Focused Ultrasound Therapy for Abdominal Organs During Respiratory Motion: Numerical Modeling and Simulation and In-Silico First-Stage Evaluation of a Novel Treatment System

by

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Abstract

Focused ultrasound (FUS) is a noninvasive method for tissue ablation that has the potential for complete and local tumor destruction with minimal side effects. Already being used for the treatment of static organs, compensating target motion is not yet clinically available due to the complexity of the treatment. We here propose a numerical model of the therapy effects during respiratory motion to study FUS for moving liver targets. A focus lies on incorporating the motion and the computational efficiency of the simulations. A temperature model is proposed predicting the temperature distributions efficiently on the graphics processing unit by mapping the problem from the moving physical world to a static motion reference state. We also investigate the accuracy of ultrasound modeling in the highly heterogeneous propagation domain including ribs. A novel angular spectrum approach for heterogeneous media is proposed as the widely used hybrid angular spectrum method is found to be ineffective. For real-time applications, we propose an approximate ultrasound propagation model. An integrated FUS model is developed combining these model with an abdominal motion model, tissue damage, and a parameter model. The patient anatomy is automatically derived from CT images. Two clinical use-cases of the integrated model are given: A simulation-driven planning tool allows a clinician to interactively explore treatment options. And a study is performed using the model to optimize the placement of the FUS device. The model is furthermore used to study a novel motion-compensation FUS treatment system by replacing hardware and patient by model predictions. We estimate the efficiency of the treatment system in combination with a clinically available FUS device and MR imaging device (6.67 Hz image rate, 20 Hz FUS control rate) to be above 80%. This estimated efficiency of the new treatment system is expected to be already suited for clinical applications.
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1.1 FOCUSED ULTRASOUND THERAPY

Focused ultrasound (FUS) is a noninvasive method for tissue ablation that has the potential for complete and controlled local tumor destruction with minimal side effects. The basic principle of the treatment of tissue with FUS is similar to a lens effect in optics. In FUS, an acoustic wave is sent into the body, shaped such that it focuses to a certain location within the body. From the viewpoint of beam theory, the wave can be decomposed into a multitude of individual ultrasound beams passing through the body. The local energy levels resulting from the propagation of each beam through the tissue are small and do not harm or destroy the tissue. However, the individual beams constructively interfere and locally introduce much higher energy levels. As a result of the introduced energy, the tissue is mechanically stressed and heated. Figure 1.1 illustrates the therapy approach.

The utilization of FUS for non-invasive localized thermal ablation has been studied for many years (ter Haar and Coussios, 2007; Orsi et al., 2010). Depending on the level of intensity, different treatment effects are predominant, ranging from mild heating at low intensities over to ablation and finally to levels where mechanical stress is the primal factor and shock-waves and cavitation implosions disrupt tissue (Histotripsy (Roberts et al., 2006)). As the latter effects are difficult to control, current clinical applications utilize predominantly the heating capabilities of FUS.

The effect on the tissue depends both on the induced temperature rise, as well as the duration of temperature elevation. This can be captured by thermal damage
models like Arrhenius formalisms or cumulative equivalent minutes CEM43 (Pearce, 2010). If tissue temperature exceeds the threshold for protein denaturation (57-60°C) for a few seconds, coagulation necrosis occurs (Jolesz, 2009). Lower temperatures can kill cells if maintained for longer durations (Pearce, 2010). Elevating the local temperature only by a few Kelvin is used for example in hyperthermia applications to stimulate local biological processes or enhance drug uptake or even trigger local drug release. Elevating the tissue temperature up to over 65°C leads to an almost immediate destruction of the tissue by coagulative necrosis (ter Haar, 2016). Higher temperatures than about 85°C are usually avoided to prevent boiling of liquids inside the tissue which would lead to the formation of gas bubbles that interact with the ultrasonic field (Tempany et al., 2011).

The induced thermal damage can be spatially very precise (Linke et al., 1973; Frizzell, 1988; ter Haar et al., 1989a), yet it is not selective and kills both normal and target tissue like neoplastic cells (Jolesz, 2009). Thus the treatment needs to be spatially controlled from outside the patient’s body and suitable imaging methods are needed to guide and track the procedure. Both magnetic resonance imaging and diagnostic ultrasound can be used for monitoring the effects of the treatment. Additionally to anatomical imaging, both imaging techniques allow to measure and estimate the spatially distributed temperature in the patient’s body.
allowing in principle to directly assess the effects of the treatment on the target tissue. This is however not without limitations, like spatial and temporal resolution limits and volume coverage. Figure 1.2 visualizes a sequence of MR thermometry images that were acquired to monitor a 16 seconds application of FUS for a single focus target (this is widely termed a ‘sonication’) and the consecutive cooling phase in a tissue-mimicking gel phantom. Furthermore, the overall assessment of treatment success needs to be done using medical imaging (Leslie et al., 2012, 2008) as the tissue is not excised for pathological assessment.

Currently, focused ultrasound is gaining acceptance for clinical applications as an alternative treatment method in different indications (Miller et al., 2012). For example in recent years, the treatment of uterine fibroids, which are benign tumors in the uterus, using focused ultrasound became rapidly accepted. Three of the benefits of FUS for this indication are the potential preservation of fertility, the short hospitalization (outpatient treatment) and the repeatability of the treatment.

Current clinical FUS applications mostly target static organs. FUS treatment of abdominal targets that move with the respiration of the patient (e.g. the liver) is not yet an available option in clinical routine due to the lack of treatment systems supporting motion compensation – the motion of the target needs to be stopped. In the short term perspective, potential clinical use cases of FUS for moving abdominal organs include both palliative treatments and patients for whom resection is impossible due to the position of the malignant tissue or co-morbidities (Aubry et al., 2013; Schwenke et al., 2015). In the long term, due to very low complication rates if done correctly, FUS might even become an alternative to surgical resection. This is discussed in more detail in the following sections.

1.1.1 Treatment physics and FUS technology

Ultrasound waves can be focused either geometrically or electronically. Geometrically, the waves can be either focused by acoustic lenses or by shaping the emitting surface. The ultrasound transducers that emit the ultrasound waves are either single-element or multi-element transducers (see Figure 1.3). For focusing a single-element transducer, the transducer needs to be shaped spherically (see Figure 1.3 a). Multi-element transducers consist of individually driven elements (phased-array transducers). With these transducers the focus position can be changed electronically. If the hardware allows to change the driving signals fast enough, such electronic beam steering can be used for motion compensation without the necessity to move the transducer.
Figure 1.2: MR thermometry during a 16 seconds test sonication and the consecutive cooling phase in a tissue-mimicking phantom. The transducer is located at the bottom sending the ultrasound waves towards the top of the domain.
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mechanically. Furthermore, these transducers allow to shape complex wave fronts and allow to compensate for tissue inhomogeneities that influence the propagation. Phased-array transducers can also be shaped such that a focused wave is produced (natural focus) when all elements are driven with the same signal phase. The possibility to drive the elements with individual signals adds additional control over the shape of the wave front. Even though in principle one-dimensional transducers (linear arrays) already show the focusing effect by constructive interference, two-dimensional transducers increase this effect and are used in therapeutic applications. These transducers have a high number of elements in the hundreds and thousands.

1.1.2 THE CLINICAL PERSPECTIVE

Already several medical applications of FUS have been approved for clinical use (Tyshlek et al., 2014; Foley, 2016). General anesthesia of the patient is in most applications not required and only sedation is applied (ter Haar, 2016). This allows to also use direct feedback from the patient during intervention. The applications include the treatment of uterine fibroids, bone metastases, essential tremor, breast cancer, breast fibroadenoma, kidney tumors, liver tumors, pancreatic tumors, Parkinsons disease, soft tissue tumors, thyroid nodules, and uterine adenomyosis (Foley, 2016). The United States Food and Drug Administration (FDA), to date, has approved the use
of FUS for treating benign prostatic hyperplasia, bone metastases, prostate cancer, and uterine fibroids (Foley, 2016; ter Haar, 2016). Ultrasound waves are furthermore used in lithotripsy to non-invasively destroy kidney stones and biliary calculi by shock-waves (Ghorbani et al., 2016). Besides the complete tissue destruction by thermal ablation, focused ultrasound can also be used for hyperthermia (lower temperature rise) in combination treatments for example to trigger local release of cancer drugs. Additionally, many more applications are in development and testing (Foley, 2016).

For complete tumor ablation, either single-focus or volumetric ablation approaches are used with FUS. A single-focus sonication of usually 30 to 90s duration only destroys a small volume, depending in size on the used ultrasound frequency, power, and focus depth. For example, at 1.6 MHz with a focal length of 90 mm an ellipsoidal ablation volume of about a 1 cm along the beam axis and 1.3 mm in transverse direction occurs (Wu et al., 2004). Destroying the entire tumor requires consecutive ablation of parts of the tumor. Volumetric ablation approaches heat a larger volume by changing the focus location during the application. This approach may result in more uniform heating and larger ablation zones though it may reduce the spatial specificity of the heated zone.

1.2 Treating abdominal organs

In summary, for abdominal organs like the liver there are severe challenges for FUS treatment (Aubry et al., 2013):

(i) the motion of the target with the respiration of the patient;

(ii) the limited accessibility of the target through the highly absorbing ribcage;

(iii) the monitoring of the therapy in the presence of motion including monitoring of adjacent risk structures; and

(iv) the anatomical complexity of the liver and the surrounding abdomen.

The following Sections discuss these in more detail.

1.2.1 Respiratory motion of the liver

Abdominal organs can move up to 20 mm during a respiratory cycle, reaching speeds of up to 15 mm/s (Korin et al., 1992; Davies et al., 1994; Aubry et al., 2013). For FUS
therapy, not only the positions of the inner organs are required to be known. Also
the positions of the ribs within the ribcage influence the treatment to a large extent.
The inner organs and ribcage move very differently: while the inner organs move up
and down (craniocaudal), the ribs predominantly move inwards and outwards with
only limited up and down motion. The inner organs thus slide along the abdominal
wall being the boundary of the abdominal cavity. Figure 1.4 visualizes temporal
motion patterns of anatomical features in the liver of three volunteers and shows
echo-planar 2D images of different respiratory states in one volunteer. Figure 1.5
visualizes two extremal configurations in 3D volume renderings and in a difference
image. The data is generated using a volumetric MR image and image deformations
based on motion data given by a respiratory motion model (Samei et al., 2012) of
the right liver lobe. The liver motion is extrapolated to the rest of the inner organs.
As the inwards and outwards motion of the ribs is very small (below 3 mm (Samei
et al., 2016)) and coincides with the direction of the FUS beam, in our studies, we
keep the ribcage static while moving only the inner organs according to the motion
model predictions.

1.2.2 Motion-compensated FUS

Compensating the respiratory motion can be achieved by electronic beam steering:
adaptively the location of the ultrasound focus is changed to follow the target motion.
This requires particular technological support and real-time control in order to enable
a safe, effective and efficient treatment.

Generally, solving the task of motion correction requires a continuous motion
observation and based on the observations a continuous derivation of control decisions
to steer the FUS system. Due to restrictions of the rates of observation and control,
in most cases it is necessary to compensate delays between observation and control by
a spatio-temporal motion prediction. Experimental treatment control systems have
been developed by several research groups and validated in ex-vivo and first animal
studies. The motion observation approaches include systems that analyze motion
surrogates like respiratory belts (Holbrook et al., 2014) or use image-based motion
tracking of ultrasound (Pernot et al., 2004; Marquet et al., 2011; Auboiroux et al.,
2012) or MR images (de Senneville et al., 2007; Ries et al., 2010; de Senneville et al.,
2011; Quesson et al., 2011) or navigators (Celicanin et al., 2014). The FUS control
approaches range from preset-based steering (Holbrook et al., 2014) to real-time beam
steering (all other above-mentioned approaches). The systems target both ablation
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![Figure 1.4: Respiratory liver motion: The plot in a) shows the motion patterns of tracked liver features derived from echo-planar imaging sequences of three different volunteers. The images in b) shows echo-planar images for three respiratory states. The dashed yellow lines are given to facilitate comparison.](image)

![Figure 1.5: Visualization of patient diagnostic images in (a) exhale and (b) inhale respiratory state highlighting the inner organs. Image c) visualizes the difference image to show the motion magnitude. The data is generated from a breath-hold volumetric image by applying motion data from a motion model (Samei et al., 2012) to the inner organs while keeping the ribcage static.](image)
and hyperthermia applications. The validations have been performed case-based as proof-of-concept validations either ex-vivo or additionally on animals (sheep and pigs). Table 4.1 in Chapter 4 summarizes the approaches in more detail.

The individual components of such motion compensation approaches can be validated individually and studies can be performed to compare alternative approaches. For example, De Luca et al. 2015 performed a large comparison of ultrasound tracking approaches including local feature tracking approaches as well as more global approaches like optical-flow-based methods. While the global approaches like optical flow may be more robust, local feature-based approaches can be faster. Both spatial accuracy and computing time were evaluated in the study to judge the fitness of tracking approaches. However, the actual integration of such components in a motion-compensation system may lead to other conclusions. For example, it may be beneficial to utilize a rather imprecise tracking method with low spatial accuracy but very fast response times. This would lead to a shorter temporal prediction horizon for compensating computational delays and thereby might lead to a better quality of motion-compensation in the actual application. Chapter 4 in this work studies such integrative effects and estimates overall error levels for different parameterizations of the entire motion-compensation pipeline.

While all above-mentioned motion-compensation approaches show considerable advancement of the methodologies for FUS of moving organs, none provides a prospect to approach any clinical trials with their systems. This is most probably due to system certification impediments and difficult patient recruitment. Establishing a treatment system for clinical use poses a great challenge, as high quality standards need to be met and pre-clinical and clinical studies need to be performed. A major effort in developing a software system for treatment planning and control is quality assurance (QA): Making sure that the system does what it is supposed to do (efficacy), and, most importantly, that it does no harm (safety). For safety-critical systems estimates for the proportion of life cycle costs spent on QA and testing go up to 80% (Reid, 2012). Thus, for industry, the hurdle to develop a FUS treatment system with motion compensation is high because of the risk that FUS may in the end turn out to not be competitive to already clinically established methods. For systems of such complexity the effort required for a change in the system grows drastically the later a defect is detected or a new feature should be incorporated (exponential cost-of-change curve (Boehm, 2001)). From the viewpoint of research and development, changing currently available clinical FUS treatment systems to make them capable of motion-compensated FUS is difficult as the clinically approved systems are not open
for extensions and are subject to closed specifications. Also, introducing changes to the certified systems means that any validation needs to be re-performed.

1.2.3 Transcostal focusing

Besides the motion of the target, a further challenge in treating liver targets with FUS arises from the anatomical location within the body. A large part of the liver is surrounded by the ribcage for protective reasons. Bones are highly absorbing and thus directly sonicating through the ribcage leads to fast heating of the ribs and unwanted side-effects like ultrasound beam defocusing and focus splitting (Gélat et al., 2011). The phased-array transducers used for electronic beam steering usually have a large number of elements. These can be individually deactivated to spare the ribs. The sonication through the ribcage sparing the ribs is termed transcostal sonication. Due to the respiratory motion of the inner organs, the target may not be accessible over the entire respiratory cycle. Furthermore, in case of motion, the transcostal focusing methods need to be real-time capable imposing an even greater challenge. Several methods have been developed to solve the task of transcostal ultrasound delivery. The simplest methods are binarized apodization and ray-casting approaches (Liu et al., 2007a; Quesson et al., 2010; Bobkova et al., 2010; Marquet et al., 2011) in which elements of the transducer that do not have a line of sight to the target are deactivated. More accurate are time-reversal and phase conjugation methods (Fink, 1992; Tanter et al., 2000) which use the principle of time inversion of the wave equation. The most accurate methods that furthermore allow for more control are for example the decomposition of the time-reversal operator (DORT) method (Prada, 2002; Cochard et al., 2009), a holographic approach (Hertzberg and Navon, 2011) and inverse-model-based optimization approaches like the approach of Gélat et al. 2012. The methods based on time-reversal and phase conjugation can be implemented without the need for image-based analysis of the patient anatomy. Yet they require an ultrasound scatterer at the target. If a scatterer is present, the methods can optimize the focusing by iteratively sending a low-energy wave into the object and measuring the reflected signals. All other methods require knowledge about the position of the ribs which might be subject to measurement errors introduced by geometric image distortions and annotation errors. The raytracing approaches can be seen as time reversal approaches in which the full wave propagation is approximated by ray theory. All above mentioned publications suggest that transcostal sonication is possible though it requires large transducer with high number of elements or
special transducer designs (Civale et al., 2006). Undesired heating of the intercostal space however results from the reduced active pass-through area and is a critical counter-effect making transcostal sonication difficult in the clinical application. A comprehensive numerical simulation-based comparison of the methods was performed by Gélat et al. 2014.

1.2.4 Treatment monitoring

Further difficulties are related to the non-invasiveness of FUS therapies (Georgii et al., 2011): Firstly, in contrast to surgical resection no pathological workup of the malignant tissue is possible and the success of the therapy must be assessed using imaging only. Secondly, the control of the thermal ablation is challenging as it results from the complex interplay of a variety of bio-physical and bio-chemical processes. Image-based treatment monitoring is thus very important to make FUS treatments possible. In principle, real-time temperature monitoring of the treatment can be performed using MR and ultrasound thermometry (Amini et al., 2005; Yuan et al., 2012). Also the change of tissue elasticity resulting from the ablation can be assessed using both ultrasound imaging (Ophir et al., 2002) and MRI (Mariappan et al., 2010). Limitations in imaging capabilities however impose challenges. The monitoring is typically restricted to a small sub-volume of the full domain of interest and limited by the available temporal and spatial resolution of the image modality. Motion of the domain furthermore makes monitoring more complicated and may introduce artifacts in the images used for monitoring the therapy. While the actual temperature distribution is a continuous physical quantity in both space and time, image-based measuring of the temperature is only a discrete view on the actual temperature process (Todd et al., 2011). In the case of motion of the domain, the quantity is furthermore subject to continuous motion. The resulting discrete measurements are average values and as such are depending on the resolution of the discrete representation (temporal update rate as well as spatial image resolution and also grid location) and need to be interpreted as such averaged discrete temperatures. Due to the small size of the ultrasound focus which is in the range of the usual spatial voxel size of MR imaging, the temperature within a voxel may not be homogeneous but may vary spatially even between body temperature and peak temperature. The resulting measured temperature for such a voxel is an average value. As such, the maximum temperature will always be underestimated in the measurements. The stronger the curvature of the actual temperature distribution is, the larger the
difference between the measured average value and the actual temperature values will be (Todd et al., 2011). Volumetric heating with FUS is thus easier to monitor as the heated region is larger and the temperature distribution within each voxel is more homogeneous. Another critical limitation of MR thermometry is signal-loss due to temperature gradients within voxels. The different temperatures lead to different proton-resonance frequencies within a voxel (Rieke and Butts Pauly, 2008). As a result of this dephasing, the MR signal strength reduces. Reducing the voxel size alleviates these effects but also reduces the measured volume of interest. For fast monitoring during motion, usually thermometry is implemented based on Echo Planar Imaging (EPI) which can provide 2D images at about 8 to 10 Hz. EPI is however subject to nonlinear geometric distortion primarily along the phase-encoding direction (Wu et al., 2008). Approaches for correcting such distortions exist (Dragonu et al., 2009), but in most cases reduce the temporal imaging resolution. These limitations in monitoring hinder the clinical application of FUS for targets in the liver.

1.2.5 THE CLINICAL COMPETITORS AND CANDIDATES FOR FUS STUDIES

The primary use case for FUS treatments of liver tumors would target both hepatocellular carcinoma (HCC) and liver metastases. For patients with early stage HCC, with a preserved liver function, the first line treatment option is surgical resection (Llovet et al., 2012; Park et al., 2014). Local ablation is considered the standard of care for patients with early tumors not suitable for surgery and the local ablation techniques currently most widely used clinically are radiofrequency ablation (RFA) and microwave ablation (MWA). Further methods include laser-induced thermotherapy (LITT) and cryoablation. Considering reported data in literature, RFA/MWA provides 5-year survival rates of 40% to 70% and even beyond in highly selected candidates (Llovet et al., 2012). As the therapeutic effect of RFA/MWA and of FUS is based on local thermal ablation, it is possible to consider these treatments suitable for the same groups of patients.

One of the main benefits of FUS is the non-invasiveness: In contrast to needle-based approaches like the above-mentioned, where tumor cells may be spread by the needle, FUS is performed completely without opening the patient’s body. In the long run, FUS might become competitive to the other thermal ablation techniques and may even become an alternative to resection and radiosurgery. Whether FUS can be competitive to these well-established techniques strongly depends on results
of current and future clinical trials of the treatment. In our research we hypothesize that the full potential of FUS in moving organs can be unleashed only with dedicated computer support in planning and control of the treatment. Potential candidates for clinical FUS studies may be divided into four general categories:

(i) *Patients who are poor surgical candidates* due to inadequate liver function, from underlying cirrhosis or prior hepatectomy, or due to comorbid conditions;

(ii) *Patients who are ineligible for surgical resection* due to the anatomic distribution of the tumors;

(iii) *Patients who are surgical candidates but for whom the test-of-time approach is favored* to limit unnecessary repeated hepatectomies in case of the occurrence of new tumors; and

(iv) *Patients who undergo ablation to control tumor* as a bridge to liver transplantation.

These patient collectives may potentially be recruited for clinical studies of new FUS treatment systems and approaches. The systems however need to already be very close to a potential clinical use to show a prospect of success for the above mentioned patient groups.

1.2.6 CLINICAL USE OF FUS FOR LIVER

The liver is a highly perfused organ with on average about 1.5 liters of blood per minute (Zoli et al., 1999) flowing through a geometrically highly complex hierarchical vascular system. The vessels locally act as heat sinks cooling the surrounding tissue and thereby considerably influence the treatment outcome (Chen et al., 1993). First reported clinical use of FUS to treat liver tissue was reported by Vallancien et al. 1993. Already before that several studies investigated the response of liver tissue to FUS treatments (ter Haar et al., 1988, 1989b). To reduce the complexity, in today’s FUS treatment of moving abdominal targets, the motion of the target still needs to be controlled with or without anesthesia (Rowland et al., 1997; Visioli et al., 1999; Kennedy et al., 2004; Wu et al., 2004; Illing et al., 2005; Anzidei et al., 2014): One option is to stop the respiration (breath-hold) for the duration of active ultrasound application and afterwards let the respiration normalize before starting the next sonication. This procedure, however, results in long treatment duration and the need for general anesthesia. Another approach that is close to clinical application
is respiratory-gated sonication (Wijlemans et al., 2015). Thereby, the therapeutic ultrasound is active during the respiratory cycle only when the target is detected to be in a certain position. This approach allows for a treatment without general anesthesia, but suffers also from overly long treatment duration due to the shut off of the FUS in parts of the respiratory cycle. To improve this, the respiration of the patient can in principle be controlled more aggressively to keep the liver almost static (jet-ventilation (Ihra et al., 2000)). This can however have adverse side-effects like pneumothorax and is not yet utilized clinically in the context of FUS treatments.

Most clinical cases of FUS liver treatments were conducted using the ultrasound-guided JC model from Chongqing Haifu (Chongqing, China) in China (Wu et al., 2004; Aubry et al., 2013). The system has been furthermore tested in the UK in a Western population (Illing et al., 2005). The system has a regulatory approval (CE mark and Chinese CFDA) for liver applications (Aubry et al., 2013). It comprises a fixed focus FUS transducer, a diagnostic ultrasound imaging device for guidance, and the possibility of mechanically moving the transducer to change the focus position in between sonications (Wu et al., 2004). The system cannot compensate respiratory motion and thus requires stopping the respiration of the patient in a precisely defined respiratory state during sonication. The patient is either in epidural or general anesthesia.

Besides the cases performed with the JC model, to date only few FUS liver treatments have been performed which are restricted to gating and breath-hold approaches. Both approaches lead to longer than necessary treatment duration due to the shut off of FUS in parts of the respiratory cycle or the necessity for normalization of respiration after long breath-hold periods.

None of the currently clinically available treatment systems supports sufficient solutions for real-time transcostal sonications and compensation of motion. Thus, the applicability for FUS in the liver is currently restricted to parts of the liver that are accessible without ribs in between transducer and target.

1.2.7 Potential complications and side-effects

Generally, FUS has the potential for very low complication rates. However, due to the non-invasive nature of the approach, side-effects may occur without even being noticed directly. For this reason, it is beneficial to perform the treatment with the patient being conscious and only mildly sedated instead of in general anesthesia.

