TARGETED DRUG DELIVERY FOR LIVER CANCER:
A PATIENT-SPECIFIC COMPUTATIONAL MODEL OF THE PARTICLE TRANSPORT DURING RADIO-EMBOLISATION

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SUMMARY

Hepatocellular carcinoma is the most common liver malignancy and it is predicted to grow to 22 million cases over the next two decades. Depending on the stage of the tumour, the therapy is chosen based on the Barcelona clinic liver cancer (BCLC) criteria. Transarterial therapies are among the possible treatments and they can be divided into transarterial embolization (TAE), transarterial chemoembolization (TACE) and radioembolization (RE). These therapies take advantage of the fact that the tumours are mostly fed by hepatic arteries instead of by hepatic veins as healthy tissue does. In this context, Computational Fluid Particle Dynamics (CF-PD) have been proven to be a powerful tool to evaluate how to maximize the targeting to the tumours as well as to assess which parameters play the most significant role in the final distribution of the drugs. Also, this technique can be used to generate particle release maps (PRMs) that link the injection points with the path that the particles will follow. Thus, they can be used to decide the injection point to target the tumours.

In this work, the possibility of targeting the tumours in a patient-specific geometry by means of CF-PD has been evaluated as well as the parameters that play the most significant role in the final distribution of the drugs. For this purpose, the geometry of the patient was extracted from Magnetic Resonance Images (MRI) by means of segmentation and computer simulations were run in it. For this patient-specific geometry, it was proven that assessing which treatment would provide the easiest target to the tumours is more than feasible by means of CF-PD. Also, that the injection location plays a significant role in terms of particle distribution and the particle density and particle diameter in terms of distal penetration. Even if the particle distribution obtained in the simulations seems to have some similarities to the ones obtained in reality, images with better resolution are needed to further assess this aspect.

Key words: Hepatocellular carcinoma, transarterial therapy, radioembolization, Computational Fluid Particle Dynamics, Particle release map, targeted drug delivery.
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RESUMEN

El carcinoma hepatocelular es el cáncer más común en el hígado y se estima que aumente hasta los 22 millones de casos en las próximas décadas. Dependiendo del estadio del tumor, el tratamiento más adecuado se elige basándose en el criterio de la clínica de Barcelona de cáncer de hígado (BCLC). Uno de los posibles tratamientos son las terapias transarteriales, las cuales se dividen en: embolización transarterial (TAE), quimioembolización transarterial (TACE) y radioembolización (RE). Estas terapias se basan en el hecho de que los tumores están irrigados mayoritariamente por arterias, en lugar de por venas como el tejido sano. En este ámbito, la dinámica computacional de fluido-partícula (CF-PD) tiene un gran potencial para asesorar cómo conseguir que la mayor cantidad posible de medicamentos llegue al tumor. También se utiliza para comprobar que parámetros tienen una mayor influencia en la distribución final del medicamento y para generar mapas de liberación de partículas (PRM). Estos PRM relacionan el punto de inyección de la partícula con la trayectoria que seguirán las mismas para así poder escoger el punto de inyección que irriga los tumores.

En este proyecto, se asesora si sería posible inyectar el medicamento de manera que llegue sólo a los tumores en la geometría de un paciente a través de CF-PD. También se ha evaluado que parámetros influyan más la distribución final de partículas. Para ello, se ha extraído la geometría del paciente de imágenes de resonancia magnética (MRI) por medio de segmentación y se han hecho simulaciones en ella. En el caso de este paciente, se ha comprobado que es posible evaluar con qué tratamiento sería más fácil llegar a los tumores usando CF-PD. También se ha concluido que el punto de inyección juega un rol muy importante en la distribución final de las partículas y la densidad y diámetro de las partículas en el alcance distal. Aunque parece haber una cierta correlación entre la distribución de las partículas en las simulaciones y la distribución real de las partículas observada en las imágenes, se necesitan imágenes con mayor resolución para poder asesorar este aspecto.

Palabras clave: Carcinoma hepatocelular, terapias transarteriales, radioembolización, dinámica computacional de fluido-partícula, mapas de liberado de partículas, tratamiento a diana.
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List of abbreviations
ATM: Angled tip microcatheter
BCLC: Barcelona clinic liver cancer
CF-PD: Computational fluid particle dynamics
CT: Computed tomography
Deb-TACE: Drug eluting beads transarterial chemoembolization
DPM: Discrete phase model
HBV: Hepatitis B virus
HCC: Hepatocellular carcinoma
HCV: Hepatitis C virus
HPC: High performance cluster
MRI: Magnetic resonance image
MSA: Mesh sensitivity analysis
MSA: Microsphere supply apparatus
NAFLD: Non-alcoholic fatty liver disease
NASH: Non-alcoholic steatohepatitis
NM: Nuclear medicine
PEI: Percutaneous ethanol injection
PRM: Particle release map
RE: Radioembolization
RECIST: Response evaluation criteria in solid tumours
RF: Radiofrequency
SMC: Smart microcatheter
TAE: Transarterial embolization
TACE: Transarterial chemoembolization
TME: Tumour microenvironment
US: Ultrasounds
WSS: Wall shear stress
Chapter 1.
Introduction to Hepatocellular carcinoma (HCC) and targeted drug delivery

In this chapter a general overview of the Hepatocellular carcinoma (HCC) is given. Epidemiology, risk factors, pathogenesis, diagnosis and treatments are among the topics discussed during the first part of the chapter. The second part of the chapter focuses on transarterial therapies used in HCC as these therapies are going to be studied in this project by means of computational simulations.
1. HEPATOCELLULAR CARCINOMA

1.1 Epidemiology

Hepatocellular carcinoma (HCC) is the most frequent malignancy of the liver [69]. It is much more common (two to four times) in men than in women, being the 5th and 7th most common cancer for each gender respectively [26]. The highest incidence rates are found within the range of 30-50 years old [33]. It mainly affects Asian countries, including China, Mongolia, South-Eastern Asia, and Sub-Saharan Western and Eastern Africa, regions in which hepatitis B is endemic, having a higher incidence in dark-skinned people [26, 33]. HCC incidence is lower in developed countries, except for Japan and Italy, as depicted in Figure 1.1.

HCC is predicted to grow to 22 million patients over the next two decades [33]. Besides, it is increasing in subgroups such as men aged from 55 to 64, especially those born in the peak era of hepatitis C virus infection [68].

![Figure 1.1: Incidence of HCC worldwide per 100,000 people, retrieved from [26].](image)

Nevertheless, the mortality of HCC has been reported to be plateauing in the United States [68] and the 5 years survival has been improved in more than a 60% from 1975 to 2005 [33, 54], thanks to an earlier detection and better treatments.

1.2 Risk factors

As previously mentioned, the higher incidence of HCC matches the countries where hepatitis viruses are endemic. These viruses compromise one of the most important risk factors of HCC. Another remarkable factors are non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), whose incidences in HCC are increasing in parallel to obesity increasing incidence.

Besides, cirrhosis is commonly found in HCC cases. It normally happens before HCC and as a result of a chronic liver disease, as depicted in Figure 1.2.
1.2.1 Hepatitis-B virus (HBV)
It is the most common cause for HCC with a 54% [33]. It increases the risk of liver cancer 15-to-20-fold in chronic carriers [33]. There are two possible mechanisms that lead eventually to hepatocellular carcinoma, one of them occurs in the presence of fibrosis and cirrhosis, while the other does not.

In the first one, HBV infection causes hepatocyte injury and chronic necroinflammation, which lead to hepatocyte proliferation, fibrosis and cirrhosis. As for the second mechanism, an integration of the HBV DNA in the host cells would act as a mutagenic agent. [27, 35, 64].

1.2.2 Hepatitis-C virus (HCV)
It compromises the second most common cause for HCC with a 10-25% [33], being the most common cause in developed countries [33]. As for its mechanisms are less well understood [35], but it is thought to increase the risk of HCC by inducing hepatic inflammation, oxidative stress, fibrosis, cirrhosis and by promoting malignant transformations in infected cells [46].

In this case, HCV cannot integrate in the DNA of the host cell.

1.2.3 Alcohol
Alcohol-related cirrhosis is the third most common cause of HCC [33]. The mechanism would consist in a recurrent inflammation and cycles of hepatocyte necrosis and regeneration with oxidative stress, which would result in cirrhosis [33]. Besides, it appears to act in synergism with HCV and HBV infection.

1.2.4 Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)
Nowadays NAFLD associated HCC incidence is increasing worldwide, parallel to obesity and diabetes [60]. NAFLD mainly occurs in the presence of cirrhosis but it can also occur without it. It is the most common liver disorder in western countries [64] and most common cause of chronic liver disease in the USA [33]. The diagnosis of HCC in the presence of NAFLD occurs normally at a late stage, owing to ultrasounds limitations in the presence of obesity, reducing the opportunities of curative treatments [60].
Both NAFDL and NASH can lead to chronic liver disease [33], cirrhosis [33] and, eventually, to HCC. Nevertheless, NASH patients only have an increased risk for HCC when they have cirrhosis [6, 33].

1.2.5 Cirrhosis
As previously exposed, cirrhosis normally occurs previously to HCC development and as a result of a chronic liver disease [64]. Most of the previously explained risk factors result in cirrhosis and, then, in HCC.

Figure 1.3: Mechanism of HCC development, retrieved from [c].

Cirrhosis occurs in around 80-90% of the cases of HCC [31]. The progression of cirrhosis to HCC is a complex process and it may involve a combination of etiologies [34]. A decrease in hepatocyte proliferation, indicative of reduced regenerative capacity of the liver [64], is associated to an increase in fibrous tissue and a destruction of liver cells, which could lead to tumour development [64] as depicted in Figure 1.3. Apart from that, telomere dysfunction, which would lead to chromosomal instability [64], and alterations in the micro and macroenvironment also play a role in HCC development [27].

1.2.6 Other risk factors
Especially in southern Africa, food contamination with aflatoxin, by producing mutations of the p53 tumour suppressor gene [64]. Other risk factor is hemochromatosis [35].

All these factors might eventually lead to HCC by different mechanisms. Now, more general pathogenesis of HCC will be discussed.

1.3 Physiological conditions and pathogenesis
Under physiological conditions the liver performs several functions. The detoxification of blood and synthesis of plasmatic proteins, clot factors and bilirubin, as well as metabolism of glucose, lipids and proteins in order to keep balance within the body are only some examples of functional processes taking place in the liver [36].
The blood supply to the liver comes from two different branches: the hepatic arteries, carrying oxygenated blood, and from the portal hepatic vein carrying blood with nutrients. They both end up in the central vein and then go to the hepatic veins, as shown in Figure 1.4. The liver receives 75% of the blood supply through the hepatic portal vein and the rest through the hepatic artery [35].

![Figure 1.4: blood supply circuit of the liver, found in [e].](image)

When the liver is affected by HCC, its normal functions are disrupted and also, its physiology is altered. Hepatocellular carcinoma occurs as a combination of intrinsic factors (acquired or inherited genetic mutations) and of extrinsic risk factors, as previously discussed. There are several mechanisms that may intervene in the development of HCC.

