Solving Inverse Problems
for Medical Applications

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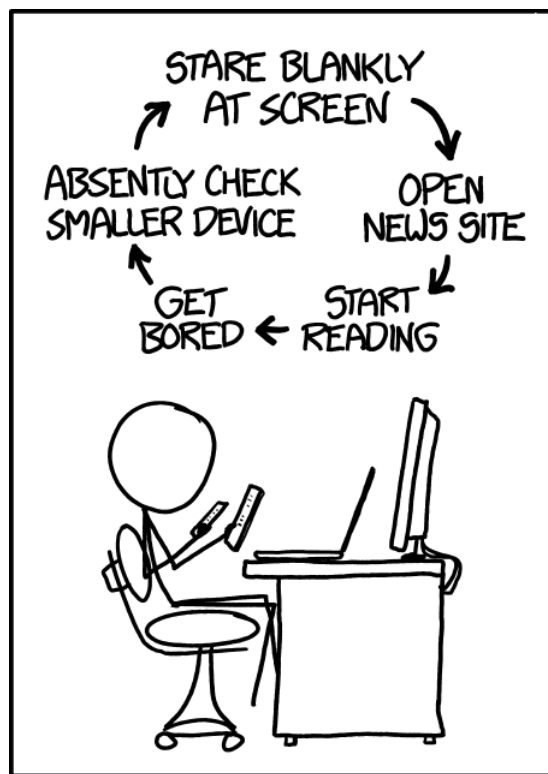
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Dedication

This is dedicated to the animal companions who were part of my life:
Muzungu, Natas, Satoru, Fridolin, and all the spiders living in my apartment.

Preface

In which right is wrong and we refuse to accept it.
– Unravel Two

One of the greatest challenges of a mathematician is when math collides with the real world. A theory can be compared to a flower. A seed is planted, and it grows over time. It might grow into a lovely flower or even a tree. But like most things in life, it must end at one point. E.g., if a new theory makes more sense, the old one becomes obsolete. Solving a problem may work theoretically, or at least the approach seems to be a great idea, but the application in the real world may not work at all. There the fun begins: Rethink, Simplify, and Repeat. This is done until, at one point, you are satisfied with the results; or give up.

https://xkcd.com/1411/

e82a8262ae6f09505e37f633e433acc95488aa22af3d288555ac21a13ea1f218

Contents

Acronyms

AR Augmented Reality. vii, 1, 2

CG Conjugate Gradient. 3, 11, 12, 14, 16–18, 72

CNN Convolutional Neural Network. 26

CqN Conjugate quasi-Newton. iv, viii, x, 3, 10, 11, 14, 16, 19–21

CT Computed Tomography. 1, 26

Er:YAG Erbium-doped Yttrium Aluminium Garnet. 1–3, 51, 73

FD Finite Difference. iv, 3, 21–24

FE Finite Elements. iv, 3, 21, 22, 24, 61

GD Gradient Descent. iv, 3, 10, 11, 13, 14, 19–21

GN Gauss Newton. iv, 3, 10, 11, 14–16, 19–21

MSELoss Mean Squared Error Loss. 11, 14, 15, 20

NN Neural Network. viii, x, 3, 26, 28, 31, 61, 73, 74

OCT Optical Coherence Tomography. 2, 3, 73

PDE Partial Differential Equation. 3, 21, 22, 24, 25

ReLU Rectified Linear Unit. 3, 32

SLN Sentinel Lymph Node. viii, x, 2, 33, 72

SLNF Sentinel Lymph Node Fingerprinting. 33

Tc^{99m} Technetium-99m. v, vii, 2, 3, 5, 7, 33, 71, 72

VR Virtual Reality. 1

WSPGL1 Weighted Projected Gradient for ℓ_1-norm Minimization. 71, 72

Acknowledgements

Summary

It is essential to have an accurate feedback system to improve the navigation of surgical tools. This thesis investigates how to solve inverse problems using the example of two medical prototypes. The first aims to detect the Sentinel Lymph Node (SLN) during the biopsy. This will allow the surgeon to remove the SLN with a small incision, reducing trauma to the patient. The second investigates how to extract depth and tissue characteristic information during bone ablation using the emitted acoustic wave.

We solved inverse problems to find our desired solution. For this purpose, we investigated three approaches: In Chapter 3, we had a good simulation of the forward problem; namely, we used a fingerprinting algorithm. Therefore, we compared the measurement with the simulations of the forward problem, and the simulation that was most similar to the measurement was a good approximation. To do so, we used a dictionary of solutions, which has a high computational speed. However, depending on how fine the grid is, it takes a long time to simulate all the solutions of the forward problem. Therefore, a lot of memory is needed to access the dictionary.

In Chapter 4, we examined the Adaptive Eigenspace method for solving the Helmholtz equation (Fourier transformed wave equation). Here we used a Conjugate quasi-Newton (CqN) algorithm. We solved the Helmholtz equation and reconstructed the source shape and the medium velocity by using the acoustic wave at the boundary of the area of interest. We accomplished this in a 2D model. We note, that the computation for the 3D model was very long and expensive. In addition, we simplified some conditions and could not confirm the results of our simulations in an *ex-vivo* experiment.

In Chapter 5, we developed a different approach. We conducted multiple experiments and acquired many acoustic measurements during the ablation process. Then we trained a Neural Network (NN) to predict the ablation depth in an end-to-end model. The computational cost of predicting the depth is relatively low once the training is complete. An end-to-end network requires almost no pre-processing. However, there were some drawbacks, e.g., it is cumbersome to obtain the ground truth.

This thesis has investigated several approaches to solving inverse problems in medical applications. From Chapter 3 we conclude that if the forward problem is well known, we can drastically improve the speed of the algorithm by using the fingerprinting algorithm. This is ideal for reconstructing a position or using it as a first guess for more complex reconstructions. The conclusion of Chapter 4 is that we can drastically reduce the number of unknown parameters using Adaptive Eigenspace method. In addition, we were able to reconstruct the medium velocity and the acoustic wave generator. However, the model is expensive for 3D simulations.

Also, the number of transducers required for the setup was not applicable to our intended setup. In Chapter 5 we found a correlation between the depth of the laser cut and the acoustic wave using only a single air-coupled transducer. This encourages further investigation to characterize the tissue during the ablation process.