The categorization in minor and major complications can be done according to the
standardized SIR (Society of Interventional Radiology) grading system (Crocetti et al., 2010). Minor complications therein require no therapy or only nominal therapy but generally have no long-term consequence for the patient. Major complications require therapy and hospitalization and might have long-term consequences including death. Among 1038 patients treated with FUS in China, a low major complication rate has been observed (Wu et al., 2004) (5-10% low-grade fever, less than 5% skin-burns, 20-30% mild local pain within 1 week after FUS, 6 cases of hepatic abscesses, 4 cases of local infections, 4 cases of bowel perforation, 4 cases of bone fracture, 4 cases of nerve damage). Illing et al. 2005 report a favorable side-effects profile when compared to more invasive techniques in their 30 patient trial. Adverse treatment effects therein are reported to be local to the treatment site, discomfort being the only clinically relevant adverse effect. Skin toxicity is reported in 27% of the cases with one grade 2 case. Low-grade fever is reported in 13% of the treated patients. The complications in FUS treatments are mostly due to high-energy US waves reflected on gas or bony structures (Kim et al., 2008; Stewart et al., 2006; Li et al., 2007). Even in the case of no major reflections, direct thermal injury of overlying skin can occur. Furthermore, tissue in the beam path and internal organs anterior or posterior to the focal zone could be injured. This is even more critical as the image-based monitoring cannot cover the entire abdomen, thereby leaving such damage unnoticed. In the presence of respiratory motion there is a much higher potential for a mismatch between the assumed position of structures and the actual physical positions than for static targets. Air-filled organs like bowel, lung, and stomach can be perforated if penetrated by the ultrasound waves. Li et al. 2007 report in their 17 patients study one case of bowel perforation, Wu et al. 2004 report 4 cases. Vascular system damage like vessel wall disruptions seem to rather not occur in larger vessels (not reported in any of the cases reported in Wu et al. 2004) but occur in smaller vessels below 2 mm diameter (Wu et al., 2004). One case of superior mesenteric artery infarction resulting in necrosis of the entire small intestines is reported by Li et al. 2007. Bile duct disruption may be more likely due to the weaker structure of the system. Skin-burn can be caused by poor acoustic coupling between the skin and the therapeutic window or a previous operation scar (Kim et al., 2008). Li et al. 2007 report skin burns in all of 17 examined patients. In cases of liver treatment, reflected US waves on ribs can induce overlying soft tissue damage including the skin (Kim et al., 2008). Furthermore, the high absorption of the ribs can lead to heating of the bone which is transferred to the surrounding tissue. Nerves may also be subject to damage. This may be due to direct heating
or heating of surrounding bone structures (Kim et al., 2008). Li et al. 2007 report Neurapraxia of the stomach and intestines, a recovering blockage of nerve conduction, to be the second most common complication in their studies. Wu et al. 2004 however report cases of complete recovery of nerve functions including sensation and motion within one year after the FUS treatment. Fever can occur after the treatment and it is observed that the severity and time of fever seems to be directly related to the amount of destroyed tissue (Wu et al., 2004). Hepatic abscesses within 2-3 weeks after FUS treatment are reported in six of 474 patients with liver cancer (Wu et al., 2004). These complications mostly appear to be minor or low grade major complications having in almost all cases no long-term effect for the patient. The major benefit over needle-based approaches appears to be that no secondary tumor formation is to be expected due to tumor cell spread by the needle. As such, if done correctly, focused ultrasound treatment can be considered to have the potential to be a safe treatment with very low risk. Software support can be a means to minimize the potential occurrences of most of the above mentioned complications.

1.3 THIS WORK

This work addresses the aforementioned challenges using computer modeling and simulation. A numerical model of the treatment effects of FUS is developed. The model accounts for the patient’s individual anatomy and respiratory motion. Besides the investigations targeting the development of the model itself and its verification and validation, we give clinically motivated application scenarios for using the numerical model to interactively plan a therapy driven by model predictions and to automatically optimize part of the therapy by finding a suitable access window to the target. The FUS model is furthermore used to extensively test a novel FUS treatment system featuring motion compensation beyond what would be feasible in real-world testing. This approach is seen as a step towards reducing the efforts necessary for establishing the system for clinical use.

1.3.1 TIMEFRAME OF THE WORK

The work described in this document is based on my work at Fraunhofer MEVIS (Bremen, Germany) in two consecutive projects funded by the European Union. Both projects received funding from the European Community’s Seventh Framework Programme (FP7/2007-2013). The first project, called FUSIMO (www.fusimo.eu), funded under grant agreement no. 270186, was dedicated to the development of an
integrated numerical model of focused ultrasound treatments for abdominal organs. The follow-up project TRANS-FUSIMO (www.trans-fusimo.eu), funded under grant agreement no. 611889, has the goal of developing an actual treatment controller system for the execution of FUS in moving organs – with the ultimate goal of the application to humans in a first clinical trial. FUSIMO started in January 2011 and lasted until December 2013. TRANS-FUSIMO started in January 2014 and is still ongoing at the time of writing this thesis.

1.3.2 Contributions

Numerical temperature simulation during respiratory motion

A fast numerical simulation method was developed. The method can predict the temperature distribution resulting from ultrasound therapy in heterogeneous moving domains. The method handles the discontinuous motion at the abdominal wall where the inner organs slide up and down along the ribcage during the respiratory cycle. GPU parallelization of the solver is used to achieve high performance and short computation times. Details can be found in Chapter 2.

Ultrasound propagation in heterogeneous media

A novel angular spectrum approach was developed and validated against a finite-difference time-domain (FDTD) model (Treeby et al., 2012) and compared to the widely used hybrid angular spectrum method (Vyas and Christensen, 2012). The novel approach adapts for tissue heterogeneity in the frequency domain for different tissue types and accurately models the pressure phase changes happening to the individual wave components, which the hybrid angular spectrum method fails to resolve. The method is a co-development together with Joachim Georgii and builds upon his efficient GPU implementation of the hybrid angular spectrum method, described in (Georgii et al., 2011). Section 3.3.2 describes the approach in more detail.

Fast patient-specific numerical FUS simulations

An integrated model was developed combining the ultrasound model, the temperature model, a tissue damage model, a predictive motion model (Samei et al., 2014), and image-based anatomical modeling. For very time-critical applications, an atlas-based ultrasound approximation model is developed and compared to the angular
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spectrum approach. The FUS model is furthermore validated exemplarily against MR thermometry data. Two clinically motivated applications of the FUS model are described. The first is a prototypical planning tool in which the FUS model is used to help the clinician to plan a suitable treatment for a certain patient. The other application case is the use of the FUS model to automatically identify an optimal transducer placement for a given target within a patient. Chapter 3 describes these studies in more detail.

IN-SILICO FIRST-STAGE VALIDATION OF A TREATMENT SYSTEM USING NUMERICAL SIMULATION

A third and more technical application case of the FUS model is described in Chapter 4. The numerical FUS model therein is used for in-silico assessment of the performance of a novel FUS treatment system with motion compensation – the treatment system is tested using a virtual replacement of the actual hardware system and the patient. The treatment system comprises a clinically available MR device and FUS transducer system. The controller is very generic and could use any suitable MR or FUS device. MR image sequences (echo planar imaging) are acquired for both motion observation and thermometry. Based on anatomical feature tracking, motion predictions are estimated to compensate for processing delays. FUS control parameters are computed repeatedly and sent to the hardware to steer the focus to the (estimated) target position. All involved calculations produce individually known errors, yet their impact on therapy outcome is unclear. This is solved by defining an intuitive quality measure that compares the achieved temperature to the static scenario, resulting in an overall efficiency with respect to temperature rise.

To allow for extensive testing of the system over wide ranges of parameters and algorithmic choices, we replace the actual MR and FUS devices by a virtual system. It emulates the hardware and, using the integrated numerical model of FUS during motion, predicts the local temperature rise in the tissue resulting from the controls it receives. Using the virtual system, design studies are performed to investigate the effect a certain parameter value (e.g. the imaging update rate) has on the overall efficiency of the system.

1.3.3 JOURNAL PUBLICATIONS

The document is based on the following three journal publications that are the result of my work in the aforementioned projects:
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1. “Fast numerical simulation of focused ultrasound treatments during respiratory motion with discontinuous motion boundaries,” (Schwenke et al., 2017a) in IEEE Transactions on Biomedical Engineering.


The following contributions are not covered by the above publications and are not yet published elsewhere:

1. the verification of the temperature simulation against an analytic reference (Section 2.5.1),

2. the CT-image-based anatomical modeling (Section 3.3.1),

3. a discussion of the error introduced by the hybrid angular spectrum method and the proposition of a novel angular spectrum approach for heterogeneous media (Section 3.3.2) and its validation against a FDTD model (Section 3.4),

4. the calibration of the FUS model to MR thermometry data (Section 3.4.4),

5. an exemplary use of the FUS model for finding optimal transducer placements (Section 3.6).
Numerical temperature simulation during respiratory motion

This chapter is closely based on the paper “Fast numerical simulation of focused ultrasound treatments during respiratory motion with discontinuous motion boundaries,” (Schwenke et al., 2017a). A numerical simulation method is presented that can simulate FUS treatments of target organs during respiratory motion in real time based on patient-specific anatomical and motion information. In particular, the partial differential equation that describes the temperature distribution in the moving patient is mathematically transformed to a static computational reference frame for both efficiency and accuracy.

2.1 Related work

The basic components in simulating thermal treatments are a temperature model, a heat source model (in case of FUS an ultrasound pressure model), and a tissue damage model to predict the tissue coagulation by thermal effects.

Thermal model. For simulating the development and distribution of heat in thermal therapy, a lot of work has been done in the context of radio frequency, microwave, and interstitial laser ablation (Kok et al., 2013). These methods include simulation of cooling effects by vascular structures. Modeling thermal ablation during motion of the domain has – to the author’s knowledge – not been considered in the literature yet.
The discretization of the models, which are usually defined as a (system of) partial differential equation(s), is widely studied. Most prominent methods include finite difference (FDM), finite volume and finite element methods (Tadmor, 2012). The solution of the ordinary differential equations resulting after spatial discretization is done with time-stepping schemes ranging from explicit methods such as forward Euler to implicit methods such as Backward Euler, Crank-Nicolson and Leapfrog stepping (Tadmor, 2012). Time stepping schemes that are not unconditionally stable, like the explicit forward Euler, potentially introduce instabilities. These can be avoided by respecting the Courant-Friedrichs-Lewy (CFL) condition for the grid resolution and time step size (Courant et al., 1928). Explicit schemes are computationally convenient since they do not require solving sparse linear systems as implicit schemes do. However due to their stability implicit schemes allow for larger time steps. Transforming the governing equations to a computational reference is an approach commonly applied in the simulation of fluid dynamics (Anderson, 1995) and adaptive moving mesh methods (Huang and Russell, 2011) for highly dynamic processes. Moving domain methods (Wang, 2015) use similar approaches to allow for spatially varying geometries. Regarding the handling of discontinuous motion boundaries (like the sliding motion of the inner organs at the abdominal wall), methods from the application area of fluid structure interaction (Hou et al., 2012) are closely related. Composite finite elements (Preusser et al., 2011) and extended finite elements (Belytschko et al., 2001) are methods to discretize discontinuous functions on (regular) meshes.

Tissue damage. Once the thermal distribution over time is known in the tissue under investigation the resulting damage due to heat can be estimated by simple temperature thresholding, the cumulative equivalent minutes (CEM43) approach, or an Arrhenius damage integral. All three approaches have been studied extensively in the context of simulation of needle-based thermal ablation (radio frequency, microwave, and interstitial laser ablation, see above) (Pearce, 2010; Kröger et al., 2010; Kok et al., 2013; Liu et al., 2007b). These models can take into account tissue type dependency and thermotolerance effects (tissue can develop tolerance to heat after a prior heating) by weighting factors (Shaw et al., 2015). For a clinically useful definition of dose for FUS treatments, the thermal damage and damage due to mechanic effects like cavitation need to be combined (ter Haar, 2013).

GPU Computing. The rapid increase in performance of graphics hardware has made it a compelling platform for computationally demanding tasks in a wide variety of application domains (Owens et al., 2007) and especially numerical simulation (Krüger
and Westermann, 2003). Recent improvements in its programmability using high-level programming frameworks like OpenCL (Stone et al., 2010) and CUDA (Nickolls et al., 2008) increased the accessibility of the hardware performance for general applications. Graphical processing units (GPUs) provide a high number of parallel units as well as efficient hardware support to hold considerably more active threads than parallel units. Parallel threads running the same instructions on multiple data (SIMD) can coalesce the memory accesses to optimally use the global memory bandwidth. Due to these properties, GPU parallelization has been applied to the simulation of bio-physical phenomena, for example elasticity (Dick et al., 2011; Han et al., 2012); wave propagation (Mehra et al., 2011; Karamalis et al., 2010); and bio-heat simulation (Kalantzis et al., 2016; Reis et al., 2016).

2.2 Contribution

We transform the problem of simulating FUS from the moving world (Eulerian approach) to a computational reference frame (Lagrangian approach). The governing equations are mathematically transformed to the reference space. Consequently, the numerical solution of the transformed problem can be performed on a fixed grid bound to the anatomical planning image. One of the key benefits of this approach is that numerical errors due to consecutive interpolations do not accumulate over time. Furthermore, the mapping to a reference frame and computational reference grid allows for an efficient GPGPU implementation using regular grids. The method is thus both accurate and efficient. Motion data can be given as irregular point clouds. The motion data is then bound to a tetrahedral mesh for geometrical flexibility. The thermal model includes the cooling of tissue by the geometrically complex vascular systems in the liver. As the simulation method is targeting abdominal FUS treatments, the models are extended to handle the discontinuous sliding motion that occurs at the abdominal wall where the inner organs slide along during the respiratory cycle (cf. Figure 1.4). The discontinuity is resolved computationally in order to accurately predict the temperature distribution within the patient.

2.3 Mathematical modeling

In the following, we focus on the modeling of heat development and distribution. The ultrasound propagation is not affected by the motion of the domain as the propagation through the tissue happens on a much smaller timescale than the tissue
motion. The medium through which the propagation takes place can be assumed to be static for the duration of the propagation. The heat however is bound to the tissue and thus follows the motion of the object.

The spatio-temporal distribution of temperature can be described by the classical heat equation with heat source and sink terms

$$\rho c_p \frac{d}{dt} T - \nabla \cdot (\kappa \nabla T) = q - s$$  \hspace{1cm} (2.1)

with unknown temperature $T$ [K], density $\rho$ [kg/m$^3$], specific heat capacity $c_p$ [J/K], thermal conductivity $\kappa$ [W/(mK)], heat source $q$ [W/(m$^3$s)], and heat sink $s$ [W/(m$^3$s)].

For modeling thermal treatment of tissue a heat source term defines the heat introduced locally by the treatment. The heat source is dependent on the specific therapy approach and will be addressed in later parts of the work.

A classical bio-heat equation was introduced by Pennes (Pennes, 1948) to describe the temperature distribution in static non-moving tissue subject to vascular perfusion on fine scale of capillaries (in the liver sinusoids). The heat sink term therein is given as

$$s(x,t) = \omega^B c^B_p \left( T(x,t) - T^B \right)$$  \hspace{1cm} (2.2)

with tissue perfusion rate $\omega^B$ [kg/(m$^3$s)], the specific heat capacity of blood $c^B_p$ [J/K], and temperature $T^B$ of in-flowing blood.

In addition to the cooling by capillary tissue perfusion expressed in Pennes’ heat sink term, we model cooling by blood flow within larger vessels by adding Dirichlet boundary conditions with body temperature for the interior of such vessels

$$T(x,t) = T_{body} \quad \forall x \in \Omega_{Vessel}.$$  \hspace{1cm} (2.3)

This means that the volume flow within the vessels is assumed to be so large that the blood is not heated considerably and the vessel wall stays at body temperature. This approach is reasonable based on the findings from other studies (Kröger et al., 2010).

Estimating the resulting tissue state after exposure to a certain temperature history can be done using the thermal dose model of cumulative equivalent minutes (CEM43) (Sapareto and Dewey, 1984):

$$t_{43}(x, t_{final}) = \int_0^{t_{final}} R^{43-T(x,t)} dt,$$

with $R = \begin{cases} 0.5 & \text{if } T(x,t) \geq 43^\circ C \\ 0.25 & \text{otherwise} \end{cases}$
An alternative to estimate the tissue damage is the Arrhenius formalism, which is also based on an integral over the history of the temperature evolution, see e.g. (Pearce, 2010).

Note that all (bio-)physical parameters in the equations above (2.1) - (2.2) and in the following expositions depend in general on space, time, temperature, and also tissue damage state. The numerical solver shall be able to handle these nonlinear dependencies. In the following, to simplify notation, we do not include all of these dependencies in the notations.

2.3.1 Modeling temperature in the breathing patient

There are basically two possible approaches to include motion and deformation of the object: an *Eulerian* and a *Lagrangian* description.

The *Eulerian* approach is to describe the problem from the viewpoint of a fixed location \( x \in \Omega \) in space. Any motion or deformation of the object in which the modeled physical process takes place results in a local change of the physical property at the fixed location \( x \) depending on the direction of motion and the local shape of the physical property function.

The *Lagrangian* approach, in contrast, is to describe the problem with respect to a reference motion state \( \Omega_r \). The physical quantity is bound to a location \( \xi \in \Omega_r \) in the reference state. The physical quantity moves with the material through space. Thereby, a change of physical location does not introduce a change of the physical property.

For a comparison of both approaches, we introduce the following mappings between the two spaces: the forward mapping from reference domain to physical world

\[
\mathbf{x} : \Omega_r \times \mathbb{R}_0^+ \to \Omega, \quad (\zeta, t) \mapsto \mathbf{x}(\zeta, t) \tag{2.4}
\]

in which points \( \mathbf{x} \) move in time \( t \) and the inverse mapping from physical world to reference

\[
\mathbf{\xi} : \Omega \times \mathbb{R}_0^+ \to \Omega_r, \quad (\mathbf{y}, t) \mapsto \mathbf{\xi}(\mathbf{y}, t), \tag{2.5}
\]

such that \((\mathbf{\xi} \circ \mathbf{x})(\zeta, t) = \mathbf{\xi}(\mathbf{x}(\zeta, t), t) = (\zeta, t)\) and \((\mathbf{x} \circ \mathbf{\xi})(\mathbf{y}, t) = \mathbf{x}(\mathbf{\xi}(\mathbf{y}, t), t) = (\mathbf{y}, t)\).

The individual vector components are denoted as (contravariant) column vectors \( \mathbf{x} = (x_1, x_2, x_3)^T \) and \( \mathbf{\xi} = (\xi_1, \xi_2, \xi_3)^T \), where \( x_i = x_i(\zeta, t) \), and \( \xi_i = \xi_i(\mathbf{y}, t) \). As we deal with real-world motion, the mappings are assumed to be physically admissible, i.e. continuous in time, continuously differentiable, globally invertible at all times.
and orientation-preserving (i.e. $\det(\frac{\partial \xi}{\partial x}) > 0$).

In the following we will simplify notation by denoting quantities in the reference domain with a hat, e.g. $\hat{f}$, defining that

$$
\begin{align*}
\hat{f}(\xi, t) &= (f \circ \xi)(\xi, t) = f(x(\xi, t), t) = f(x, t), \\
f(x, t) &= (\hat{f} \circ \xi)(x, t) = \hat{f}(x(\xi, t), t) = \hat{f}(\xi, t).
\end{align*}
$$

(2.6)

Bio-heat equation under motion in Eulerian description. All physical quantities in the Eulerian approach are defined as functions of position in physical space and time. Now, with $x$ being time-dependent, the change of a physical quantity $p(x, t)$ at location $x$ at time $t$ is the material derivative

$$
\frac{d}{dt}p(x, t) = \frac{\partial p(x, t)}{\partial t} + \nabla p(x, t) \frac{dx}{dt}
$$

(2.7)

and thereby is the result of a change in physical quantity over time (first term) or a change due to a changed physical location of the object in combination with a locally changing quantity (second term).

Physical model parameters that are naturally given in the reference space (from a static view of the object), need to be mapped to the moving and deformed state at each time-point with the mappings introduced above, cf. (2.6).

Inserting Eq. (2.7) into Eq. (2.1) we get the bio-heat equation during motion of the domain in Eulerian description as

$$
\rho c_p \left( \frac{\partial}{\partial t} T(x, t) + \nabla T(x, t) \frac{dx}{dt} \right) - \nabla \cdot (\kappa \nabla T(x, t)) = q(x, t) - s(x, t).
$$

(2.8)

Thus, using the Eulerian approach results in an additional advection term compared to the heat equation in the static domain.

Bio-heat equation during motion in Lagrangian description. In the Lagrangian approach in contrast, all physical quantities are defined as a function of position in a reference space and time, i.e. $\hat{T}(\xi, t) = T(x(\xi, t), t)$, cf. (2.6). This includes all physical model parameters that are naturally given in the reference space. Using Eq. (2.6) and the fact that the position in the reference domain is not changing with time by design of the mappings, the temporal change of a physical quantity $\hat{p}$
at a location $\xi$ at time $t$ is

$$\frac{d}{dt} p(x, t) = \frac{d}{dt} \hat{p}(\xi, t) = \frac{\partial \hat{p}(\xi, t)}{\partial t} + \nabla_\xi \hat{p}(\xi, t) \frac{d\xi}{dt} = \frac{\partial \hat{p}(\xi, t)}{\partial t}. \quad (2.9)$$

Inserting Eq. (2.9) into Eq. (2.1), the bio-heat equation under motion of the domain in the Lagrangian description is

$$\rho c_p \frac{\partial}{\partial t} \hat{T}(\xi, t) - \nabla_x \cdot \left( \kappa \nabla_x \hat{T}(\xi, t) \right) = q(\xi, t) - s(\xi, t). \quad (2.10)$$

Here, the subscript in $\nabla_x$ denotes that the operator is defined with respect to the Euclidean coordinate frame and not the reference coordinate frame. Notice that in this formulation the equation does not contain an advection term. The partial differential operators however are defined with respect to a different coordinate frame ($\Omega$) than the function ($\Omega_r$). To resolve this we need to also transform the operators.

Let $\nabla_\xi$ denote the gradient operator with respect to the reference coordinates $\xi \in \Omega_r$. The inverse Jacobian is defined as

$$J^{-1}(x, t) = \frac{\partial \xi}{\partial x}(x, t) = \begin{bmatrix} \frac{\partial \xi_1}{\partial x_1} & \frac{\partial \xi_1}{\partial x_2} & \frac{\partial \xi_1}{\partial x_3} \\ \frac{\partial \xi_2}{\partial x_1} & \frac{\partial \xi_2}{\partial x_2} & \frac{\partial \xi_2}{\partial x_3} \\ \frac{\partial \xi_3}{\partial x_1} & \frac{\partial \xi_3}{\partial x_2} & \frac{\partial \xi_3}{\partial x_3} \end{bmatrix} (x, t) = \begin{bmatrix} (a^1(x, t))^T \\ (a^2(x, t))^T \\ (a^3(x, t))^T \end{bmatrix}$$

with the contravariant vectors denoted by

$$a^i(x, t) := \nabla_\xi(x, t) = \left( \frac{\partial \xi_i}{\partial x_1}(x, t), \frac{\partial \xi_i}{\partial x_2}(x, t), \frac{\partial \xi_i}{\partial x_3}(x, t) \right)^T, \quad i = 1, 2, 3.$$

Using the chain rule, the individual components of the gradient of some scalar function $p$ with respect to physical space $p(x, t) = p(x(\xi, t), t) = \hat{p}(\xi, t)$ can be stated in terms of the gradient with respect to the reference space

$$\frac{\partial p}{\partial x_j} = \sum_{i=1}^3 \frac{\partial \hat{p}}{\partial \xi_i} \frac{\partial \xi_i}{\partial x_j}. \quad (2.11)$$
With $\frac{\partial \xi}{\partial x_j}$ being the j-th component of $\hat{a}_i^j$, the gradient can be written as

$$\nabla_{x} p(x,t) = \nabla_{x} \hat{p}(\xi(x,t),t) = \left( \frac{\partial \xi}{\partial x} \right)^T(x,t) \nabla_{\xi} \hat{p}(\xi,t)$$

$$= \sum_{i=1}^{3} \hat{a}_i^i(\xi,t) \frac{\partial}{\partial \xi_i} \hat{p}(\xi,t). \quad (2.12)$$

Similar to this, the divergence of a vector field $\mathbf{v}(x,t) = \mathbf{v}(\xi(t)) = \hat{v}(\xi,t)$ is given by

$$\nabla_{x} \cdot \mathbf{v}(x,t) = \sum_{i=1}^{3} \hat{a}_i^i(\xi,t) \cdot \frac{\partial}{\partial \xi_i} \hat{v}(\xi,t). \quad (2.13)$$

The diffusion term follows with Eqs. (2.12) and (2.13) as

$$\nabla_{x} \left( \kappa \nabla_{x} \hat{T}(\xi,t) \right) = \sum_{i=1}^{3} \hat{a}_i^i(\xi,t) \cdot \frac{\partial}{\partial \xi_i} \left( \hat{\kappa} \sum_{j=1}^{3} \hat{a}_j^j(\xi,t) \frac{\partial}{\partial \xi_j} \hat{T}(\xi,t) \right)$$

$$= \sum_{i=1}^{3} \sum_{j=1}^{3} \hat{a}_i^i(\xi,t) \cdot \hat{a}_j^j(\xi,t) \frac{\partial}{\partial \xi_i} \left( \hat{\kappa} \frac{\partial}{\partial \xi_j} \hat{T}(\xi,t) \right). \quad (2.14)$$

Inserting the transformed diffusion term, the bio-heat equation completely transformed to reference space is

$$\rho c_p \frac{\partial}{\partial t} \hat{T}(\xi,t) - \sum_{i=1}^{3} \sum_{j=1}^{3} \hat{a}_i^i(\xi,t) \cdot \hat{a}_j^j(\xi,t) \frac{\partial}{\partial \xi_i} \left( \hat{\kappa} \frac{\partial}{\partial \xi_j} \hat{T}(\xi,t) \right)$$

$$= q(\xi,t) - s(\xi,t). \quad (2.15)$$

Discussion of the approaches: In the Eulerian approach (PDE (2.8)) the change of the temperature at a given location consists of both temporal changes (partial derivative with respect to time) and motional changes (advection term). The discretization of the advection term inevitably introduces numerical diffusion due to interpolations. Thus, high-order energy-conserving discretization schemes are needed to decrease accumulation of errors when the physical quantity, in our case temperature, is transported relative to the discretization grid. This fact is the main reason not to choose the Eulerian approach in our given application area.

