifically, the SMC simulation achieved the highest convergence rate of 94.08%, closely followed by SHC 0.2 at 93.42%, and SHC 0.4 slightly lower at 92.74%. These high convergence percentages were consistently maintained throughout all cardiac cycles. Importantly, even timesteps that did not fully satisfy the convergence criteria still achieved at least a two-order magnitude drop in residuals and maintained normalised residuals below 10^{-5} . However, as demonstrated in Figure 10.10, attempts to improve convergence simply by increasing the number of iterations per timestep proved ineffective. The observed plateau in residual values suggests that further iterations alone cannot enhance convergence due to inherent limitations in the numerical setup or mesh configuration.

One notable issue affecting convergence was the occurrence of reverse flow at several outlets. This reverse flow can disrupt numerical stability and affect convergence behaviour. To address

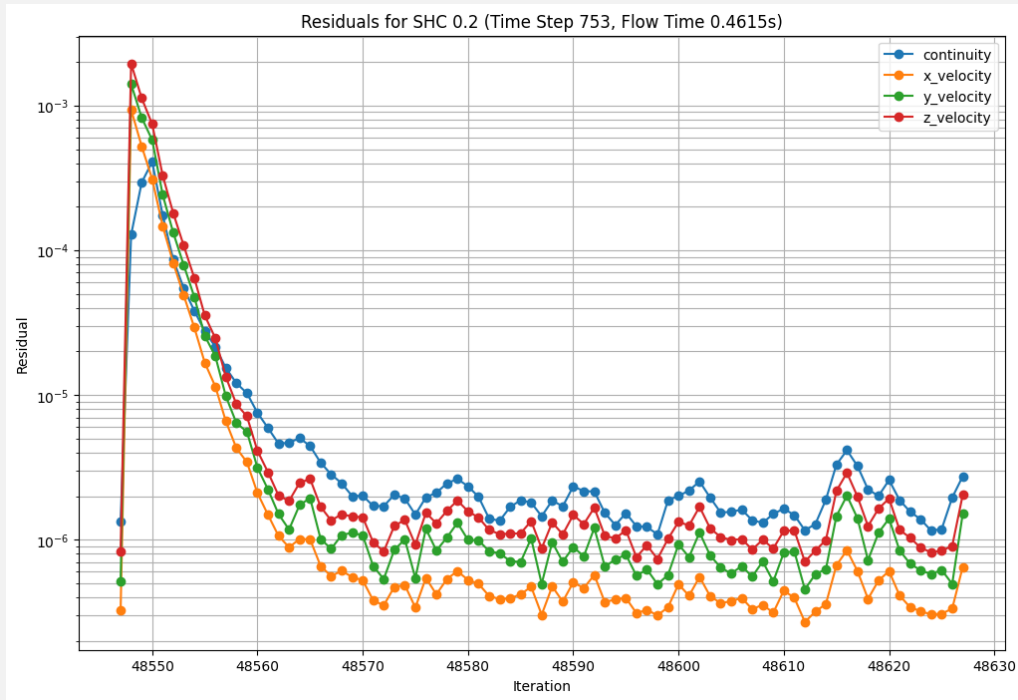


Figure 10.10 Visualisation of the residuals (continuity, x-velocity, y-velocity and z-velocity) at the timestep equal to 0.4615 s for the SHC 0.2 simulation.

this, lengthening the outlet geometries is recommended to ensure proper flow development at the boundaries, thereby potentially reducing reverse flow and improving overall convergence rates. Moreover, convergence issues can be substantially mitigated by enhancing mesh quality, as increasing orthogonal quality and reducing skewness.