Some of the most common mechanisms found in HCC are:

- **Chronic oxidative stress.**
- **Cirrhosis.**
- **Affected signalling pathways:** activation of proinflammatory pathways [64].
- **Fibrosis:** there are several factors that lead to persistent inflammation as depicted in Figure 1.5. Then, chronic damage and inflammation can lead to liver cirrhosis, fibrosis and even carcinogenesis. Because of fibrosis, there is an increase of the matrix quantity and its stiffness leading to a poor oxygen exchange [33]. This hypoxia promotes angiogenesis.
Figure 1.5: pathways for developing HCC from cirrhosis/fibrosis and chronic inflammation, found in [71].

- **Tumour microenvironment (TME):** TME has been proved to play a really important role in the development of HCC. It is composed by tumour cells, stromal cells, immune cells and cancer-related fibroblastic cells as depicted in Figure 1.6. Hepatic stellate cells influence tumour progression as they create a fibrotic environment where the tumour can proliferate rapidly [11].

Figure 1.6: Microenvironment of HCC, retrieved from [20].
• **Pro-angiogenic growth factors:** they are secreted thanks to fibrosis. This results in HCC being highly vascularised by arteries [31]. The blood supply to tumorous tissue consists of 90% hepatic arterial blood [47]. This differs from healthy liver tissue which is mainly supplied by the hepatic portal vein. Because of that, many therapies target the hepatic arteries that supply blood to HCC, either by blocking them or by releasing drugs there so that they only reach the tumour. Such techniques are transarterial embolization (TAE), conventional transarterial chemoembolization (cTACE), drug-eluting bead-TACE (deb-TACE) and radioembolization (RE) [35]. They will be further discussed in the treatment section (1.6.2.4 Transarterial therapies) and in the second part of the chapter (2. Transarterial therapies).

All these underlying process lead to several symptoms because of a disruption of the liver functions. These alterations also allow for different diagnostic tools and classification of the tumour.

### 1.4 Symptoms and diagnosis

The main symptoms that HCC produces at first are similar to the ones of chronic hepatitis and cirrhosis [35]. If the tumour is small, it is normally asymptomatic. For more advanced tumours, possible symptoms are [30, a]:

- Deterioration of liver function.
- Fever and weight loss.
- Jaundice: yellowing of skin and eyes.
- Pain in the abdomen.
- Tiredness and weakness.

Even though the symptoms do not appear until later stages of the tumour, they are used as part of the diagnosis.

In patients suffering from any of the HCC risk factor, a **surveillance** is normally carried out in order to try to diagnose HCC at an early stage.

As for the **diagnosis**, the main methods used are imaging techniques and biopsy when the imaging techniques are not sufficient [30, 35]. Ultrasound imaging (US), computed tomography (CT) and magnetic resonance images (MRI) can be acquired to diagnose HCC. In some cases two techniques are used, as shown in Figure 1.7. In the case of HCC, large hepatic masses with arterial hypervascularity are expected to be found in the images [28, 30]. Also, because of the high amount of arterial blood feeding the HCC tumours, tumorous tissue will be brighter during the arterial phase in the image than the surrounding tissue, that also contains venous blood [16].
1.5 Prevention

HCC is detected many times when it is too late for treatment or when the only option to cure it is transplantation. In order to avoid so, surveillance methods are used for people with high risk, as previously mentioned, and preventive measures are taken to avoid the development of HCC. As displayed in Figure 1.8, some of the measures adopted for this purpose are:

- HBV vaccination: by reducing HBV, the incidence of HCC is also reduced [51].
- Interferon treatment for patients with HCV: it is associated with a lower risk of HCC [64].
- Treating chronic or viral hepatitis which may lead eventually to HCC [64].

Avoiding the risk factors, such as massive consumption of alcohol, food contaminated by aflatoxin, reducing NASH by weight loss and control of diabetes [60, 67, b].
When prevention is no longer possible and HCC has already developed, anticancer therapy is used.

1.6 Treatment

1.6.1 Staging

The treatment is chosen based on the stage of HCC. Different staging systems are used, but the Barcelona Clinic Liver Cancer (BCLC) stage system is the one most commonly used [14, 28] in order to do prognostic predictions and for treatment allocation [28]. It divides patients in 5 stages: 0, A, B, C and D.

- Stage 0 corresponds to patients with a single tumour <2cm in diameter without vascular invasion and well-preserved liver function.
- Stage A corresponds to patients with a single tumour >2cm or with 3 nodules <3cm in diameter.
- Stage B corresponds to patients with multinodular asymptomatic tumours.
- Stage C corresponds to patients with macrovascular invasion or extrahepatic spread, they are symptomatic tumours.
- Stage D corresponds to patients with very poor performance status.

Then the treatment is chosen based on the stage of HCC.

1.6.2 Therapies overview

Treatment can be chosen based on the Barcelona Clinic Liver Cancer (BCLC) stage system. According to this criteria, the stage 0 of HCC should be treated with a resection of the tumour. The next stage (stage A) of HCC can be treated by either transplantation, provided that there are no other diseases, or with Radiofrequency (RF) or Percutaneous Ethanol Injection (PEI). Stage B is treated by transarterial therapies such as TAE, TACE or radioembolization and in the next stage, sorafenib is used. During the terminal stage or stage D only supportive care is provided. This is summarised in Figures 1.9 and 1.10 and a more detailed explanation of each technique can be found below.

![Figure 1.9](image-url)

Figure 1.9: Graphical association of the stage of the tumour to the treatment given, extracted from [16].
1.6.2.1 Liver resection
It consists of removing the part of the liver where the tumour is located. It is performed when the tumour has not spread within the liver and is smaller than 2 cm [35]. Several resections can be performed as displayed in Figure 1.11.

Figure 1.11: Possible liver resections that can be performed, retrieved from [35].

1.6.2.2 Liver transplantation
Liver transplantation is performed in patients with early stage HCC or stage A, that have single or 3 nodules of less than 3 cm [35]. Because of the shortage of donors, the procedure might be
delayed. This permits the tumour to progress and then, transplantation might be no longer an option [32].

1.6.2.3 Radiofrequency ablation (RF)/Percutaneous ethanol injection (PEI)
These treatments are used on patients with associated diseases in stage A. Both methods induce coagulative necrosis of the tumour, in the case of RF because of the produced heat (60 °C to 90 °C) and in the case of PEI because of cellular dehydration, protein denaturation, and chemical occlusion of small tumour vessels. Another analogous technique is cryoablation, in which the tissue is frozen (-20 °C to -60 °C). RF and PEI are displayed in Figures 1.12 and 1.13 respectively.

![Figure 1.12: Radiofrequency (RF) ablation in HCC, extracted from [35].](image1)

![Figure 1.13: Percutaneous ethanol injection (PEI) to treat HCC, found in [35].](image2)

1.6.2.4 Transarterial therapies
Several procedures are included here. These are: transarterial embolization (TAE), transarterial chemoembolization (TACE), displayed in Figure 1.14, and radioembolization (RE). They are used in patients in stage B, with more than 3 nodules but without macrovascular invasion nor cancer symptoms. These treatments take advantage of the fact that the tumour receives most of its blood supply from the hepatic artery and not from the portal vein as healthy tissue does [9]. These therapies are based on targeted drug delivery and are going to be the main focus of this project. Because of that, they are further explained in the second part of this chapter.
1.6.2.5 Sorafenib
Sorafenib is used in patients in advanced stage or stage C. It is an inhibitor of kinases leading to a reduced tumour cell proliferation and angiogenesis and increased apoptosis [13].

1.6.2.6 Palliative care
Palliative care is given to patients in terminal stage of HCC. It consists of management of pain, nutrition and physiological support [28].

2. Transarterial therapies
In these techniques, the tumour blood supplying arteries are occluded by the injection of particles, which can be either a chemotherapeutic (TACE) or radiologic agent (RE) or only embolic (TAE). In comparison to conventional chemotherapy, where less than 0.1% of drugs reaches the tumour [57], most of the drugs reach the liver, up to 85%, reducing that way the toxicity to the rest of the system, thus, the toxicity to healthy tissue [9].

In TAE, the embolization is performed without any chemotherapy or radiation. It aims to cause ischemia of the tumour [45], as depicted in the left top of Figure 1.15.

In the case of TACE and radioembolization, either a cytotoxic agent or a radiologic agent is injected respectively.

TACE can be divided in two subtechniques: conventional TACE (cTACE) and drug-eluting beads TACE (DEB-TACE):

- **Conventional TACE (cTACE):** it implies the delivery of chemotherapeutic drugs to the arteries that feed the tumour, followed by embolic materials that restrict the flow to the tumour [45]. This results in a cytotoxic and ischemic effect [28]. The most common agents used are doxorubicin and cisplastin [28]. The most common embolic materials are Gel-foam microspheres and polyvinyl alcohol (PVA) particles. This procedure is depicted in the top at the right of Figure 1.15.

- **Drug-eluting bead (deb-TACE):** in this technique, an embolic product that gradually releases the drug over time (drug-eluting embolic bead) is used in order to achieve more sustained levels of chemotherapy. These beads are loaded with a drug solution, normally doxorubicin [45]. This procedure can also be found in Figure 1.15.
As for radioembolization (RE), radioactive substances are injected, commonly microspheres containing Yttrium-90 ($^{90}$Y) or Iodine-131 ($^{131}$I). These particles emit high-energy but low-penetration radiation to the tumour and they do not cause substantial ischemia [16]. This treatment was performed in the patient whose data was used for this project. Because of that, more details of this technique are given below.

Figure 1.15: Transarterial therapies, extracted from [62].
2.1 Radioembolization

As mentioned above, $^{90}$Y is commonly used in radioembolization as the radioactive agent. Two Yttrium-90 particles are commercially available: one made out of glass (TheraSphere; Biocompatibles UK, Farnham, United Kingdom) and the other of resin (SIR-Spheres; Sirtex, North Sydney, Australia) [16], whose properties are displayed in Table 1. SIR-Spheres are kept with water in a vial of 5 mL that contains around 40 to 80 million particles. The vial is mixed with sterile water to infuse around 20-40 mL of mixture to the patient [61]. In the case of TheraSpheres, around 27-90 mg of TheraSpheres, which equals 1.2-8 million particles, are contained in a vial. They are injected mixed with a saline solution, being the volume injected equal to 20-60 mL [61].