The main advantage of the Lagrangian approach in our setting is that PDE (2.15) is free of advection terms. Instead we are dealing with a modified second order differential operator in space which can be treated more robustly. Using the
Lagrangian formulation, we can get to a solution where no motion-induced transport of the physical quantity relative to the grid occurs and hence a solution that can be applied to accurately simulate long duration treatments.

2.3.2 Multiple independently moving objects

Consider the case of the liver moving in the abdomen during respiration of the human. The liver slides up and down along the abdominal wall. The global motion field is thus not continuous and a discontinuity is present at the abdominal wall. As a result, in the Lagrangian approach, the mapping $\xi$ from physical space to reference space is discontinuous at the boundaries of the objects. Thus, the mapping is not differentiable and the mapping of the differential operators from $\Omega$ to $\Omega_r$

$$\nabla_x \hat{T}(\xi, t) = \sum_{i=1}^{3} \hat{a}_i(\xi, t) \frac{\partial}{\partial \xi_i} \hat{T}(\xi, t)$$

is undefined due to the undefined mapping components gradient $\hat{a}_i$.

However the global motion is just a combination of multiple continuously moving objects – the liver and the ribcage – that happen to move independently of each other. The motion is piecewise continuous and the discontinuities can be resolved: The exchange of heat occurs between neighboring points in the physical domain and these need not be neighboring points in the reference due to the discontinuous motion. However, within each physically admissible independently moving object the mapping is well-defined. To resolve the discontinuity at the boundary between the moving objects we establish the coupling using boundary conditions on the temperature. Inside each object, the mapping is continuous and can be differentiated and the operators can be mapped to the reference as described. On the boundary, computations of the gradient operator need to take into account the discontinuity of the temperature field and thus need to utilize the mapping to the physical world to access the required temperature values. Details on this are given in Section 2.4.5.

2.4 Numerical solution

In the following the numerical solution of the Lagrangian approach (PDE (2.15)) is described in detail.
2.4.1 Choosing the computational reference grid

As a result of the Lagrangian approach, the choice of the computational mesh or grid is independent of the possible motion and deformation of the patient in physical space: deformations of the patient in physical space do not change the grid in the computational reference space but solely introduce local changes in the partial differential operators via the Jacobian of the mapping between physical space and computational reference space.

As the goal is an efficient simulation allowing high update rates, a GPGPU implementation has been developed. To this end, a regular hexahedral grid is employed in conjunction with a finite difference (FD) discretization of Eq. (2.15). Regular computational grids with fixed neighborhood relations are particularly well-suited for parallel implementations and efficient execution on GPUs with coalesced memory access. We apply an explicit Euler method to solve the ordinal differential equation in time. The explicit time-stepping leads to locally independent operations that fit well to the SIMD paradigm. The time steps for the explicit Euler method are chosen according to the CFL condition (Courant et al., 1928). In most cases the small time steps that are required for the resolution of motion already lead to a stable solution. In all of our experiments a time step of 0.1 s was sufficient to guarantee stability and an accurate resolution of the motion.

Additionally to the regular grid used for the temperature simulations, a tetrahedral mesh is utilized to discretize the motion of the domain. Figure 2.1 shows the relation of the deformation mesh to the regular computational grid. The tetrahedral mesh is utilized to allow for an accurate resolution of object boundaries between moving objects already at low resolutions. Furthermore, the simulation of ultrasound propagation (as described in the next chapter) is performed on a regular grid which is of higher resolution than the temperature simulation grid and may be arbitrarily oriented with respect to the temperature grid.

2.4.2 Motion information

Aiming at an efficient computation of the mappings between reference domain $\Omega_r$ and physical world $\Omega$ we define them on the basis of point cloud correspondences. Therefore, in both domains $\Omega_r$ and $\Omega$ we define point clouds, $M_\xi = \{ \xi_j \mid j \in 1, \ldots, n \}$ be the set of points in the reference state and $M_x(t) = \{ x^j(t) \mid j \in 1, \ldots, n \}$ the corresponding set of points in the physical world at time $t$. Using the notation $\overline{x}$ to denote that the function $\overline{x}$ is a discretization of $x$, the discrete forward and backward
mappings can be defined as

\[ \mathbf{x} : M_\xi \times \mathbb{R}_0^+ \rightarrow M_\mathbf{x}(t), \quad \mathbf{x} (\xi^j, t) = x^j(t), \]  
and

\[ \overline{\mathbf{\xi}} : M_\mathbf{x}(t) \times \mathbb{R}_0^+ \rightarrow M_\xi, \quad \overline{\mathbf{\xi}} (x^j(t), t) = \xi^j. \]  

To evaluate the forward mapping \( \mathbf{x} \) at arbitrary locations \( \xi \) not necessarily located on points in \( M_\xi \), a tetrahedral mesh is built based on the point cloud \( M_\xi \). The continuous mapping function is then approximated linearly inside the mesh elements using barycentric interpolation. Indeed, for a given point \( \xi \in \Omega_r \), the physical world position \( \mathbf{x} \in \Omega \) can be determined from the displacements given at the mesh nodes of the containing tetrahedron. With \( \xi^i \in \mathbb{R}^3 \) being the position of node \( i \), the barycentric coordinates of \( \xi \in \mathbb{R}^3 \) are

\[ \lambda(\xi) = \begin{bmatrix} \xi^1 \\ 1 \\ \xi^2 \\ 1 \\ \xi^3 \\ 1 \\ \xi^4 \\ 1 \end{bmatrix}^{-1} \cdot \begin{bmatrix} \xi \\ 1 \end{bmatrix} =: T_{\xi}^{-1} \cdot \begin{bmatrix} \xi \\ 1 \end{bmatrix}. \]  

Furthermore, with \( \mathbf{v}^i(t) \) being the corresponding physical world position of the
vertex $i$ of the tetrahedron at time $t$, we can compute the corresponding world point $\mathbf{x}$ to $\mathbf{\xi}$ and $t$ as
\[
\bar{x} = \bar{x}(\mathbf{\xi}, t) = \sum_{i=1}^{4} \lambda_i(\mathbf{\xi}) \cdot \mathbf{v}_i(t) = T_{v(t)} \cdot \lambda(\mathbf{\xi})
\] (2.19)

The determination of the tetrahedron that contains the grid point $\mathbf{\xi}_g$ in the reference domain is computationally expensive. However, since the reference domain is static, the determination of the containing tetrahedron for a grid node can be precomputed.

### 2.4.3 Jacobian matrix of motion

To be able to solve Eq. (2.15), the row-vectors $\mathbf{\hat{a}}^i$ of the Jacobian matrix of the mapping $\mathbf{\xi}(\mathbf{x})$ from physical space $\Omega$ to reference space $\Omega_r$ are required. Given the barycentric interpolation approach these can be evaluated efficiently. For a given point $\mathbf{x}(t) \in \Omega$ in physical space and time $t$, the point $\bar{\mathbf{\xi}}$ in the reference system is analogously to Equations (2.18) and (2.19) given by
\[
\bar{\mathbf{\xi}} = \bar{\mathbf{\xi}}(\mathbf{x}) = T_{\mathbf{\xi}} \cdot \lambda(\mathbf{x}), \text{ with } \lambda(\mathbf{x}) = T_{\mathbf{x}}^{-1} \cdot \begin{bmatrix} \mathbf{x} \\ 1 \end{bmatrix}.
\] (2.20)

The inverse Jacobian of $\bar{\mathbf{\xi}}$ with respect to physical coordinates $\mathbf{x}$ is given by
\[
\mathbf{J}^{-1} = \frac{\partial \bar{\mathbf{\xi}}}{\partial \mathbf{x}} = \frac{\partial \bar{\mathbf{\xi}}}{\partial \lambda} \frac{\partial \lambda}{\partial \mathbf{x}} = T_{\mathbf{\xi}} \cdot T_{\mathbf{x}}^{-1}
\]
and is constant inside each tetrahedral element of the deformation mesh for a fixed time $t$.

### 2.4.4 Discretization of the transformed bio-heat-equation

The different parts of PDE (2.15) to be discretized are the temporal derivative $\frac{\partial}{\partial t} \hat{T}$, the diffusion term
\[
Q_{\text{diffusion}}(\mathbf{\xi}, t) = \sum_{i=1}^{3} \sum_{j=1}^{3} \hat{\mathbf{a}}^i(\mathbf{\xi}, t) \cdot \hat{\mathbf{a}}^j(\mathbf{\xi}, t) \frac{\partial}{\partial \xi_i} \left( \hat{k} \frac{\partial}{\partial \xi_j} \hat{T}(\mathbf{\xi}, t) \right)
\] (2.21)
as well as the heat sink $s(\mathbf{\xi}, t)$ and source term $q(\mathbf{\xi}, t)$. 

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We group the spatial operators as

\[ Q(\xi, t) := Q_{\text{diffusion}}(\xi, t) - s(\xi, t) + q(\xi, t). \]  

(2.22)

Inserting this into Eq. (2.15), we arrive at

\[ \frac{\partial}{\partial t} \hat{T}(\xi, t) = \frac{1}{\rho(\xi, t) c_p(\xi, t)} Q(\xi, t) \]  

(2.23)

which can be discretized using the forward Euler method

\[ \frac{\partial}{\partial t} \hat{T}(\xi, t) \approx \frac{\hat{T}(\xi, t + \tau) - \hat{T}(\xi, t)}{\tau} \approx \frac{1}{\rho(\xi, t) c_p(\xi, t)} Q(\xi, t) \]  

(2.24)

and leads to the explicit local update formula for a time step \( \tau \)

\[ \hat{T}(\xi, t + \tau) = \hat{T}(\xi, t) + \frac{\tau}{\rho(\xi, t) c_p(\xi, t)} Q(\xi, t). \]  

(2.25)

In the following we focus on the spatial discretization, thereby introducing a grid only on the reference domain. Let us denote a 3D uniform hexahedral grid of computational nodes \( n \) with indices \( (u, v, w) \in \mathbb{N}^3 \) and with the corresponding reference coordinates \( \xi_n \in \Omega_r \). The spacing of the grid in all directions are denoted by \( dx = (dx, dy, dz) \). Based on this grid we define the discrete temperature function \( \bar{T}_n := \hat{T}(\xi_n, t) \) at some time \( t \). Similarly we define discrete quantities for all other functions and material parameters involved in the above equations. Note that in the following we omit denoting the dependence on \( t \) as it is clear that the right hand side of (2.24) is evaluated explicitly, i.e. at the old time \( t \).

We now can describe the finite difference discretization of

\[ \bar{Q}_n = \bar{Q}_{\text{diffusion}} - \bar{s}_n + \bar{q}_n. \]  

(2.26)

Defining local index offsets in the three spatial dimensions by \( \Delta_1 = (0.5, 0, 0), \Delta_2 = (0, 0.5, 0), \Delta_3 = (0, 0, 0.5) \) we can denote the centered difference derivative of a function \( f \) at node \( n \) in direction \( \Delta_i \) by

\[ \delta_{\Delta_i}[f]_n := \frac{1}{|2\Delta_i \cdot dx|} ([f]_{n+\Delta_i} - [f]_{n-\Delta_i}), \]  

(2.27)

in which \([f]_n\) means evaluating function \( f \) at node \( n \).

Using the discrete motion derivative \( \bar{a}_c^i := \bar{a}^i(\xi_c, t) \) of the center node \( c \) for the
\[ Q_{\text{diffusion}} = \sum_i \sum_j [\mathbf{a}_i]_e \cdot [\mathbf{a}_j]_e \delta \Delta_i \kappa \delta \Delta_j [\mathbf{T}]_e \]

\[ = \sum_i \sum_j [\mathbf{a}_i]_e \cdot [\mathbf{a}_j]_e \frac{1}{4|\Delta_i| \cdot |\Delta_j|} \left( \kappa_{\Delta_i \Delta_j} (T_{e+\Delta_i} - T_{e-\Delta_i}) - \kappa_{\Delta_i \Delta_j} (T_{e+\Delta_j} - T_{e-\Delta_j}) \right) \]

Figure 2.2 visualizes the discretization stencil for the diffusion term Eq. (2.28). Whereas the actual computations are done in 3D, the illustration is in 2D for simplicity. The stencil uses the temperature values at the center \( c \) and all six direct neighbors, the motion derivative \( \mathbf{a}_i \) at the center, and \( \kappa \) at the grid nodes. It interpolates \( \kappa \) on the in-between nodes. The temperature gradient discretizations \( \delta \Delta_i [\mathbf{T}]_{\pm \Delta_i} \) are computed on the in-between grid nodes using interpolated temperature values at the hanging nodes.
Both heat source and sink terms are local point operators. The Pennes heat sink term is discretized by
\[ s(\xi_n, t) \approx s_n = \omega^B c^B_p (\bar{T}_n - T^B) \] (2.29)
and the ultrasound heat source term by
\[ q(\xi_n, t) \approx q_n = \bar{\alpha} f \bar{\rho} \bar{c} |p(x(\xi_n, t))|^2. \] (2.30)

Note that the ultrasound pressure \( p \) is defined in the moving world.

### 2.4.5 Coupling object boundaries

As described in Section 2.3.2, in abdominal applications, there are multiple independently moving objects in the domain. This section describes how we numerically treat this case.

**Splitting of the tetrahedral mesh.** A point cloud with displacements is given for each independently moving object: Let \( K = \{A, B, C, \ldots\} \) denote the set of all objects and \( \Omega_o \subset \mathbb{R}^3, \; o \in K \) the domain covered by the respective objects. The entire domain is covered by the union of the objects, \( \Omega_r \subseteq \bigcup_{o \in K} \Omega_o \). For each of the objects, correspondences between reference domain and physical space are defined analogously to Equations (2.16) and (2.17) and denoted by an additional index, e.g. \( x_o(\xi, t) \) for a specific object \( o \in K \).

A tetrahedral mesh is first build on basis of the union of all object point clouds in reference space. The resulting tetrahedral mesh is then split into the individual objects to assure compatibility of the object meshes at the interfaces.

Given a label image that stores for each grid point the object identifier in the reference coordinate frame, the tetrahedral mesh can be split into individual meshes for the objects that share a triangular surface as boundary similar to the methods described in (Bey, 1995). Figure 2.3 illustrates the splitting procedure with a 2D example. It starts by collecting all edges that connect nodes with different object identifiers, see Fig. 2.3a. The splitting of elements is then performed in an iteration over all those edges. For each edge to be split, we first determine the object boundary point along the edge using the label image. At that location, two new nodes (one for each motion object) are added to the mesh. All elements incident to the split edge are then split into two tetrahedra using the respective new boundary node, see
Figure 2.3: Mesh splitting procedure. For simplicity the example is in 2D. First, the motion mesh is analyzed for edges that connect different motion objects (the boundary is the orange contour), shown dash-dotted in (a). Figure b) shows the result of a first split, c) after the second split and d) shows the result after the procedure finished.

Fig. 2.3b and 2.3c. Therefore, the procedure does not need to detect special splitting cases like for example the splitting into prisms. The splitting finishes when there are no more edges that connect different objects, see Fig. 2.3d. Every mesh element is afterwards uniquely assigned to one of the motion objects.

**DIFFUSION TERM DISCRETIZATION OVER MOTION OBJECT BOUNDARIES.** If the stencil that discretizes the diffusion term Eq. (2.28) at some location in the domain needs to use grid nodes of different motion objects, the direct neighbor values that do not belong to the center motion object need to be remapped according to their location in physical space.

Figure 2.4 shows a case of one object sliding along another object. $\xi_1$ and $\xi_2$ in Fig. 2.4a are neighboring grid nodes in the computational reference space. However, as the two nodes are from different objects, the two points are not necessarily close...
to each other in physical space. In fact, in the given example, object B has moved downwards sliding down object A and thus the two nodes do not influence each other by heat diffusion. The actual heat diffusion process happens between points that are close to each other in physical space. In the given example, Fig. 2.4b, heat diffusion takes place between $x_A(\xi^A_1)$ and $x_A(\xi^A_2)$ as well as $x_B(\xi^B_1)$ and $x_B(\xi^B_2)$. The superscript to a coordinate, e.g. $\xi^A$, shall denote that the center of the stencil is located within object A and the connection is seen from this direction.

To remap the neighboring nodes for a diffusion stencil the following procedure is performed: Let object A be the object the stencil center is in, and let object B be the adjacent motion object. The remapped neighboring grid-node $\xi_n$ is computed by $\xi_n^A = \xi$. This involves the evaluation of the inverse mapping $\xi$ which is computed as described in the following Section 2.4.6. As the new neighbor $\xi'_n$ is generally not a grid node but lies in between the grid nodes, the temperature values at this location are interpolated. The interpolation is performed using solely temperature values from the same motion object as the temperature function may have a discontinuity at the object boundary. If the new neighbor $\xi'_n$ is not on the boundary of object B, we assume there is a gap between the two objects and use body temperature as defaulting value. The motion in our application does not show this as the liver slides closely down the abdominal wall without introducing a gap.

### 2.4.6 Computing the inverse transformation

The forward mapping $x$ can be sampled efficiently after the computation of the spatial correspondence of grid nodes and tetrahedral elements (cf. Fig. 2.1, i.e. after computing for each grid node in which tetrahedron it is contained). This computation is performed only once since the mapping does not change in the reference space. For the inverse mapping $\xi$ however, the spatial correspondence of a point $x$ in physical space and tetrahedral elements changes continuously with the motion of the object and it is not efficient to re-compute it in every time step of the simulation. A search on the mesh would be needed for each point $x$ to find the containing tetrahedron. Instead, an iteration similar to the Stencil-walk algorithm (Buning, 1989) is performed. The goal is to estimate $\xi_{\text{Source}} = \xi(x(\text{Target}))$ given a position $x(\text{Target}) \in \Omega$ and the forward mapping $x$. The iteration is initialized with $\xi_0 = x$. Each iteration updates the estimate of $\xi_{\text{Source}}$ by $\xi_i = \xi_{i-1} - \epsilon_i^{\xi} - 1$ with $\epsilon_i^{\xi} = \frac{\partial \xi}{\partial x} \cdot \epsilon_x$ and $\epsilon_x = x(\xi_i) - x(\text{Target})$. Usually, only a few iterations (less than 20) are required to converge to a good source estimate.
Figure 2.4: Remapping of neighborhoods to resolve discontinuities of the motion over object boundaries. In this example object B slides down with respect to the non-moving object A. a) Shows the object locations and neighborhoods in the reference space, whereas b) shows the object locations and neighborhoods at time $t$ in physical space.
2.5 Results

In the following we present results of the experiments performed, including the verification of the accuracy of the temperature simulation in the static computational reference at an increasing level of complexity of the underlying motion and shape of the sliding boundary as well as studies of the computational performance.

The described methods were implemented in C++ and OpenCL (Stone et al., 2010) utilizing VTK (Schroeder et al., 2006) and ITK (Johnson et al., 2013). The simulation method has been integrated in MeVisLab (Ritter et al., 2011) for sophisticated visualization, support for building the standalone treatment simulation application, and graphical user interface design. The utilized hardware system is a commercially available off-the-shelf consumer notebook with an Intel® Core(TM) i7 CPU @2.5GHz, 16 GB RAM, NVIDIA GeForce GTX 860M with 2GB RAM, Samsung SSD 512GB hard drive.

2.5.1 Verification

For verification purposes we define three artificial motion cases, see Figure 2.5. The motion cases present increasing level of motion complexity ranging from axis-aligned translational motion (Figure 2.5a), over to not axis-aligned diagonal motion (Figure 2.5b), and finally to a rotational motion case (Figure 2.5c) with similar characteristics as the motion that is expected in the human abdomen at the abdominal wall during respiration. These cases are simulated without any heat source solely as diffusion processes from an initial temperature distribution. In the case of Figure 2.5, the initial temperature is a hot 3D cube at 40°C (red) with surrounding 20°C base temperature (blue).

The dashed line marks the location of a motion boundary that may be introduced separating the two parts of the domain. Both sides may be assigned individual motion pattern resulting in discontinuous motion. The motion function in all cases is a sinusoidal pattern in the direction of the specific motion direction (marked by the arrow in the Figure). The size of the domain is 50 mm × 50 mm × 30 mm.

Fundamental solution as reference solution

For the initial condition of a point source (Dirac delta function) the analytic solution for the temperature distribution at some time in the future is given by the fundamental
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Figure 2.5: Motion cases for temperature model verification.

Figure 2.6: Analytic solution on center slice for the temperature distribution at a) 5 s, b) 10 s, c) 15 s, and d) 20 s from an initial Dirac delta distribution.

solution to the heat equation in three variables (Evans, 1998):

\[ T(x, t) = \frac{1}{\sqrt{(4\pi kt)^3}} \exp \left( \frac{-x \cdot x}{4kt} \right) + T_b, \]  

(2.31)

with coefficient \( k = \frac{\kappa}{\rho c_p} \), \( \kappa \) being the thermal conductivity, \( \rho \) being the density, \( c_p \) being the specific heat capacity, \( T_b \) being the base temperature, and \( x \) being the three-dimensional coordinate relative to the source point.

CONVERGENCE ANALYSIS

In the following, to verify the overall temperature model we compute the convergence of the results when refining the sampling of the spatial domain. In case we have an analytic solution we take it as the reference towards which the solution should converge. In case of no analytic solution (discontinuous motion cases), the finest resolution is taken as the reference. To compare the solutions, we compute the mean absolute error (MAE)

\[ \text{MAE}_{dx} = \frac{1}{n} \sum_{i \in \text{grid}} |T^i_{dx} - [T_{GT}]^i_{dx}| \]  

(2.32)
between $T_{GT}$ and the result $T_{dx}$ on a specific grid resolution. The number of nodes in the grid is denoted by $n$. In case of no analytic solution, the reference solution on the specific resolution grid is computed by linearly sampling down $T_{\text{finest}}$ to the coarser grid (denoted here by the $[\cdot]_{dx}$ operator). Afterwards the computation of the $\text{MAE}_{dx}$ is a simple point-wise operation and $n$ denotes the number of nodes on the grid at the specific resolution. The analyzed grid voxel sizes are $dx \in \{3 \text{ mm}, 2 \text{ mm}, 1 \text{ mm}, 0.5 \text{ mm}, 0.25 \text{ mm}\}$.

The rate of convergence $q$ is estimated using

$$q \approx \frac{\log \frac{\text{MAE}_{dx, \text{finer}}}{\text{MAE}_{dx, \text{coarser}}}}{\log \frac{dx_{\text{finer}}}{dx_{\text{coarser}}}}. \quad (2.33)$$

This equation is evaluated for each experiment and for each step of refinement individually.