Chapter 11

Concluding Remarks

11.1 Conclusions

HCC remains the third leading cause of cancer-related deaths globally. For intermediate-stage HCC, transarterial radioembolisation (TARE) represents a crucial locoregional therapy, leveraging the liver's distinctive vascular architecture, where healthy tissue predominantly receives blood from the portal vein. In contrast, tumour tissue primarily draws from the hepatic arteries. TARE administers radioactive microspheres directly into the hepatic arterial network to effectively target tumour tissue. Despite its clinical efficacy, the effectiveness of TARE depends on clinical parameters such as catheter type, radial position, and radial orientation, factors that are often challenging to optimise in clinical practice, resulting in variable treatment outcomes. Moreover, each patient has a unique arterial tree, making optimisation patient-specific.

The research presented in this thesis addressed these challenges by exploring novel catheter designs aimed at reducing variability and improving alignment of particle distribution with blood flow and tumour perfusion patterns. Specifically, the side-hole catheter (SHC), proposed by Ortega et al. (2022) [43], was investigated. This design aims for improved particle mixing and distribution with the blood flow, taking advantage of tumour hyperperfusion characteristics and the unique liver blood supply.

The goals of this thesis were threefold. First, a refined workflow was developed to insert catheters into patient-specific geometries without losing anatomical detail, thus enabling a more precise impact assessment of catheter design. Second, the study quantified the effect of the catheter's radial orientation on particle distribution and treatment outcomes. Third, the research expanded upon steady-state simulation results to transient simulations, reflecting more realistic clinical scenarios.

The main conclusions can be summarised as follows :

1. The new workflow, leveraging Ansys Discovery, improved the insertion process compared to the previous methodologies, which relied on SpaceClaim and Design Modeller. This workflow introduced a deviation from the native segmentation of only 0.0003%, compared to the prior deviation of 0.7091%. It enhanced anatomical accuracy, streamlined catheter insertion, and eliminated time-consuming reverse-engineering processes, notably accelerating computational modelling.
2. Comparative steady-state simulations involving three catheter designs (SMC, SHC 0.2, and SHC 0.4) at an injection speed of 0.1254 m/s demonstrated that smaller side-holes enhanced crossflow, creating distinct injection streams positioned closer to arterial walls. This proximity increased particle-wall interactions, leading to greater spread across arterial outlets. Consequently, SHC 0.2 showed substantial particle spread variability depending on radial orientation, which resulted in tumour dose variations up to 46.72% between orientations compared to a modest 4.18% for SHC 0.4. Although SHC 0.4 consistently achieved higher tumour doses than SHC 0.2, its narrower dispersion resulted in lower tumour coverage.

From a clinical optimisation perspective, the Matching Deviation Index (MDI), reflecting the alignment of particle distribution with blood flow, consistently favoured SHC designs over the SMC. SHC 0.2 presented lower MDI in most orientations, suggesting improved general distribution with blood flow. However, when evaluating the Targeting Deviation Index (TDI), a metric aligning particle distribution with tumour perfusion, SHC 0.4 demonstrated superior performance across all orientations. However, SHC 0.4's superior performance was not due primarily to an inherently better catheter design but rather because its injection streams were positioned closer to those of the SMC, achieving a perfect tumour dose of 100%. By enhancing dispersion with four injection streams, SHC 0.4 achieved improved alignment with tumour perfusion.

3. Transient simulations underscored the necessity of evaluating catheter performance under physiologically realistic conditions. The pulsatile nature of blood flow dynamically influenced particle distribution, especially altering the radial extent of injection streams between systole and diastole. Notably, SHC 0.2 exhibited a higher difference in radial extent between these cardiac phases compared to SHC 0.4, due to the greater difference in ratio between the outlet velocity and the blood flow. The transient simulations led to a marked increase in particle dispersion, with a 12-fold enhancement in particle spread compared to steady-state conditions. SHC 0.2 showed the most uniform spread, attributable to its injection characteristics, whereas the SMC exhibited the least uniform spread. Additionally, the particle spread was demonstrated to be cyclical. Due to substantial particle dispersion across all catheter designs, particles consistently targeted 13 out of the 17 arterial outlets. Furthermore, all transient simulations yielded consistently lower MDI and TDI values, with values remaining below 3%. SHC 0.2 displayed the optimal

MDI due to its uniform particle spread, but this also led to diminished targeting specificity, resulting in the highest TDI.