Zusammenfassung

Um die Navigation von chirurgischen Instrumenten zu verbessern, ist ein genaues Feedbacksystem unerlässlich. In dieser Arbeit wurde untersucht, wie ein inverses Problem bei zwei medizinischen Prototypen gelöst werden kann. Das erste zielt darauf ab, die Sentinel-Lymphknoten (SLN) während der Biopsie zu erkennen, damit diese minimal invasiv entfernt werden, was das Trauma des Patienten verringert. Das zweite Projekt befasst sich mit der Frage, wie wir während der Knochenabtragung mithilfe der emittierten akustischen Welle Informationen gewinnen können.

Wir untersuchten drei Ansätze, wie wir die inversen Probleme lösen können: In Kapitel 3 hatten wir eine gute Simulation des Vorwärtsproblems. Wir verglichen die Messung mit den Simulationen des Vorwärtsproblems. Die Simulation, die der Messung am ähnlichsten war, stellt eine gute Lösung dar. Je nachdem, wie fein das Gitter ist, dauert es jedoch sehr lange, alle Lösungen für das Vorwärtsproblem zu simulieren, bzw. es wird viel Arbeitsspeicher benötigt, um auf alle Simulationen zuzugreifen.

In Kapitel 4 lösten wir die Helmholtz-Gleichung (Fourier-transformierte Wellengleichung). Hier verwendeten wir einen Conjugate quasi-Newton (CqN)-Algorithmus um die Form der Quelle und die Mediumgeschwindigkeit zu rekonstruiert. Wir haben dies in einem 2D-Modell durchgeführt. Die Berechnung für das 3D-Modell war sehr lange und rechenintensiv. Wir weisen darauf hin, dass wir einige Bedingungen vereinfachten und die Ergebnisse unserer Simulationen nicht in einem *Ex-vivo*-Experiment bestätigen konnten.

Daher beschlossen wir in Kapitel 5 einen anderen Ansatz zu verwenden. Wir führten mehrere Experimente durch und erfassten viele akustische Messungen während des Ablationsprozesses des Knochens. Dann trainierten wir ein Neurales Netzwerk (NN), um die Tiefe des Schnittes in einem End-to-End-Modell vorherzusagen. Es handelte sich um ein End-to-End-Netzwerk, was bedeutet, dass fast keine Datenvorverarbeitung benötigt wird. Allerdings gab es auch einige Nachteile, z. B. war es mühsam, die akustische Messung mit der dazugehörigen Tiefe zu kennzeichnen.

In dieser Arbeit wurden mehrere Ansätze zur Lösung inverser Probleme in medizinischen Anwendungen untersucht. Aus Kapitel 3 lernten wir, dass wir, wenn das Vorwärtsproblem gut bekannt ist, die Geschwindigkeit des Algorithmus erheblich verbessern konnten, indem wir den fingerprinting-Algorithmus verwendeten. Dies ist ideal für die Rekonstruktion einer Position oder als erster Ansatz für komplexere Rekonstruktionen. Die Schlussfolgerung aus Kapitel 4 ist, dass wir die Anzahl der unbekannten Parameter mit der adaptiven Eigenschaftsmethode erheblich reduzieren können. Ausserdem können wir die Mediumgeschwindigkeit und den akustischen Wellengenerator rekonstruieren. Allerdings war das Modell für 3D-Simulationen sehr

rechenintensiv. Die Anzahl der Mikrophone, die für das Experiment erforderlich waren, war für unsere geplante Einrichtung nicht anwendbar. In Kapitel 5 haben wir eine Korrelation zwischen der Tiefe des Laser-Schnitts und der akustischen Welle unter Verwendung nur eines luftgekoppelten Mikrophones gezeigt. Das ermutigt weitere Untersuchungen, um das Gewebe während des Ablationsprozesses zu charakterisieren.

Chapter 1

Introduction

1.1 MIRACLE – Project

An important feature of modern medicine is not only treating and curing patients but also improving their quality of life. One way of improving a patients quality of life is to decrease the recovery time after medical procedures such as surgery. The reduction of the recovery time has an additional advantage, namely, that the risk of accompanying illnesses is reduced. This reduction can be achieved by performing minimally invasive procedures [36, 56]. For example, in an osteotomy (the surgical cutting of a bone), the recovery time is decreased by replacing the mechanical tools used in open osteotomies with laser-based ablation [5, 7, 50, 55]. Another development is using robots during surgery, to improve the quality of the cut [16, 46]. Using such robots not only reduces the patient's healing process but also improves the lifespan of an implant if cement-less fixation is used [70].

The first robotic device in clinics with a free-space laser used for laser-osteotomy is called CARLO® (short for "Cold Ablation Robot-guided Laser Osteotome") [4, 6, 7, 19]. This robot guides the Er:YAG laser along a preplanned cutting path with the help of an optoelectronic tracking system which is previously registered with the Computed Tomography (CT) data from the patient. However, the surgeon's incision on the patient has to expose the bone so that CARLO® can proceed with the ablation of the bone.

To further improve the recovery time, the Flagship project *MIRACLE*[1] (short for "Minimally Invasive Robot-Assisted Computer-guided LaserosteotomE") was founded at the Department of the Biomedical Engineering of the University of Basel [73]. Their vision is to enable laser osteotomy in minimally invasive surgery, meaning that not the entire bone has to be exposed, but solely a one-centimeter wide incision is needed. Four research groups tackle the MIRACLE project: The group *Planning and Navigation*[2] dedicate themselves to improving the planning process using Virtual Reality (VR) and Augmented Reality (AR) glasses [27, 43, 57, 91–93] and to have an automated labeling system of the CT images from bones [75–77]. In addition, they develop novel approaches to navigate the endoscope, namely to reconstruct the position of the endoscope accurately [37–39, 58, 59, 74]. Finally, we opt to control the depth of the cut

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[1]17.03.2023, dbe.unibas.ch/en/research/flagship-project-miracle
[2]17.03.2023, dbe.unibas.ch/en/planning-navigation

during laser ablation and to analyze the surrounding using the acoustic wave emitted during the ablation process [65, 67, 78]. The second group is called *Biomedical Laser and Optics Group (BLOG)*[3]. They study the ablation process of different lasers [1, 13–15, 15] and develop a fiber-based laser that can be integrated into the endoscope. In addition, they want to integrate Optical Coherence Tomography (OCT) to get additional information of the tissue being ablated [8, 9] and investigate tissue differentiation using acoustic waves [44, 68]. The third group is called *Bio-Inspired RObots for MEDicine-Laboratory (BIROMED-Lab)*[4], and their goal is to build the robotic endoscope. They are facing the challenge of making the flexible endoscope and controlling it safely [20, 24–26, 28]. The last group, called *Smart Implants*[5], develops personalized bio-implants with durable 3D printed bio-materials [80] and will further investigate developing implants compatible with minimally invasive surgeries.