**Convergence towards analytic solution with space refinement**

To assess the accuracy of the transformed PDE operator and the re-mapping over the boundary between the motion objects, initial temperature maps are diffused over time. To be able to compare to the analytic solution, we construct a diffusion process that is independently of any rigid motion of the domain. Moving the entire scene (object and temperature distribution) with the test motion cases should not change the diffusion process and comparison can be done to the analytic solution. We perform this analysis for two scenarios: a single motion object for the entire domain (no motion boundary), as well as the case of two equally moving objects divided by a boundary over which the diffusion needs to be calculated correctly. The calculations of the operator at the boundary in this case are the same as if the motion was discontinuous in the physical space, cf. Figure 2.4.

Figure 2.7 shows the results of the analysis for increasing simulation duration. In all cases, the solution converges to the analytic solution. Independent of the kind of motion, the three whole domain motion cases (grid-aligned, diagonal, and rotational) show identical error. The cases with boundary (grid-aligned-split, diagonal-split, rotational-split) show additional errors that are introduced by the remapping and interpolations over the boundary. These errors however also reduce with refinement of the grid. The estimated mean convergence rate over all experiments is $q = 2.0748$ with a standard deviation of 0.275. As a result of the discretization using a centered finite difference operator, the expected convergence rate is quadratic ($q = 2$).
Figure 2.7: Convergence towards analytic solution with space refinement for four different simulation duration.
Convergence of discontinuous motion examples with space refinement

The artificial motion cases from Figure 2.5 are now used with motion only on the left part of the domain while keeping the right side of the domain static – thereby producing sliding motion at the boundary. An initial temperature peak (35°C with surrounding 20°C base temperature) centered in the domain is diffused with time. As we cannot give an analytic solution due to the discontinuous boundary in this case, we assess the convergence of the solutions to the solution on the finest level.

Figure 2.8 shows the results of the analysis for increasing simulation duration. All three motion cases converge similarly towards the finest solution (0.25 mm spacing) for all simulation duration. While the expected convergence rate is again quadratic...
(\(q = 2\)), the estimated mean convergence rate over all experiments here is only \(q = 1.358\) with a standard deviation of 0.222. This is still a super-linear convergence rate but the quadratic convergence of the discretization within the moving objects is reduced by errors of the discretization at the discontinuous boundary.

### 2.5.2 Visual assessment on artificial cases

The three artificial discontinuous motion scenarios from Figure 2.5 are now simulated and visualized for consecutive times to allow a visual assessment of the simulation in the reference space.

**Translatory motion along the grid**

The hot-cube temperature distribution is diffused over time during sliding motion of two objects. The left part of the domain translates up-down with a sinusoidal motion while the right part remains static (see Fig. 2.9). We show the temperature distribution in the static computational domain and also transformed to the moving physical world. It is visible that the method successfully resolves the sliding boundary between the two parts of the domain. In the computational domain this is noticeable as discontinuities in the temperature distribution at the sliding boundary. The corresponding temperature distribution in the physical domain is smoother. This is however dependent on motion speed: if the motion is faster than the diffusion process, discontinuities will also develop in the moving world.

**Diagonal motion**

The underlying motion is now the diagonal translational motion pattern not aligned to the computational grid (Fig. 2.10). The temperature distribution in the computational domain shows the characteristic discontinuities introduced by the motion of the domain while the temperature distribution in the moving physical world is smooth and plausible.

**Rotational motion**

The last experiment with artificial motion is based on the rotational motion pattern. The hot cube temperature distribution is diffused over time while the left part of the domain slides up and down along a spherical boundary (Fig. 2.11). Again, sharp discontinuities are evident in the computational temperature distribution (top row). The actual corresponding motion states (bottom row) show smooth distributions.
Figure 2.9: Simulation during motion: Temperature diffusion over a boundary for six time-points during motion of the left half domain. The first time-point visualizes the geometrical setting of the experiment. Temperature maps are given in the reference space (top row) and also mapped to the actual moving space (bottom row). The Figure shows the results for the sliding translatory up-down sine motion.
FIGURE 2.10: Simulation during motion: Temperature diffusion over a boundary for six time-points during motion of the left half domain.

The first time-point visualizes the geometrical setting of the experiment. Temperature maps are given in the reference space (top row) and also mapped to the actual moving space (bottom row).
Figure 2.11: Simulation during motion: Temperature diffusion over a boundary for six time-points during motion of the left half domain. The first time-point visualizes the geometrical setting of the experiment. Temperature maps are given in the reference space (top row) and also mapped to the actual moving space (bottom row). The Figure shows the results for the sliding rotational sine motion.
2.5.3 Computing time

In this section, we assess the performance of the simulation method on our test system. Figure 2.12 summarizes the results of the performance analysis of the heat stencil. We examine the influence of the size of the computational grid and the motion mesh on the run time. Given a time step of 0.1 s a computing time below 100 ms represents grid sizes that can be handled in real time. The upload of motion data to GPU memory is included in the timings. We investigate deformation mesh sizes up to $10^6$ nodes and computational grid sizes up to $120^3$ nodes. All examples finished below 20 ms. Both grid size and motion mesh size influence the performance similarly.

2.6 Discussion

In this part we presented our simulation approach and its efficient GPU-based implementation for abdominal thermal treatments during respiratory motion. Especially, we propose a novel approach to simulate the heating during motion by solving Pennes’ bioheat equation in a computational reference grid. The governing partial differential equation is mathematically transformed from the moving world to the computational reference grid. The key characteristic of the method is that by the transformation of the problem to the reference space, the calculations can be performed without transport of the quantities relative to the grid (no advection). The approach is extended such that it allows for discontinuities, i.e. sliding motions of the objects. Such kind of motion discontinuities occurs at the abdominal wall during respiration:
the inner organs slide along the ribcage during the respiratory cycle.

Using artificial motion examples, we verify that the implementation indeed solves the heat equation and that the solutions converge to the analytic solutions as well as converge with refinement of grid.

We aim for high computational performance of the method to make the method as usable for clinical applications as possible. Therefore we implemented the model using GPU calculations. The heat solver in the computational reference frame shows high performance. All tests finished under 20 ms for motion meshes up to $10^6$ and computational grids up to $120^3$ voxels. These problem sizes are assumed to be very much suited for real-world applications.
Patient-specific numerical FUS simulations

This chapter is in parts based on the paper “An integrated model-based software for FUS in moving abdominal organs (Schwenke et al., 2015) and also the paper “Fast numerical simulation of focused ultrasound treatments during respiratory motion with discontinuous motion boundaries (Schwenke et al., 2017a). The goals in this chapter are two-fold: On the one hand we aim at solving the task of patient-specific simulation of focused ultrasound treatments during motion on a level of quality that is usable for clinical applications. On the other hand we aim at providing these predictions in computing times that are also feasible for the clinical application. For this work, we define this to be in real time, meaning that the simulated time is greater than the required computing time. This performance requirement was the driver for the development of an approximation model for ultrasound propagation.

3.1 Related work

Ultrasound simulation. In modeling FUS treatment, the heat source is proportional to the squared pressure magnitude (Zeng and McGough, 2009):

\[
q(x,t) = \frac{\alpha f}{\rho c} |p(x,t)|^2,
\]

with acoustic absorption coefficient \(\alpha\) [Np/m], density \(\rho\) [kg/m\(^3\)], speed of sound \(c\) [m/s], physical frequency \(f\) [Hz] of the ultrasound transducer and ultrasound pressure \(p\) [Pa]. Thus, for estimating the heat source for the thermal ablation
simulation, the pressure distribution in the medium needs to be estimated. This involves two steps: first, given the spatially heterogeneous tissue medium, the transducer orientation and target position, the focusing parameters (driving signals for the transducer elements) need to be estimated; then, using the driving signals, the propagation of the resulting pressure wave through the medium is simulated. To avoid heating of the ribs, we implemented a fast ray-casting-based focusing approach similar to the method described by Quesson et al. 2010 to shut off elements that are shadowed by ribs in the beam path.

For the simulation of ultrasound propagation, several methods have been proposed in literature. One of the most efficient simulation approaches is the linear angular spectrum approach (Goodman, 1996; Zeng and McGough, 2009). The ultrasound propagation therein is simulated in a slice-by-slice sweep through the computational volume. The pressure distribution is propagated from one slice to the next starting at the ultrasound transducer. The hybrid angular spectrum method (Vyas and Christensen, 2012) is an extension of this approach to incorporate heterogeneous tissue properties. For nonlinear ultrasound propagation simulation, the KZK equation (Bakhvalov et al., 1987) as an extension of Burgers’ equation is widely applied. Commercial general purpose simulation packages can be utilized for flexible definition and solution of the models (see e.g. (Scott et al., 2014)). The application area of these packages is however restricted due to insufficient performance for real-time applications. Furthermore, several freely available ultrasound simulation tools have been developed (HIFU simulator (Soneson, 2009), Field II (Jensen, 1996), k-wave (Treeby et al., 2012)). GPU parallelization has been applied to allow efficient treatment planning in the static scenario (Georgii et al., 2011). The few attempts addressing the numerical ultrasound simulation during motion have been contributed by the author of the present work and Georgii et al. 2014. Using the GPGPU implementation of the angular spectrum method (Georgii et al., 2011) reduces the computation time of a single ultrasound field to about two seconds on our test system (consumer notebook with an Intel Core(TM) i7 dual core CPU @2.5GHz, 16 GB RAM, NVIDIA GeForce GTX 860M with 2GB RAM, Samsung SSD 512GB hard drive). However, in case of a continuously changing domain and beam steering to follow a moving target, simulating FUS requires several ultrasound field simulations per second. For real-time capable simulations, the ultrasound pressure field computations thereby become the bottleneck.
Numerical simulation for therapy planning. Numerical thermal therapy simulations are applied in minimally-invasive and non-invasive therapies: e.g. prostate thermal therapy (Bellil et al., 2015), radio-frequency ablation (Villard et al., 2005; Kok et al., 2013; Kröger et al., 2010; Berjano, 2006; Altrogge et al., 2006), microwave ablation (Prakash, 2010), laser-induced thermal therapy (Feng and Fuentes, 2011), and focused ultrasound (Georgii et al., 2011). Common goals in these approaches are to utilize the numerical simulations for either treatment planning or optimizing treatment parameters. Treatment planning can be useful in multiple stages of preparing an intervention: firstly, virtually planning the intervention can support the decision making process whether a patient is suited for the specific intervention. Secondly, treatment planning can be an actual preparation of the intervention for a specific patient. In this planning stage, e.g. strategic decisions for the actual treatment can be made (access paths, identification of risk structures, specifying dose parameters). Furthermore, the tools used for the planning can be utilized also to train clinical personnel. Software support can be a means to improve the planning: for example in radiotherapy, numerical simulations are used to predict the target dose coverage resulting from different plans (Gintz et al., 2016). This can be used in a forward planning fashion, where the clinician alters the plan and assesses the predicted outcome, or in an inverse planning fashion, where an optimization method is used to find the best plan covering a target volume (Gintz et al., 2016). Surgical interventions can be prepared using predictive models. For example in liver resection planning, models can predict the remaining liver functional tissue associated to a certain cut through the organ (Lang et al., 2007; Mise et al., 2013). This helps in finding a suitable resection plan.

In-therapy use of numerical models. Numerical modeling and simulation of the treatment effects of minimal- and non-invasive therapies can furthermore be used during therapy execution. For example the performance limits of image-based monitoring can be pushed by fusing the model predictions with the measured data. Model-predictive filtering approaches like (Todd et al., 2010) and (Roujol et al., 2012) show promising ways to improve current therapy monitoring. Both approaches only include a temperature model. The use of a full FUS treatment model including an ultrasound model has not yet been proposed to date. This is most likely due to performance constraints imposed by such use-cases and furthermore the necessary validation efforts associated with the clinical applicability. Model predictions can furthermore in principle be used in automated control loops to achieve more robust
control of the treatment execution (Goharrizi et al., 2014).

3.2 Contribution

An integrated model for FUS in moving organs is proposed that combines the temperature model from the previous chapter with an ultrasound model, a thermal damage model, and a predictive liver motion model (Samei et al., 2012). Patient-specific anatomical modeling is done based on CT-images.

To the end of ultrasound modeling, we here propose an alternative approach to utilize the angular spectrum method originally solely suited for homogeneous media for simulating the propagation through a heterogeneous medium. In contrast to the hybrid angular spectrum (HAS) method (Vyas and Christensen, 2012) in which a spatial correction step is introduced that accounts for heterogeneous medium parameters, we here already account for the heterogeneity in the frequency domain. This results in the method being able to model the interference patterns which the spatial correction step of the hybrid angular spectrum method is not capable of. A detailed discussion of the approximations of the hybrid angular spectrum method is performed to show what kind of error is introduced. In our novel method, the accounting for heterogeneity in the frequency domain is done by propagating multiple angular spectra – hence we call it multiple angular spectra (MAS) method. Section 3.3.2 provides more details. The implementation of the MAS method bases on the GPU implementation of the hybrid angular spectrum method (Georgii et al., 2011).

The original publication of the HAS method (Vyas and Christensen, 2012) presents only a single validation case for a heterogeneous domain. The comparison therein is also performed against a FDTD method, but before comparing the simulated pressure fields, the fields were normalized to the maximum pressure value without giving any motivation. Therefore, to strengthen the trust in the predictions of the angular spectrum method, we compare both methods, HAS and MAS, to a pseudo-spectral finite-difference time-domain (FDTD) method (Treeby et al., 2012) as a reference model. The pseudo-spectral FDTD method models acoustic wave propagation accounting for acoustic heterogeneity, power law absorption, and nonlinear effects. The computing demands of the method are rather intense, but we can construct 2D validation cases for which it is feasible in our case.

Furthermore, to remedy the computational demands of the ultrasound simulations in the moving domain in real-time applications, we develop an approximation
model for the ultrasound simulation (see Section 3.3.3). For the numerous 3D cases in the simulation studies of the integrated FUS model using the pseudo-spectral FDTD model as reference is too elaborate. Instead, in these cases we choose the MAS method as the reference model.

We give two exemplary clinically motivated application use-cases of the FUS model. A treatment planning application prototype allows a clinician to interactively plan a treatment during respiratory motion guided by feedback from the numerical simulation. In a second application scenario we use the FUS model to automatically improve the placement of the transducer to treat a certain target location within the liver of a specific patient.

3.3 Methods

3.3.1 An integrated model for FUS in moving organs

The numerical temperature simulation described in Chapter 2 in this chapter will be integrated with an ultrasound propagation model, a tissue damage model, a physiological model, and a predictive abdominal motion model to enable the prediction of abdominal FUS therapy outcomes.

Predictive motion model

A liver motion model (Samei et al., 2012) was included to obtain realistic motion data. The motion model predicts the motion of 290 points within the right liver lobe. The model is derived from 4D-MRI images of the liver of multiple individuals. The 4D-MRI images are constructed based on an interleaved sequence of navigator and measurement slice scans and subsequent sorting according to respiratory states. To generate motion information for the entire domain we interpolate and extrapolate the motion model data using an inverse-distance-based interpolation (Shepard, 1968) approach for the inner organs. The ribcage is kept static in our experiment resulting in realistic sliding motion along the abdominal wall, cf. also Figure 1.5 c).

Integrated FUS model

Figure 3.1 visualizes the resulting integrated FUS model with the interconnections of the models. Motion predictions from the motion model are fed into the ultrasound propagation and the temperature model. The resulting ultrasound pressure distribution is fed into the temperature model as a heat source in the moving space. Based
on the temperature distribution over time, the tissue damage model predicts the local state of the tissue. The result is fed into a physiological model that describes the interplay between the FUS treatment and the patient’s organ physiology. It can adapt model parameter values based on the tissue state. The physiological model adjusts the ultrasound absorption, the speed of sound, and the local tissue perfusion rate based on a dependency on the grade of tissue damage. For example this can be used to model the stop of local tissue perfusion due to coagulation of the tissue and vascular structures. The parameter values are fed back into the ultrasound and temperature model.

**Parameterization and anatomical modeling**

The model parameterization is done patient-individually, mostly for the anatomical part, by analyzing medical image data. The model parameter values (e.g. thermal diffusivity, acoustic absorption) are taken from literature. The parameter values can be estimated by model calibration approaches given example sonications (for example low-power test sonications that are routinely being performed before the treatment). Section 3.4.4 will later address this, here we focus on the anatomical modeling.

The patient anatomy is one of the main influencing factors for the treatability of targets within the liver and we aim at providing an automatic method to generate anatomy models to capture some of the variability of anatomies among a larger population of patients. To construct the anatomical models, we here use a method
based on x-ray computed tomography (CT) images of patients. In principal, MR images can also be used for deriving anatomical models, but CT images bear the great advantage of the image values directly corresponding to tissue types (Hounsfield unit). This considerably simplifies the automatic processing. Table 3.1 lists the Hounsfield value intervals for the most important tissue types for the anatomical modeling. Figure 3.2 visualizes ten of the resulting anatomical models. In the following, we briefly explain how each anatomical structure is detected. The segmentation methods used here are not validated against ground truth annotations by medical experts. For the use of the methods for treating an actual patient a thorough validation would be crucial. Here, the intended use is less critical: the methods are used solely for the task of deriving plausible example patient anatomies. The level of plausibility was confirmed solely by visual inspection and the derived models are visualized in Figure 3.2 for the reader.

A wide range of medical image segmentation methods is available in literature. Usually there are many suitable approaches to solve a specific segmentation task. Available methods range from manual to semi-automatic and automatic methods. Often with automatic methods, a manual correction step is necessary which is basically a verification stage in which a clinical expert inspects the segmentation results and the image data and has suitable tools at hand to interactively change the segmentation. Very basic segmentation methods are for example intensity thresholding, region growing, and watershed algorithms (Nosrati and Hamarneh, 2016). These methods work solely on the intensity values of the image and thereby incorporating prior knowledge, like for example knowledge about the typical shape of the object, is difficult. Optimization-based image segmentation allow for incorporation of such information (Nosrati and Hamarneh, 2016). These approaches formulate the identification of the object within the image as an optimization problem in which the goal function consists of several terms representing different constraints. An optimizer then is used to identify the best segmentation being a good compromise of the different terms. Different weights can be assigned to each term to control the outcome. Approaches include discrete graph cut methods, for example max-flow/min-cut algorithms or graph partitioning methods, as well as continuous formulations based on partial differential equations and calculus of variations (Nosrati and Hamarneh, 2016). Prior knowledge about the shape of the object can be incorporated by penalizing deviations from observed shapes of similar objects as well as statistical shape derived from a multitude of observations. Furthermore, also machine learning can be applied to solve segmentation problems. In this domain, one can separate approaches into
### Table 3.1: Hounsfield unit intervals of the most important tissue types for deriving the anatomical models.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Hounsfield interval/values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>-1000 HU</td>
</tr>
<tr>
<td>Water</td>
<td>0 HU</td>
</tr>
<tr>
<td>Fat</td>
<td>-120 HU to -90 HU</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>100 HU to 300 HU</td>
</tr>
<tr>
<td>Bone</td>
<td>200 HU to 3000 HU</td>
</tr>
</tbody>
</table>

classical approaches in which the developing expert tries to extract features from the images and only afterwards machine learning is applied based on the derived features. More advanced approaches use machine learning directly on the images and let the machine learn discriminant features itself. The most successful type of such kind are convolutional neural networks which are increasingly being used successfully for the task of medical image analysis (Litjens et al., 2017). Lastly, while many of the methods are originally designed for segmentation of a single object, often multiple objects need to be segmented in a given patient. The individual objects can either be segmented sequentially or can be identified simultaneously which may lead to more robust results (Nosrati and Hamarneh, 2016).

Given this wide range of existing methods, the methods used here and are described below are just a set of the simplest methods that sufficiently work for the intended use case of deriving plausible anatomical models. Determining these anatomical models is a multi-object segmentation problem which is here solved in a sequential approach in the order of description below. The first structure to identify is the patient body.

**BODY.** The entire body volume of the patient is segmented by a region growing from an outside voxel with an inclusion interval from negative infinity to -1000.

**LIVER.** The liver is our main target organ and we want to discriminate between liver and other soft tissue with similar Hounsfield values. In our database of CT cases a liver segmentation was already available and was directly used. Generally, automatic CT-based liver segmentation remains a challenging task in medical image processing, even though nowadays methods begin to be available that can provide sufficient accuracy levels in some cases.
Figure 3.2: Abdominal anatomy models derived from CT images of ten patients. For each case we give a 3D rendering as well as a 2D slice showing the different structures: bone (white), air-filled (black), liver (dark red), liver vessels (darkest red), other soft-tissue (light red), and fatty tissue (yellow). The abdominal wall estimate is marked by a green contour in the 2D images.
Abdominal wall. The abdominal wall separating the inner organs from the ribcage is challenging to detect directly based on the images. To estimate its location, we perform geometric operations from the other structures: we shrink the segmentation of the body surface to such extent that it is as small as possible while still containing the entire liver volume. The resulting mask divides the liver and lungs from the ribcage. It still contains the spine which we remove in another step. Based on an existing spine detection we push the contour of the segmentation mask towards the center such that the spine is completely outside the mask.

Bones. The hard part of bones is detected using a threshold filter for the Hounsfield interval of 250 HU to 3000 HU. To prevent false positives within the liver, the liver mask is used to remove any bone classification within the organ. The sternum and cartilage of the ribs connecting them to the sternum have lower Hounsfield values in the range of soft tissue and are segmented in an additional step. Starting from the hard bones mask a region growing is performed with an inclusion interval of 100 HU to 300 HU. This includes the softer parts of the ribcage but also includes inner organs like the kidneys and the heart. To remove these inner organs, we use the abdominal wall segmentation and remove all bone classifications that are inside the mask.

Fat. Fat is detected using a simple threshold filter for the Hounsfield interval of -120 HU to -90 HU and is constrained to be within the body mask.

Liver vessels. The vascular system of the liver is computed by image filters detecting tubular structures (Frangi et al., 1998). The filters are used at multiple resolutions to capture different vessel sizes and the results are merged afterwards. The analysis is solely performed within the liver mask.

The individual structures are then merged into a combined label image, see Figure 3.2. The resulting patient models can then directly be used to parameterize the FUS model.

3.3.2 Ultrasound modelling: A novel angular spectrum method for heterogeneous media

To the end of patient-specific focused ultrasound therapy simulation, we need to provide the integrated FUS model from the previous section with an ultrasound
propagation model. The model needs to be able to account for the medium heterogeneity that is the result of different tissue types of anatomical structures and bone structures. The acoustic parameter values are spatially varying which influences the wave propagation.

The angular spectrum approach (Zeng and McGough, 2009) is a very efficient approach for the simulation of wave propagation through a medium, yet it is restricted to homogeneous media with constant parameter values. The hybrid angular spectrum method (Vyas and Christensen, 2012) was designed to extend the angular spectrum approach to heterogeneous media. The method is similarly efficient to the angular spectrum approach, leading to its wide use and several medical applications (de Greef et al., 2015; Dillon et al., 2015; Farrer et al., 2016; Vyas et al., 2014). Yet to the authors’ knowledge, to date no discussion of the errors of the method has been performed and such medical applications should take the errors into account.

As we need for a discussion of the errors a precise understanding of the method, we in the following give all necessary details. We will see that the approximations that the hybrid angular spectrum method introduces impose severe limitations of the method.

As a consequence, we then propose a new method for extending the angular spectrum approach to allow the simulation of propagation of ultrasonic pressure waves through heterogeneous media.

Angular spectrum approach

The angular spectrum method (Goodman, 1996; Zeng and McGough, 2009) allows the simulation of wave propagation in a predominant direction through a homogeneous medium, i.e. constant medium parameter values for the entire volume. The method requires as input an initial pressure distribution on the first slice. Several methods are available to compute this initial pressure distribution: the Rayleigh-Sommerfeld diffraction integral (Goodman, 1996) can be solved for all transducer elements that produce the wave (Zeng and McGough, 2009) leading to quadratic computational effort with respect to the number of elements. A more efficient approach is the Fast Nearfield method (McGough, 2004; Chen and McGough, 2008).