Overall, integrating Ansys Discovery into the computational workflow proved beneficial, enhancing the precision and efficiency of catheter modelling. The orientation of the side holes notably introduced variability in treatment outcomes under steady-state conditions, with higher variability observed for smaller side holes. The necessity of transient simulations to obtain valid conclusions regarding SHC designs, specifically in terms of dispersion, was clearly demonstrated. SHC designs featuring smaller side holes consistently provided better alignment with blood flow in this patient-specific case.

This thesis has thus demonstrated the potential for patient-specific catheter optimisation through detailed computational fluid dynamics modelling, with SHC designs offering notable advantages in targeted particle delivery.

11.2 Limitations

Due to its computational modelling approach, the present study has several limitations, each of which presents opportunities for future refinement.

Some conclusions primarily rely on steady-state simulations, particularly concerning the impact of catheter radial orientation. These steady-state findings require further validation under transient conditions, as some transient simulations demonstrated increased dispersion, improved matching (MDI), and better targeting (TDI) indices. Transient simulations provide a more physiologically accurate representation due to the naturally pulsatile nature of arterial blood flow. Therefore, the observed effect of catheter orientation in steady-state conditions may be diminished under realistic transient conditions, highlighting the need for comprehensive validation in pulsatile physiological settings.

The transient scenarios examined in this study remain limited, as simulations were conducted only at a single injection velocity (0.1254 m/s) and across solely three catheter configurations. The effects of different injection velocities have not been explored, which is particularly noteworthy given that higher injection velocities have been shown to increase the performance of SHCs. Additionally, transient simulations were conducted over just five cardiac cycles following injection. While approximately 85% of particles exited during this period, the exit fractions had not stabilised, indicating that longer simulations are necessary to confirm equilibrium states and accurately validate outflow predictions. Moreover, convergence criteria were met in only about 93% of the timesteps. The plateau observed in residuals during the unconverged timesteps suggests potential issues with mesh quality or boundary conditions, particularly concerning

reverse flow phenomena at the outlet surfaces. Extending the outlet geometries and using a mesh with higher orthogonal quality and lower skewness could alleviate these convergence challenges.

The catheter models used in this study were rigid and straight, which simplifies the representation of real-world clinical devices that are typically flexible and curved to navigate the complex pathways to the hepatic arteries. Additionally, the catheter injection fluid was modelled in the same way as blood, ignoring the unique rheological properties of clinical drug carriers. This oversight could affect dispersion patterns.

All computational analyses utilised a single, truncated geometry derived from one patient-specific hepatic arterial tree, inherently limiting the generalizability of the results across diverse patient anatomies, including variations in vessel diameters, branching angles, and tumour locations. Additionally, the simplification of the model from 48 to 17 arterial outlets introduces further uncertainty, as this truncation could potentially skew particle distribution by as much as 4–11%. Furthermore, the vessel walls were modelled as rigid, no-slip surfaces, which neglect fluid-structure interactions and arterial deformation under physiological pressures. The assumption of elastic particle-wall interactions oversimplifies the more complex physical behaviours that occur in clinical settings.

A simplified Quemada shear-thinning model with fixed rheological parameters was employed to characterise blood viscosity without explicitly modelling variations in hematocrit, which can influence viscosity and, consequently, impact dispersion metrics, as outlined in Section 8.6.

Injection protocols, encompassing velocities, hole diameters, catheter orientations, axial positions, and hole shapes, were narrowly defined, which limits the broader applicability of the investigation's findings. Exploring a wider range of injection velocities and diverse catheter configurations could yield deeper insights into optimal clinical practices. Additionally, the physiological blood flow conditions applied at the hepatic artery inlet were derived from existing literature rather than from direct patient-specific measurements, potentially compromising clinical accuracy. Incorporating patient-specific hemodynamic data would enhance the physiological realism and predictive reliability of the computational models.