1.2 Contribution

The aim of this PhD thesis was to investigate inverse problems that occur in two potential medical devices. The first project investigates a new method to detect the Sentinel Lymph Node (SLN) during the biopsy in real time [66, 79, 84–86]. We helped design a pinhole collimator [66] using the optimal design algorithm [31]. In addition, we improved the computational speed to pinpoint the Tc^{99m} source using a fingerprinting algorithm [66]. One of the major achievements was that we were able to reconstruct the Tc^{99m} source using just a single measurement from the detector, hence reconstructing a 3D subspace using a 2D projection from the detector. The design of the collimator and the fingerprinting were then used for further research and as a base-line for the reconstruction [86, 87] to have a real-time reconstruction of the sources visualized with the AR glasses [85, 87]. Our vision is that our research will help the surgeon conduct a minimally invasive SLN biopsy.

In the second part, we investigated multiple approaches to aid the MIRACLE robot in navigating the endoscope and controlling the Er:YAG laser. An acoustic wave is emitted during tissue ablation with the Er:YAG laser. My task was to extract from these acoustic waves properties of the tissue being ablated. We solved the mathematical optimization problems to simultaneously reconstruct an unknown source of an acoustic wave and its surrounding medium velocity. Using the Adaptive Eigenspace method introduced in [63], we showed in [65] that this is, in fact, possible in the 2D subspace. We also managed to do so in a 3D subspace, but we noticed one major drawback: the computational time is very high. For real-time implementation, we either had to optimize the program and use high-performance computing or find another approach. When we tried to reconstruct the mathematical approach in the real world, we found some additional challenges we had not yet included in our simulations, one of them being the impedance between the bone and the air. A different challenge was that our simulation needs over 100 point transducers (simulated measurement at a single point on the coordinate system, but in reality, it stretches over multiple grid points) and did not include that the shape of the transducer that may influence the acoustic wave.

Therefore, we decided to change the methodology to analyze the acoustic wave. We bought tissue samples from the local grocery store, ablated the bone with our Er:YAG laser, and measured the depth of the cut with the OCT. An acoustic wave is created during the ablation process, which we measured with an air-coupled transducer. The data were then used to train the NNs. In our publication [78], we concluded that depth information is embedded in the acoustic wave. Although the experiments were performed in a dry environment, they encourage future scientists to further investigate this problem for deep bone ablation using an irrigation system.

1.3 Outline of the Thesis

In this chapter, we give an overview of the MIRACLE project and explain our contribution to the project. Chapter 2 will provide the reader with an understanding of the technical background. It will help the reader to understand what *Forward* and *Inverse Problems* are. Then we will explain what *Linear* and *Non-linear Models* are and give examples on how to solve them. We further introduce some *Optimization Algorithms*: *Conjugate Gradient (CG)*, *Gradient Descent (GD)*, *Gauss Newton (GN)*, *Conjugate quasi-Newton (CqN)*, and how to implement an adaptive step size with the *Armijo–Goldstein* condition. Then the *Partial Differential Equation (PDE)* is introduced, and how this can be solved with the help of *Finite Difference (FD)* and *Finite Elements (FE)*. In the final part, we give an overview of the *Neural Network (NN)* and describe the concepts of a *Fully Connected Layer*, *Convolutional Layer*, *Maxpool Layer*, and the *Rectified Linear Unit (ReLU)* activation function. Chapters 3-5 comprise the main contribution of this thesis, namely the publications. Chapter 3 introduces a method to find a good design for a pinhole collimator and how spatial distribution of a Technetium-99m (Tc^{99m}) source can be reconstructed efficiently. Chapter 4 investigates the propagation of the acoustic wave and how to reconstruct the medium velocity and the source in an unknown environment. In Chapter 5, we use a NN to approximate the depth of the cut using the acoustic wave emitted during the bone ablation with an Erbium-doped Yttrium Aluminium Garnet (Er:YAG) laser. In Chapter 6 we discuss our results and what we learned from the project. Finally, Appendix in Chapter 7 has proofs of theorems used to explain some of the technical backgrounds in Chapter 2.

Chapter 2

Technical Background

2.1 Forward Problem

According to the encyclopedia[1], a forward problem is

> *"[. . .] the problem of calculating what should be observed for a particular model"*.

This means that a forward problem can fit or predict the results of an outcome for a particular condition. In everyday life, we apply forward problems without even noticing. For example, when we buy groceries, each grocery is mapped to a particular value, or when we play billiards, we approximate how the ball rolls according to its surroundings and the angle at which we hit the ball.

We now look at a more mathematical example. Assume, we have two sets of numbers. $\mathcal{A} = \{0, 1, 2, 3, 4, \cdots\} = \mathbb{N}_0$ with all the natural numbers (including 0) and $\mathcal{B} = \{0, 1, 2, 3, 4\}$. Our function g maps each of the numbers in $\mathcal{A}$ to a number in $\mathcal{B}$

$$
\begin{aligned}
g : \mathcal{A} &\longrightarrow \mathcal{B} \\
a &\longmapsto b
\end{aligned}
\quad \text{with} \quad a \in \mathcal{A}, \, b \in \mathcal{B} \,.
\tag{2.1}
$$

There exists a simple function g, namely the *modulo* 5 function, that maps $\mathcal{A}$ onto $\mathcal{B}$: We can write each number $a \in \mathcal{A}$ as a combination of $n \in \mathbb{N}$, $p = 5$, and $b \in \mathcal{B}$

$$
a = np + b \,,
$$

hence, the function g can be written as follows

$$
g(a) = g(np + b) = a \;(\mathrm{mod}\; p) = b \,.
\tag{2.2}
$$

In other words: a divided by p is n remainder b. In this example, an element $a \in \mathcal{A}$ represents a condition and $b \in \mathcal{B}$ the corresponding outcome. The function g maps the element a to the element b; hence, the function g is a forward problem. We show, in Table 2.1, some mapping from elements of the subset $\mathcal{A}$ onto the elements of the subset $\mathcal{B}$ using the mapping function

a	0	1	2	3	4	5	6	7	8	$314\,159\,265\,359$	$2^{82\,589\,933} - 1$
b	0	1	2	3	4	0	1	2	3	4	1

Table 2.1: Sample mapping of the *modulo* 5 function $g(a) = b$.