The angular spectrum method afterwards can be used to compute the change of the wave due to the propagation through a medium. From the initial pressure profile on the first slice, the propagation is computed slice by slice sweeping through the volume. To this end, the pressure distribution \( p_n(x, y) \) is resolved into a spectrum of
plane wave components traveling in different directions by the use of a fast Fourier transform (FFT):

\[ P_n(k_x, k_y) = \text{FFT}\{p_n(x, y)\}, \]

in which the subscript \( n \) denotes the slice index and \( k_x \) and \( k_y \) are the transverse wavenumbers \( k_x^2 + k_y^2 + k_z^2 = k^2 \) with \( k = \frac{2\pi}{\lambda} = \frac{\omega}{c} \) being the wavenumber of the wave. Spatial coordinates are denoted by \( x \) for left to right, and \( y \) for top to bottom, while the \( z \)-axis is orthogonal to the slices and points from the first slice through the medium. The propagation angles, \( \alpha \) around \( y \)-axis and \( \beta \) around \( x \)-axis, associated to each plane wave relate to the transverse wavenumbers by \( \tan \alpha = \frac{k_x}{k_z} \) and \( \tan \beta = \frac{k_y}{k_z} \).

Due to the individual propagation angles of the plane waves, each plane wave experiences a different phase change while propagating through the slice which can be expressed using the spectral propagator according to (Zeng and McGough, 2009)

\[ H_p(k_x, k_y, \Delta z) = \begin{cases} 
 e^{-j\Delta z \sqrt{k^2 - k_x^2 - k_y^2}} & \text{for } k_x^2 + k_y^2 \leq k^2 \\
 e^{-\alpha k \Delta z / \sqrt{k^2 - k_x^2 - k_y^2}} & \text{for } k_x^2 + k_y^2 > k^2.
\end{cases} \]  

(3.3)

Furthermore the attenuation of the plane waves can be incorporated also in the spatial-frequency domain according to (Zeng and McGough, 2009):

\[ S(k_x, k_y, \Delta z) = e^{-\alpha k \Delta z / \sqrt{k^2 - k_x^2 - k_y^2}} \]  

(3.4)

Thus, the spectrum after the propagation through the slice \( n \) follows as

\[ P_n(k_x, k_y) = S(k_x, k_y, \Delta z) \cdot H_p(k_x, k_y, \Delta z) \cdot P_{n-1}(k_x, k_y), \]

(3.5)

and the resulting pressure distribution can be computed using the inverse Fourier transform

\[ p_n(x, y) = \text{FFT}^{-1}\{P_n(k_x, k_y)\}. \]  

(3.6)
Algorithm Angular Spectrum Method

1: procedure AngularSpectrumPropagate($p_n(x,y)$ at $z=0$, $c$, $\alpha$)
2:   $p = \text{createDomain(sizeX, sizeY, sizeZ)}$
3:   propagator = createPropagator($c$) \Comment{acc. to Eq. (3.3)}
4:   attenuator = createAttenuator($\alpha$) \Comment{acc. to Eq. (3.4)}
5:   fillSlice(0, $p_{in}$, $p$)
6:   for $z = 0$, $z < \text{numSlices-1}$, $z += 1$ do
7:     planeWaveSpectrumZ = $\text{FFT}(p_{in}(x,y,z))$
8:     planeWaveSpectrumNextZ = elementWiseMultiply(planeWaveSpectrumZ, propagator)
9:     planeWaveSpectrumNextZ = elementWiseMultiply(planeWaveSpectrumNextZ, attenuator)
10:    pressureNextZ = $\text{FFT}^{-1}(\text{planeWaveSpectrumNextZ})$
11:    fillSlice($z+1$, pressureNextZ, $p$)
12:  end for
13: return $p$
14: end procedure

Subroutine:

15: procedure fillSlice(slice, pressureSlice, outVolume)
16:   for voxel in slice do
17:     outVolume(voxel) = pressureSlice(voxel.x, voxel.y)
18:   end for
19: end procedure

Hybrid angular spectrum approach

The hybrid angular spectrum method (Vyas and Christensen, 2012) tries to extend the very efficient angular spectrum approach to heterogeneous media. The motivation for the approach starts in the space domain. Each plane-wave component can be individually propagated to the next slice ($n$) at some location ($x, y$) also in the space domain by (Vyas and Christensen, 2012)

\[ p_n(x, y) = p_{n-1}(x, y) \cdot t_n(x, y), \quad (3.7) \]

with the transmission function

\[ t_n(x, y) = e^{j \frac{2\pi f}{c_n(x,y)}} r'(k_x, k_y) - \alpha_n(x, y) r(k_x, k_y), \quad (3.8) \]

in which $c_n(x, y)$ is the space-dependent speed of sound, and $\alpha_n(x, y)$ is the space-dependent pressure attenuation coefficient. The traveling distance between the two slices for the plane wave traveling in direction $k$ is $r = \frac{\Delta z k}{\sqrt{k_x^2 + k_y^2}}$ and is used for the attenuation computation. To compute the phase change, the effective path length $r' = \Delta z^2 / r$ is used, see Figure 3.3 for a schematic.

Directly using Equation (3.7) is computationally demanding as it requires for each point of the slice the evaluation of the equation for all plane-wave components.
CHAPTER 3. PATIENT-SPECIFIC NUMERICAL FUS SIMULATIONS

Figure 3.3: A plane wave (yellow lines denote equal wave states) propagates through a slice of voxels. The traveling distance \( r \) and effective path length \( r' \) are depicted. The phase change is computed using \( r' \), the attenuation using \( r \).

To reduce computational efforts, the hybrid angular spectrum method introduces approximations to solve Equation (3.8) as described in the following. The phase shift part of the transmission function is split into two terms

\[
e^{j \frac{2\pi f}{c_n(x, y)} r'(k_x, k_y)} = e^{j \frac{2\pi f}{c_n(x, y) - c_{n\text{-average}}} r'(k_x, k_y)} e^{j \frac{2\pi f}{c_n(x, y) - c_{n\text{-average}}} r'_{\text{average}}(k_x, k_y)} \quad (3.9)
\]

in which the first phase shift term is space-independent. The second term is space-dependent and corrects the phase shift to match the locally deviation of the speed of sound from the computed average. This is equivalent to Equation (3.8) and does not yet introduce any error if used individually for each plane wave.

Due to its space independence, the first term can be evaluated efficiently and accurately in the frequency domain with the angular spectrum approach treating each plane wave component individually: let \( p_{n-1} \) denote the pressure on the previous slice, the standard angular spectrum approach can be applied to propagate the pressure distribution through the slice

\[
P'_{n-1} = \{H_p(\cdots, \Delta z, c_{n\text{-average}}) \cdot \text{FFT}\{p_{n-1}\}\}, \quad (3.10)
\]

\( P'_{n-1} \) being the plane-wave spectrum after the propagation. The speed of sound

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\(c_{n\text{-average}}\) used for the propagation in the spatial frequency domain is chosen as the averaged speed of sound weighted with the pressure magnitude:

\[
c_{n\text{-average}} = \frac{\int |p(x, y, z)|c_n(x, y)dx \, dy}{\int |p(x, y, z)|dx \, dy}. \tag{3.11}
\]

The pressure in the spatial domain can then, as in the original angular spectrum method, be computed by

\[
p_{n-1}'(x, y) = \text{FFT}^{-1}\{P_{n-1}'(k_x, k_y)\}. \tag{3.12}
\]

To accurately evaluate the second term in Equation (3.9) would now still require a loop over the full set of plane waves for each location \((x, y)\)

\[
p_n(x, y) = \sum_{k_y} \sum_{k_x} P_{n-1}'(k_x, k_y) \cdot e^{j \frac{2\pi f}{c_n(x,y)-c_{n\text{-average}}} r'(k_x, k_y)}. \tag{3.13}
\]

This would correct the phase shift locally for each plane waves traveling in individual directions. However, this being too elaborate for the practical implementation, to reduce efforts, the HAS method now approximates Equation (3.13) using an averaged propagation direction \(r'_{n\text{-average}}\). It does not treat the plane-waves individually but shifts the phase of the resulting sum of plane waves:

\[
p_n(x, y) = \sum_{k_y} \sum_{k_x} P_{n-1}'(k_x, k_y) \cdot e^{j \frac{2\pi f}{c_n(x,y)-c_{n\text{-average}}} r'_{n\text{-average}}} \cdot e^{-\alpha_n(x,y)r_{n\text{-average}}}. \tag{3.14}
\]

\[
\approx p_{n-1}'(x, y) \cdot e^{j \frac{2\pi f}{c_n(x,y)-c_{n\text{-average}}} r'_{n\text{-average}}}. \tag{3.15}
\]

To minimize the introduced error, the speed of sound used for the propagation in the spatial frequency domain needs to be as close to the correct local speed of sound value, hence the use of the average speed of sound in Equation (3.9).

Adding attenuation of the pressure to Equation (3.15), the spatial domain step in the hybrid angular spectrum method is

\[
P_{n\text{-attenuated}}(x, y) = p_n(x, y) \cdot e^{-\alpha_n(x,y)r_{n\text{-average}}} \tag{3.16}
\]

\[
= p_{n-1}'(x, y) \cdot e^{j \frac{2\pi f}{c_n(x,y)-c_{n\text{-average}}} r'_{n\text{-average}}} \cdot e^{-\alpha_n(x,y)r_{n\text{-average}}}. \tag{3.17}
\]

with \(r\) and \(r'\) being average weighted by the magnitude of the angular spectrum.

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taken as constants for each plane

\[ r_n^{'} \text{-average} = \frac{\int |P_n(k_x, k_y)| r^{'}(k_x, k_y) \, dk_x dk_y}{\int |P(k_x, k_y)| \, dk_x dk_y}, \quad (3.18) \]

respective

\[ r_n^{'} \text{-average} = \frac{\int |P_n(k_x, k_y)| r(k_x, k_y) \, dk_x dk_y}{\int |P(k_x, k_y)| \, dk_x dk_y}, \quad (3.19) \]

The entire hybrid angular spectrum method follows as:

**Algorithm**  Hybrid Angular Spectrum Method

1: procedure HybridAngularSpectrumPropagate(p in (x,y) at z=0, c_{medium}(x,y,z), \alpha_{medium}(x,y,z))
2: \quad p = createDomain(sizeX,sizeY,sizeZ)
3: \quad fillSlice(0, p_{in}, p)
4: \quad for z = 0, z < numSlices-1, z+=1 do
5: \quad \quad planeWaveSpectrumZ = FFT(p(x,y,z))
6: \quad \quad averageSpeedOfSound = computeWeightedAverage(p, c_{medium}) \quad \triangleright \text{acc. to Eq (3.11)}
7: \quad \quad propagator = createPropagator(averageSpeedOfSound) \quad \triangleright \text{acc. to Eq (3.3)}
8: \quad \quad planeWaveSpectrumNextZ = elementWiseMultiply(planeWaveSpectrumZ, propagator)
9: \quad \quad pressureNextZ = FFT^{-1}(planeWaveSpectrumNextZ)
10: \quad \quad pressureNextZ = spaceDomainAdjust(pressureNextZ) \quad \triangleright \text{acc. to Eq (3.17)}
11: \quad \quad fillSlice(z+1, pressureNextZ, p)
12: \quad end for
13: \quad return p
14: end procedure

**Subroutine:**

15: procedure fillSlice(slice, pressureSlice, outVolume)
16: \quad for voxel in slice do
17: \quad \quad outVolume(voxel) = pressureSlice(voxel.x, voxel.y)
18: \quad end for
19: end procedure

**The novel multiple angular spectra (MAS) approach**

It is very difficult to anticipate or estimate the error for general application cases that is introduced by the approximations of the hybrid angular spectrum approach in Equation (3.15). Not shifting the phase of the plane waves individually but shifting the phase of the resulting sum of plane waves results in the method not being able to correctly predict the interference pattern. Figure 3.4 a) shows an example of the kind of error that is introduced. A focused wave is sent into the domain from below. The wave is focused in such a way that the focus appears at the black cross in a medium with speed of sound \( c = 1500 \text{ m/s} \), see Figure 3.4 a) leftmost image. Using the same pressure for the first slice in a medium with a higher speed of sound of \( c = 2000 \text{ m/s} \) leads to a shift of focus towards the source, see Figure 3.4 a) center image. Using a split domain, left half with \( c = 1500 \text{ m/s} \), right half with
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\[ c = 1500 \text{ m/s} \]
\[ c = 2000 \text{ m/s} \]
\[ c = 1500 \text{ m/s} \]
\[ c = 2000 \text{ m/s} \]

\[ a) \] Results of the hybrid angular spectrum method.

\[ b) \] Results of the novel multiple angular spectra method.

Figure 3.4: Artificial example highlighting the error introduced by the hybrid angular spectrum method. A focused wave is sent into the domain from below. The wave is focused such that the focus appears at the black cross in a medium with \( c = 1500 \text{ m/s} \) (leftmost), moving closer to the source in \( c = 2000 \text{ m/s} \) (center). A split medium (rightmost) should lead to a shift of focus only in the right half of the domain, yet the hybrid angular spectrum method erroneously moves the focus for the entire domain (rightmost a). The multiple angular spectrum method b) successfully moves only the right half of the focus to the expected depth.
\( c = 2000 \text{ m/s} \) should result in a slit of focus – different focus depths for each half of the domain. The pressure waves of one half of the domain surely influence the other half of the domain, but predominantly the foci should be the result of the constructive interference of the waves in their individual half domain. The pressure field computed with the HAS method for the split medium is shown in the rightmost image in Figure 3.4 a). A single focus appears at the same depth for both halves of the medium. The depth of the focus is exactly the mean of both expected focus depths for \( c = 1500 \text{ m/s} \) and \( c = 2000 \text{ m/s} \). The hybrid angular spectrum method is thus not able to correctly predict this example. This suggests that the method should not be used for trans-costal or trans-cranial simulations.

This was the initial motivation to develop another method extending the angular spectrum approach to heterogeneous domains. Figure 3.4 b) shows the results for the novel method that effectively is able to handle the split medium case, see the rightmost image, producing two foci at the expected depths.

The method is detailed in the following. The method does not impose assumptions on the geometry of the media (e.g. layered media) but assumes that the media can be approximated sufficiently well by a finite number of materials. For the applicability of the method to simulate FUS in the human body we think this assumption is tolerable and usually it should be sufficient to discriminate bones \((c \geq 2000 \text{ m/s})\), soft-tissue \((c \approx 1540 \text{ m/s})\), and fatty tissue \((c \approx 1450 \text{ m/s})\). In the case of any pathology in the domain (i.e. a tumor) there might be the necessity to introduce another tissue type.

The approach is conceptually very simple. The main idea is to use the propagation step in the spatial frequency domain for each material individually and merge the results afterwards. We therefore term the approach \textit{multiple-angular-spectra-method} and abbreviate it as the MAS method. It correctly computes the phase changes for all plane waves at all locations. The computational effort increases due to the additional inverse fast Fourier transforms per tissue types. The algorithm is summarized in the following:
Algorithm Multiple Angular Spectra Method

1: procedure \textsc{MultipleAngularSpectraPropagate}(p_{in}(x,y) \text{ at } z=0, \text{ cs (speed of sound per tissue type)},
\text{ alphas (attenuation per tissue type)})
2: \hspace{1em} \text{p} = \text{createDomain(sizeX, sizeY, sizeZ)}
3: \hspace{1em} \text{fillSlice(0, p_{in}, p)}
4: \hspace{1em} \text{for } z = 0, z < \text{numSlices}-1, z+=1 \text{ do}
5: \hspace{2em} \text{planeWaveSpectrumZ} = \text{FFT}(p(x,y,z))
6: \hspace{2em} \text{tissueTypes} = \text{determineTissueTypes(z)}
7: \hspace{2em} \text{for } t \in \text{tissueTypes} \text{ do}
8: \hspace{3em} \text{propagator} = \text{createPropagator(cs(t))} \triangleright \text{acc. to Eq. (3.3)}
9: \hspace{3em} \text{attenuator} = \text{createAttenuator(alphas(t))} \triangleright \text{acc. to Eq. (3.4)}
10: \hspace{3em} \text{planeWaveSpectrumNextZ} = \text{elementWiseMultiply}(\text{planeWaveSpectrumZ}, \text{propagator})
11: \hspace{3em} \text{planeWaveSpectrumNextZ} = \text{elementWiseMultiply}(\text{planeWaveSpectrumNextZ}, \text{attenuator})
12: \hspace{3em} \text{pressureNextZ} = \text{FFT}^{-1}(\text{planeWaveSpectrumNextZ})
13: \hspace{3em} \text{fillSliceForTissueType(z+1, t, pressureNextZ, p)}
14: \hspace{2em} \text{end for}
15: \hspace{1em} \text{end for}
16: \hspace{1em} \text{return p}
17: \text{end procedure}

Subroutines:

18: \text{procedure} \text{determineTissueTypes}(\text{slice})
19: \hspace{1em} \text{foundTissueTypes} = \text{empty}
20: \hspace{1em} \text{for voxel in slice do}
21: \hspace{2em} \text{if voxel.getTissueType()} \text{ not in foundTissueTypes then}
22: \hspace{3em} \text{insert voxel.getTissueType()} \text{ into foundTissueTypes}
23: \hspace{2em} \text{end if}
24: \hspace{1em} \text{end for}
25: \hspace{1em} \text{return foundTissueTypes}
26: \text{end procedure}

27: \text{procedure} \text{fillSliceForTissueType}(\text{slice, tissueType, pressureSlice, outVolume})
28: \hspace{1em} \text{for voxel in slice do}
29: \hspace{2em} \text{if voxel.getTissueType()} \text{ equals tissueType then}
30: \hspace{3em} \text{outVolume(voxel)} = \text{pressureSlice(voxel.x, voxel.y)}
31: \hspace{2em} \text{end if}
32: \hspace{1em} \text{end for}
33: \text{end procedure}

Reflections

To account for reflections of the waves at interfaces, we use the method proposed in (Vyas and Christensen, 2012). During the forward propagation of the wave through the medium, the reflection $R_n(x, y)$ and transmission $T_n(x, y)$ factor are determined locally based on the impedance mismatch between the voxels as

$$R_n(x, y) = \frac{Z_n(x, y) - Z_{n-1}(x, y)}{Z_n(x, y) + Z_{n-1}(x, y)},$$  \hspace{1em} (3.20)
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with $Z = \rho c$ depending on the local density $\rho$ and speed of sound $c$. By conservation of energy the transmission factor results as

$$T_n(x, y) = 1 + R_n(x, y).$$

(3.21)

The direction of wave propagation with respect to medium interfaces is neglected. After the forward propagation, another backpropagation step of the reflective portions is applied starting from a zero pressure distribution at the farthest slice. This approach could in principle be done multiple times to simulate multiple reflections, but in practice already the first reflection is small and thus we compute only a single backpropagation.

The methods are validated against a FDTD method later in Section 3.4.1.

3.3.3 Real-time-capable atlas-based ultrasound simulation approximation

The MAS method proposed in the previous section is already very efficient due to the angular spectrum approach. For some clinical applications of the FUS model, however, it still is too slow. For example, a clinician that plans a therapy guided by predictions of the FUS model will need fast feedback of prediction results. Another clinical use-case of the FUS model would be to support and augment therapy monitoring (e.g. in model-predictive filtering approaches like (Todd et al., 2010) and (Roujol et al., 2012)). This use-case, while being a promising way for improving current therapy monitoring, also imposes even harder computational challenges, as the model needs to be at least real-time capable.

As the ultrasound simulations are the bottleneck in simulations during motion, we need to develop approaches to speed up the models. The goal is to compute a realistic ultrasound-induced heat source several times per second. At the current performance level of personal computers, this can only be achieved using approximation methods.

We here describe an approach based on pre-computing a generic atlas of pressure fields that are adapted to the specific anatomical setting during the fast simulations. Clearly, the reduction in model accuracy will lead to errors in the heat source for the temperature simulations. In validation studies in this chapter, this error will be assessed to judge whether the approximation is useful.

For our atlas-based approximation, we assume that the utilized beam forming algorithm in the real treatment is able to focus the ultrasound pressure through the ribcage as sharply as in homogeneous tissue. As we have seen in Section 1.2.3 on
transcostal focusing, methods exist to solve this task. Following our assumption, we approximate the ultrasound propagation through the heterogeneous patient medium based on a pre-computed ultrasound pressure simulation in a homogeneous medium. The ultrasound fields are pre-computed for different target points in the homogeneous medium and stored in an atlas. Then, the pressure fields from this atlas are altered to emulate the effects of the actual heterogeneous medium on the propagation.

**Building the atlas**

We build an atlas of ultrasound pressure fields for a multitude of focus positions relative to the transducer in a homogeneous medium. The atlas is specific to the transducer geometry and ultrasound frequency. We build the atlas with a regular grid of focal spots with a spacing of 5 mm. For each focal spot target, the angular spectrum ultrasound simulation is performed for a homogeneous volume of $256^3$ voxels of size $0.5 \times 0.5 \times 0.75 \text{mm}^3$ covering a domain of $128 \times 128 \times 192 \text{mm}^3$. The voxel size is chosen dependent on the transducer frequency and fixed for the atlas for a specific transducer. The simulations are performed solely for 1 W acoustic power. The pressure magnitude fields are downsampled to a volume of $128^3$ voxels and stored on the hard drive.

**Utilizing the atlas**

For a given target in transducer coordinates $\mathbf{x}_{\text{target}}$, the pressure field in the atlas for a target $\mathbf{x}_{\text{target-atlas}}$ is determined that is closest to the given target with respect to the Euclidean norm. The corresponding file is loaded from the hard drive. The remaining deviation of focus location is then compensated for by a translation of the atlas pressure field by $\mathbf{x}_{\text{target}} - \mathbf{x}_{\text{target-atlas}}$. The pressure field is then uploaded to the GPU and all following calculations are performed on the GPU for efficiency. An interpolation of multiple nearest pressure fields could be used to reduce the effect of the translational compensation: each of the fields used in the interpolation would need to be translated such that the focus is at $\mathbf{x}_{\text{target}}$ and afterwards a weighted averaging could be performed using the inverse of the distance $\mathbf{x}_{\text{target}} - \mathbf{x}_{\text{target-atlas}}$ as weighting factors. However, this approach is not used here as the fields do not vary largely due to the homogeneity of the medium and the density of pre-computed targets. Thus, to maximize performance, only the closest field is selected as described above and the adaption to heterogeneous medium is performed as follows. First, the acoustic power is adjusted by multiplying the pressure magnitudes
of the atlas field by the square root of the total power. Second, we introduce spatially varying acoustic absorption. We adjust for heterogeneous attenuation using power-law attenuation $p(x + \Delta z) = p(x)e^{-\alpha \Delta z}$. We split the total attenuation by absorption $\alpha_{\text{actual}}(x) = \alpha_{\text{atlas}} + \alpha_{\Delta}(x)$ into a homogeneous component $\alpha_{\text{atlas}}$ and a local deviation $\alpha_{\Delta}(x)$ from the homogeneous absorption. Starting from the transducer plane, we sweep through the volume slice-by-slice adjusting for different local medium parameters and accumulating the deviations: $p(x) = p_{\text{atlas}}(x)e^{-\alpha_{\Delta}\Delta z}$ where $\alpha_{\Delta}$ is accumulated from slice to slice, similar to Equation (3.4) in the angular spectrum method.

As in the abdominal FUS application the shadowing of ribs is very important and a critical factor in the applicability of the therapy for a patient, we also adjust for the ribs in the beam path. The goal is to determine shutoff regions, being regions that cannot reach the target directly because the pressure wave hits bone structures where it is almost completely absorbed. In contrast to the ray-casting-based transcostal focusing method, here, to compute the shutoff parts of the transducer, we sweep back from the target slice to the transducer plane in a slice-by-slice fashion computing a “shadow” map of bone structures. First, the shadow map from the previous slice is propagated to the current slice using the target location position. Second, we determine the bone structures on the current slice from the material image and add them to the shadow map. For each slice, the acoustic pressure magnitude is afterwards adapted: The acoustic pressure in shutoff regions is decreased to 10% of the original pressure magnitude. We do not reduce it to zero, as no perfect reduction of pressure is possible by shutting off transducer elements. To conserve the acoustic energy, the pressure in the active region is increased accordingly by distributing the remaining power. Therewith, the method can approximate the higher deposit of heat to the smaller beam path of the intercostal space. Figure 3.5 shows example results for an abdominal case.

3.4 Results

3.4.1 Angular Spectrum Method Validation

To validate the angular spectrum methods, we compare the models’ predictions to a pseudo-spectral FDTD method that models acoustic wave propagation accounting for acoustic heterogeneity, power law absorption, and can model nonlinear effects and multiple frequencies (Treeby et al., 2012). We chose this model as a reference model because it is publicly available, well-documented and provides evidence based
Figure 3.5: Comparison of the multiple-angular-spectra simulation a) with the atlas-based simulation b) for a human abdomen case. The degeneration of the focus visible in a) introduced by the ribs in the beam path cannot be mimicked by the atlas simulation b). A rendering of the difference volume is shown in c). Note that the largest error is in the side foci while the center focus is approximated well.