Moreover, the computational predictions lack support from experimental or clinical validations, including controlled in vitro setups or in vivo animal models. Such experimental validation is essential for ensuring the reliability of catheters and their translational effectiveness. Therefore, it is imperative to conduct additional validation studies and to expand the range of patient-specific anatomies examined.

11.3 Future Work

Future work should address several key aspects to enhance the accuracy, applicability, and clinical relevance of this study. First, transient validation of the effects of catheter orientation is crucial. Repeating the three-catheter study under time-dependent flow conditions would reveal more realistic dynamic particle behaviour and orientation-dependent dispersion.

Extended cardiac cycle simulations are recommended to improve the completeness of particle tracking data. These simulations should run until the total outflow fraction plateaus, ensuring a comprehensive assessment of particle fate.

Improvements in mesh and boundary refinement are also necessary. Lengthening outlets that show reverse flow and enforcing stricter mesh quality criteria, such as improved orthogonality and reduced skewness, could eliminate convergence issues and minimise artefacts at outlets.

To optimise catheter designs, a broader transient parameter sweep is suggested. Systematic variations in injection speeds, injection pulse timings, and durations should be investigated to identify optimal conditions for achieving minimal Matching Deviation Index (MDI) and Targeting Deviation Index (TDI).

Future simulations should incorporate fluid-structure interaction (FSI) modelling. Including vessel wall compliance would reveal the influence of arterial elasticity on flow dynamics and particle distribution, more accurately reflecting physiological conditions.

Rheology sensitivity studies and detailed modelling of the catheter fluid are recommended to quantify their effects on dispersion. Alternative viscosity models, such as Casson, should be compared alongside modelling of actual catheter carrier fluids.

Expanding the catheter design space by exploring curved, flexible geometries and diverse side-hole patterns could improve clinical performance. Patient-specific boundary conditions, obtained from Echo Doppler or 4D flow MRI and angiographic data, would further enhance simulation fidelity.

Validation of tumour-region models through in vivo experiments and expanded preclinical trials with compliant, transparent 3D-printed hepatic models is an essential next step. Ultimately, multi-patient cohort studies and the development of real-time surrogate models will be pivotal for clinical translation, enabling rapid, personalised catheter planning.

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Appendix A

Ethical Remarks

Ethical aspects directly related to the work done in this thesis

This thesis uses a dataset that comprises patient-specific CT images illustrating hepatic arteries alongside a hepatocellular carcinoma tumour nodule. This dataset is the same as employed in previous study by Bomberna et al. (2022) [45], and additional research by the same author. The CT scans were not specially collected for this thesis; they were already available from earlier research. Therefore, no new human data collection was necessary for this thesis.

The use of this dataset was approved by the Ethical Committee of the University Hospital in Leuven. As Bomberna et al. (2022) [45] stated: "The studies involving human participants were reviewed and approved by the Ethical Committee of the University Hospitals Leuven. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements." Since the current thesis utilises the same dataset, the previously mentioned ethical approval and informed consent statement remain valid.

The primary objective of this thesis is to evaluate transarterial treatments in individual patient cases, making the use of a patient-specific dataset essential. Considering the unique nature of the data, no other datasets could effectively meet the requirements of this research.

Reflection about the potential (future) impact of study results

The findings presented in this study are highly preliminary, as they focus exclusively on one patient-specific case and explore a limited set of distinct parameters, including side-hole diameter and catheter orientation. Despite this, these initial CFD results provide valuable insights into the potential performance of the SHC. Nonetheless, these preliminary results must be validated through rigorous in vitro testing and subsequent preclinical studies to confirm their applicability

and robustness. Moreover, any future expansions to larger patient cohorts must ensure rigorous de-identification, secure storage, and full compliance with GDPR to safeguard patient privacy.