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>SIR-Spheres</th>
<th>TheraSphere</th>
<th>Pretreatment particles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotope location</td>
<td>Attached to surface</td>
<td>Incorporated into glass matrix</td>
<td>Attached to surface</td>
</tr>
<tr>
<td>$\beta$ emission (MeV)</td>
<td>2.28 (100%)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>$\gamma$ emission</td>
<td>None</td>
<td>141 KeV (89%)</td>
<td></td>
</tr>
<tr>
<td>Matrix material</td>
<td>Resin</td>
<td>Glass</td>
<td>Aggregated human serum albumin</td>
</tr>
<tr>
<td>Density (g/mL)</td>
<td>1.6</td>
<td>3.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Av diameter (µm)</td>
<td>32±10</td>
<td>25±10</td>
<td>10-60</td>
</tr>
<tr>
<td>Number of particles (range)</td>
<td>40-80-10⁶</td>
<td>1.2-8-10⁶</td>
<td>0.15-10⁶</td>
</tr>
<tr>
<td>Bq per sphere</td>
<td>50</td>
<td>2500</td>
<td>-</td>
</tr>
<tr>
<td>Embolic effect</td>
<td>Mild-moderate</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Available activity (GBq)</td>
<td>3</td>
<td>3, 5, 7, 10, 15, 20</td>
<td>Any</td>
</tr>
<tr>
<td>Shelf life</td>
<td>24 hours</td>
<td>12 days</td>
<td>Dissociation after 2 hours</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Target Activity/stasis</td>
<td>Target Dose</td>
<td>Target Activity</td>
</tr>
</tbody>
</table>

Table 1: properties of the SIR-Sphere, of the TheraSphere and of $^{99m}$Tc-MAA, retrieved from [55].

Secondary effects owing to irradiation to other organs may occur [16] as well as dispersion of the particles to other sites due to the impossibility to come closer to the tumour. Because of that, achieving the highest targeting to the tumour reports high benefits.

In order to achieve the highest targeting, there is a preparation phase previous to treatment. This phase consists of several procedures [25]:

1. Angiography: to identify the arterial liver anatomy in order to decide the position of the catheter as well as to predict the deposition of $^{90}$Y.
2. Pretreatment with $^{99m}$Tc-MAA: $^{99m}$Tc spheres, whose properties are displayed in Table 1, try to mimic the particles used during the treatment. These particles are injected to verify if the $^{99m}$Tc are going to end up in the tumour, the lung shunting (percentage of MAA shunted in the lungs) and if there is any vessel going to the stomach so as to prevent ulcers by closing the vessel [61]. Nowadays, $^{166}$Ho-PLLA is starting to be used to replace $^{99m}$Tc [55] since, unlike to $^{99m}$Tc, $^{166}$Ho does not disintegrate, reducing possible errors in the pulmonary lung shunting. Besides, $^{166}$Ho is visible in MRI.
3. Calculation of the dose of particles that it is going to be injected. The dose delivered is adjusted based on the results of the pretreatment. If the lung shunting is more than the 20%, the treatment is contraindicated.

Then, the treatment is performed. It consists of different phases:

1. Tumour targeting [63]: the catheter is placed at the target location. This is made by using fluoroscopic guidance [50].
2. Once that the catheter is located at the right position, the activity vial is injected [50].
3. Patients are discharged 4-6 hours after treatment [50].
4. Follow-up of the treatment to monitor the response and toxicity [50].

Radioembolization techniques are going to be the main focus of this project since they were used to treat the patient whose geometry was used.
Chapter 2.
State of the art on targeted drug delivery for HCC by means of Computational Fluid Particle Dynamics (CF-PD)

In this chapter the situation and advances of targeted drug delivery for HCC by means of Computational Fluid Particle Dynamics are discussed.
Even if transarterial techniques are targeted therapies, there might be still some particles not reaching the targeted tissue, ending up in healthy tissue. This can lead to patients responding to treatment (responder patients) and patients in which the treatment is not effective (non-responder patients). Because of that, several approaches have been developed to try to maximize the target to the tumour:

1. **Ligand-receptor particles** [43]: these particles attach specifically to receptors in the tumour cells; e.g. multikinase inhibitor directed against several molecular components of the tissue microenvironment. However, many of these particles are removed by the immune system before reaching the tumour.

2. **Magnetic drug targeting** [43]: by using an external magnetic field, the particles are directed to the target place; e.g. biodegradable microparticles loaded with iron-cobalt nanoparticles and doxorubicin (DOX). Their main limitations are that the tumour must be close to the surface and the flow rate has to be very small.

3. **Direct drug-targeting** [43]: here the radioembolization techniques previously discussed are included. By making use of computational fluid-particle dynamics (CF-PD), the location of the catheter as well as the infusion velocity among other parameters are chosen. This allows to specifically choose the injection parameters for each patients in order to achieve the best targeting possible. This technique is going to be the main focus of this project.

**Direct drug-targeting by computational fluid-particle dynamics (CF-PD)**

This technique consists in simulating the drugs injection in the hepatic artery system by means of computational fluid-particle dynamics (CF-PD). A computational domain of the hepatic arteries is extracted from medical images and the flow of hepatic arteries and the treatment are simulated in it.

Thanks to the use computational fluid-particle dynamics (CF-PD), the injection point of the drugs could be chosen in such a way that the targeting achieved is much higher than when injecting the particles at any point. As depicted in Figure 2.1 by choosing the position of the catheter, the particles can be more accurately directed to the tumour.

![Figure 2.1: advantages of targeting the particles injection (right), versus not (left), extracted from [58]. As it can be seen, by moving the catheter within the cross-sectional area the target is much more accurate.](image)
The position of the catheter within the cross-sectional area would be chosen by means of the particle release maps (PRM) generated by CF-PD. These PRM are generated by backtracking the particles trajectories to the injection point. That way, the PRM links the place of injection with the trajectory (branch) that the particles will follow as can be seen in Figure 2.2. By making use of the PRM, the optimal position of the catheter to reach the branch that feeds the tumour could be determined.

![Particle release map](image)

**Figure 2.2:** Particle release map, it shows where the particles will preferentially end depending on the location of the catheter-tip over the cross-sectional area, retrieved from [43].

The potentials of this technique have been shown both experimentally [59] and, also, computationally under different conditions [8, 21, 22, 23, 42, 59]. CF-PD has proven to be a powerful tool for assessing targeting in transarterial therapies [2, 39, 42] and that it could even be used for treatment planning [43]. In this aspect, refinements done in the models, such as the implementation of boundary-conditions dependent on the tumour burden [3], can lead to more accurate results and the models can even be used to test new devices or check what treatment (TACE or radioembolization) or what particles (SIR-Spheres or TheraSpheres) would be best for a specific patient. Nevertheless, according to previous studies, there are not significant differences in the trajectory between using one kind of particles or other (tested with Theraspheres, SIR-Spheres and $^{99m}$Tc), and the differences would be noticeable only on the penetration depth [38]. This was validated by experiments [19, 54] and computational simulations [1, 7]. What studies do prove is that both catheter location and position within the cross-sectional area plays a significant role.

As discussed by Aramburu et al [1], the catheter tip location within the hepatic artery plays a very significant role. By shifting the catheter-tip only 5 mm, the particles pathlines changed drastically, as depicted in Figure 2.3. According to their study, the presence of near-by bifurcations as well as the tumour burden play a very important role in the particles distribution. Parameters of less importance in the general target are the tip orientation (Figure 2.4), which plays a minor role in segment-to-segment distributions [2]. This same author also claimed the importance of the catheter-tip position within the cross-sectional area [4] for the downstream particle distribution. This confirmed what had been previously demonstrated by Basciano et al [7].
Figure 2.3: Streamlines at the hepatic artery with the catheter-tip near the bifurcation (left) and with the catheter tip-near the bifurcation with a 5-mm shift (right), directly extracted from [1].

Figure 2.4: Catheter tip orientations changed to verify the influence of the orientation. It was changed so it pointed upwards, rightwards, downwards and leftwards, retrieved from [2].
Among other potentials of using CF-PD is the fact that the influence on the blood hemodynamics of different catheters, such as an angled-tip microcatheter (ATM) (in Figure 2.4) [2] or an antireflux microcatheter (Figure 2.5) [5, 70], can be assessed and it even allows to test the possible performance of new catheters before its implementation in the clinic. This was done by Kleinstreuer et al [21, 42] that developed a Smart Microcatheter (SMC) and evaluated its hemodynamics in the hepatic artery by means of CF-PD. This catheter consist of some struts, as depicted in Figure 2.6, that provide a precise and stable positioning within the vessel cross section, allowing much more accurate targeting, as depicted in Figure 2.7. The SMC is connected to an automated microsphere supply apparatus (MSA), forming the SMC system [42]. The MSA resides externally and is operated together with the SMC. The MSA is composed by a syringe with a well-mixed microsphere solution, a piston-displacement motor actuated by a transient function, and MSA-SMC connecting tubing [21]. Thanks to the MSA, the particles can be injected with different distributions: step, ramp or S curve, among others.
By using the above mentioned SMC, a targeting methodology has been proposed to be implemented in the clinic following the Computational Medical Management Program proposed by Kleinstreur [43]. It is performed in three steps depicted in Figure 2.8 [43]:

I. Evaluation of the patient: tumour classification in order to choose the treatment.
II. Computer modelling: in order to choose the catheter placement.
III. Clinical implementation: injection of the therapeutic drugs by making use of the Smart Micro-Catheter (SMC), to accurately locate the catheter, and the Medicine Supply Apparatus (MSA), which supplies the particle stream at the computed instant.

Figure 2.8: Computational medical management program stages, found in [43].
Furthermore, this technique could be more easily implemented thanks to the recent advances of Simoncini et al [65] that allow to create successive bifurcations from principal branches. Thus, the geometry generation will be faster and it would be possible to include more terminal vessels in the model.

Even if the potentials of using CF-PD to target more accurately the tumours have been proven to be huge, the above mentioned studies have some limitations [1, 2, 4]. First of all, the results cannot be generalised for every hepatic artery, since the results are highly dependent on the specific patient geometry and on the tumour distribution. This is because the flow to tumour-bearing segments is higher [1, 3, 5], which strongly influences the flow split in the arteries. Besides, most of the models do not take into account the variability in the sphere diameters, the elasticity of the walls, the embolic effects that may arise after the injection of the spheres or the possible displacements of the catheter while the injection is being done, since the catheter is fixed in the domain. Nevertheless, this problem could be solved in reality by using the SMC.

Based on this literature review, it has not been studied by means of CF-PD the possible differences in outcome on a patient when using different treatments nor the possibilities of this technique to evaluate what treatment to choose for a patient. To the author’s knowledge, chemoembolization particles have never been inspected in any study. Hence, the aim of this study was to evaluate whether changing some treatment parameters, such as the particles, the injection point or the velocity, in a patient could have meant any significant differences in their outcome as well as which one had the most significant impact in the particle distribution. The inspected particles are the particles used in radioembolization, both SIR-Spheres and TheraSpheres during the treatment, and the $^{99m}$Tc during pre-treatment, and in chemoembolization, the HepaSpheres. Also, the easiness of targeting the tumours was assessed by means of CF-PD for all the cases. The ultimate goal of this project was to inspect the similarities between the simulations and the reality by comparing the distribution of $^{99m}$Tc particles in the simulation with the real images of the pre-treatment taken to the patient.
Chapter 3.
Creation of the computational domain

In this chapter the geometry in which the simulations will be run is created. This is done by means of segmentation of the medical images of a patient. The first part of the chapter focuses on the composition of the image studies used to extract the geometry and the second part explains how the geometry is extracted. Even though there were images from two different patients, only one patient was used in the end, as explained in 2.2 Non-responder patient. The third part of the chapter explains the generation of the volume mesh and how it was chosen based on a mesh sensitivity analysis.
1. Patient datasets

Thanks to the collaboration that was setup with prof. dr. Geert Maleux (Leuven University Hospital), the images used for this study are images from two real patients. These patients had both been treated with radioembolization, one of them was a responder to the treatment and the other a non-responder. This classification is done based on the RECIST (Response Evaluation Criteria In Solid Tumours) criteria. According to this criteria the patient outcome is examined 6 weeks after the first treatment and it is classified as follows [i]:

- Completely shrinkage of the tumour: absolute response.
- At least 30% shrinkage of the tumour: partial response.
- Less than 20% shrinkage or growth: stable disease.
- More than 20% growth: progression.