Figure 3.6: Ultrasound pressure simulation validation cases. The ultrasound transducer is depicted by the thick black line at the bottom. For each medium type, the speed of sound $c$, the absorption $\alpha$ and the density $\rho$ are denoted.
on experimental validations (Cox et al., 2004; Wang et al., 2012). The computing demands of the method are rather intense, but we can construct 2D validation cases for which it is feasible in our case. Figure 3.6 shows 2D medium cases that we use for validation studies of the angular spectrum methods against the pseudo-spectral FDTD method. In all cases, the domain size is 256 × 256 voxel with a voxel size of 0.39 mm × 0.39 mm. For each of the medium cases, we simulate two different incoming waves: a plane wave and a spherical wave, both at 0.5 MHz driving frequency. Figure 3.7 shows the resulting pressure fields for each case.

All these 2D validation cases are now simulated with the angular spectrum methods. Four algorithmic variants are evaluated: the hybrid angular spectrum method HAS, and the multiple angular spectra method MAS, both also with a single reflection pass HAS-Refl and MAS-Refl. As comparison metric, we compute for each method \( m \) in the above mentioned algorithmic variants the relative root-mean-square-deviation

\[
\frac{\text{RMSD}(p_m, p_{\text{FDTD}})}{\text{max } p_{\text{FDTD}}} = \frac{1}{n} \sum_{i}^{n} \frac{\sqrt{(p^i_m - p^i_{\text{FDTD}})^2}}{\text{max}_{j \in \{1, \ldots, n\}} \| p^j_{\text{FDTD}} \|} \tag{3.22}
\]

with \( n \) being the number of grid voxels.

<table>
<thead>
<tr>
<th>Test case</th>
<th>HAS</th>
<th>HAS-Refl</th>
<th>MAS</th>
<th>MAS-Refl</th>
</tr>
</thead>
<tbody>
<tr>
<td>homogeneous/spherical wave</td>
<td>0.016</td>
<td>0.016</td>
<td>0.016</td>
<td>0.016</td>
</tr>
<tr>
<td>oblique-interface/spherical wave</td>
<td>0.080</td>
<td>0.081</td>
<td>0.072</td>
<td>0.073</td>
</tr>
<tr>
<td>curved-interface/spherical wave</td>
<td>0.069</td>
<td>0.068</td>
<td>0.052</td>
<td>0.050</td>
</tr>
<tr>
<td>obstacles/spherical wave</td>
<td>0.060</td>
<td>0.059</td>
<td>0.036</td>
<td>0.034</td>
</tr>
<tr>
<td>homogeneous/plane wave</td>
<td>0.055</td>
<td>0.055</td>
<td>0.055</td>
<td>0.055</td>
</tr>
<tr>
<td>oblique-interface/plane wave</td>
<td>0.120</td>
<td>0.122</td>
<td>0.114</td>
<td>0.112</td>
</tr>
<tr>
<td>curved-interface/plane wave</td>
<td>0.080</td>
<td>0.080</td>
<td>0.065</td>
<td>0.063</td>
</tr>
<tr>
<td>obstacles/plane wave</td>
<td>0.121</td>
<td>0.122</td>
<td>0.111</td>
<td>0.113</td>
</tr>
</tbody>
</table>

Table 3.2: Comparison of the angular spectrum methods against the FDTD reference solution for the 2D validation cases. The listed values are the relative root-mean-square-deviation \( \frac{\text{RMSD}(p_m, p_{\text{FDTD}})}{\text{max } p_{\text{FDTD}}} \).

Table 3.2 lists the results for all cases. Figure 3.8 and Figure 3.9 visualize the deviation of the fields for all medium cases for spherical and plane wave propagation.

All methods solve the homogeneous medium case for the spherical wave equally well with an deviation of 1.6% from the FDTD result. The exact same values are expected for HAS and MAS as in this case no reflections occur and the MAS method with one medium type equals the HAS method. The plane wave case in the homogeneous medium case shows 5.5% deviation. Looking at the deviation
Figure 3.7: Simulated reference 2D pressure fields for validation as predicted by the pseudo-spectral FDTD method (Treeby et al., 2012). The four medium configurations are shown in the first column (see a), d), g), j)), the plane wave pressure fields in the corresponding medium configuration are shown in the second column (see b), e), h), k)), and the spherical wave pressure fields in the corresponding medium configuration are shown in the third column (see c), f), i), l)). The pressure value ranges in kPa are: b) $[-11.155, 11.051]$, c) $[-21.931, 16.356]$, e) $[-11.019, 11.812]$, f) $[-17.017, 14.310]$, h) $[-18.198, 17.976]$, i) $[-19.645, 19.751]$, k) $[-31.529, 31.475]$, l) $[-24.354, 20.496]$. 

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Figure 3.8: Relative deviation $\frac{\sqrt{\sum_{m=0}^{\infty} p_{n}^{m} - p_{\text{FDTD}}^{m}}}{\max_{j \in \{1, \ldots, n\}} \|p_{\text{FDTD}}^{j}\|}$ from the FDTD simulation (top row) for the propagation of a spherical wave through the four test media (columns) simulated with the different angular spectrum approaches (rows) being HAS, MAS, HAS-Refl, MAS-Refl.
Figure 3.9: Relative deviation $\frac{\sqrt{(p_{im} - p_{FDTD})^2}}{\max_{j \in \{1, \ldots, n\}} \|p_{FDTD}\|}$ from the FDTD simulation (top row) for the propagation of a plane wave through the four test media (columns) simulated with the different angular spectrum approaches (rows) being HAS, MAS, HAS-Refl, MAS-Refl.
fields for this case (Figure 3.9 left column) we see that the error is larger at the boundary of the domain. The perfectly matched layers at the boundary in the FDTD approach lead to imperfect plane wave fronts (see Figure 3.9 top of left column). On the other hand, the wave fronts computed by the angular spectrum methods fade towards the boundary making a comparison difficult. As an overall result from Table 3.2, we see that the MAS method results in smaller deviations in all cases. In the 'oblique-interface/plane wave' and the 'obstacles/planewave' case, all methods show greater deviations than in the other cases. Figure 3.9 (second column) shows large deviations at the right boundary of the domain for the 'oblique-interface/planewave' case.

The added reflection pass does not show a great improvement in any of the cases. This might be due to a small reflection coefficient or may be due to the determination of the reflection part not being done in dependence of propagation direction.

Looking at the case of the spherical wave propagation through the oblique interface medium and the curved interface medium (see Figure 3.8 second and third column, second and third row) it is apparent that the HAS method with and without reflection calculation makes the largest error in the range of the interface. This is the key motivation for using the MAS instead of HAS method: In the HAS method, for each slice, the mean propagation speed is calculated and used for the spectral propagation. In the range of the interface the mean propagation speed is therefore a continuous fade from the speed of sound value in the material below the interface to the speed of sound value of the material above the interface. The MAS method reduces these errors by propagating each part separately. To investigate this further, Figure 3.10 gives pressure profile plots for the HAS-Refl and MAS-Refl method for the spherical wave propagation through the oblique interface medium. In these plots, we can also assess the pressure phase and see that in the range of the interface, the HAS-Refl method is out-of-phase, yet the MAS-Refl method is in-phase with the FDTD pressure profile. For applications of the angular spectrum method to focused ultrasound simulations, the correct phase values are however of utmost importance as these determine the interference pattern of the individual waves. Figure 3.11 and 3.12 give additional pressure profile plots for all test cases for comparison. As a summary it can be concluded that the multiple angular spectra method with reflections is the best of the tested methods. It appears applicable for transcostal simulations as it correctly predicts the phase change through heterogeneous media.
Figure 3.10: Comparison of pressure profiles for the oblique interface medium case with a spherical wave. The profile is read out along the depicted arrow and shown only for the thick part of the arrow in the plot. Note how the HAS-Refl pressure profile runs out of phase compared to the FDTD pressure profile and how this does not happen with the MAS-Refl method.
Figure 3.11: Pressure profiles for the four test cases with spherical wave propagation.
Figure 3.12: Pressure profiles for the four test cases with plane wave propagation.
### 3.4.2 Atlas-based ultrasound approximation

**Accuracy of the atlas-based ultrasound simulation**

Table 3.3 shows the results of an accuracy study of the atlas-based ultrasound simulation. The reference solution that we compare against is computed with the MAS method. As comparison metrics, the root-mean-square deviation (RMSD) is computed for the pressure magnitude fields $\text{RMSD}(p_{\text{atl}}, p_{\text{sim}})$ related to the maximum pressure value of the direct simulation. Furthermore, we compute the RMSD for the resulting heat source terms computed according to Equation (3.1) $\text{RMSD}(Q_{\text{atl}}, Q_{\text{sim}})$.

The accuracy of the atlas-based simulation was assessed for a homogeneous medium and also a heterogeneous medium case of a human abdomen. The simulations were performed for three power levels (10 W, 50 W, 100 W) and 27 focus locations. For all of these 81 simulations, we computed the RMSD values separately. Table 3.3 shows the respective mean, minimum, and maximum value over all simulation runs. The mean RMSD values for pressure field and heat source terms are of similar magnitude. The simulation results in relative errors of around 1% on average in the homogeneous medium, and 2.5% on average in the heterogeneous abdominal case.

Additionally to this, we compare the atlas-based ultrasound approximation to the MAS-method for different anatomical models (100 cases, ten targets within the liver for ten different anatomical models). Given the sonication target position, first an initial transducer positioning is computed by finding the skin point closest to the target and then orienting the transducer using the skin surface normal vector. The transducer is then moved 2 cm away from the skin surface as in the real scenario acoustic coupling needs to be established by a water-filled membrane bag or some similar approach. Figure 3.13 plots the results of this study. We assess the following metrics: the pressure magnitude within a 2 mm vicinity of the target (Figure 3.13 a)), the 95%ile of the pressure magnitude in a slice half-way to the target (Figure 3.13 b)), the active elements ratio of the transducer elements (Figure 3.13 c)), and the 95%ile pressure magnitude in the transducer slice (Figure 3.13 d)). The 95%iles are computed by analyzing all pressure magnitude values in the corresponding slice, sorting them.

<table>
<thead>
<tr>
<th>Medium</th>
<th>$\text{RMSD}(p_{\text{atl}}, p_{\text{sim}})$</th>
<th>$\text{RMSD}(Q_{\text{atl}}, Q_{\text{sim}})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogeneous</td>
<td>1.0e-2 [2.9e-4, 1.3e-2]</td>
<td>1.1e-2 [3.2e-4, 1.4e-2]</td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>2.4e-2 [2.2e-2, 2.7e-2]</td>
<td>2.3e-2 [1.9e-2, 3.1e-2]</td>
</tr>
</tbody>
</table>

Table 3.3: Ultrasound simulation approximation error evaluation.
Figure 3.13: Comparison of atlas-based ultrasound approximation to results computed with the MAS method for 100 cases (ten targets within the liver for ten different anatomical models).
and choosing the entry for which 95% of all values are smaller. We use the 95%iles for the pressure magnitude as this metric is more stable than the maximum and leads to better comparability. The plots relate the simulation results of the atlas-based approximation (y-axis) to the reference simulation with the MAS-method. Ideally, all results should lie on the depicted dashed line of equal values. The pressure at the focus location is slightly underestimated by the atlas-based method in higher pressure cases and overestimated in lower pressure cases. The half-way slice pressure is almost never overestimated. A lot of the cases around $0.4 \cdot 10^6$ Pa are estimated correctly, but several cases do not correlate between both methods. The estimation of the transducer slice pressure (both active elements ratio as well as pressure magnitude) show a wide spread of results and is in all cases underestimated by the atlas-based method. As the transducer slice is not part of the heated body and thus not critical for estimating the temperature within the body we did not try to further improve these results by changing the atlas-based model.

**Performance evaluation**

The atlas-based ultrasound pressure simulation takes on average 47 ms per field computation, including data loading and all post-processing steps to adapt for the heterogeneous medium. Detailed timings can be found in Table 3.4. Most of the computing time is needed on the one hand to load the pressure fields from the hard drive and on the other hand to emulate the element shutoff to compensate for ribs in the beam path. The current version of the atlas is thus capable to approximate about 20 ultrasound pressure fields per second.

**3.4.3 Overall FUS simulation performance analysis**

A short abdominal FUS treatment of 100 s consisting of ten consecutive targets, each active for 10 s, was simulated. We simulate a new ultrasound field every three
heat equation time-steps of 0.1 s using the atlas-based simulation method. Table 3.5 lists the timings of the individual computation steps. The main time is spent on the ultrasound and temperature simulations. As a result of using the GPU for the heat solver and combining it with an atlas-based ultrasound simulation approach, we achieve super real-time performance of FUS treatment simulations (less than 50 s computing time for 100 s of treatment time) on a modern off-the-shelf laptop.

### 3.4.4 Validation against MR thermometry data

To further validate the integrated FUS model, we here compare the simulation to actual measurements of a real sonication. The sonication is performed with the Conformal Bone System 2100 Transducer (InSightec Ltd, Tira Camel, Israel) within a tissue-mimicking gel phantom. During the sonication, MR images are acquired to monitor the temperature within the object. The temporal resolution is 5 s, voxel size is $1.09 \text{ mm} \times 1.09 \text{ mm}$ with a slice thickness of 4 mm. The sonication duration is 16 s with 145 Watt acoustic power.

Several parameters are missing for a direct re-simulation of the sonication: firstly, the experimental setup is known only to a certain degree of accuracy (transducer position and orientation, focus position, exact start of sonication compared to the MR image sequence); and secondly as would be the case in a patient, the acoustic properties of the phantom are here assumed to be unknown (most important parameters are acoustic absorption and thermal conductivity). These parameters need to be estimated prior to a potential comparison. As such, we here assess the model’s general capability to describe the observations only after being calibrated to the measurements.

To determine the open parameter values we implemented a calibration method. First we estimate the MR timing correction to compensate for the unknown exact
start of the sonication. To this end, we simulate the temperature resulting from
the sonication and determine the time of maximum temperature $t_{\text{max-T-Sim}}$ using
an initial set of medium parameter values. The time of maximum temperature
is then also determined for the MR thermometry sequence $t_{\text{max-T-MR}}$. The timing
correction $t_{\text{offset}}$ is then estimated as the difference between these two timings
$t_{\text{offset}} = t_{\text{max-T-MR}} - t_{\text{max-T-Sim}}$. An optimization method afterwards simultaneously estimates
a focus position correction $dx \in \mathbb{R}^3$, as well as the medium parameter values for
acoustic absorption $\alpha \in \mathbb{R}$ and thermal conductivity $\kappa \in \mathbb{R}$ while minimizing the
sum of squared differences between simulation and MR thermometry. The reason for
not including the determination of $t_{\text{offset}}$ in the optimization is that adapting it can
have similar effects as adapting the acoustic absorption: Increasing $t_{\text{offset}}$ increases
the peak temperature in the early time-points of the sequence until sonication end;
a very similar effect can be achieved by increasing the acoustic absorption. The
optimizer therefore may converge to local minima which we prevent by first correcting
the timing and then afterwards only calibrate the acoustic absorption. We use the
Nelder-Mead-simplex optimization method (Nelder and Mead, 1965).

Figure 3.14 illustrates the calibration method. First step is a simulation with
initial parameter values and the determination of the timing correction to compensate
for the unknown exact start of sonication. Afterwards, the optimizer iteratively
adapts the parameter values, simulation is done with the current parameters, and the
similarity of simulation result and MR thermometry is fed back into the optimizer.
This is done until convergence which is determined by a threshold on the improvement
in between iterations. An important step in the calibration is the resampling
of the simulation result to the MR image grid: the MR slice thickness is four times
the simulation voxel size and the focus size normal to propagation direction can be
estimated from the MR images as 5-10 mm. The MR measures the signal within
the entire voxel and thereby averages the temperature within the voxel volume almost over the complete focus size with temperature ranging from almost baseline temperature to maximum temperature. We emulate this and sample the simulation result to the MR grid by averaging the temperature within the voxel volume. Only after this step, we compare the temperature values.

Figure 3.15 compares the simulation results with the MR thermometry for different time points in the sequence. For each time, the temperature maps of the slice containing the focus are shown for both MR thermometry and resampled simulation result. Temperature profile curves are furthermore shown along and across the focus. After calibration, the FUS simulation shows a very good agreement with the measurements over all time-points of the sequence. Figure 3.16 visualizes the convergence of the calibration method. The optimizer maximizes the negative sum of squared differences value (first graph) by adjusting the simulation parameters (other graphs).

To assess the quality of the calibration, we compare the spatio-temporal temperature distributions after the calibration. The resulting temperature difference between simulation and MR thermometry is only evaluated at voxels for which the simulated temperature exceeds 20.5 °C. This is done to assure independence of image size and to not include noise outside the focus area. The mean temperature difference is found to be 0.72 K, the standard deviation is 0.7 K, the 95%ile is 1.67 K, and the maximal difference is 16.16 K. In percentages of the maximal temperature rise found in the MR thermometry (+20.437 K) these metrics are: (mean) 3.51%, (standard deviation) 3.4%, and (maximum) 79%.
Figure 3.15: Comparison of MR thermometry of an actual sonication with the FUS simulation after model calibration. For each time-point (rows) we show column-wise the MR thermometry image, the simulation result, the temperature profile along the focus (1), and the temperature profile across the focus (2).
Figure 3.16: Convergence of the calibration method. The optimizer maximizes the negative sum of squared differences (SSD) value a) by adjusting the acoustic absorption $\alpha$ b), the thermal conductivity $\kappa$ c), and the focus position x- d), y- e), and z-coordinate f). After 150 iterations there is no considerable improvement noticeable.

3.5 Exemplary clinical use case I: Interactive treatment planning

The integrated simulation is incorporated into a prototype treatment planning software. Figure 3.17 shows screenshots of the tool in use. The treatment planning is performed interactively by defining a suitable transducer position and orientation in a planning image as well as targets to cover the specified target volume. Using the FUS simulation the outcome of the planned treatment is predicted taking into account the respiratory motion. The results are then visualized to the user, see Fig. 3.17 a)-c), to allow for manual treatment optimization. The temperature and tissue damage overlays are shown on top of the planning image in the static computational reference to facilitate the assessment for the user. The treatment plan in this example consists of ten consecutive targets that are marked by red squares in the visualizations. No cooling is prescribed in-between the heating of the individual targets leading to a complex temperature distribution. The intercostal space is however considerably heated which could be prevented by introducing cooling phases.
CHAPTER 3. PATIENT-SPECIFIC NUMERICAL FUS SIMULATIONS

Figure 3.17: Simulated liver treatment during respiratory motion. Ten consecutive sonications (marked by red squares) each active for ten seconds without in-between cooling. The transducer is visualized in blue. The evolving simulated temperature and tissue damage is shown in the temperature and damage legend. The temperature color legend is shown.

Temperature legend:
- 37°C
- 43.5°C
- 60°C
3.6 Exemplary clinical use case II: Optimal transducer placement

We here want to assess whether the FUS model can be utilized to help solving one of the challenges the clinician is faced with while treating a patient: finding a suitable transducer placement for treating a specific target. The task is to find a placement to firstly effectively ablate the intended target and secondly to do this efficiently by sparing risk structures, minimizing acoustic energy and sonication duration. This needs to account not only for a single location of the target but for all target positions over the entire respiratory cycle. Solving this manually by inspection of a three-dimensional image in a single respiration state is a very difficult if not practicably unfeasible task and the results will be highly depending on the clinician’s experience and understanding of the respiratory motion as well as the ultrasound propagation. We here want to facilitate this by dedicated computer support.

3.6.1 Optimization approach

The integrated FUS model is combined with an optimization method to try to identify a suitable transducer placement on the patient skin. Given the sonication target position, first an initial transducer positioning is found as described in Section 3.4.2 based on the closest skin point. Starting from the initial transducer orientation, an optimization procedure is performed. The optimizer iteratively changes the transducer position and evaluates whether using the new orientation is superior or inferior to the prior orientation. We use again the Nelder-Mead-simplex optimization method (Nelder and Mead, 1965).

For evaluating the quality of a transducer position, a sonication is simulated that automatically shuts off the transducer as soon as the target is ablated. The first optimization goal (effectively reaching the target) is checked by making sure that the sonication is automatically stopped before a specified maximal duration (30 s in our case). Whenever a transducer position leads to the target not being treated within these 30 s, the position can be disregarded as the target appears not treatable. The second goal from above (efficiency) is captured after assuring treatability by minimizing (!) the ablated volume of tissue. This is somewhat counterintuitive as generally the clinical goal will be to ablate as much target volume as possible with a single sonication. The argument for minimization is the following: Besides the goal for fast treatments, there is also the clinical goal of treating with great spatial specificity and to only treat target tissue and no surrounding structures. Minimizing the ablated volume while assuring target ablation means that while the target is
treated, no other part of the volume is ablated. This can only be the result of an efficient access path and a sparing of other anatomical structures in the domain.

For example, assuming a bone structures behind the target, a bad transducer orientation may lead to heating of the bone and an ablation volume that is the sum of the target ablation volume and the bone ablation volume. Changing the transducer orientation however might lead to a reduction of energy deposition at the bone while still allowing the target to be treated. The resulting ablation volume in the best case would be solely the target volume and no part of the bone structure.

The ablation volume as a metric for the optimization also incorporates the favoring of short sonications: the longer the sonication the more energy is deposited into the volume and the more likely it is that somewhere off-target tissue is ablated resulting in a larger ablation volume.

The perfect sonication with respect to the minimization of ablation volume therefore has the following properties:

- it effectively ablates the target point
- it is as short as possible
- it does not ablate any other part of the domain (minimal nearfield-, farfield-, sidelobes-heating).

This results in the maximization of the spatial specificity and control of the treatment.

Consequently, for our optimization approach we chose the objective function that the optimizer shall maximize to be

$$f(x) = \begin{cases} 
\frac{1}{1 + V_{\text{ablated}}(\text{TX}(x))}, & \text{if target was successfully ablated,} \\
0, & \text{otherwise}
\end{cases} \quad (3.23)$$

in which $V_{\text{ablated}}$ denotes the damage volume at end of the sonication. If the target can be treated within the $30 \text{ s}$ duration, $f(x)$ will be maximal ($=1$) if only the target is ablated (minimal $V_{\text{ablated}}$) and will decrease with larger ablation volumes converging to zero ($\lim_{V_{\text{ablated}} \to \infty} f(x) = 0$). If the target cannot be successfully ablated, $f(x)$ will be set to zero being the worst possible value of $f$.

Using the multiple angular spectrum (MAS) as ultrasound simulation method within this optimization appears impractical due to its computing time and the numerous evaluations of the optimizer. Each evaluation is potentially a full thirty seconds sonication with three ultrasound simulations per second of treatment. Using
the atlas-based ultrasound simulation, however, the computational burden becomes manageable.

3.6.2 Evaluation study

The optimization approach is used to find optimal transducer placements for ten sonication target positions in each of the ten patient models (cf. Section 3.3.1) – resulting in 100 test cases in different anatomical situations. The targets are single voxels to be ablated that are evenly distributed over the entire liver.

The first goal of our study is to assess whether the posed problem is solvable by optimization. Figure 3.18 a) gives the results of the study as a scatter plot relating the ablation volume resulting from the initial transducer placement (x-axis) to the ablation volume resulting after optimization (y-axis). The smaller the ablation volume the better the placement as the ultrasound energy is introduced to a smaller volume (remember that we make sure that the target itself is ablated). Just by visual assessment it is clear, that in almost all cases the optimizer successfully improved the placement resulting in a smaller ablation volume outside the target.

As the atlas-based ultrasound simulation is only an approximate model, we need to furthermore assess whether it captures and represents the critical effects for the optimization. To assess this we simulate using the multiple angular spectrum (MAS) method the end-points of the optimization: we simulate the sonication using the initial transducer orientation and furthermore using the orientation determined by the optimization with the atlas-based ultrasound simulation.

If the atlas-based ultrasound simulation predicts all critical effects, the damaged volume computed using the integrated model with the MAS method should also decrease from initial orientation to optimized orientation. Figure 3.18 b) shows the results for the resimulation of the optimization end-points using the MAS method. In case of unsuccessful target ablation within 30 s, the case is marked on the maximum of the axis range. We label four selected cases for reference in the following part of the section. The selection was done manually after inspecting the plots and for each selected case we give 3D visualizations in Figures 3.19-3.22.