$g(a) = b$. Note, that we prove Theorem 7.1 in the appendix, that $g\left(2^{82\,589\,933} - 1\right) = 1$ ($2^{82\,589\,933} - 1$ is the biggest known prime-number, at the time of writing).

The following example is more applied. The goal is to detect a Tc^{99m} source with a detector, and describe the relationship between the position of the source and the resulting image of the detector. Let the pinhole collimator be in front of a γ-ray detector, as visualized in Figure 2.1, and a Tc^{99m} source in front of the collimator. In this case, the forward problem is the projection of the Tc^{99m} source onto the detector. This can be done by simulating photons as a straight line from the Tc^{99m} source, through any of the pinholes, onto the detector.
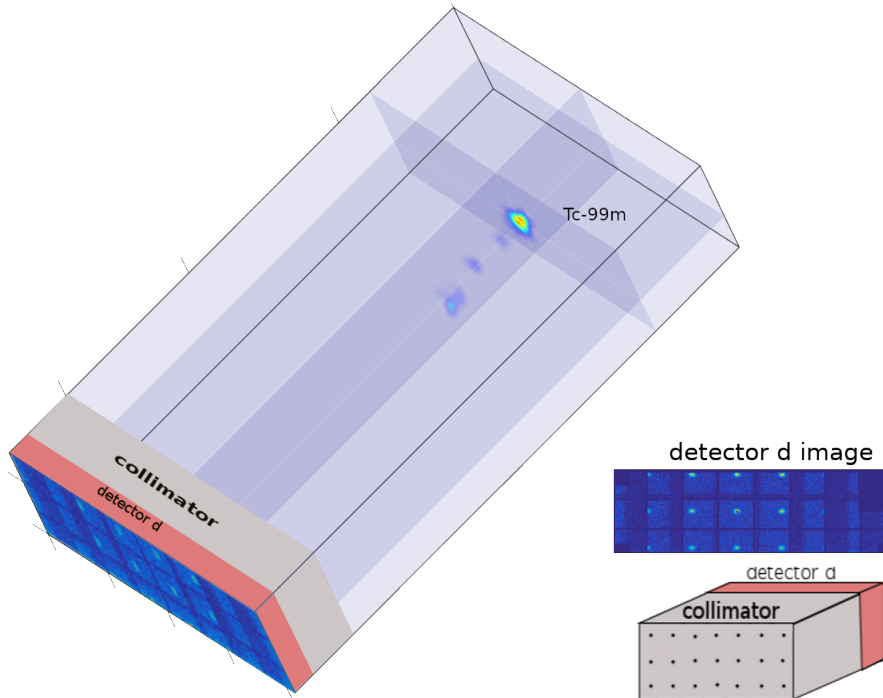
Figure 2.1: The schematic visualizes the setup: γ-rays from the Tc^{99m} source pass through the pinholes of the collimator and are projected onto the detector. The right side depicts an image from the detector, which is a measurement, and the front view of the collimator. The forward problem (Section 2.1) can thus be formulated as: For a given Tc^{99m} source simulate the projection on the detector; and the inverse problem (Section 2.2) as: Reconstruct the position of the Tc^{99m} source with the measurement from the detector.

For the final example, we look at the frequency spectrum of a standing wave. An acoustic

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[1]14.10.22, encyclopedia.com/science/dictionaries-thesauruses-pictures-and-press-releases/forward-problem
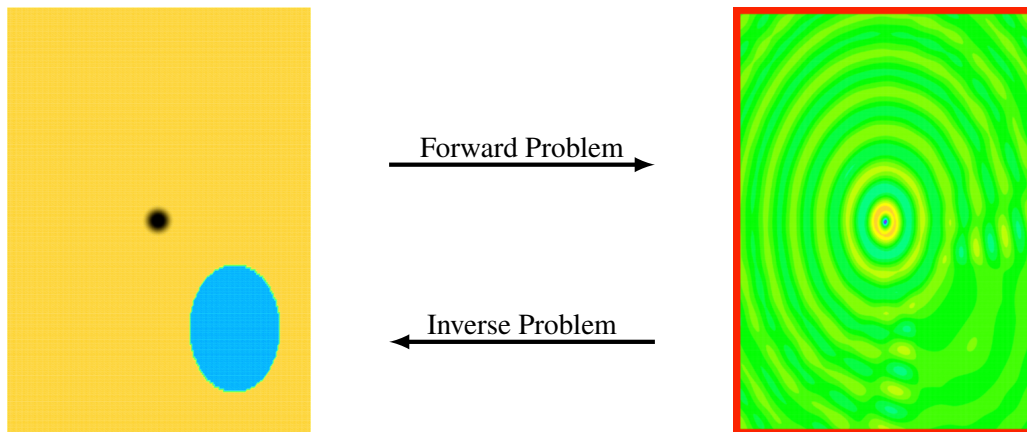
Figure 2.2: On the left side, we visualize an area of interest. In its center is an acoustic wave generator (black), and the area has two different medium velocities (yellow and blue). On the right side, we visualize the acoustic propagation through the various medium velocities, respectively the pressure variation at each point (variation of the colors means different amplitude of the pressure variation). The red box represents the positions of the transducers measuring the acoustic wave. The forward problem (Section 2.1) is then: We have the source information and the medium velocity of the objects (left side) and simulate the propagation of the acoustic wave (right side). The inverse problem (Section 2.2): Under which condition (for which source and for what medium velocity) the measured wave is created (information from the right side to reconstruct the left image).

wave is created from a source or wave generator, e.g., a loudspeaker. The acoustic wave has different propagation speeds within different mediums. For example, in air its medium velocity of $343\,\mathrm{m\,s^{-1}}$ and in water it is $1482\,\mathrm{m\,s^{-1}}$. On the left side of Figure 2.2, we show an area with two different medium velocities and in its center, an acoustic source or wave generator is located. The forward problem simulates the propagation of the acoustic wave, respectively the pressure variation at each point, as is shown on the right side of Figure 2.2.