In terms of future implications, the insights gained from this preliminary investigation represent crucial steps toward enhancing transarterial therapies utilising SHCs. This research provides tools and methodologies that could potentially enhance clinical outcomes by mitigating the impact of variable catheter parameters. Furthermore, the study of the SHC has the potential to align pre-treatment planning more closely with actual clinical treatment, optimising radiation dose delivery to targeted tumour tissue while minimising exposure to healthy tissue. Such advancements could greatly reduce treatment-related toxicity, diminish patient side effects, and ultimately facilitate quicker patient recovery.

This study also contributes to a broader goal: the establishment of a CFD-based pre-treatment planning framework. Such a framework would enable the fine-tuning of catheter parameters tailored specifically to each patient, thereby optimising both the planning and the treatment itself. The adoption of this CFD-based methodology would be highly beneficial, as it utilises CT scans, which are already routinely acquired during standard clinical procedures, negating the need for additional invasive or diagnostic interventions.

An important consideration for future implementation is the substantial computational resources and time required to perform these simulations. Addressing these computational challenges will be critical before such an approach can be feasibly integrated into routine clinical practice.

Scientific Integrity

This master's thesis is my own work, except where I reference the work of others. Information retrieved from external sources is properly cited and included in the References chapter. Parts of this dissertation have been revised with assistance from ChatGPT (OpenAI) and Grammarly, specifically to improve grammar, spelling, and style. However, the intellectual content remains solely my own, and the use of these AI tools has been strictly limited to language refinement and enhancing clarity. All data obtained from the mentioned simulations is presented and discussed in the 'Results and Discussion' part, unless otherwise stated to enhance clarity and reduce repetition.

Appendix B

Remarks on Sustainability

Sustainability concerns are primarily related to the computational and systemic effects of running simulations on a high-performance computing (HPC) cluster. HPC clusters require a considerable amount of electricity, particularly during intensive CFD simulations. Proper management of computational nodes and responsible use of HPC time can help minimise unnecessary energy use. Sensitivity analyses were performed to establish the minimum necessary computational complexity, including mesh size and solver type. Initial steady-state simulations assessed performance, with transient simulations only implemented when necessary to account for the intricate pulsatile characteristics of blood flow. A minimum of seven complete cardiac cycles were simulated to achieve physiological accuracy while keeping computational demands manageable.

Efficient storage, organisation, and reuse of simulation data can decrease the need for repeated runs and excessive data creation. This approach leads to reduced energy consumption, less server strain, and enhanced long-term sustainability of computational infrastructure. CFD simulations facilitate virtual testing of catheter designs, enabling the discarding of ineffective options before proceeding to in vitro validation. This reduces the requirement for physical prototypes, conserves materials, minimises manufacturing demands, and lessens laboratory waste.

Additionally, a deeper understanding of transarterial treatment via CFD can improve medical outcomes. More accurate catheter designs might decrease procedural complications and shorten patient recovery periods. Consequently, this could lead to shorter hospital stays, decreasing the strain on hospital resources and reducing consumption of energy, medications, food, and disposable medical supplies. Cost-effective treatment approaches could also lower healthcare costs and free up financial resources for other priority areas in the healthcare system.

Appendix C

Technical Remarks

To ensure the reproducibility of this study, the technical configuration of the simulations performed is detailed in this chapter. All simulations were set up according to the methodology outlined in Chapter 6. Following initial validation of the simulation settings, the viscosity model was temporarily set to a constant value. This simplified case file was uploaded to the High Performance Computing (HPC) cluster (Shinx or Doduo) for simulation.