The cases were selected due to the following characteristics: EX-1 and EX-4 are cases that show similar improvements after the optimization with the atlas-based ultrasound simulation yet the assessment with the MAS ultrasound simulation shows a great improvement in EX-1 but a worsening for EX-4. In the EX-2 case, the optimization reduces the ablated volume to around 85% and the assessment using
Figure 3.18: Comparison of the ablated volumes resulting from the initial transducer placement and the optimized placements for all of the 100 cases. a) Shows the results for the atlas-based ultrasound simulation model that is used by the optimizer. b) Shows the ablated volumes for the same transducer placements as a) simulated with the more accurate MAS ultrasound simulation method. Note that we plot the cube root of the volume to increase visibility of the result. A '+' mark cases for which the other models’ (i.e. atlas-based for b), MAS for a)) result improves with respect to the ablated volume from initial to optimized placement, the ‘x’ mark cases for which the other model’s results worsens. Selected cases (EX-1 to 4) are labeled here and visualized later in detail in the following parts.
the MAS ultrasound simulation shows also an improvement. EX-3 marks a case, that shows almost no improvement following the optimization and shows a clear worsening in the assessment with the MAS method.

Figure 3.19 visualizes the results of case EX-1. The target was not treatable within 30 seconds with the initial transducer position. After optimization it is treatable efficiently.

Figure 3.20 shows another successfully treated target case (EX-2) that however can not be improved much by the optimizer. Compared to the atlas-based method, the MAS method predicts a slightly larger ablation volume and less improvement, but both methods produce rather comparable results.

Figure 3.21 shows the results for case EX-3. It represents a case that cannot be improved by the optimizer, as it already produces an ideal target heating with the initial transducer position. The simulation using the MAS method however shows considerable more heating in the beam-path and a longer sonication duration. The initial transducer placement results in a smaller damage volume than the damage volume after optimization.

The case in Figure 3.22 (EX-4) shows a good improvement after optimization using the atlas-based simulation. The MAS method however results in an increased damage volume compared to the initial transducer orientation. A visual comparison of the resulting temperature distributions on the other hand shows a good agreement.
Figure 3.19: Visualization of optimization case EX-1. The top row shows that the optimizer in this case successfully changes the transducer orientation from the initial (gray transducer) to improved orientation (yellow transducer) effectively reducing the damage outside the target. The simulation with the MAS method (lower row) also shows an improvement for the transducer orientation.
Figure 3.20: Visualization of optimization case EX-2. This case shows a successfully treated case that however can not be improved much by the optimizer. Compared to the atlas-based method, the MAS method predicts a slightly larger ablation volume in the intercostal space and less improvement, but both methods produce rather comparable results.
Figure 3.21: Visualization of optimization case EX-3. This case shows a case that cannot be improved by the optimizer, as it already produces an ideal target heating with the initial transducer position. The simulation using the MAS method however shows considerable more heating in the beam-path and a longer sonication duration. The initial transducer placement results in a smaller damage volume than the damage volume after optimization.
Figure 3.22: Visualization of optimization case EX-4. This case shows a good improvement after optimization using the atlas-based simulation. The MAS method however results in an increased damage volume compared to the initial transducer orientation. A visual comparison of the resulting temperature distributions on the other hand shows a good agreement.
3.7 Discussion

An integrated FUS model was developed that combines the fast GPU-based temperature solver described in Chapter 2 with ultrasound pressure simulation models, a thermal damage model, and a predictive motion model (Samei et al., 2014). The parameterization of the integrated model is mainly driven by an anatomical model generation that was developed. Starting from a liver segmentation mask, it automatically derives from a CT image a full anatomical model for the simulation, including the identification of skin, bones, air-filled organs, liver vasculature, fat tissue, soft tissue, and the abdominal wall for the motion modeling. The physical tissue parameters are defined on basis of the tissue types and values from literature are used for the simulations. Additionally to this, a model calibration approach is described (cf. Section 3.4.4) that allows to fit the model to measurements and thereby identify the most critical parameter (acoustic absorption, thermal diffusivity).

To the end of simulating the propagation of ultrasound through the heterogeneous tissue medium, a novel angular spectrum method which we call *multiple angular spectra* method was developed. The method shows less errors than the hybrid angular spectrum method in validations against a FDTD ultrasound simulation in 2D cases (cf. Section 3.4.1). The results suggest that the MAS method effectively predicts the propagation through heterogeneous tissue and that the application of the hybrid angular spectrum method has severe limitations.

*Performance.* For the simulation of FUS during motion, the ultrasound simulation is a performance bottleneck. To alleviate this, an atlas-based ultrasound simulation was furthermore developed to generate realistic heat source maps for abdominal FUS treatments. The atlas-based ultrasound simulation requires about 50 ms per pressure field generation including effects of trans-costal propagation and heterogeneous tissue adaption while still showing suitable accuracy (below 2.5% RMSD compared to the direct simulation using the hybrid angular spectrum method). As a result of using the GPU for the heat solver and combining it with an atlas-based ultrasound simulation approach, we achieve super real-time performance of FUS treatment simulations (less than 50 s computing time for 100 s of treatment time) on a modern off-the-shelf laptop. An exemplary comparison of the integrated FUS model prediction to an actual sonication observed by MR thermometry was done showing good spatial and temporal agreement of the model with the real world measurements.

*Applications.* The simulation method is incorporated into a treatment planning demonstration application that allows to simulate real patient cases including
respiratory motion. Interactively, a treatment plan can be designed and adjusted driven by feedback from the model predictions. Furthermore, in combination with an optimization method, the model is utilized to find a suitable transducer placement for a given target to treat. This is done for ten targets within each of ten different anatomical models. The problem appears to be solvable for a general-purpose black-box optimizer and in the majority of cases a better transducer placement is found by the optimizer. The atlas-based ultrasound simulation that is used in the optimization appears to not be fully descriptive of all effects of the abdominal treatments: not in all cases, the MAS-method also shows an improvement from initial transducer placement to optimized transducer placement. For the cluster of cases around cube-root ablation volume interval $[1.0 \text{ mm}, 2.0 \text{ mm}]$ in Figure 3.18 a), we see similar numbers of cases for which the MAS method result also improves as for which it worsens. One reason for this could be that these cases already have a suitable transducer position at the beginning of the optimization. The optimizer in these cases is not able to reduce the ablated volume (the results are plotted close to the line of equivalence). For example, cases that have a direct access-path to the target without bones in the way will already be well-treatable from the initial transducer position being the closest skin point to the target. Other cases show greater improvement from the initial to the optimized orientation (cube-root ablation volume $> 2.0 \text{ mm}$) using the atlas-based optimization, however, when assessing this with the MAS method we see similar numbers of cases improving and degrading. This effectively means that the atlas-based ultrasound simulation fails to predict some of the effects that the MAS method can predict. This also shows in Figure 3.18 b) where we see that the results appear around the threshold line of improvement. To better understand these results, four exemplary cases are shown for a visual assessment. In these cases, we can see promising agreement of the atlas-based method with the MAS method, even though we also see potential for improvements: For example, in case EX-1 the MAS method results in a higher level of subcutaneous heating and in case EX-4 we see that the focus resulting from the MAS method simulation is less sharp than estimated by the atlas-based method. This is in alignment with the results in Figure 3.13 where we also see that the focus pressure (cf. a) is not always estimated correctly by the atlas-based method and we see that in some cases, (cf. b) the pressure on a slice half-way to the transducer is underestimated by the atlas-based method. Future work might utilize learning methods to identify parameters of a more heuristic approximation model based on example pressure fields to capture the remaining ultrasound propagation effects. The main parameters to identify appear
to be the pressure increase in the beam-path as well as the focus change due to shut off of some part of the transducer. It appears likely that these are dependent on the actual geometry of the remaining active parts of the transducer.
4

In-silico first-stage validation of a novel treatment system

The numerical simulation method described in the previous chapters is now encapsulated in a virtual system that is used here to test, validate, and assess the performance of a novel FUS treatment system for moving targets that we developed. The section is closely based on the paper “A Focused Ultrasound Treatment System for Moving Targets (part I): Generic System Design and In-silico First-stage Evaluation” (Schwenke et al., 2017b) published in the Journal of Therapeutic Ultrasound.

4.1 Related work

Motion compensation for FUS. The challenges for FUS treatment systems imposed by respiratory motion have been addressed by several studies in the literature. Table 4.1 lists and categorizes the reported approaches. Experimental treatment control systems have been developed by several research groups and validated in ex-vivo and first animal studies. The motion observation approaches include systems that analyze motion surrogates like respiratory belts or use image-based motion tracking of ultrasound or MR images. The FUS control approaches range from gating approaches to real-time beam steering. The systems target both ablation and hyperthermia applications. The validations have been performed case-based as proof-of-concept validations either ex-vivo or additionally on animals (sheep and pigs). While all these approaches show considerable advancement of the methodologies for
FUS of moving organs, none provides a prospect to approach any clinical trials with their systems. This is most probably due to system certification impediments or difficult patient recruitment.

**System emulation as a driver for development.** Industry uses emulation of hardware systems that can be employed in the software development process, for example in aerospace software development (Ard et al., 2014). Clearly, high priority is assigned to safety and reliability in these applications. To allow for a parallel development of hardware and software, in (Ard et al., 2014), the authors propose simulation-based hardware emulation. Therewith, the hardware and software can be developed iteratively and dependencies are minimized. This also facilitates the application of agile development approaches, in which requirements are not only specified at the beginning of the development but rather evolve during the development and adapt in short cycles. Contrary to the use of numerical simulations for periodic performance assessment (as being done in several industrial applications), in the emulation-based development, simulation is used to provide continuous feedback for collaborative design and development (Ard et al., 2014).

### 4.2 Contribution

In this Chapter we report on our development of a FUS treatment system including motion compensation with the long-term goal of meeting the
### Table 4.1: Approaches to FUS control systems with motion compensation.

The work of Marguet et al. (Marquet et al., 2011) is the only one addressing both motion compensation and transcostal sonication (using binarized apodization).
requirements for a "Class III Medical Product". The system allows to perform
a single-target motion-compensated sonication during respiratory motion. It is
specified and defined in a generic way abstracting from actual hardware components.
A first implementation of the system has been performed with clinically available
hardware, i.e. an MR device (GE Healthcare Systems, Chicago, USA) and FUS
device (Conformal Bone System 2100, InSightec Ltd., Tirat Camel, Israel). To
facilitate the translation of FUS research results to the clinic, the treatment system
is defined open for extensions and the use with hardware devices of other vendors
and may be used as a research platform for FUS experimentation.

A virtual system using numerical FUS simulations is presented and used
for first-stage numerical experimental validation of the treatment system.
The treatment system interacts with the emulation in the same way it does with
real hardware and is provided with realistic data that is influenced by its control
commands. The comprehensive numerical FUS simulation during respiratory motion
(Chapter 2 and 3) is used to predict the treatment effects that would happen in a real
FUS experiment. Using this virtual system, automatic execution of system tests is
possible and system design parameter studies are performed to analyze the efficiency
of the system. One advantage of this approach is that the numerical experiments can
easily be observed in the simulation whereas physical measurements in real-world
experiments are challenging, time-consuming, and require a lot of resources.

4.3 Methods

In the following, we first define the generic treatment system that abstracts from
actual vendor-specific hardware details. While the system allows the use of different
methodological approaches to solve FUS-related tasks (thermometry, focusing), it
abstracts also from any implementation details of these. After the definition of
the generic treatment system, we provide details for our implementation of the
system with a clinically available MR device (GE Healthcare Systems, Chicago,
USA) and a FUS device (Conformal Bone System 2100, InSightec Ltd., Tirat Camel,
Israel). Closing the section, the numerical-simulation-based approach for a first-stage
validation of the system is presented.

4.3.1 Specification and quality assurance approach

A thorough requirements analysis involving a multi-disciplinary team of radiologists
and engineers was performed. According to these stated requirements, a detailed
design specification of a generic system was defined. The details of these specifications go beyond this thesis. We only briefly describe the main components and concepts of the system as needed for the studies. The main hardware devices of the system are the MR imaging device and the therapeutic ultrasound transducer. Both devices have a software representation within the system controlling the devices by using their programming interfaces. The most important software components of the system include the motion compensation system and the temperature calculation component.

**MR IMAGING DEVICE**

The generic specification states that an MR device shall be able to acquire a breath-hold planning image. It does not specify a certain MR sequence. Furthermore, it shall allow the acquisition of a transducer calibration image that can be used by the system to identify the spatial orientation of the FUS transducer with respect to the patient. Most importantly, the MR device shall allow to acquire monitoring images with a high update rate and as little delay as possible. The treatment controller system derives motion observation and temperature information from these images. To simplify the system, we have restricted our developments to MR imaging although, generally, the system could use multiple sources of tracking data (respiratory belt, US tracking, MR tracking) simultaneously. The main intention for our restriction is to avoid the introduction of another hardware system like an MR-compatible diagnostic imaging device in the current development stage. For future versions, we expect a benefit from combining US tracking with MR tracking. We do not plan to use external tracking (like respiratory belts) as external motion is not necessarily correlated with the liver motion (Durichen et al., 2013).

**ULTRASOUND TRANSDUCER SYSTEM**

One of the key requirements defined for the transducer system is the capability to change the focus very fast by electronic steering (phased-array system) in a suitable range to cover the respiratory motion. Two kinds of ultrasound transducer control approaches can be handled by the generic treatment system:

(i) Transducer systems with a real-time interface (fast enough to be controlled with a full parameter set of phases and amplitudes for all individual elements in real time);
(ii) Hardware that works with preset configurations, which need to be uploaded before the actual sonication and that can be activated sufficiently fast during sonication.

Transducers that provide a real-time interface are easier to handle, since a preset-based interface requires pre-computing a suitable set of presets based on an observed motion trajectory. In our system, in case of a multi-baseline thermometry approach, the presets can be determined from the motion information in the baseline image collection. This assumes that the motion states in the baseline collection are representative for the duration of the sonication. Focusing of the ultrasound beam is computed within the system using a ray-based method (Schwenke et al., 2017a). For complex focusing approaches that are not real-time capable, a preset-based approach can be used also with transducer systems with a full real-time API. The treatment system provides the focusing component with deformed anatomical structure maps to allow for trans-costal focusing approaches.

**Motion compensation system**

For motion compensation, the following steps are repeatedly performed during monitoring of the therapy. The computational pipeline starts with the image acquisition: image reconstruction, image send over network, receive and image assemble on the treatment controller. Based on each newly received image, the controller performs a motion analysis: Feature tracking is used to identify local motion of anatomical structures. The features are then related to the reference respiratory state of the planning image to allow for a mapping of planning data to the current motion state. To steer the ultrasound focus to the current target position, a temporal prediction needs to be performed compensating any delays (the delay from image acquisition to the analyzed motion state, the delays introduced by focusing, sending the FUS control parameters to the hardware, and the hardware delay of the FUS device).

Instead of implementing all this in a feed-forward loop, we propose to decouple the observation part of the loop from the control part. Figure 4.2 a) illustrates the problems of a feed-forward approach: The FUS system is controlled with the same update rate as the imaging rate. As a remedy, a motion model is introduced (see Fig. 4.2 b)) to break the forward loop into two concurrently executing loops: i) The motion observation loop starts with each new monitoring image and performs the tracking, relates the data to the reference motion state and feeds the new motion information into the motion model to update its state. ii) The FUS control loop
Figure 4.2: Motion compensation: Decoupling the FUS control from the image update rate. The forward loop a) restricts the FUS control loop to run with the same rate as the monitoring imaging. To decouple both loops, in b), a motion model is introduced allowing for a flexible choice of control update rate.
simultaneously uses the temporal prediction functionality available in the motion model to compute FUS control parameters for a predicted motion state and upload the parameter set to the FUS hardware.

Thereby, the observation and control loops can be executed with different update rates and can be adapted to the actual constraints of the hardware devices with great flexibility. This comes at the cost of slightly higher overall system latency that needs to be compensated by the motion model.

**Temperature calculation component (MR Thermometry)**

The specified interface of the temperature calculation component would allow both multi-baseline and reference-less proton-resonance frequency shift MR thermometry approaches. Currently only the multi-baseline approach is implemented. The temperature calculation component is queried by the treatment system core whether it requires baseline images. Accordingly, the system acquires as many baseline images during respiratory motion as the component requested. Then, in case of a multi-baseline thermometry approach, for each new monitoring image the most similar baseline image is determined based on the magnitude images. Consequently, the temperature is computed using the phase information of the current and baseline image. The resulting temperature image is mapped to the reference respiratory state and can be easily overlaid on the planning image to allow for a static-like monitoring of the therapy. This is intended to facilitate the visual inspection by the physician. For the reference-less thermometry, the only difference is that no baseline collection is acquired and for each new monitoring image, the baseline phase image would need to be estimated from the current image itself. A combination of both approaches would also be possible and would be an implementation detail of the temperature calculation component.

4.3.2 FUS system implementation

We have implemented a fully functional system according to the above-mentioned specification. The system is integrated with MR devices from GE (GE Healthcare Systems, Chicago, USA) and the Conformal Bone System 2100 (CBS) (InSightec Ltd., Tirat Camel, Israel) FUS device. Echo planar imaging (EPI) is used for fast monitoring and the proprietary GE API is used to receive the image data after reconstruction on the scanner side. The monitoring images are used for both motion observation and temperature monitoring. The current system consists of a
multi-baseline thermometry component and a preset-based transducer controller.

4.3.3 Emulating the hardware system and modeling the patient and therapy.

For a first-stage validation of the system, we have replaced the actual hardware by a virtual system. The hardware and the effects of the treatment to the patient are emulated and numerically simulated. To simulate the resulting temperature in the patient’s body, we incorporated the integrated model for FUS during respiratory motion (described in the previous Chapters and in (Schwenke et al., 2017a)). The key advantages of using simulation in the process of system development are flexibility, responsive feedback, automatic execution of tests, and the possibility of checking the system efficiency for a wide range of hardware system characteristics like update rates and motion patterns. A detailed view into the inner state of the numerical experiment allows for a better assessment of the effectiveness of the system. Automated testing and evaluation of new components and its influences are possible through this. Elaborate and time-consuming real-world experiments still need to follow, but only after the emulation-based numerical experiments have shown the effectiveness of the system.

The hardware emulation replaces the two main hardware devices involved: The MR imaging device and the FUS device. The treatment system interacts with the emulated system as with the real hardware unaware of which execution system is actually connected. The emulation needs to produce realistic and meaningful data for the treatment system, e.g. monitoring images showing organ motion in real time. To this end, GPU-based image deformation is used to generate the required monitoring image data. The underlying respiratory motion pattern is replayed from actual recorded patient data. We then use our numerical FUS simulation during respiratory motion to simulate the patient status and to generate the image data for the application. This involves simulating ultrasound propagation and heat diffusion during the deformation and motion of the organs as described in the previous chapters. For the present studies, the FUS simulation does not need to be performed in real time as the treatment system does not change controls based on temperature feedback yet. It solely compensates the motion and executes a sonication for a predefined duration and power. This allows to perform the simulations after the execution of the sonication: during execution of the sonication, all control commands are recorded and after the execution the temperature resulting from the sequence of controls is
CHAPTER 4. IN-SILICO FIRST-STAGE VALIDATION OF A NOVEL TREATMENT SYSTEM

simulated. This approach also minimizes performance side effects on the real-time treatment system.

To test the application we let the following emulation parameters vary:

(i) the monitoring image duration (the rate at which monitoring images are produced);

(ii) the ultrasound shot duration for which the focus is kept static (the motion trajectory is broken down into multiple discrete short static foci called shots);

(iii) the transducer type (preset-based or real-time control);

(iv) and the temporal motion prediction algorithms.

4.3.4 TEMPORAL MOTION PREDICTORS

A motion predictor uses the latest tracking information to predict the target position for a requested time in the future. We here compare two prediction approaches:

(i) a linear-extrapolation-based predictor uses the last two tracking samples and extrapolates by a linear fit into the future;

(ii) a history-based predictor that (assuming periodic motion) uses the latest tracking samples to find the most similar motion state in the history of motion states. The prediction of the target position then is performed by an interpolation in the historical data (the history continuously grows with new motion samples).

Figure 4.3 illustrates the history-based prediction approach. Another motion model that we have investigated which is not yet part of the evaluation is described in (Tanner et al., 2016).

4.3.5 VALIDATION

As mentioned above, quality assurance (QA) is the main effort in translation from research demonstrators to clinical prototypes that may be used in studies. From the two major aspects of efficacy and safety that have to be shown by QA and validation we focus on the efficacy in the following. Further results on experimental validation have been reported in (Mihecin et al., 2017).

We have designed a suite of test scenarios that is based on the emulated system in order to analyze the performance of the treatment system. To quantify the
Figure 4.3: Example of the temporal motion prediction approaches: The linear-extrapolation-based predictor (+) overshoots at the turning point of motion. The history-based predictor (x) better handles this case by finding the best match in the history of samples and uses the historical state for the prediction.

For performance of the system, i.e. its efficacy, we aim at comparing it with static sonications. Thus, we determine an efficiency factor for a certain choice of component implementations and system parameter values. This efficiency factor quantifies how much energy is delivered to a moving target in contrast to a static target, see below.

**Numerical study**

In our in-silico study the system parameters are varied over the following ranges:

- monitoring image duration (100 ms, 200 ms, 300 ms);
- ultrasound shot duration (50 ms, 100 ms, 200 ms, 300 ms);
- monitoring image delay is fixed to 150 ms;

Furthermore, we test different choices for motion tracking, motion prediction, and emulated transducer types:

- a Bayesian tracking (Rothlübbers et al., 2014; De Luca et al., 2015);
- the linear-extrapolation-based and the history-based motion predictors described above;
- emulated real-time and preset-based transducers with varying number of available preset configurations.
To identify the efficiency limit of a system constrained to the above system parameter values, we need to use ground-truth tracking and prediction components. The ground-truth components fulfill the software interface definitions of the tracking and the prediction components and they internally know the underlying test motion at all times. Using these test components the system is provided with exact motion information.

**Ground-truth respiratory motion and generation of test data**

To generate suitable and controllable test data for respiratory motion we acquired EPI image sequences of volunteers (Tanner et al., 2016). Respiratory motion patterns are derived from the EPI images for a feature point in the liver. Figure 4.4 a) shows 40 s of the acquired respiratory motion patterns for some feature points in the liver. The motion patterns $p(t) \in [p_{\text{min}}, p_{\text{max}}]$ are then used as a basis for generating image displacements. Additionally, a scale parameter $s$ is introduced, to scale the motion pattern. The displacement function $d(t) \in \mathbb{R}^3$ at time $t$ is

\[
d(t) = s \, p(t) \, v,
\]

where $v \in \mathbb{R}^3$ is the motion direction unit vector (superior-inferior direction). Using the scale parameter $s \geq 0$, the motion can be reduced to the static case ($s = 0$) or increased to simulate exaggerated motion ($s > 1$).

To generate an EPI magnitude image at some time $t$, we first find the EPI magnitude image that is most similar to the planning image respiratory state. Figure 4.4 b) shows this image in the leftmost column. We then add noise to this image as described below. Using Eq. (4.1) we translate the noisy image to the moving state. Note that in fact we use just a single translation vector $d(t)$ here. Thus no deformation of the liver is modeled. A manual marking of the abdominal wall is used to keep the ribcage static by applying the displacements only to the inner organs that slide along the abdominal wall. Figure 4.4 b) visualizes the generated test data for different respiratory states.

To be able to introduce noise we build a noise model based on the EPI images. To this end, we register 50 images of the EPI sequence to the reference EPI magnitude image. Registration was only applied to the inner organs and was based on a translation model. The differences between the registered images and the reference image were visually inspected to ensure that they contained negligible motion artifacts in the liver. During data generation, these difference images were then sequentially
Figure 4.4: Generation of test-data: The plot in a) shows the motion patterns of tracked liver features derived from EPI image sequences of three different volunteers. For our studies, we use the black-solid motion pattern to generate monitoring images. The images in b) show data for different motion states comparing the real EPI images and the generated data for the same respiratory state. The dashed yellow lines are given to facilitate comparison. The green solid contours show the manually delineated sliding boundary between inner organs and ribcage. The last column shows images highlighting the differences between the EPI and the generated image, normalized with respect to the range of the EPI image.
added to the reference EPI image to simulate appearance changes. Compared to directly using the original sequence with the registration results, this approach has the advantage of full control over the motion (especially image rate and furthermore magnitude to simulate exaggerated motion). Changing the image rate in a replay of the original sequence would also change the speed of motion, which is undesired.