2.2 Inverse Problem

Contrary to the forward problem, the inverse problem uses a given observation or measurement to calculate under which conditions the measurement is observed.

Using previous examples, we will explain inverse problems and how to formulate them. The first example is grocery shopping. An example of an inverse problem is if a person goes grocery shopping and only knows how much they paid but does not know the price of each item. Hence, they have an observation "*how much they paid*" and are searching for the initial condition "*how much each item costs*". It is obvious that without any additional boundary condition, or if the person does not have multiple receipts to evaluate, the problem has no unique solution. Gathering additional data will help the person estimate an initial validated condition: How much they paid for each item. The second example is a billiard game. Here, we observe how the ball

moves on the table and want to deduce the angle at which the ball was hit. Hence, our observation is *the movement of the ball*, and the unknown initial value is at *at what angle the ball was hit*. There are also some unknown factors, like the friction of the table. Another parameter for the initial value is at what strength the ball was hit, for this, we need additional boundary conditions, e.g., the weight of the ball and its speed.

The example of Equation 2.1 can be transformed into an inverse problem: We have an observation $b \in \mathcal{B}$, and we are searching for the initial condition $a \in \mathcal{A}$. This can be written as follows

$$\text{for a given } b \in \mathcal{B} \text{ find } a \in \mathcal{A} \text{ s.t. } g(a) = b \,.$$

Hence, the solution for the inverse problem can be written as

$$\arg \min_a |g(a) - b| \,. \tag{2.3}$$

Solving this equation can give one or multiple different results. For example, let us assume that function g is the modulo function from Equation 2.2 with $p = 5$. Further, we now search for an initial condition $a \in \mathcal{A}$, which yields $g(a) = 1$. In Table 2.1 we see some possible solutions. We can generalize the results for all $a \in \mathcal{A}$ where

$$a = np + 1 \,, \text{ for } n \in \mathbb{N}_0 \text{ and } p = 5 \,,$$

hence, infinitely many solutions exist. Although all of these results are correct, we may search for a specific result, or better: A result that fulfills certain additional conditions. To this end, we can add some regularization $R(a)$ to Equation 2.3

$$\arg \min_a \left(|g(a) - b| + \gamma R(a) \right) \,, \tag{2.4}$$

where $R(a) \geq 0$ is an arbitrary function $R : \mathcal{A} \longrightarrow \mathbb{R}_{\geq 0}$ and γ is the regularization parameter $\gamma \in \mathbb{R}_{\geq 0}$. A simple example is when $R(a) = ||a||_2$ is the Euclidean norm and $\gamma = 1$. When we solve Equation 2.4, then there exist exactly one solution for our example in Equation 2.2, namely,

$$a = 1 \,.$$

Therefore, adding an appropriate regularization function can help find the desired minimum, hence, getting the initial conditions we are looking for.

Another example, is the inverse problems solved in Chapter 3. As previously described and visualized in Figure 2.1, the γ-rays emitted by the Tc^{99m} source pass through the pinholes of the collimator and are detected by the detector. Let us formulate the inverse problem: For a given measurement, here, the image from the detector, we search for the condition under which the measurement was observed, i.e., the position of the Tc^{99m} source.

The final example we give, is the propagation of the acoustic wave, which is an important part of Chapter 4. As described earlier, the Figure 2.2 visualizes the propagation of the wave in the frequency spectrum through various types of media. Solving the inverse problem involves reconstructing the different medium velocities in the area of interest from the measured acoustic waves.

2.3 Linear Models

This subsection describes how to solve an inverse problem using a linear model. We define

$$x \in \mathbb{R}^K \quad \Longleftrightarrow \quad x = [x_1, \cdots, x_K] \quad \text{with} \quad x_i \in \mathbb{R} \quad \text{for all} \quad i \in \{1, \cdots, K\}.$$

Let the multivariate function g be

$$
\begin{array}{rcl}
g : \mathbb{R}^K & \longrightarrow & \mathbb{R} \\
x & \longmapsto & y
\end{array},
$$

with the observation $y \in \mathbb{R}$ and the initial condition $x \in \mathbb{R}^K$. During an experiment, we might only know some initial condition parameters. We divide x into two parts: $t \in \mathbb{R}^{\tilde{K}}$ the experimental condition (known parameters of the initial condition) and $\theta \in \mathbb{R}^k$ the unknown parameters of the initial condition. Solving the inverse problem will find the initial condition θ with the given experimental condition t and the corresponding observation y. We can thus write

$$
\begin{array}{rcl}
g : \mathbb{R}^K & \longrightarrow & \mathbb{R} \\
{[t, \theta]} & \longmapsto & y
\end{array} \quad \text{with } K = \tilde{K} + k \text{ and } x = [t, \theta].
$$

During data collection, some random error ε distorts the model. Hence, we can write

$$y^{obs} = g(t^{obs}, \theta) + \varepsilon, \tag{2.5}$$

where ε can result from inaccuracies in the measuring device or a distorting of the model g.

The simplest relationship of a deterministic linear model [72] is when the parameters θ are linearly dependent on the known experimental condition t. Then, there are functions $f_i(t) : \mathbb{R}^{\hat{K}} \longrightarrow \mathbb{R}$, that approximate the function g as a linear combination of the unknown parameters θ and the functions f_i:

$$f(t) = \begin{bmatrix} f_1(t) \\ \vdots \\ f_k(t) \end{bmatrix} \in \mathbb{R}^{k \times 1} \quad \text{and} \quad \theta = \begin{bmatrix} \theta_1 \\ \vdots \\ \theta_k \end{bmatrix} \in \mathbb{R}^{k \times 1} \quad s.t. \quad g(t, \theta) \approx f(t)^T \theta.$$

We note that $f(t)^T \in \mathbb{R}^{1 \times k}$ is the transpose of $f(t) \in \mathbb{R}^{k \times 1}$. Hence, we can deduce from Equation 2.5

$$y^{obs} = g(t^{obs}, \theta) + \varepsilon = f(t^{obs})^T \theta + \hat{\varepsilon}, \tag{2.6}$$

where $\hat{\varepsilon}$ is an error. To solve the inverse problem, we find the unknown parameters θ. When just a single unknown $\theta = \theta_1$ exists, then we have just a single function $f(t) = f_1(t)$. A good approximation θ_1, can be found, when we use Equation 2.6 and get

$$y^{obs} = g(t^{obs}, \theta_1) + \varepsilon = f(t^{obs})^T \theta_1 + \hat{\varepsilon}.$$