The examination of these patients is done by different imaging modalities which are presented next.

1.2 Image studies

For each of the two patients, there are 4 different studies: 2 are MRI studies, one X-ray Angiography study and a CT and Nuclear Medicine (NM) study. Each study is composed of different series of images. Each series corresponds to a certain time instant within the study. All these studies are done with different purposes that are described below.

1.2.1 MRI

One of the two MRI studies was performed prior to treatment (MRI1) and the other typically a few months after the treatment (MRI2). In the case of the patients inspected here, MRI2 was done 4 months after the treatment for the responder and 2 weeks after the treatment for the non-responder.

The MR images are used for diagnosis (MRI1) and treatment response (MRI2). MRI is performed with contrast-enhancement which provides more information about the liver function and the perfusion of blood to the tumour. The contrast travel through the liver vasculature allows to differentiate in phases depending on the location of the contrast: arterial when the contrast is in the arteries and venous when it is in the veins.

The early arterial phase is used to detect the lesions. As seen in Figure 3.1, some features of this phase are that the aorta is seen brighter as well as the spleen and the tumours if they are hypervascularised. The tumours may be hypervascularised because of the angiogenesis that takes place in HCC, as described in 1.3 Physiological conditions and pathogenesis. The angiogenesis leads to the tumour being preferentially fed by arteries instead of veins as the rest of the liver tissue does.
Figure 3.1: Hyperintense tumour during the early arterial phase, marked with the circle. The other bright area corresponds to the aorta.

On the other hand, on the later phases (venous phase), there is a washout of the contrast and the veins are seen. During this phase, the lesions are hypointense (darker than the surrounding) because of the washout. Tumours appear darker with a bright ring around them during this phase as depicted in Figure 3.2.

Figure 3.2: tumour appearance in the venous phase. The tumour is hypointense with a brighter ring surrounding it.

In order to segment (extract) the arteries and look at the tumours, it is better to use the arterial phases, since during this phase those structures are brighter. Only axial slices with a pixel size of around 1 mm are used in this diagnostic technique. The other views have much lower resolution due to high slice thickness which is in the order of 3.5 to 5 mm. The high slice thickness later on led to complications in the segmentation of the arteries, such as elliptic bumpy vessels, enlarged in the longitudinal direction as it can be seen in 2. Geometry segmentation.
1.2.2 CT and NM images
CT and NM study is performed prior to the treatment.

These imaging techniques are used during the pre-treatment, described in 2.1 Radioembolization. The final distribution of the $^{99m}$Tc spheres is evaluated by means of SPECT. The medical doctors then compare this distribution to the MRI to see if there is a good match between the tumours and the hot spots (locations at which most $^{99m}$Tc particles have ended up) in order know if the treatment will be effective or not.

1.2.3 X-ray angiography (XA)
X-ray angiography is performed during the treatment so that the medical doctors can know the location of the catheter tip.

1.3 Studies composition
Each of the before-explained studies was composed of several series each representing one time instant. Hence, there was a huge amount of data from each patient. A summary of all the data for each patient can be found in Table 2.

<table>
<thead>
<tr>
<th>Study</th>
<th>Responder</th>
<th>Non-responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI pre-treatment</td>
<td>13 series</td>
<td>9 series</td>
</tr>
<tr>
<td></td>
<td>Contrast travelling through the vasculature, differences in resolutions, noise and so on.</td>
<td>Same as in the responder patient.</td>
</tr>
<tr>
<td>MRI post-treatment</td>
<td>15 series</td>
<td>9 series</td>
</tr>
<tr>
<td></td>
<td>2 series of lung shunting, 3 series of axial CT images, SPECT: 6 series of the final distribution of $^{99m}$Tc: in a volume, different views, different slices 1 topogram: coronal slice of the patient reconstructed from the axial CT slices</td>
<td>2 series of lung shunting, 5 series of CT in different views SPECT: 2 series of the final distribution of $^{99m}$Tc 1 topogram: coronal slice</td>
</tr>
<tr>
<td>CT/NM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XA angiography</td>
<td>7 series of the catheter tip location</td>
<td>3 series of the catheter tip location</td>
</tr>
</tbody>
</table>

Table 2: Summary of all the data series available for each patient.

All the MRI series were carefully inspected in order to use the images with the best resolution and where the hepatic arterial tree was best seen. Since portal veins and hepatic arteries run in parallel, identifying whether the vessels seen are arteries or veins was challenging.

In the case of the non-responder patient, the phase of each series was labelled in the dataset, so the arteries could be more easily identified. Nevertheless, in the case of the responder patient, the phase of each series was not specified. Among all the series two different structures were identified, being one of them larger in diameter than the other. In general, veins are larger than the arteries. Thus, the arteries were assumed to be the smaller vessels. The correct identification of the arteries for both patient was confirmed afterwards by the medical doctor who had provided the images.

For both patients, the images chosen were the ones with the best balance between image resolution, contrast and clearness of the arterial path and noise. The characteristics of the images chosen for each patient can be found in Table 3.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Responder</th>
<th>Non-responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image chosen</td>
<td>MRI pre-treatment, series 10</td>
<td>MRI pre-treatment, series 7</td>
</tr>
<tr>
<td>Image size</td>
<td>320x260 px</td>
<td>384x384 px</td>
</tr>
<tr>
<td>Pixel size</td>
<td>1.3125 mm</td>
<td>0.976562 mm</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>3.5 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Slice increment</td>
<td>3.5 mm</td>
<td>2.5 mm</td>
</tr>
<tr>
<td>Number of slices</td>
<td>72</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3: Parameters of the images chosen for each of the patients.

Once that the best series were chosen, the images were opened in Mimics (Materialise, Leuven, Belgium) to extract the geometry.
2. Geometry segmentation

This step was performed in three different software programs, being all from the same company (Materialise®, Leuven, Belgium): Mimics, 3-Matic and Magics. In the first one, the geometry was segmented based on the images and the 3D model was reconstructed. The segmentation is done to separate the hepatic artery pixels in order to extract the geometry. In the second one, the geometry was modified. In the last one, the model obtained in Mimics was improved to achieve a good surface mesh from which the volume mesh could be generated. In order to generate the volume mesh (described in 3. Volume mesh), another software program, ICEM (Ansys, Canonsburg, PA, USA) was used.

As previously explained, the images were from two different patients. The first intention was to obtain the geometries of both patients and compare why the treatment had worked in one of them whereas not in the other. However, owing to the images limited resolution, the extraction of the geometry took longer than expected and only the responder patient images were used in the end.

2.1 Responder patient

2.1.1 First geometry

The geometry was segmented in Mimics by using Dynamic region growing tool. This segmentation is made based on the grey values of a seed point within a certain range. A lot of manual editing had to be done since the arteries did not have much contrast and, in many cases, parts of the artery were not selected in the mask with Dynamic region growing.

From the masks drawn in 2D, a 3D part was generated. Then, further manual editing was done in order to get the best possible geometry. All this process was mainly done in the images of the axial plane since in the other views the pixels were too big, as displayed in Figure 3.4, and identifying the arteries paths was more challenging. Nevertheless, they were also used for confirmation when the path was not clear in the axial view.

![Figure 3.4 Pixels in the sagittal plane, its rectangular shape lead to elliptic or even rectangular vessels.](image)

A first attempt of generating a surface mesh was done in the geometry depicted in Figure 3.5. To do so, it was imported to 3-matic in order to smoothen it and to generate the surface mesh. In 3-matic the geometry was smoothed both globally and locally and remeshed afterwards. Nevertheless, the geometry was not suitable to incorporate in the computer simulations since it was very bumpy and irregular and the radius of the daughter vessels were sometimes bigger.
than the ones of the parent vessels. Hence, it was imported back to Mimics in order to do further refinements on it.

![Figure 3.5: First geometry generated in Mimics. It had to be improved in order to use it for simulations.](image)

2.1.2 Resliced geometry

2.1.2.1 Editing the geometry in Mimics

Since one of the main problems of the geometry was the bumps due to the larger pixel size in one of the views, this problem was tried to be solved by reslicing the project in Mimics. That way, more slices were created by means of interpolation of the existing ones. As a result the vessels could be better refined along the longitudinal axis but at a cost of a decreased contrast. This contrast reduction would make the path of the vessels less well defined. The project was resliced to a size of two fold the pixel size (2.6 mm) along the longitudinal direction because this size fulfilled the best relation between pixel size and contrast.

In this step, a more realistic geometry was achieved by always trying to reduce the radius of the vessels after bifurcations and by trying to smooth the geometry as much as possible. Also, some new vessels were recognised and created along the longitudinal direction thanks to the enhanced resolution in that direction.

Even though the reslicing improved the geometry a lot, the limitations of the bigger pixel size did not completely disappear and they were still perceptible in the elliptical shape of the vessels and the still existing bumps. The geometry displayed in Figure 3.6 was imported again in 3-matic.
2.1.2.2 Smoothing and surface mesh generation in 3-matic

The geometry was smoothened both globally and locally, giving special attention to the areas with bumps. In these areas the amount of triangles was reduced drastically and, then, the geometry was smoothened to remove the bumps. Once it was smooth, the triangles were subdivided again. During this process, the maximum geometrical error was set to 10% of the smallest detail that should be preserved [48], being 1.31 mm. All this process lead to a more uniform and round geometry. The smoothed geometry can be seen in Figure 3.7, where the cross-sectional area of two terminal branches is depicted for both the smooth and the original geometry. There are two different contours: the more rounded filled in blue corresponds to the smooth geometry and the sharper and more rectangular contour corresponds to the original geometry.