**System efficiency factor**

The peak temperature rise $dT_{\text{static}}$ at the target resulting from a 10 s single-focus application of 200 W ultrasound energy in a non-moving domain will be used as the reference for establishing an efficiency factor for the FUS system validation in the moving case. Clearly, the temperature rise $dT_{\text{moving}}$ during motion will be less or equal to $dT_{\text{static}}$. Based on this, we define the efficiency of the moving system for a specific motion case to be

$$\eta = \frac{dT_{\text{moving}}}{dT_{\text{static}}}, \quad 0\% \leq \eta \leq 100\%. \quad (4.2)$$

For example, if the system has an efficiency of 80% for a certain motion pattern, the resulting temperature rise at the target during motion is equivalent to 80% of the temperature rise introduced in the static case. The value of $\eta$ can also be interpreted as an energy efficiency: A 100 W sonication in the moving case results in the same peak temperature rise as an 80 W sonication in the static case.

We use the peak temperature rise at the planned target position as the metric for our studies as it gives good results only if the focus in the moving case is both as sharp as in the static case and also at the correct location. Assessing an average over a region around the target might underestimate an unintended focus dislocation. The main effects influencing the peak temperature rise at the planned target are firstly the quality of motion compensation (how accurately was the actual target motion followed by the moving focus) and secondly the heat diffusion process (how much heat is conducted from the heated target to the surrounding tissue). The second effect is largely influenced by the choice of tissue parameters. By using a relative metric that compares static and moving case for the exact same tissue parameters, however, we eliminate this dependency to a large extent.
4.4 Results

4.4.1 Maximum efficiency during motion

For a certain choice of ultrasound shot duration and specific type of motion, the maximum efficiency that can be reached is identified using the test-ground-truth tracking and prediction components together with an emulated real-time ultrasound transducer. Figure 4.5 shows the efficiency plots over ultrasound shot duration for different motion scaling. These results give the efficiency limits of the treatment system if provided with perfect motion predictions. For subtle motion \((s = 0.5)\), even with a long ultrasound shot duration of 300 ms, the system efficiency can reach \(\eta = 99\%\) and can increase to almost 100% for decreasing the ultrasound shot duration to 50 ms. In case of normal respiratory motion \((s = 1.0)\), the efficiency can be better than 95% for 300 ms shot duration and can increase to above 99% for 50 ms shot duration. Exaggerated motion \((s = 1.5)\) might be compensated with an efficiency of 90% in case of 300 ms shot duration and can increase to about 99% for 50 ms shot duration. By design, the ground-truth motion prediction is invariant to the imaging update rate which can be seen in Fig. 4.6 below (similar efficiency limits across columns).
Figure 4.6: Efficiency evaluation of the system using temporal motion predictors in combination with the ground-truth tracking data. The rows represent different motion scaling factors while the columns represent different monitoring image duration (inverse of image rate).
4.4.2 Efficiency of temporal motion predictors

We here evaluate the system efficiency when equipped with different motion predictors. The reference again is the achieved temperature rise in the sonication with no motion. Tested motion predictors are the linear-extrapolation-based and the history-based predictor. As stated before, the ultrasound focus is kept static for the shot duration. During this shot, the target moves continuously along a trajectory.

Since we have de-coupled the observation loop from the control loop (cf. Fig. 4.2) we may purely concentrate on the small time window of the shot duration. For the focusing we can choose any point on the predicted trajectory within this time window to achieve the short-time static sonication. However, we also need to take into account that the error of the prediction increases with prediction time.

Theoretically, shooting at the trajectory point in the middle of the shot duration should best approximate the trajectory. But this shooting at the center of the trajectory also increases the prediction time by half of the shot duration. To assess this effect, we evaluate both prediction methods for targeting at the predicted trajectory at i) the beginning and ii) the center of the shot duration time window.

To separate from tracking errors, the test-ground-truth tracking is used providing accurate tracking data to the motion predictors. All experiments are performed using an emulated real-time transducer. We thus can evaluate the error introduced by the different predictors. Figure 4.6 shows the efficiency plots over ultrasound shot duration for different motion amplitude factors (0.0, 0.5, 1.0, 1.5) for different monitoring image durations (100 ms, 200 ms, 300 ms; columns). The first row shows the efficiency for all motion predictors for the static case ($s = 0.0$) to verify that all of them can handle the static case. The other rows show the efficiency over shot duration for scaling factors of $s = 0.5$, $s = 1.0$, and $s = 1.5$. We see that all motion predictors can handle the static case and have near-perfect efficiency. In all cases, the efficiency limit for targeting the trajectory center (dashed limit line) is higher than for targeting the beginning of the trajectory. This, however, represents the limit that is computed using the ground-truth predictor that provides the system with error-free motion predictions. When analyzing the imperfect predictors, firstly it is evident that in almost all numerical experiments, the history-based motion prediction performs better than or equally well as the linear-extrapolation-based predictor. Only in the case of 100 ms image duration and reduced motion ($s = 0.5$), the linear prediction is slightly better. The plots furthermore show decreasing efficiency for increasing monitoring imaging duration (meaning decreasing image update rate).
Table 4.2: Efficiency loss associated with the Bayesian tracking in combination with the motion predictors.

<table>
<thead>
<tr>
<th>motion predictor</th>
<th>mean $\eta_\Delta$</th>
<th>95%ile $\eta_\Delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>linear-extrapolation</td>
<td>6.4 %</td>
<td>12.9 %</td>
</tr>
<tr>
<td>history-based</td>
<td>3.3 %</td>
<td>7.9 %</td>
</tr>
<tr>
<td>overall</td>
<td>4.9 %</td>
<td>10.8 %</td>
</tr>
</tbody>
</table>

Sources of this error are the greater temporal prediction horizon and the associated greater prediction error, and also the inferior temporal sampling of the motion. The history-based predictor shows better efficiency and less dependency on image update rate than the linear-extrapolation-based predictor. This meets the expectations as the history-based predictor can better handle the inversion of motion directions at the turning points (see also Fig. 4.3). The linear-extrapolation-based predictor cannot handle the turning points and thus shows greater dependency on image update rate. We conclude that the history-based predictor is better suited for the available image update rates. Regarding the choice of targeting the beginning or the center of the motion trajectory during a shot with fixed focus, we do not see a clear improvement of shooting at the center. The better approximation of the trajectory on the one hand and the increasing prediction error on the other hand cancel each other out. As targeting the center should be theoretically better and in our tests it does not show worse efficiency than targeting the beginning of the shot, we favor shooting at the center of the trajectory.

4.4.3 Efficiency of motion tracker

The efficiency of the Bayesian motion tracking is evaluated in the combination with the temporal motion predictors. All tests are performed using the emulated real-time transducer. We compute the efficiency loss $\eta_\Delta$ associated with the Bayesian motion tracking by subtracting the efficiency when using the Bayesian tracking ($\eta_{\text{Bayesian-tracking}}$) from the efficiency when using the test-ground-truth tracking ($\eta_{\text{ground-truth}}$), with both employing the same temporal prediction:

$$\eta_\Delta = \eta_{\text{ground-truth}} - \eta_{\text{Bayesian-tracking}}.$$  \hspace{1cm} (4.3)

Table 4.2 lists the results of this investigation. The mean efficiency loss $\eta_\Delta$ over 120 simulated experiments with varying image durations and ultrasound shot durations is 4.9 % with a 95%ile loss of 10.8 %. In combination with the history-
based motion predictor, the efficiency loss is far less than in combination with the linear-extrapolation-based motion predictor.

4.4.4 Efficiency of preset-based ultrasound transducers

To assess the error that is introduced by using a preset-based transducer instead of a real-time transducer, we vary the number of presets and compute the resulting system efficiency. To discriminate the error introduced by using transducer configuration presets from the errors introduced by tracking and motion prediction, we use again the ground-truth tracking and prediction components that know the underlying respiratory test motion. As the ultrasound shot duration is a critical parameter for this assessment, we also vary over this parameter. Figure 4.7 shows the resulting system efficiency. The reference is the temperature rise achieved with a real-time transducer (dashed plot). For subtle motion (scale factor $s = 0.5$ a)) even 8 presets result in an efficiency of over 99%. For larger motions in b) and c) the efficiency with 8 preset quickly degrades. Using 32 or 64 presets is efficiency-wise close to using a real-time interface without presets. In some cases it can happen that the preset-based approach results in higher efficiency than the real-time transducer: the closest preset in these cases is slightly better than choosing the center point of the trajectory for the active shot duration. To minimize this effect, the numerical experiment simulations were repeated 5 times and the results represent the mean efficiency.

4.4.5 Estimated efficiency of the actual hardware FUS system

Using the GE MR device, EPI (reduced field-of-view) images can be acquired with about 150 ms imaging duration and a delay of about 150 ms. The delay includes coil averaging and image reconstruction on the scanner, sending the data over the network and receiving it in our application. The InSightec CBS transducer is used in a preset-based approach that can handle 64 preset configurations. Switching between the presets is a matter of a few milliseconds. The system is equipped with Bayesian tracking, history-based motion prediction and a 50 ms shot duration. The presets are computed at the beginning of the monitoring session for a sonication based on the observed motion. Figure 4.8 gives the results as a plot of efficiency over motion scaling factor $s$. The overall efficiency of the virtual system with respect to temperature for normal motion is about 80%. For exaggerated motion ($s = 1.5$) the efficiency goes down to about 70%. Less motion can be compensated with an efficiency greater than 80%.
Figure 4.7: Efficiency evaluation of preset-based transducers against real-time transducers for respiratory test motion with scale factor a) $s = 0.5$, b) $s = 1.0$, and c) $s = 1.5$.

Figure 4.8: Estimated efficiency of the actual hardware FUS system based on the virtual system.
4.5 Discussion

In this chapter, we describe the development of a novel FUS treatment system capable of performing motion-compensated application of FUS. Motion compensation is achieved by deriving motion information from MR monitoring images and computing motion predictions to compensate delays in the processing loop. The system is developed with the goal of clinical use. A major problem is that developing a whole treatment system under such high quality regulations is a huge effort for research groups which normally is not compatible with short research projects of a few years. Usually, research groups are furthermore not trained and certified for the high quality standards necessary for the application of the system to humans. This challenge requires a change of the development process in the research context using more automatic testing of the system. To reduce the efforts necessary for testing and particularly real-world experimental validation, we here propose a simulation-based hardware emulation to test and analyze the efficiency of the system. The emulation internally uses a full numerical simulation of FUS during respiratory motion. Using this virtual system, choices of system parameters and algorithms can be determined with less effort. The actual real-world testing is thereby minimized to performing tests on the system resulting from the in-silico design stage.

In this work, we focus our attention to the motion compensation of the system. Firstly, we compute the limits of motion compensation for different choices of system parameter values for image duration and ultrasound shot duration. Even exaggerated motion \((s = 1.5)\) can theoretically be compensated in the case of an ultrasound shot duration of 300 ms with an efficiency above 90\%. However, it would require a perfect temporal prediction which in practice is clearly not possible. To see how good the actual predictors can forecast the motion, we first individually analyze their influence on the system efficiency. This testing is done in combination with perfectly accurate tracking information. Afterwards, also the influence of motion tracking and also the transducer types is quantified. The motion tracking reduces the efficiency on average by only 4.9\%. The effect of using a preset-based transducer instead of a real-time transducer is also analyzed. For the sole task of motion compensation, 32 presets should be enough to compensate even exaggerated motion. However, for the additional task of trans-costal delivery we assume that a larger number of presets is required. The temporal motion prediction is the most influential component. The history-based motion prediction is found to perform better than a linear-extrapolation-based predictor. We, however, see potential for improving the
temporal predictions. A spatio-temporal motion model for liver motion (Tanner et al., 2016), which currently is being integrated, is expected to improve the predictions. The model includes a temporal prediction method extending (Tanner et al., 2014).

Finally, a virtual model of the actual hardware system with the same specifications (150 ms monitoring imaging delay, 150 ms image duration, 64-preset transducer) is tested and found to be capable of motion compensation of normal respiratory motion with an efficiency above 80%. Exaggerated motion \((s = 1.5)\) can be compensated with an efficiency of about 70%.

Potential for improving the system efficiency lies also in decreasing the overall computational delays in the system including computational delays introduced by the motion tracking, the motion predictors, and also imaging delays and update rates. Furthermore, we see potential in improving the temporal motion predictions by the combination of different tracking sources like external motion surrogates and ultrasound tracking.

4.6 CONCLUSION

The reported efficiency values for the virtual model of our target hardware system are expected to be already suited for the clinical use of the motion compensation. We currently work on confirming the estimated efficiency of our system in real-world FUS experiments. Animal studies for further validation are in preparation. The long-term goal is to bring the technology to clinical use. Furthermore, we want to ease the translation of future research and build upon our current work in the future. The system might be a candidate for a platform for research developments in the FUS context. Research partners could contribute individual component implementations that are used in the system in a plugin fashion. A further long-term goal is to implement a challenge-style evaluation framework to automatically evaluate and compare the plugins using the simulation-based emulation. This approach could lead to more research results being transferred to clinical practice.
In this thesis we propose a numerical model of focused ultrasound therapy within the abdomen during respiratory motion. The model can be used to study the effects of FUS for liver targets during respiratory motion. Potential use-cases of the model are numerous, ranging from studies of feasibility of the treatment for a certain patient and target, over pre-therapy planning and training of clinical staff, to in-therapy planning and even real-time use to improve treatment monitoring and execution.

A special focus was laid on the incorporation of the respiratory motion and the efficiency of the simulations. A temperature model is proposed that solves the prediction of temperature distributions efficiently on the graphics processing unit by mapping the problem from the moving physical world to a static motion reference state.

Due to the highly heterogeneous propagation domain including ribs, we also investigate the accuracy of the ultrasound modeling. A novel angular spectrum approach for heterogeneous media is proposed and found to be more accurate than the widely used hybrid angular spectrum method when compared to a state-of-the-art reference computational model. A detailed discussion of the approximation error of the hybrid angular spectrum method is performed and suggests that the error is critical for medical applications (like for example trans-cranial phase-aberration studies (Vyas et al., 2014) and trans-costal propagation simulations (de Greef et al., 2015)). The error in practical applications is reduced by computing an average speed of sound per slice for the original angular spectrum propagation step – but the main novelty of the hybrid angular spectrum method being its spatial correction step...
cannot, by design, model phase aberrations through heterogeneous media. Our novel MAS method can provide this. Ultrasound model validations are performed against a publicly available finite difference time domain method (Treeby et al., 2012).

To the end of real-time applications, we propose an approximate ultrasound propagation model to allow for the computation of multiple simulations per second. Having established the two main parts of FUS modeling, we propose an integrated FUS model combining the ultrasound propagation model and the temperature model with a predictive abdominal motion model and a tissue damage and parameter change model. As the patient anatomy is a key influence factor of the therapy, we propose a mainly automatic anatomical model generation from CT images. This leads to the model being easily adapted to an unseen patient which would be necessary for clinical use. Using the predictions of the model, studies can be performed that would not be feasible in real-world experimentation: a very detailed view into the treatment effects can be established which would not be provided by measurements. Automatic execution of extensive experiments is possible. Therefore, the models already can progress the understanding of the complex treatment effects of FUS during respiratory motion. The use of the model during the therapy could in principle be used to monitor risk structures that are not covered by the image-based monitoring. This could lead to a reduction of treatment complexity, yet it is one of the toughest applications for modeling as there is no real-world measurement that can be used for calibration. Clearly, the model will not yet be descriptive of all effects that occur in the real-world and for each application scenario, a thorough validation needs to be performed. The error associated to the predictions will be consistent of modeling errors but also measurement errors and uncertainties due to spatial inaccuracies introduced by imaging, image processing, device position detection, as well as temporal inaccuracies, and unknown patient-individual model parameter values. For a robust clinical applicability it will be key to calibrate the model to as many measurements as possible from as many sources as possible.

To show the applicability of the models for clinical relevant use-cases, two examples are given. Firstly, a simulation-driven treatment planning tool that allows a clinician to explore treatment options interactively by providing feedback from the simulations. Secondly, a study is being performed for using the model to optimize the placement of the FUS device which is a critical task in treating a wide range of targets in the liver. While in this second use-case the model can be used to show that the problem of transducer placement can be effectively approached by automatic optimization – it also shows that the atlas-based ultrasound approximation method is not yet fully
descriptive of all ultrasound propagation effects. Thus, for a clinical application, either the atlas-based approximation needs to be improved or compromising on computational speed, the MAS method needs to be used in the optimization.

As a more technical, yet clinically highly relevant, use case of the model, an in-silico design and validation study is performed using the numerical simulation to study the characteristics of a novel motion compensation FUS treatment system. Motion compensation is achieved by deriving motion information from MR monitoring images and computing motion predictions to compensate delays in the processing loop. In the in-silico studies, the actual patient and the FUS and imaging hardware system are replaced by a virtual system incorporating the FUS model. The treatment system interacts with the virtual system as with a real hardware system. Using this setup allows extensive testing of the treatment system with varying parameters and to study the influence these parameters have on the treatment outcome. We assess the influence of the focus update rate, the imaging update rate used to derive motion information, the motion model predictions, as well as the influence of using a discrete set of focus targets instead of continuous focus updates. The experiments can be re-performed as part of the development cycle (e.g. automatic overnight evaluation) and thereby drive the system development by providing quantitative metrics of the current performance of the system. The tests show that currently, the greatest error is associated with the motion prediction to compensate delays between motion observation and FUS control. Incorporation of the liver motion model (Samei et al., 2012) into the system might improve the efficiency. Finally, we estimate the efficiency of the treatment system in combination with a clinically available FUS device and MR imaging device for which an integration has been developed. These tests suggest that, in combination with these clinically available hardware systems, the system is found to be capable of motion compensation of normal respiratory motion with an efficiency above 80%. This is expected to be a tolerable efficiency loss for clinical applicability.

5.1 Future work

Facilitate translation of research results to the patient. The in-silico evaluation framework might be used to facilitate translation of research results to the actual application in the clinical practice. The treatment system might be a candidate for a platform for research developments in the FUS context. Research partners could contribute individual treatment system component implementations that are
used in the system in a plugin fashion. These could be motion predictors, motion tracking algorithms, focusing algorithms, and monitoring approaches. The in-silico evaluation would then allow for automatic assessment and comparison of all available components. This approach could increase the comparability of approaches and facilitate the determination of best candidates for the full translation to a clinical system.

Learning of a heuristic ultrasound model. In this thesis, the atlas-based ultrasound model introduces several simplifications compared to the angular spectrum methods. The shut-off of certain parts of the transducer is done completely geometrically and no influence other than pressure reduction of the active parts on the focus shape is modeled. The actual focus spot appears however to be oriented towards the direction of the largest active area on the transducer. Furthermore, the focus splitting behind several parallel ribs is not modeled but may be estimated based on the active areas. These effects could be modeled either directly or learned on basis of a large number of simulated cases. In any case, it appears promising to further improve the approximate modeling due to its performance benefits.

Improving monitoring by model predictions. The model calibration approach from Section 3.4.4 can be seen as the first step towards fusing model predictions and MR thermometry measurements. The model predictions could be used to either improve spatial resolution, temporal resolution, or even volume coverage of the monitoring of the therapy. This however requires further work on model validation, further speed improvements, and accurate anatomical models as well as motion detection.

Automatic treatment planning and optimization. The interactive planning of treatments will in the long run be replaced by automatic approaches. Using the FUS model in a similar fashion as for the transducer placement optimization for a single target (cf. Section 3.6) could be used to optimize the treatment for a full tumor volume coverage. The parameter space for such an optimization is rather large: the goal is to find the optimal sequence of focus position and cooling times, potentially also power levels for each focus. This is even harder if the goal is a volumetric heating with each focus position in the sequence being active for only some seconds and not individually reaching ablation. In such cases the interdependence of the individual sequence steps is very high.

On-line treatment control. In this thesis, we concentrate on single focus ablation as this is the most suited setting for assessing the spatial specificity of the treatment. For current approaches to volumetric ablations, the focus position is changed to cover a larger anatomical region by executing a predefined trajectory (like a spiral). For more
sophisticated volumetric ablations that are not predefined but dynamically changed based on temperature feedback, the FUS model could be used to automatically determine the next best focus position by forward simulations. This requires again a good calibration of the model to the individual patient and poses very hard performance constraints that need to be addressed.

*Experimental validation.* Before the described computer models can be applied in clinical settings as described above, further experimental validation is required. The efforts in numerical validation studies described in this work are to be seen as a starting point for further experimental validations based on real measurements. The required level of validation is highly dependent on the impact of the model predictions in the intended use case. For example, if the MAS method would be used within a focusing algorithm to treat a target within a patient, it would be required to experimentally validate that the model is fit for this use. Additionally, any imaging and segmentation method providing the anatomical model based on which the ultrasound propagation is simulated, would need to be validated with respect to the accuracy in spatial description of the patient. For the clinical use of the integrated FUS model further validation is needed to verify the combination of the ultrasound and temperature model. The comparison to thermometry measurements described in Section 3.4.4 will need to be extended to a multitude of experiments including heterogeneous tissue domains and in-vivo experiments. Studies of the predictive power of the model need to be performed in which the model is calibrated based on some example data and is used to predict unseen sonication experiments.

All these directions of future work appear challenging yet they might have a great impact on the feasibility of FUS treatments of abdominal targets during respiratory motion. While FUS has been available as a treatment technique already for quite some time it continues to bear great potential for improving medical treatments in the future.
References


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Personal thanks

It has been quite a journey to finally write these words into this document being my PhD thesis. A series of major interest sparks occurred and led me to this. Some of these inspirations I found by myself, some came from people surrounding me and for which I am deeply grateful. Leaving aside all the inspirations during childhood, I like to think in my case the journey began in 10th grade, if I recall correctly. I don’t know why and what exactly it was, but somehow during that year in physics class my interest awakened (very bad before, very good afterwards, something happened). This spark of interest also formed in math – maybe due to the same teacher (Thanks Mr. Napp). This vulnerable interest spark eventually led me to my choice of math and physics as majors (Thanks to Mr. Napp and Mr. Ueckert who kept this interest alive and growing). During these years another interest was highly influencing my developments: audio processing for producing electronic music and recording my rock band. Driven by this interest in math and physics and engineering as well as sound recording, processing and furthermore computer-generated 3D animation movie production, I started my engineering studies of media technologies in Hamburg. During these studies, the combination of 3D animation and real-world footage (matchmoving) led me to computer vision topics and the algorithms and methods behind that. Computer vision sparked the interest in image processing. Image processing felt quite like home due to my interests and studies of audio signal processing. And it led me eventually to a great and inspiring application domain: medical image processing – and led me to great time of research at the IMI at the UKE Hamburg (Thanks to Heinz Handels for giving me the opportunity and to the entire group). During these studies in medical image processing, I focused on the Fast Marching method which opened up the field of mathematical methods and partial differential equations for image processing. The end of this period was marked by my diploma thesis at the IMI. Afterwards, I started to study computer science in Lübeck which opened a lot of new interesting fields like software architectures, robotics, and hardware design. Yet, I was able to also put some focus on numerical methods for image processing enjoying inspiring lectures by Bernd Fischer, Stefan Heldmann, and Nils Papenberg. So, not loosing contact to (medical) image processing even though
numerous interesting new paths were laid out for me in Lübeck, I decided to apply for doing my master’s thesis at Fraunhofer MEVIS in Bremen. Thanks to Bernd Fischer who initiated the contact, I was actually given the opportunity to do these studies at MEVIS. A pretty perfect fit of topic was found with Ola Friman at MEVIS: studies on anisotropic Fast Marching, being a generalization of the Fast Marching method, and its application in medical image processing. I was already deep in Fast Marching, Ola was interested in anisotropic Fast Marching; plus we found interesting medical applications of the method leading to my master thesis. Finished with the master studies, Ola supported me in applying at MEVIS for being a researcher in the fields of numerical simulations with the goal of writing a PhD thesis. Thanks to Tobias Preusser, Horst Hahn, and Heinz-Otto Peitgen, I was given the chance to actually start working at MEVIS in 2011. A special thanks to Tobias Preusser for having the faith in my abilities to dig into the (related to my previous research fields yet to a large extent new) field of numerical simulations and providing me with a continuous research task in high intensity focused ultrasound for years. During these years, additionally to the advice by Tobias, Joachim Georgii has been closely involved in my research and has been a constant source of methodological inspirations and guidance. More general thanks I would like to address to my colleagues at MEVIS, my soccer mates, and band mates for making it all more fun. Special thanks I would like to address to my parents and family for every bit of support and for letting me freely explore my interests and choice of profession. My wife for everything that we are, every day of the long path that we already went together, and for reassuring motivations in clouded times of doubt during the long journey of my PhD studies. Believing people that always tell that ‘there is a life after the PhD’, I’d like to openly close this section by writing ‘To be continued...’.