For a sufficiently small error $||\hat{\varepsilon}||_2$ we can approximate

$$y^{obs} \approx f(t^{obs})^T \theta_1,$$

and a solution is found by minimizing the difference

$$\arg \min_{\theta} \left|\left| y^{obs} - f(t^{obs})^T \theta_1 \right|\right|_2 .$$

In fact, to find a solution for a single unknown it is sufficient to use one observation y^{obs}

$$\theta_1 = \frac{y^{obs}}{f_1(t^{obs})} ,$$

and therefore a good approximation for the unknown parameter θ, if $||\hat{\varepsilon}||_2$ is small enough. However, in most cases, we have multiple unknowns. We will now generalize the Equation 2.6 to a statistic linear model, with N observations and k unknown parameters θ. We assume that the unknown parameters stay the same for all N known experimental conditions $t_i^{obs} \in \mathbb{R}^{\tilde{K}}$. Hence, the i-th observation $y_i^{obs} = g(t_i^{obs}, \theta) + \varepsilon_i$, can be approximated with the linear Equation 2.6 as

$$y_i^{obs} = g\left(t_i^{obs}, \theta\right) + \varepsilon_i = f\left(t_i^{obs}\right)^T \theta + \hat{\varepsilon}_i ,$$

with some error $\hat{\varepsilon}_i$. Further, generalizing for N observations, we get a $Y^{obs} \in \mathbb{R}^N$ with

$$
\begin{aligned}
Y^{obs} = \begin{bmatrix} y_1^{obs} \\ \vdots \\ y_N^{obs} \end{bmatrix} &= \begin{bmatrix} f\left(t_1^{obs}\right) & \cdots & f\left(t_N^{obs}\right) \end{bmatrix}^T \begin{bmatrix} \theta_1 \\ \vdots \\ \theta_k \end{bmatrix} + \begin{bmatrix} \hat{\varepsilon}_1 \\ \vdots \\ \hat{\varepsilon}_k \end{bmatrix} \\
\\
&= \begin{bmatrix} f_1(t_1^{obs}) & \cdots & f_1(t_N^{obs}) \\ \vdots & \ddots & \vdots \\ f_k(t_1^{obs}) & \cdots & f_k(t_N^{obs}) \end{bmatrix}^T \begin{bmatrix} \theta_1 \\ \vdots \\ \theta_k \end{bmatrix} + \begin{bmatrix} \hat{\varepsilon}_1 \\ \vdots \\ \hat{\varepsilon}_k \end{bmatrix} \quad\quad (2.7) \\
\\
&= F\left(t^{obs}\right)^T \theta + E \quad \text{for} \quad t^{obs} = [t_1^{obs}, \cdots, t_N^{obs}] ,
\end{aligned}
$$

where $F\left(t^{obs}\right) \in \mathbb{R}^{k \times N}$ is the linear combination of the observations $t^{obs} \in \mathbb{R}^{\hat{K} \times N}$, the unknown parameter $\theta \in \mathbb{R}^k$, and the error $E \in \mathbb{R}^k$. Again, we exploit that for a sufficiently small $||E||$ we have

$$Y^{obs} \approx F\left(t^{obs}\right)^T \theta . \quad\quad (2.8)$$

Therefore a good solution for θ can be found when solving Equation 2.8.

For simplification, we assume that all the linear equations are independent; hence, all columns of $F\left(t^{obs}\right)$ are linearly independent. Then, we have three cases: The first case is when the number of k unknown parameters θ and number of N observations y_i^{obs} are equal ($k = N$); then there exists exactly one solution $\theta \in \mathbb{R}^k$. The second case is when we have more observations N than unknowns k. This is more robust against outliers in the observations, especially when $N \gg k$. In [72], many classical methods are described to find a good approximation in such a case. The third case is when the number of unknown parameters exceeds the number of observations. In fact, such a case is an ill-posed problem because more than one result exists. Therefore, additional boundary information to the unknown parameters θ can be given to find the desired solution. In [31], some numerical methods are proposed to solve an ill-posed statistical linear equation.

2.4 Non-linear Models

We can describe a non-linear model similarly to the beginning of Section 2.3 and Equation 2.6. For a given experimental condition $t \in \mathbb{R}^{\tilde{K}}$ and an observation $y \in \mathbb{R}$ we search for the initial condition $\theta \in \mathbb{R}^k$

$$
\begin{aligned}
g: \mathbb{R}^K &\longrightarrow \mathbb{R} \\
[t, \theta] &\longmapsto y
\end{aligned}
\quad \text{with } K = \tilde{K} + k \text{ and } x = [t, \theta].
$$

As before, some random error ε can accrue that distorts the model. Hence, we write

$$
y^{obs} = g(t^{obs}, \theta) + \varepsilon. \tag{2.9}
$$

Some mathematical models, like the wave-equation, cannot be linearized. Therefore, we introduce an approach to solve non-linear inverse problems. Unlike in Section 2.3, we do not linearize the problem; we will not have a linear equation like Equation 2.8. Therefore, we will use optimization algorithms to solve Equation 2.9. In Section 2.5, we give some examples of algorithms to solve inverse problems, namely: GD, GN, and CqN. A further reading recommendation is the thesis of Eriksson [22] which gives an excellent overview of some optimization methods for non-linear models.

To solve the inverse problem, we need to rewrite Equation 2.9 into a minimization problem. If $||\varepsilon||_2$ is sufficiently small, then a good result for a given t^{obs} and the corresponding measurement y^{obs} is

$$
\arg \min_{\theta} \left|\left| g(t^{obs}, \theta) - y^{obs} \right|\right|_2^2.
$$