Along this process, the geometry was remeshed several times. At first, a Uniform remesh was used since this is recommended when there is less need to preserve the geometry of the part [48]. Once the geometry was smooth and regular, Gradient remesh was used in order to achieve a smoother transition between the more finely meshed bifurcations and the other regions.
Two extra modifications were performed in the geometry. The first one was that the outlets and the inlet were cut perpendicular to the vessel walls so that the sections were perfectly flat. This was necessary since it ensured that the flow imposed by the boundary conditions was parallel to the walls. This was done in Mimics by Cut with Polyplane and Cut perpendicular to screen. The second modification was that the inlet was extended to a final length of 30 mm in 3-matic to make sure that the inflow was fully developed by the time it reached the first bifurcation. In order to have fully developed flow in laminar regime the length of the tube (L) has to be [g]:

\[
L = 0.06 \cdot Re \cdot D = 0.0297 \text{ m}
\]  

(1)

where Re stands for the Reynolds number=\(\rho \cdot v \cdot D / \mu\), with \(\rho\), the density of blood; \(v\), the velocity of blood; \(\mu\) the viscosity of blood, all defined in the Numerical modelling section (1. Numerical modelling); and \(D\), the diameter of the tube (\(2 \cdot 4.56 \times 10^{-3} \text{ m}\)).

The final surface mesh is depicted in Figure 3.8 and Figure 3.10, where it can be compared to the first created geometry. It had around 26400 triangular elements, all of which had a skewness value higher than 0.4, as shown in Figure 3.9, with skewness defined as ‘the ratio of the area to the area of an equilateral triangle with the same circumradius’ [49]. That surface mesh was exported in order to generate the volume mesh in the next step.

![Figure 3.8: Final surface mesh generated in 3-Matic for the responder patient.](image)

![Figure 3.9: Final quality histogram of the surface mesh. The quality was inspected based on the skewness, which was set to be more than 0.4.](image)
2.2 Non-responder patient

In this case, the Dynamic region growing tool worked better to select the arteries since they had more contrast so less manual editing was needed. Also the Smart Expand tool was very useful to select parts that had not been selected with the first segmentation. Nevertheless, the paths were more tortuous at certain regions and difficult to follow. In Figure 3.11, the latest version of the geometry is displayed. It is clear that it is very different from the arterial morphology of the responder patient. In the end only the geometry of the responder patient was used since the paths of the arteries were easier to follow and recognise.
3. Volume mesh

3.1 Volume mesh generation in ICEM

The surface mesh generated in 3-Matic was exported as an STL file and imported into ICEM in order to generate the volume mesh.

Ten different volume meshes were created with the values as found in Table 4. The maximum element seed size was set to a value of 2, since it is recommended to be a power of 2 [j], and the minimum size limit was set to 0.5. A mesh sensitivity analysis was performed to choose the best mesh which provided accurate enough results with the least number of elements possible.

<table>
<thead>
<tr>
<th>Mesh</th>
<th>Number of elements</th>
<th>Scale factor</th>
<th>Number of refinements</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.62·10^6</td>
<td>1</td>
<td>18</td>
<td>Octree</td>
</tr>
<tr>
<td>2</td>
<td>0.85·10^6</td>
<td>0.5</td>
<td>18</td>
<td>Octree</td>
</tr>
<tr>
<td>3</td>
<td>1.56·10^6</td>
<td>0.25</td>
<td>10</td>
<td>Octree</td>
</tr>
<tr>
<td>4</td>
<td>1.73·10^6</td>
<td>0.25</td>
<td>18</td>
<td>Octree</td>
</tr>
<tr>
<td>5</td>
<td>3.54·10^6</td>
<td>0.25</td>
<td>18</td>
<td>Octree</td>
</tr>
<tr>
<td>6</td>
<td>6.9·10^6</td>
<td>0.15</td>
<td>18</td>
<td>Octree</td>
</tr>
<tr>
<td>7</td>
<td>9.38·10^6</td>
<td>0.135</td>
<td>18</td>
<td>Octree</td>
</tr>
<tr>
<td>8</td>
<td>15·10^6</td>
<td>0.115</td>
<td>18</td>
<td>Octree</td>
</tr>
<tr>
<td>9</td>
<td>2.26·10^7</td>
<td>0.1</td>
<td>20</td>
<td>Octree</td>
</tr>
<tr>
<td>10</td>
<td>2.26·10^7</td>
<td>0.1</td>
<td>10</td>
<td>Octree</td>
</tr>
</tbody>
</table>

Table 4: Parameters of all the meshes generated in ICEM.

The generated meshes were composed by tetrahedral elements and by 3 layers of prisms elements close to the wall to improve the accuracy next to the wall and because the flow is aligned with the wall near the boundary. The Octree method was used for all the meshes except for one. The latest was created with the Delaunay method in order to compare which method gave better results in coarser meshes. Both of these methods allow for Mixed Meshing. The Octree Mesh Method ensures refinement of the mesh where necessary, but maintaining larger elements where possible [h]. The Delaunay Method allows for a smoother volume transition between the two layers of elements [h].

The generated meshes were imported into Fluent (Ansys, Canonsburg, PA, USA) to perform the mesh sensitivity analysis. Based on the results of the mesh sensitivity analysis, the final chosen mesh, mesh number 7, had 9379897 elements.

3.2 Volume mesh selection

The parameters inspected to choose the final mesh were: average pressure (Figure 3.12), average velocity (Figure 3.13), average WSS (Figure 3.15), 99-percentile of the velocity (Figure 3.14), 99-percentile of the WSS (Figure 3.16), and the percentage of particles exiting through each outlet (Figure 3.17). They are calculated based on the values of every cell. The 99-percentile was used in order to prevent the influence of possible outliers. As it can be seen in the Figures below for the inspected parameters the results for the mesh with 9 million elements have converged with the results of the meshes of 22 million of elements. In the case of the average pressure even if the difference looks larger, it is only a relative difference of the 4.7% while with the mesh of 6.9·10^6 elements the relative difference was larger (7%). That is why the mesh with 9.4·10^6 was used instead. The Delaunay mesh gives better results for the
pressure, but for the other parameters the results are worse than the ones of the meshes with a similar number of elements.

![Average pressure (Pa)](image)

Figure 3.12: Average pressure (Pa) values in all the meshes of the MSA.

![Average velocity](image)

Figure 3.13: Average velocity (m/s) values in all the meshes of the MSA.
Figure 3.14: 99-percentile velocity (m/s) values for all the meshes of the MSA.

Figure 3.15: Average WSS (Pa) values for all the meshes of the MSA.
Figure 3.16: 99-percentile WSS (Pa) values in all the meshes of the MSA.

Figure 3.17: Percentage of particles that exit through each outlet for each mesh. The non-filled bar corresponds to the Delaunay mesh.
Chapter 4. Computer simulations

In this chapter the whole process of the computer simulations is explained. In the first part, how the computer simulations were performed is explained. Here, a detailed description of the blood flow, particle properties and how they are transported and injected in the blood as well as the boundary conditions of the model can be found. The second part of the chapter focuses on the results extracted from these simulations and the third part in the limitations of the model and future perspectives.
1. Numerical modelling

The numerical modelling is needed in order to implement the blood flow, the particles and its transport in the blood as well as how they are injected into the domain.

1.1 Blood

Blood was modelled as an isothermal, incompressible (1050 kg/m³) and non-Newtonian fluid, meaning that its viscosity depended on the shear rate or shear rate history [i]. For this, a simplified Quemada viscosity model proposed by Buchanan et al. was used [18]. This model has been used in other similar works for target drug delivery in HCC [1, 2, 7, 42]. It defines the apparent blood viscosity dependence with the shear rate as follows:

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

with \( \mu_0 = 0.00309 \, Pa \cdot s \) being the minimum viscosity; \( \mu_\infty = 0.0020654 \, Pa \cdot s \) being the asymptotic viscosity; \( \tau_0 = 0.004360 \, Pa \cdot s \) being the apparent yield stress; and \( \lambda = 0.02181 \, s^{-1} \) being the shear stress modifier [4]. The shear rate (\( \dot{\gamma} \)) is

\[ \dot{\gamma} = \sqrt{\nabla \cdot \vec{u} + (\nabla \cdot \vec{u})^T} \]  

The viscosity function defined by this model is depicted in Figure 4.1, in which a comparison with other models, such as the Power law model, can be seen.

![Figure 4.1: Blood viscosity dependence with shear rate according to Quemada’s viscosity model, with \( \mu \) the apparent blood viscosity; and \( \dot{\gamma} \) the shear rate. Figure extracted from [18].](image)

Blood flow was governed by the Navier-Stokes equations of continuity (4) and momentum (5) in laminar regime and tracked in an Eulerian frame.

\[ \nabla \cdot \vec{u} = 0 \]  

\[ \frac{\partial \vec{u}}{\partial t} + \nabla \cdot (\vec{u} \vec{u}) = \frac{1}{\rho} (-\nabla p + \nabla \cdot \vec{\tau}) + \vec{f}_G \]  

being \( \vec{u} \), the blood velocity vector; \( \rho \), blood density; \( \vec{\tau} \), the second order stress tensor; and \( \vec{f}_G \), the gravity force per unit mass.
1.2 Blood-particle dynamics

The interaction between blood and particles can be modelled either by a one-way or by a two-way coupling system. In the one-way coupling system the discrete-phase trajectories are predicted based on a fixed continuous phase flow field whereas in the two-way coupling system the effect of the discrete phase on the continuum is also taken into account and vice versa, as shown in Figure 4.2. Therefore, in the latter the flow is influenced by the particles and the calculations between the continuous and discrete phase are alternated until the convergence is achieved \([k]\). It has been already shown that the two-way coupling does not have a significant influence on the outcome \([1]\), where the computational particles-haemodynamics for HCC was studied. Hence the one-way coupled approach was preferred here as in \([7, 39, 42, 59]\).

![Diagram of trajectory calculations](image)

Figure 4.2: Trajectory calculations in the left with the one-way couple and in the right with the two-way couple, retrieved from \([k]\).

The particle transport in blood was solved by Newton’s Second Law of Motion by tracking the particles in a Lagrangian frame; i.e. the particles are followed as they move, which differs from the Eulerian frame, where the motion is evaluated at fixed points in space. Newton’s Second Law of Motion can be written as follows:

\[
\frac{d\vec{u}_p}{dt} = \vec{f}_P + \vec{f}_G + \vec{f}_D
\]

(6)

being \(\vec{u}_p\) the particle velocity vector; \(\vec{f}_P\) the force vector because of the fluid pressure gradient (7); \(\vec{f}_G\) accounts for the gravity force vector (8) and \(\vec{f}_D\) for the drag force (9).

The forces are defined as follows:

- \(\vec{f}_P = \frac{\rho}{\rho_p} \left[ (\vec{u}_p \cdot \nabla) \vec{u} - \frac{d\vec{u}_p}{dt} \right]\) (7)
- \(\vec{f}_G = \frac{\rho_p - \rho}{\rho_p} \vec{g}\) (8)
- \(\vec{f}_D = \frac{18\mu}{\rho_p d_p^2} \frac{C_D Rep}{24} (\vec{u} - \vec{u}_p)\) (9)

being \(\rho_p\) the particle density; \(\vec{g} = 9.81 \ m/s^2\) in the positive \(y\)-direction to account for the lying position of the patient while the treatment is performed as shown in Figure 4.3; \(d_p\) the particle diameter; \(C_D\) the drag coefficient \([52]\); and \(Re_p\) the particle Reynolds number, which equals:

\[
Re_p = \frac{\rho |\vec{u}_p - \vec{u}| \cdot d_p}{\mu}
\]

(10)

The sum of forces taken into account was proposed by Basciano et al. \([7]\), justifying that most of the forces can be neglected except for the fluid pressure gradient force, the gravity force
and the drag force which must be included. This model was validated later on by Richards et al. [59].