A shell script (.sh file) was created to execute the case file on the cluster using one compute node. The number of processors per node (ppn) was varied between 48 and 192. Ansys Fluent 2024 R2 (Ansys Inc., Canonsburg, PA, USA) was used as the solver. The commands employed in the shell script are provided below for reference:

Shell script contents

```
#!/bin/bash
#PBS -N # Name of the simulation
#PBS -l walltime=12:00:00 # the amount of time needed
#PBS -l nodes=1:ppn=96 # the amount of nodes and ppn
#PBS -m abe -M ...@ugent.be # provide e-mailadress after

FLUENT_PPN=96 # the amount of nodes used for calculating
FLUENT_INPUTFILE=$VSC_DATA/...
# provide directory to journal file
INPUT_DIR=$VSC_DATA/... # provide directory with all input files

export ANSYSLI_SERVERS=... # provide ansys license
export ANSYSLMD_LICENSE_FILE=... # provide ansys license

module load FLUENT/2024R2
```

```
module load iimpi/2023a

# For multinode jobs on delcatty use:
cd $INPUT_DIR

# setup syncing
#while sleep 1799;do rsync -ruazq $WORK_DIR/* $OUTPUT_DIR ; done &
# sync workdir with output dir every 1800 seconds (half an hour)

# Run fluent
FLUENT_HOSTFILE=fluent.hosts.'date +%s'
TMP1_HOSTFILE=tmp1.hosts.'date +%s'
TMP2_HOSTFILE=tmp2.hosts.'date +%s'
cat $PBS_NODEFILE | uniq | sed -e 's/\.rome.*$//' > $TMP1_HOSTFILE
for ((i=0;i<$FLUENT_PPN;i++)) ; do cat $TMP1_HOSTFILE >> $TMP2_HOSTFILE ;
done cat $TMP2_HOSTFILE | sort > $FLUENT_HOSTFILE
rm $TMP1_HOSTFILE $TMP2_HOSTFILE
export FLUENT_PROCESSES='cat $FLUENT_HOSTFILE | wc -l'

fluent 3ddp -gu -driver null -i$FLUENT_INPUTFILE -t$FLUENT_PROCESSES
-cnf=$FLUENT_HOSTFILE -ssh &>logfile_$PBS_JOBID.log

#rm -Rf $WORKDIR
```

The corresponding journal file was configured to perform the following sequence of operations:

- Load the specified case file,
- Replace the constant viscosity with the Quemada viscosity model (described in Appendix E),
- Apply hybrid initialization,
- Set the time step size,
- Execute the transient simulation for a predefined number of timesteps and iterations.

The complete journal file commands are listed below:

Journal file contents

```
/file/read-case ....cas # name input case-file

/define/user-defined/compiled-functions
compile
"libudf"
yes
"Final_viscosity_Quemada.c"
""
"Final_viscosity_Quemada.c"
""

/define/user-defined/compiled-functions
load
"libudf"

/define/materials/change-create
blood
blood
no
no
no
yes
user-defined
"cell_viscosity::libudf"
no
no
no

/solve/initialize hyb-initialization

/solve/set/time-step 0.001
/solve/dual-time-iterate 70 80 # number of timesteps and iterations per timestep
...
/file/write-case-data ....dat # write final case and data files

exit
```

Appendix D

Workflow Simulations

D.1 Workflow Materialise

Segmentation and Model Generation

Using **Mimics**, the following steps are performed:

1. Segment the desired anatomy:

Identify and isolate anatomical structures such as the liver tumours and arteries.

2. Generate a 3D surface model:

- Create a part based on segmented data.
- Remove unwanted noise or small floating components.
- Apply smoothing if necessary to reduce rough surfaces.
- Fit a centerline to the model and cut the ends perpendicularly.
- Extrude the inlet by 80 mm to ensure proper flow development.

3. Export model data:

- If available, export the centerline as .IGES or .STEP format for catheter placement.
- Export the part to **3-Matic** via **File > Export > 3-Matic**.

Model Optimization in 3-Matic

1. **Enable Expert Mode** and run the 'Fix Wizard' to resolve geometry issues (e.g., intersecting/overlapping triangles).