However, this may not give the desired output for multiple unknowns ($k > 1$). Hence, either some regularization needs to be added, or the number of observations has to be increased. When we have N observations, we get an observation y_i^{obs} for each experimental condition t_i^{obs}, with $i = 1, \cdots, N$. We define the loss function $\mathcal{L}(\theta)$ as a dot product, with

$$
G\left(t^{obs}, \theta\right) = \begin{bmatrix} g(t_1^{obs}, \theta) \\ \vdots \\ g(t_N^{obs}, \theta) \end{bmatrix} \quad \text{and} \quad Y^{obs} = \begin{bmatrix} y_1^{obs} \\ \vdots \\ y_N^{obs} \end{bmatrix}
$$

as follows

$$
\begin{aligned}
\mathcal{L}(\theta) &= \frac{1}{2} \sum_{i=1}^N \left(g(t_i^{obs}, \theta) - y_i^{obs} \right)^2 \\
&= \frac{1}{2} \left(G(t^{obs}, \theta) - Y^{obs} \right)^T \left(G(t^{obs}, \theta) - Y^{obs} \right) \\
&= \frac{1}{2} \left|\left| G(t^{obs}, \theta) - Y^{obs} \right|\right|_2^2,
\end{aligned} \tag{2.10}
$$

and thus we have a good result for θ when solving the minimization problem

$$
\arg \min_{\theta} \mathcal{L}(\theta) = \arg \min_{\theta} \left(\frac{1}{2} \sum_{i=1}^N \left(g(t_i^{obs}, \theta) - y_i^{obs} \right)^2 \right).
$$

We note that we use the Mean Squared Error Loss (MSELoss); however, a different loss function can be used. The condition that a loss function should fulfil is that it has a minimum at the desired result.

2.5 Optimization Algorithms

Optimization algorithms are an important part of numerical mathematics. In this section, we show, how to solve a linear model of the form

$$Ax = y \,, \tag{2.11}$$

with $A \in \mathbb{R}^{N \times M}$ and $x, b \in \mathbb{R}^M$ using the CG method and how to find the minimum of a function

$$\arg \min_{\theta} \mathcal{L}(\theta) \,,$$

where $\mathcal{L} : \mathcal{A} \longrightarrow \mathcal{B}$ is a derivable multi-variable function with $\mathcal{A} \subset \mathbb{R}^N$ and $\mathcal{B} \subset \mathbb{R}$, using the GD, GN, and CqN algorithms. These algorithms can also be used to solve non-linear models.

2.5.1 Conjugate Gradient (CG) algorithm

The CG Algorithm [34] is a popular numerical method to solve linear equations in the form of Equation 2.11. It is advantageous for solving large linear systems since it only uses matrix-vector multiplications. Hence, it is not as computationally heavy as matrix-matrix multiplications or finding the inverse of a matrix. To solve a linear equation of the form

$$Hx = b$$

with the CG algorithm the matrix H has to be positive definite, meaning

$$H \in \mathbb{R}^{M \times M} \text{ is positive definite} \iff x^T H x > 0 \,, \; \forall x \in \mathbb{R}^M \backslash \{0\} \,, \; H \text{ is a symmetric real matrix} \,.$$

We note that the matrix H can be written as

$$H = A^T A \in \mathbb{R}^{M \times M}$$

and is therefore symmetric, as shown in Theorem 7.2. In fact, we show in Theorem 7.3 that if H is invertible, it is positive definite. Hence, to solve the linear Equation 2.11 we multiply A^T on the left side and we get

$$Hx = b \,, \quad \text{with} \quad b = A^T y \quad \text{and} \quad H = A^T A$$

so that it can be solved with the CG algorithm. In Algorithm 1, we give a detailed description of the CG algorithm. We note that nowhere in the CG algorithm we compute

$$H = A^T A \,.$$

This is avoided by computing the matrix-vector multiplication

$$Hx = A^T(Ax).$$

To add additional regularization and to ensure that the matrix H is invertible and therefore positive definite, we can use

$$H = A^T A + \lambda E$$

for a $\lambda \in \mathbb{R}_{>0}$, where E is the identity matrix (instead of $H = A^T A$), as shown in Theorem 7.4. We note, if H is positive semidefinit

$$H \in \mathbb{R}^{M \times M} \text{ is positive semidefinite} \iff \begin{cases} x^T H x \geq 0 \,, \forall x \in \mathbb{R}^M \setminus \{0\} \\ H \text{ is a symmetric real matrix} \end{cases},$$

and b is in the range space of H, then the CG method converges as well [33, 41].

Algorithm 1: The algorithm shows an implementation of the CG method, with three possible implementations to update β_n: (a.1) Polak-Ribière, (a.2) Fletcher-Reeves, and (a.3) Hestenes-Stiefel

---

Data: solve $Hx = b$, for H real, symmetric, positive definite matrix, b vector, x unknown

Result: find unknown x

x_0 initial guess ;

$r_0 \leftarrow b - Hx$;

$p_0 \leftarrow r_0$;

$n \leftarrow 0$;

while $||r_n||$ *is not small enough* **do**

$\qquad \tau_n \leftarrow \dfrac{r_n^T r_n}{p_n^T H p_n}$;

$\qquad x_{n+1} \leftarrow x_n + \tau_n p_n$;

$\qquad r_{n+1} \leftarrow r_n - \tau_n H p_n$;

$\qquad$ calculate β_n;

$\qquad$ (a.1) $\beta_n \leftarrow \dfrac{r_{n+1}^T r_{n+1}}{r_n^T r_n}$ $\qquad$ (Polak-Ribière);

$\qquad$ (a.2) $\beta_n \leftarrow \dfrac{r_{n+1}^T (r_{n+1} - r_n)}{r_n^T r_n}$ $\qquad$ (Fletcher-Reeves);

$\qquad$ (a.3) $\beta_n \leftarrow \dfrac{r_{n+1}^T (r_{n+1} - r_n)}{p_n^T (r_{n+1} - r_n)}$ $\qquad$ (Hestenes-Stiefel);

$\qquad p_{n+1} \leftarrow r_{n+1} + \beta_n p_n$;

$\qquad n \leftarrow n + 1$;

end

2.5.2 Gradient Descent (GD)

The gradient descent algorithm [17, 51] is one of the most commonly used and elementary algorithms to find a local minimum of a function. In order to minimize a function, the function $\mathcal{L}(\theta)$ has to be $\mathcal{L} \in \mathcal{C}^1(\mathcal{A})$, meaning that $\mathcal{L}$ is at least one time differentiable in $\mathcal{A}$. In Algorithm 2, we visualize the gradient descent. First, the gradient of $\mathcal{L}$ is computed with the initial guess $\theta^{(0)}$. Then, the negative gradient of $\mathcal{L}$ is applied with a certain step size α. This is done until a certain breaking condition is fulfilled. In this example, we take the relative error breaking condition

$$\left| \frac{\mathcal{L}\left(\theta^{(0)}\right) - \mathcal{L}\left(\theta^{(n)}\right)}{\mathcal{L}\left(\theta^{(0)}\right)} \right| > (1 - \varepsilon), \tag{2.12}$$

where $\theta^{(0)}$ is the initial guess of θ and $\theta^{(n)}$ is its value after n updates, with $0 < \varepsilon < 1$. The algorithm is terminated when Equation 2.12 is fulfilled. We note that for a big step size α, the algorithm may not converge, and that for a small step size α, it might take a long time to converge (assuming there exists a minimum). We note that choosing a fixed step-size of α can either lead to very slow convergence or to oscillation around a minimum, as can be seen in Figure 2.4 and Figure 2.5. To avoid such behavior, we can implement the Armijo–Goldstein condition [3], as described in the Subsection 2.5.3.