![Diagram of axis system definition](image)

**Figure 4.3: Axis system definition.**

### 1.3 Particles and injections

Different particles were implemented in order to check if there were significant differences in the targeting and, therefore, in the outcome of the patient. The particles that were modelled included radioembolization and chemoembolization particles. For the first one, that includes: SIR-Spheres and TheraSpheres, which are used during the treatment and $^{99m}$Tc-MAA, which is used during the pre-treatment. The chemoembolization particles used were the HepaSpheres. The $^{99m}$Tc-MAA was used to evaluate the correspondence between the computer simulation results and the distribution seen in the images of the patient after the pre-treatment procedure.

Other cases used to check possible differences in the particles distribution and, thus, in the possible treatment outcome were: an injection with a reduced velocity, approximated to the one used in reality, changing the position of the injection to the one used in the real treatment, extracted from the patient images dataset. A summary of all the particle characteristics and injection parameters can be found in Table 5 and the detailed calculation of some of the parameters can be found below. This variations were also done to investigate which parameters had the highest impact on the final distribution.

<table>
<thead>
<tr>
<th>Simulation</th>
<th>Particle density (kg/m³)</th>
<th>Particle diameter (µm)</th>
<th>Injection velocity (m/s)</th>
<th>Injection location</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIR-Spheres</td>
<td>1600</td>
<td>32</td>
<td>0.070215</td>
<td>Inlet</td>
</tr>
<tr>
<td>$^{99m}$Tc-MAA</td>
<td>1100</td>
<td>35</td>
<td>0.070215</td>
<td>Inlet</td>
</tr>
<tr>
<td>Thera-Spheres</td>
<td>3290</td>
<td>25</td>
<td>0.070215</td>
<td>Inlet</td>
</tr>
<tr>
<td>Hepa-Spheres</td>
<td>1008</td>
<td>300</td>
<td>0.070215</td>
<td>Inlet</td>
</tr>
<tr>
<td>Velocity</td>
<td>1600</td>
<td>32</td>
<td>0.056588</td>
<td>Inlet</td>
</tr>
<tr>
<td>Injection point</td>
<td>1600</td>
<td>32</td>
<td>0.070215</td>
<td>Before bifurcation</td>
</tr>
</tbody>
</table>

**Table 5: Summary of all the particles injected and the different injection properties.**

In total 6 simulations were run in Fluent in order to check how changing the before mentioned parameters, namely the type of injected particles, the injection velocity and the injection location, would influence the distribution of the drugs in the vasculature of the patient. They
were also used to check the tumour targeting and try to validate the results of the simulations with the pre-treatment performed in the patient.

The particles were included by activating the discrete phase model in Fluent and were modelled as inert particles. A surface injection from the inlet was used in all the simulations except for one, in which the particles were released close to the bifurcation of the left and right hepatic arteries, as displayed in Figure 4.4, which was more similar to the position actually used during the treatment, as displayed in Figure 4.5. This position was determined by inspecting the X-ray Angiography images of the patient taken during the treatment, as described in 1.2.3 X-ray angiography (XA).

The injection velocity of the particles was set to be the same as the one of the blood, calculated in the Boundary conditions section (1.4.1 Inlet). The velocity was set to the same as

Figure 4.4: Surfaces from which the injection of particles was done indicated by the arrows. All the injections were done from the inlet except for one that was done near the bifurcation.

Figure 4.5: Catheter tip location during the treatment, extracted from the X-ray Angiography study (1.2.3 X-ray angiography (XA)). In the left, full view of the catheter and the hepatic artery tree and, in the right, zoom region with the catheter-tip indicated by the green arrow.
blood since it has been reported [2, 4, 42] that when the velocity is similar, the particles follow more easily the blood streamlines and the delivery to the target is easier. A reduced velocity approximated based on the injection velocity used during the treatment, was also implemented. It was estimated as follows:

- 40 mL of particles and liquid are typically infused to the patient [61].
- Treatment takes around 15 minutes according to Prof. dr. Geert Maleux.
- The injection area of a catheter 3F, which is normally used to inject the drugs, is 0.7854·10⁻⁶ m² [i].

Then,

\[ v = \frac{Q}{\text{area}} = \frac{40 \cdot 10^{-6} \text{m}^3}{15 \cdot 60 \cdot 0.7854 \cdot 10^{-6} \text{m}^2} = 0.056588 \text{m/s} \]  \quad (11)

The density of the HepaSpheres was calculated based on:

- There are 139000 particles in each vial [i].
- For one vial the weight is 25 mg [10].
- The dry diameter of each particle is 75 µm for the model of HepaSpheres chosen (V525 HS) [10].

\[ \rho_{\text{Dry HepaSpheres}} = \frac{\text{mass}}{\text{volume}} = \frac{25 \cdot 10^{-6} \text{kg}}{4/3 \pi (75 \cdot 10^{-6}/2 \text{ m})^3 \cdot 139000} = 814.22 \text{ kg/m}^3 \]  \quad (12)

- Then, the particles are hydrated, by mixing the 25 mg of HepaSpheres with 10 mL of 100% NaCl 0.9% aqueous solution (ρ=1009 kg/m³), and they expand to their final diameter of 300 µm. The increase in volume (from a diameter of 75 µm to 300 µm) that the particles experience equals 1.93 mL, so it was assumed that this is the amount of solution that the particles absorb. Thus,

\[ \rho_{\text{final HepaSpheres}} = \frac{\text{mass}}{\text{volume}} = \frac{25 \cdot 10^{-6} \text{kg} + (1.93 \cdot 10^{-6}) \text{m}^3 \cdot 1009 \text{ kg/m}^3}{4/3 \pi (300 \cdot 10^{-6}/2 \text{ m})^3 \cdot 139000} = 1008 \text{ kg/m}^3 \]

Once that the Discrete Phase Model (DPM) is defined, the boundary conditions can be defined.

1.4 Boundary conditions

1.4.1 Inlet

A velocity boundary condition was defined in the inlet. Since the specific flow characteristics of the patient were not measured at any point during treatment, flow values from literature of the hepatic artery system, depicted in Table 6, were used instead of patient-specific values.

From these values, the velocity was calculated as:

\[ v = \frac{\text{Inflow}}{A_{\text{Inlet}}} = \frac{4.595 \cdot 10^{-6} \text{m}^3/\text{s}}{\pi (4.564 \cdot 10^{-3})^2} = 0.070215 \text{ m/s} \]  \quad (13)

The constant velocity was imposed to be orthogonal to the inlet surface, since it is a steady-flow simulation. Since the steady condition may provide a good approximation for the transient PRM [22], the steady state was used in order to reduce the computational times.
<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Measurement method</th>
<th>Mean flow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Duplex Doppler US</td>
<td>212±75</td>
</tr>
<tr>
<td>10</td>
<td>Eco Doppler US</td>
<td>235±76</td>
</tr>
<tr>
<td>10</td>
<td>Eco Doppler US</td>
<td>313±117</td>
</tr>
<tr>
<td>10</td>
<td>Eco Doppler US</td>
<td>318±144</td>
</tr>
<tr>
<td>10</td>
<td>Eco Doppler US</td>
<td>271±94</td>
</tr>
<tr>
<td>30</td>
<td>Duplex Doppler US</td>
<td>224±56</td>
</tr>
<tr>
<td>9</td>
<td>PC-MRI</td>
<td>215±101</td>
</tr>
<tr>
<td>9</td>
<td>Doppler US</td>
<td>541.5±272</td>
</tr>
<tr>
<td><strong>Total sample size</strong></td>
<td></td>
<td><strong>Average weighted mean flow (ml/min)</strong></td>
</tr>
<tr>
<td>98</td>
<td></td>
<td>275.7</td>
</tr>
</tbody>
</table>

Table 6: Hepatic artery flow values, directly extracted from [44].

### 1.4.2 Outlets

Outflow boundary conditions were also defined. According to Aramburu et al [3], hepatic arteries bifurcate dichotomously and the flow of the parent branch is divided equally among the daughter vessels. Nevertheless, the radii of the daughter vessels were very different in many cases so Murray’s law [53] was used instead.

Murray’s law states that the arteries in human body branch in such a way that [i]

$$R_{\text{parent}}^3 = \sum_i R_i^3$$  \hspace{1cm} (14)

being \(i\) the daughter vessels branching from that parent and \(R\) the radius of the branches. This law is only valid in the case of mass-conservative vessels with laminar flow.

Then, as \(Q = \alpha R^3\), being \(\alpha\) a proportionality constant, the following relation can be extracted:

$$Q_i = Q_{\text{parent}} \cdot \frac{R_i^3}{R_{\text{parent}}^3}$$  \hspace{1cm} (15)

being \(i\) the daughter vessels branching from that parent.

For this purpose, the centrelines of each branch were extracted in Mimics in order to calculate the cross-sectional area of the vessels at different points along the vessel length and, then, the average radius for each branch. The average radius was used instead of the radius at the entrance point due to the high variability in the radius along the branch.

In some cases, Murray’s law (Eq. 14) was not perfectly accomplished. In that cases, the cubic radius of the daughter vessels was divided by the sum of the cubic radius of the daughter vessels instead of by the real cubic radius of the parent vessel (Eq. 15). This was done in order to ensure that the inflow was equal to the sum of the outflows. The final outflow distributions for each outlet can be found in Figure 4.6. These values were imposed in Fluent.
1.4.3 Hepatic arteries
The walls of the hepatic arteries were modelled as inelastic walls. The no-slip boundary condition was imposed; i.e. the blood velocity at the wall is zero. The particle collisions with the wall were modelled as elastic, meaning that the particles conserve their kinetic energy after the collision.

1.5 Solution methods
All the simulations were run in a computer cluster: HPC (High Performance Cluster), with 126 nodes, each 2x8-core Intel E5-2670 (Sandy Bridge @2.6 GHz). Here 180 cores were used. The time of simulation was normally inferior to 1 hour of wall time, the iterations needed were around 1300 and the absolute residuals were always lower than $10^{-5}$, which equals to a drop of 5 orders of magnitude.

The flow was solved with SIMPLE scheme for the pressure-velocity coupling. The spatial discretization used for the gradient was Least Squares Cell Based, for the pressure the Standard and for the moment the Second Order Upwind.

The particles were tracked for 50000 timesteps, which was enough to allow particles to exit the hepatic artery domain, and prevented particles of being caught in a recirculating region and tracked infinitely. The tolerance control was enabled so that the solution of the equations were within a specified tolerance ($10^{-5}$). That way, the step would be reduced if the computing error was too large. Besides, the tracking scheme was set to auto, meaning that the tracking scheme switches automatically between numerically stable lower order schemes and higher order schemes.
2. Results and discussion

The results section is divided into three parts. The first one focuses on the differences between the different injections. The other two rely on the data provided by dr. Prof. Geert Maleux. In section 2, the tumour distribution seen in the images is used to check if the tumours were targeted according to the results of the simulation with the SIR-Spheres or not. In section 3, the model is validated by comparing the images of the pre-treatment with the results of the $^{99m}$Tc-MAA simulation.