2. Optimize the Surface Mesh:

- Use **Adaptive Remesh** and **Smoothing** to refine the surface (globally and locally).
- Maintain a shape skewness threshold of **0.4**.
- Ensure 'Preserve Surface Contours' is enabled when remeshing.

3. Export the Optimized Model in .STL format.

D.2 Workflow ANSYS Discovery

Preparing Geometry in ANSYS Discovery

1. Open Ansys Discovery 2024 R1.

2. Click **File > Import** and select the exported **STL file** from 3-Matic.

3. Check and clean the geometry:

- **Check for multiple facets.** If multiple disconnected facets exist, separate them and delete non-connected parts.
- Run a **facets check for errors** (to detect holes, overlapping triangles, etc.).
- Duplicate geometry and **convert to solid body** (fully tessellated).
- **Verify visually** and with an area metric if there is a difference between the solid and the facets. If there is no difference, keep only the solid.

4. Define inlet & outlet boundaries:

- Place **faces** on the **inlet & outlet** of the vessel (needed for meshing).
 - Double click face, copy and paste.
 - Rename with an appropriate name.
- Remove **extra faces (in- and outlets from wall)** by double-clicking and pressing delete.

Catheter Creation and Insertion

Create the Catheter Solid Body

- **[Option 1] Centerline Approach:** Import the pre-segmented centerline and generate a hollow cylindrical catheter by:

1. Importing the centerline:

- Open the **IGES file** exported from Mimics.
- Ensure the centerline is correctly aligned with the solid body of the vessel.

2. Creating the catheter along the centerline:

- Select the **centerline** and then click on **DESIGN > CYLINDER**.
- Define the **inner diameter** and **outer diameter** according to catheter specifications.
- Ensure the catheter is hollow by selecting and deleting the inner volume.

3. Adjusting the length of the catheter:

If modifications are needed, use the **Pull Function** to extend or shorten the catheter length.

4. Positioning the Catheter Inlet:

Pull the inlet of the catheter out of the solid body of the vessel to facilitate further operations.

• [Option 2] Straight Catheter: Define a straight catheter manually by:**1. Selecting the inlet face:**

Identify the correct inlet region of the vessel where the catheter should be placed.

2. Creating the catheter sketch:

- Enter **Sketch Mode** when the inlet is selected and define the catheter cross-section using **two concentric circles**.
- Ensure the circles represent the **inner** and **outer diameters** of the catheter.

3. Generating the hollow catheter body:

- Use the **Pull Function** to extrude the catheter walls in both directions.
- Confirm that the catheter remains hollow and is correctly aligned with the vessel inlet.

Define the inlet and outlet**1. Copy the Catheter Solid Body:**

- Select the catheter model and create a duplicate to preserve the original structure.
- Delete all components of the copy except for the outer layer.

2. Split the inlet with the outer catheter layer:

- Use the **Split Face** tool to divide the inlet region along the boundary of the outer layer.
 - Ensure the split maintains a clean division between the blood inlet and the remaining geometry.
 - Retain only the blood inlet.
3. **Remove any remaining duplicates of the catheter** geometry that are not needed.
 4. **Split the Catheter at the inlet:**
 - Use **DESIGN > SPLIT** to further divide the geometry of the catheter at the location of the blood inlet.
 - Delete the portion of the catheter that extends outside the vessel geometry, ensuring correct positioning within the arterial structure.
 5. **Define the catheter inlet & outlet:**
 - Utilize the **Fill Hole** function by navigating to **DESIGN > FILL**.
 - Select the edges of both the catheter inlet and outlet to create the catheter inlet and outlet.

Make Side-holes (optional)

1. **Create a closed frontal tip:**
 - Extend the outlet inside the catheter with a predefined thickness.
 - Combine the newly created part with the wall of the catheter.
2. **Create side-holes:**
 - **Define the side-hole positioning:**
 - Select the catheter tip and create a reference plane using **DESIGN > PLANE**.
 - Move the plane along the catheter's axis using **DESIGN > MOVE** to align with the desired side-hole centers precisely.
 - **Sketch side-hole guide lines:**

Enter **Sketch Mode** and draw two **perpendicular lines** on the reference plane connecting the side-hole centers through the center of the catheter.
 - **Create cylindrical cutouts for side-holes:**

Select one of the guidelines and create a **cylinder** with the desired side-hole radius. Do the same for the other guideline.