2.1 Comparison of simulations

2.1.1 Particle release maps (PRM)

In Figure 4.7, the correspondence of the outlet number with the terminal branch of the model is depicted. That way, outlets 1 and 2 correspond to the terminal vessels of the left hepatic artery and the other outlets are terminal vessels of the right hepatic artery.

In general, all the Particle Release Maps (PRM) are very similar for all the simulations (except for the one near the bifurcation) as it can be seen in Figure 4.8. Also, the particle distribution exiting through each outlet seems to be alike as well, as seen in Figure 4.9, but with significant differences in the number of particles that did not exit the domain. The particle distribution can be seen in Figure 4.10 as well but in this case the percentage variation with respect to the SIR-Spheres is plotted, where the differences among the simulations is more noticeable.
Figure 4.8: Outlets and colour correspondence. Outlet 0 implies that the particle injected at that point did not exit the domain. SIR-Spheres corresponds to the injection of SIR-Spheres, Techne corresponds to the injection of $^{99m}$Tc-MAA, Thera corresponds to the injection of Thera-Spheres, Chemo to the injection of HepaSpheres, Velocity to the injection with reduced velocity and Injection near bifurcation to the injection done from the other location. The details of every simulation can be found in Table 5 in Chapter 4 in 1.3 Particles and injections section.
First the different particles are compared. Those are the radioembolization particles, SIR-Spheres, TheraSpheres, $^{99m}$Tc-MAA, and the chemoembolization particles, which are the HepaSpheres. For all the particles used, the most significant differences are in the number of particles that exit the domain (Figure 4.10), meaning that the distal penetration is quite affected by the particle properties, which matches what had been stated in [38, 44]. The particles that exit the most are the $^{99m}$Tc-MAA, whose density is smaller than the one of the SIR-Spheres. The ones that exit the least are the TheraSpheres, whose density doubles the one of the SIR-Spheres, and the HepaSpheres, in which even if the density is close to the one of $^{99m}$Tc-MAA, the huge difference in diameter (the diameter is almost 10 times the one of $^{99m}$Tc-MAA) would difficult the particle transport in the blood. This was also the case in [44], where the bigger particles and the denser particles were also the ones that mainly remained in the domain.
In the case of the **velocity**, using a reduced velocity did not make any significant difference when compared to injecting with blood’s velocity. The particles follow the same streamlines as blood when the velocity is reduced in a 20% with respect to blood’s velocity. This is not the case when injecting with velocities larger than blood’s velocity. Nevertheless, since this affirmation had already been reported several times [1, 4, 42], it was not inspected in this study.

When the injection is initiated near the **bifurcation**, targeting the left hepatic branch (outlets 1 and 2) is easier than in the previous cases and the amount of particles that exit through this branch increases (from a 30.50% to a 46.41%, which translates into an increase of the 50%). Therefore, if the tumour was fed by the left hepatic artery, the targeting would have been easier if performed near the bifurcation. On the other hand, the amount of particles exiting through outlets 3 and 4 decreases from a 32.93% to 21.79%, so targeting these branches would be easier from the inlet. Here, the PRM is clearly divided into a half that targets the left side and the other half that targets the right side so targeting only one of the two sides would be easier from that location. Still, these results are patient-specific and they cannot be generalised.

As a clear example of the patient-specificity, in the Master’s thesis of Ghazal A. Koudehi [44], the injection was also done from different locations: one very near the bifurcation and other two more distant from it. In that work, the PRMs for the 3 different injection points were more similar and did not vary as much as in this work. Besides, the area targeting the left side
reduces a bit when the injection is near the bifurcation, which opposes to what happens here. Another example of the patient-specificity and variability among the hepatic artery tree is seen in the other segmented geometry of this project (shown in Chapter 3, section 2.2 Non-responder patient). The geometry of this patient is very different from the one of the responder so many of the results cannot be generalised for every case. The PRMs for instance are very patient-specific and should be extracted for every patient.

Other meaningful remark is that, in general, the percentage of particles exiting through each outlet tends to match the outflow boundary condition imposed at each outlet, being the most alike case with $^{99m}$Tc-MAA. When injecting near the bifurcation it differs more. A possible refinement to do in this model would be to use boundary conditions dependent on tumour burden in order to have more realistic and more patient-specific conditions. For this purpose, the boundary conditions proposed by Aramburu et al [3], which allow to impose boundary conditions based on the tumour burden of the patient, can be used. The flow feeding each segment of the liver is calculated based on the tumour masses and on the arterial perfusion characteristics of normal and tumorous tissue masses.

2.2 Tumour-targeting

The final distribution of the particles obtained from the computer simulations was used to check when more particles reach the tumour. This was done to inspect what treatment would have given the best targeting and how easy the targeting was according to the PRMs.

The tumour distribution within the liver can be seen in Figure 4.11 and the branch that targets each tumour is depicted in Figure 4.12. As it can be seen, the tumours are being targeted by the branches whose outlets are labelled as 6 and 8.

The amount of particles exiting through branch 6 increases in an 11% with respect to SIR-Spheres when $^{99m}$Tc-MAA is used. For branch 8, there is a particle increase of the 8% in comparison to the SIR-Spheres when TheraSpheres are used. The amount of particles exiting through these branches is specially reduced when the injection is done near the bifurcation for both outlets (36% reduction through outlet 6 and 32% reduction on 8) and when the HepaSpheres are used (11% reduction on 6 and 31% reduction through outlet 8). Thus, it would be better to use radioembolization, as in reality, instead of chemoembolization and to inject from further away from the bifurcation.
Figure 4.11: Location of the tumours within the whole liver. On the left top the coronal view is depicted, on the right top, the axial view and on the bottom left the right side view. The axis system is depicted on the right bottom. Abbreviations: T, top; B, bottom; R, right; L, left; P, posterior; A, anterior. The liver figures were retrieved from [n] and [o].

In Figure 4.13 the PRMs are displayed with a different colour-scale. Here, the locations that target the outlets that feed the tumours, outlets 6 and 8, are coloured in green. This was done in order to check how easily the tumours could be reached by setting the catheter in a specific position within the cross-sectional area. According to the PRMs, the area going to the tumours is larger when the SIR-Spheres are used, both with blood’s velocity and with the reduced velocity. The distance between where the targeting area starts and where it ends is around 3 mm. Since the diameter of the catheter 3F used in the radioembolization procedures is 1 mm [i], it could be possible to locate the catheter within the area that targets the tumours. Besides, as the other spotted tumours are on the right side and no tumours have been seen in the left side, targeting only one of the sides can be easily done. This is specially the case near the bifurcation, where the area that targets the right side is very large. That ensures that even if the catheter shifts, the particles will end up in the right side, sparing the left liver lobe.
Figure 4.12: Branches targeting each tumour. The vessels feeding the tumours displayed in yellow and white were not segmented due to the low resolution. The arrows depicted at the outlet of each branch show the direction of the branch, meaning that it is contained in the axial plane if the arrow is green and, if it is blue, along the longitudinal direction.

Still, there are some limitations in this section:

i. Because of the reduced quality of the images, the vessels that feed the other tumours were not segmented. Consequently, the targeting to these tumours could not be evaluated by computer simulations.

ii. There might be some tumours that the author has missed.
Figure 4.13: Outlets and colour correspondence. Non-escaped implies that the particle injected at that point did not exit the domain. SIR-Spheres corresponds to the injection of SIR-Spheres, Techne corresponds to the injection of $^{99m}$Tc-MAA, Thera corresponds to the injection of Thera-Spheres, Chemo to the injection of HepaSpheres, Velocity to the injection with reduced velocity and Injection near bifurcation to the injection done from the other location. The details of every simulation can be found in Table 5 in Chapter 4.

2.3 Pretreatment comparison

In this section the results of the simulation with $^{99m}$Tc-MAA are compared with the SPECT images taken during the pre-treatment in which the distribution of the $^{99m}$Tc-MAA is seen. This was done in order to check if the distribution of the particles seen in the simulation is similar to the real distribution. Even though the radiation of the $^{99m}$Tc-MAA seen in the images spreads over the whole liver, there are some areas where it is more concentrated. These areas are known as ‘hot spots’ and they imply that there is a larger concentration of particles there.

The comparison was done by inspecting in parallel the slices of the pre-treatment images with the slices of the MRI where the geometry had been created. The relation between the hot
spots and the vessels of the model was done visually while going through the slices so there might be some mismatches between the compared slices.

From the comparison of the slices, it could be established some relations between the distribution of hot spots and the branches of the model. Some examples of the analogies between the two images are displayed below (Figures 4.14, 4.15, 4.16 and 4.17). Thus, there is some correlation between the results of the simulation and the pre-treatment done in reality as it can be seen. Nevertheless, this could only be established for a few vessels since the majority of the radiation ended up in terminal vessels that could not be extracted from the images because of the reduced resolution. In order to have more similarities, the resolution of the images must be improved so that the branches can be segmented until more terminal vessels.

From the images it can also be extracted that the left lobe is being radiated since particles are ending up there. By using the information of the PRMs, the damage to this lobe could be diminished.

As previously explained, the link between the slices of both images was established visually, so there could be some mismatches between the compared slices. Such a pitfall can be overcome with the use of $^{166}$Ho-PLLA which is visible in MRI. This particle is started to be used for the pretreatment, as explained in Chapter 1, section 2, in 2.1 Radioembolization, since it proves to have some advantages compared to $^{99m}$Tc-MAA. These are that it does not disintegrate and that it is visible in MRI.
Figure 4.15: Analogy between the hot spots and the model. The vessel should go a bit further to completely match the hot spot. The blue arrow shows the location of the other branch of the model (outlet 1 in Figure 4.7) which is not captured in this slice but it emits radiation as seen in the left image. Again, the radiation reaches till more terminal points (left image) than the model branches (right image).

Figure 4.6: Correspondence in the coronal view between a hot spot and a branch of the created model. The correspondence of the hot spot in the top of the liver is shown below.

Figure 4.7: Another correspondence in the coronal plane. Again, the radiation goes to more terminal areas that are not captured by the model.
3. Limitations, potential and future perspectives

In this section, the main limitations are listed as well as the potential of the CF-PD and the future perspectives.

One of the main limitations during the whole project was the images. Because of the large slice increment, several challenges were encountered. These were the difficulty to determine the arterial path, the vessels being elliptic, sharp and with a lot of bumps. Even though they were clear improvements by reslicing the images and by smoothing the geometry, the vessels were still more enlarged than they should along the longitudinal direction.