- **Perform Boolean Subtraction:**
 - Use the **Combine Tool** with the **Subtract from Target** option enabled.
 - Select the catheter wall as the target and the two cylinders as the subtracting bodies.
- **Finalize the side-hole geometry:**
 - Delete the guidelines used for construction.
 - Use the **Fill Hole** tool in **DESIGN > FILL** to create catheter outlets for the side-holes (repeat for all side-holes).

Merge and Prepare for Export

1. Move all catheter and artery parts to 2 separate components by right clicking on the components
2. Apply **Share Topology** on catheter & vessel parts.
3. **Check and validate geometry**
 - Run an **interference check** to verify the catheter and vessel **do not overlap improperly**.
 - Ensure all **surfaces are smooth** and **have no gaps**.
4. Export the final geometry to Fluent Meshing using the Watertight Workflow (**Prepare > Export to fluent > Watertight Workflow**).

D.3 Mesh Sensitivity Analysis

Use the watertight workflow and import the discovery file as geometry.

Geometry without Catheter (MSA Arteries)

1. Apply a surface mesh with sizes ranging from **0.17 mm to 4.47 mm** and a growth rate of **1.2**.
2. Define three boundary layers with a default growth rate of **1.2**.
3. Find the optimal maximum cell length of the tetrahedral elements (MSA).

Geometry with Catheter (MSA Catheter)

1. Apply a **local face size of $3\text{e-}2$ mm** at the catheter inlet to ensure accurate particle injection [45].
2. Find the optimal **local body sizing** for the catheter (MSA).
3. Implement a surface mesh similar to the arterial geometry (0.17 mm – 4.47 mm, growth rate: 1.2).
4. Define boundary layers and select the optimal maximum cell length based on the MSA of the arterial geometry outcomes.

Running Steady State Simulations

1. Mesh transfer to fluent solution:

Export the generated mesh for simulation processing.

2. Simulation parameter definition:

- Configure models, materials, boundary conditions, and solver settings (explained in Chapter 6).
- Use an absolute convergence criterion of **$1\text{e-}6$** .

Choosing the optimal mesh

- Parameters to export from the steady state simulations :
 - Pressure on the wall, WSS and velocities at a cross-section downstream of injection:
 - * Average
 - * 95th percentile
 - Distribution of particles to each outlet.
 - * Calculate the difference between cases.
 - * Look at the average and the 95th percentile of the differences between cases for each outlet.
- Define the optimal mesh settings:

If parameter variations remain below **1%** between consecutive refinements and the densest mesh, select the coarser mesh.

D.4 Workflow ANSYS Fluent

This workflow is detailed in Chapter 6 for the simulation settings and in Chapter 7 for the post-processing. Additional information can be found in the Ansys Fluent Theory Guide [49].

Appendix E

Quemada Model - Code

```
#include "udf.h"

DEFINE_PROPERTY(cell_viscosity, cell, thread)
{
    real mu = 0;
    real mu_zero = 0.00309;
    real mu_inf = 0.002654;
    real tau = 0.00436;
    real landa = 0.02181;
    real shear_rate = 0;
    real y = 0;
    real mu_Quemada = 0;

    shear_rate = C_STRAIN_RATE_MAG(cell, thread);
    y = sqrt(mu_inf) + (sqrt(tau) / (sqrt(landa) + sqrt(shear_rate)));
    mu_Quemada = pow(y, 2);

    if (mu_zero > mu_Quemada)
        mu = mu_zero;
    else
        mu = mu_Quemada;

    return mu;
}
```