On the other hand, some possible refinements to do in the model are:

1. Imposing a transient inflow as in reality.
2. Modelling the catheter in order to take into account the possible influences that it may have in the flow.
3. Injecting particles with a distribution of diameters instead of all being of the same size.
4. Injecting more particles. In reality, around 40-80 million particles are injected in the case of the SIR-Spheres, while here only around 3300 particles were injected.
5. Using the outflow boundary conditions proposed by Aramburu et al [3] in order to account for the differences in the flow rate resulting from the presence of tumours, instead of the standard Murray's law. These conditions represent the flow of the tumour feeding arteries more realistically.

Still, the model allows for good results and similarities to the distribution in the reality, as shown with the pre-treatment images. These refinements are tasks to work in the future. Another task to conclude would be to finish the geometry of the non-responder patient in order to try to find a possible cause of why the treatment did not work in his/her case. Also, an experimental validation similar to the one described in the Appendix (1. Experimental validation) could be done by using the geometry model of the responder patient and the non-radioactive SIR-Spheres provided by SIRTEX® Medical Europe GmbH (Bonn, Germany).

As seen in this project, this technique allows to extract the specific geometry of the patient, permitting a much personalised treatment. Besides, the possibilities of targeting either one side of the liver or only the tumours have shown to be more than feasible in the PRMs. Also, which treatment would be better to each patient could be assessed by means of CF-PD.

As proposed by Kleinstreuer [43] and with the model developed by Simoncini et al [65] to reconstruct the global hepatic arterial tree, the implementation of CF-PD in the clinic to determine the optimal location of the catheter in order to target the tumours should be more than possible. As shown in here, the differences between using one treatment or other could also be inspected in order to choose the treatment that achieves the best possible targeting.

Furthermore, in the future, specific measures of the velocities and pressure values of the hepatic arterial system of the patient could be taken in order to impose more personalised boundary conditions. This combined with the results of the simulations and the use of the smart micro-catheter would permit a very patient-specific targeting to the tumours, as well as a reduction in the amount of damage to the healthy tissue.
Conclusions

This project had several purposes. First, to verify the possible influences in the particle distribution and in the particle release maps (PRMs) of several parameters. Those parameters are: different particles used during the treatments, namely SIR-Spheres, TheraSpheres and $^{99m}$Tc-MAA for radioembolization, and HepaSpheres for chemoembolization, also the injection velocity and the injection location. Second, evaluate by means of CF-PD if a better targeting of the tumours could be achievable and evaluate which treatment could have worked better. Also, try to relate the results of the pre-treatment simulation with $^{99m}$Tc-MAA to the pre-treatment results that occurred in reality.

From this analysis it can be concluded:

- The particle properties play a role in terms of particle distribution, being the distal penetration the most affected.
- A reduced injection velocity (only 20% reduction), to a value closer to the injection velocity used during treatment, did not have any significant differences in the particle distribution nor in the PRMs.
- Injecting near the bifurcation has a significant impact on the final particles distribution. There is an increase of the 50% with respect to the SIR-Spheres simulation in the amount of particles that going to the left lobe. This statement is very patient-specific though.
- In this specific-patient, both radioembolization treatments (SIR-Spheres and TheraSpheres) provide higher amount of particles in the outlets with tumours, outlet 6 and 8, with respect to the chemoembolization. Thus, radioembolization should be used according to the results. This matches what was done in reality.
- When injecting near the bifurcation, the amount of particles going to the tumours is reduced. Nevertheless, targeting only one of the lobes of the liver is much easier from the bifurcation than when injecting further away since, in this case, the cross-sectional area of the injection plane is clearly divided into two areas, one that mainly targets the left branch and the other targeting the right branch. Still, these results are very patient-specific and cannot be generalised to every patient.
- The generation of the PRMs by means of CF-PD has allowed to evaluate whether the targeting to the tumour was possible and with which configuration it was easier. This technique has also allowed to evaluate which treatment could provide better results.
- In terms of the particle release maps (PRMs), the targeting would be easier when using SIR-Spheres since there is an area targeting the tumour in which the catheter can perfectly fit.
- From the conducted comparison between the $^{99m}$Tc-MAA simulation results and the images of the pre-treatment some correlation was observed in the distribution of particles. Still, in reality, many of the particles end up in terminal vessels which were not segmented in the model due to the low resolution of the images.
- Better images would be needed in order to speed up the segmentation process and to reach to more terminal vessels. This would be very important for the implementation in the clinic of the Computational Medical Management Program proposed by Kleinstreur [43], as explained in Chapter 2.
• The hepatic artery trees are very different for every patient. So the specific geometry of each patient should be used in order to assess the treatment and targeting.

As shown in this project, by using the PRMs, targeting only the branches where there are tumours should be more than possible. Besides, the best treatment as well as with which one the targeting is easier can be assessed by CF-PD. That way, a lot of the damage that the healthy receives could be avoided or, at least, reduced. Thus, the potentials of this approach are very high, and it should be implemented in the clinic. Moreover, thanks to the recent advances proposed by Simoncini et al [65], the segmentation could be done much quicker and it would be much more than feasible to use it in daily use. Also, by using the Smart Micro Catheter in order to set the catheter in a certain location within the cross-sectional area, the target should be very high and patient-specific.
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Appendix

1. Experimental validation

The results of the simulations were going to be validated by an experimental set-up previously used by [44]. This experiment consisted of a 3D printed model of the liver vasculature, displayed in Figure 1.1, in which particles were injected through the inlet and collected at the outlets to compare the final distribution to the one of the simulations performed, which can be found in Figure 2.1. Nevertheless, that set-up had some shortcomings that needed to be solved.

Figure 1.1: 3D printed model of the liver vasculature used for the experiment, directly extracted from [44].

Figure 2: Experiment set-up used in [44]. In the containers the particles were collected to measure the final distribution. Figure directly retrieved from [44].
One of the most important changes to make to the previous experiment were the particles, since they were not similar to the particles used for treatment. Because of that, it was decided to look for non-radio-active particles that would mimic SIR-Spheres to make the validation more similar to reality. That is because the University Hospital of Leuven, entity which provided the images of the patients, mainly uses SIR-Spheres for radioembolization instead of TheraSpheres. Another shortcoming to solve was how the particles were injected into the model. They were implemented into the liver vasculature mixed with water from a reservoir instead of being injected by a catheter preloaded by a syringe of around 20-40 mL as in reality [61].

From all the inspected options, the best particles were the Polybeads provided by Polyscience, whose properties can be found in table ... together with the particles that are actually used for the treatment.

<table>
<thead>
<tr>
<th>Particle</th>
<th>Diameter</th>
<th>Density</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polybeads</td>
<td>25 µm (22.5–27.5 µm)</td>
<td>~1.05 g/mL-1.19 g/mL</td>
<td>185€/5mL</td>
</tr>
<tr>
<td></td>
<td>40 µm (40.5-49.5 µm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIR-Spheres</td>
<td>20-60 µm</td>
<td>1.6 g/mL</td>
<td>Not useful for experiments (radioactive)**</td>
</tr>
<tr>
<td>TheraSphere</td>
<td>20-30 µm</td>
<td>3.29 g/mL</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Possible options of particles to buy. **Later on, SIRTEX® Medical Europe GmbH (Bonn, Germany) agreed to provide some non-radio-active vials of SIR-Spheres which they use within the enterprise for teaching purposes.

Based on those particles, an estimation of the costs to do one experiment was made as depicted in table ... As previously described, the maximum injected activity to one patient is 3 GBq, which results in the need for 40 to 80 million particles in the case of SIR-Spheres. Therefore, 4 vials of Polybeads of 25 µm, which equals 740€, would be needed to simulate one injection of 60 million SIR-Spheres on average. Owing to the limited budget for the project, the main focus was redirected towards the simulations.

<table>
<thead>
<tr>
<th>Particles</th>
<th>Particles/mL</th>
<th>Particles in one package</th>
<th>Number of packages needed for 1 dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polybead 25 µm</td>
<td>2.91*10⁶</td>
<td>14.55*10⁶</td>
<td>SIR (~60 million partic) 4 (740€)</td>
</tr>
<tr>
<td>Polybead 45 µm</td>
<td>4.99*10⁶</td>
<td>2.495*10⁶</td>
<td>Thera (~25 million partic) 1.66 (370€)</td>
</tr>
</tbody>
</table>

Table 2: Estimation of the costs of performing one experiment with the Polybead particles.

2. Very small density of the HepaSpheres

2.1 Particle pathlines

At first, the density of the HepaSpheres (chemoembolization particles) was wrongly calculated and it was set to a very small value (12.72 kg/m³). That was because the expansion process that the particles go through was not taken into account and the density was calculated directly from the expanded volume. This led to a different phenomenon in which all the particles remained in the domain. The particles pathlines were explored in order to verify why all the chemoembolization particles had stayed in the domain. These pathlines can be seen in Figures 2.1 and 2.2 and be compared to the particle pathlines of the SIR-Spheres, Figure 2.4
and 2.5. As it can be seen, the chemoembolization particles go straight to the right wall at the entrance of the domain which does not happen in the case of the SIR-Spheres, nor with the TheraSpheres, nor with $^{99m}$Tc-MAA, that follow the blood stream. Several options were considered in order to try to explain that:

a. The inlet not being perfectly perpendicular to the artery walls. To inspect this, the velocity vectors of the blood were also visualised. This is important to be checked because blood flow was imposed to be orthogonal to the inlet, same as the injection of particles. Hence, if the inlet was not orthogonal to the wall, the flow would be also be directed towards the wall. This option was rejected since the direction of these vectors were not towards the wall but within the centre as seen in Figure 2.1 on the right.

b. According to Aramburu et al [1], particles with larger diameters tend to travel more centripetally and exit through the main branches, while particles with lower diameters tend to travel more peripherally, through side branches. Nevertheless, in this case, HepaSpheres tend to travel more peripherally despite having larger diameter. As a result, this does not justify the direction followed by the particles either.

c. The gravity affecting the pathlines of these particles more. Even if at first this option was also rejected since the gravity was imposed in the positive Y-direction and the particles deviate towards the negative Y-direction as shown in Figure 2.2, later on by rechecking the formula it was checked that in this case the gravity force was equal to:

$$\vec{f}_G = \frac{1}{2} \rho_p g \bar{z} \vec{g} = 12.72 \cdot 10^{-50} \cdot 12.72 \cdot \vec{g} = -81.5 \text{ N.}$$

This explains the direction that the particles follow and why they deviate, since the force is very large.

![Figure 2.1](image)

**Figure 2.1:** On the left, the legend of the velocity used for the particles velocity, on the middle, the particle pathlines followed by the HepaSpheres and, on the right, the velocity vectors of the blood are displayed in uniform colour red at the entrance of the domain.
Figure 2.3: On the left, zoomed lateral view of the paths followed by the HepaSpheres (particles displayed at their real size), on the right, top view of the paths followed by the particles with its corresponding axis system.

Figure 2.4: Pathlines of the SIR-Spheres. In this case they do not collide with the wall at the entrance which can be seen more clearly bellow. On the left, over view and zoom lateral view of the entrance of the particles and, on the right, zoomed top view of the SIR-Spheres pathlines.