Algorithm 2: A visualization of the gradient descent algorithm. We note that α can be updated after each iteration, with, e.g., the Armijo-Goldstein condition described in Subsection 2.5.3 and Algorithm 3.

Data: $\alpha > 0$ step size; ε breaking condition
Result: $\arg \min_{\theta} \mathcal{L}(\theta)$

$\theta^{(0)}$ initial guess ;
$n \leftarrow 0$;
while $\left| \dfrac{\mathcal{L}\left(\theta^{(0)}\right) - \mathcal{L}\left(\theta^{(n)}\right)}{\mathcal{L}\left(\theta^{(0)}\right)} \right| < (1 - \varepsilon)$ **do**

   $n \leftarrow n + 1$;
   $p \leftarrow -\nabla\mathcal{L}\left(\theta^{(n-1)}\right)$ set gradient as search direction;
   $\theta^{(n)} \leftarrow \theta^{(n-1)} + \alpha p$ apply search direction;
end

2.5.3 Armijo–Goldstein condition

A constant step size can lead to very slow optimization, or even to the optimization algorithm oscillating around a minimum. Therefore, it is important to update the step size during the optimization. One well-known method is the Armijo–Goldstein condition [3], which can be applied if the function being minimized is $\mathcal{L}(\theta) \in C^1(\mathcal{A})$. We show this method in Algorithm 3.

Algorithm 3: The Armijo-Goldstein condition to reduce the step size during the optimization process. In our examples we use $\alpha = 1$, $\sigma = \delta = 0.1$.

Data: α step size, search control parameters $0 < \sigma < 1$ and $0 < \delta < 1$, p search direction

Result: α new step size

while $\mathcal{L}(\theta + \alpha p) > \mathcal{L}(\theta) + \alpha \delta \nabla \mathcal{L}(\theta)^T p$ **do**
  $\quad \mid \quad \alpha \leftarrow \sigma \alpha$ reduce step size;
end

2.5.4 Gauss–Newton (GN) and Conjugate quasi-Newton (CqN) algorithm

---

Algorithm 4: A visualization of the gradient GN and the CqN algorithm. Either use (a.1) or (a.2): (a.1) is the standard approximation (a.2) can have the advantage of additional regularization and ensures that H is positive definite, which can be important for the CG algorithm. Solving $Hp = -\nabla \mathcal{L}(\theta^{(n)})$ with (b.1) is the GN method, (b.2) is the CqN method, which solves it with maximal c iteration (e.g., $c = 2$). We note, that α can be updated with e.g. the Armijo-Goldstein condition described in Subsection 2.5.3 and Algorithm 3.

Data: ε breaking condition

Result: $\arg \min_\theta \mathcal{L}(\theta)$

$\theta^{(0)}$ initial guess ;

$n \leftarrow 0$;

while $\left| \dfrac{\mathcal{L}(\theta^{(0)}) - \mathcal{L}(\theta^{(n)})}{\mathcal{L}(\theta^{(0)})} \right| < (1 - \varepsilon)$ **do**

  $\quad \mid \quad n \leftarrow n + 1$;
  $\quad \mid \quad J \leftarrow \nabla G(t^{obs}, \theta^{(n-1)})$ calculate Jacobian matrix ;
  $\quad \mid \quad$ approximate the Hessian Matrix H;
  $\quad \mid \quad \quad$ (a.1) $H \leftarrow J^T J$;
  $\quad \mid \quad \quad$ (a.2) $H \leftarrow J^T J + \lambda E$;
  $\quad \mid \quad$ solve $Hp = -\nabla \mathcal{L}(\theta^{(n)})$;
  $\quad \mid \quad \quad$ (b.1) standard (GN);
  $\quad \mid \quad \quad$ (b.2) maximal c iterations using CG (CqN) ;
  $\quad \mid \quad$ adapt step size α with Armijo-Goldstein condition;
  $\quad \mid \quad \theta^{(n)} \leftarrow \theta^{(n-1)} + \alpha p$;
end

In contrast to the GD, the GN Algorithm [29, 30, 90] can be more robust and faster in the optimization. The GN algorithm locally converges quadratically when we minimize the MSELoss.

We apply the GN algorithm on the MSELoss in Equation 2.10. For simplification, we write

$$\mathcal{L}(\theta) = \frac{1}{2} \left|\left| G(t^{obs}, \theta) - Y^{obs} \right|\right|_2^2 = \frac{1}{2} ||d(\theta)||_2^2 = \frac{1}{2} \sum_{n=1}^{N} (d_n(\theta))^2 \;, \tag{2.13}$$

with the residual vector

$$d(\theta) = \begin{bmatrix} d_1(\theta) \\ \vdots \\ d_N(\theta) \end{bmatrix} = \begin{bmatrix} g(t_1^{obs}, \theta) - y_1^{obs} \\ \vdots \\ g(t_N^{obs}, \theta) - y_N^{obs} \end{bmatrix}.$$

The second order of the Taylor-Approximation of $\mathcal{L}(\theta)$ is

$$\mathcal{L}(\theta) \approx \mathcal{L}(\hat{\theta}) + \nabla\mathcal{L}(\hat{\theta})^T (\theta - \hat{\theta}) + (\theta - \hat{\theta})^T \nabla^2\mathcal{L}(\hat{\theta})(\theta - \hat{\theta})$$

and is a polynomial approximation of the order two of the function $\mathcal{L}(\theta)$ evaluated at $\hat{\theta} \in \mathbb{R}^M$ that is close enough to θ. To find the minimum of $\mathcal{L}(\theta)$, we need to search for a θ s.t. $\nabla\mathcal{L}(\theta) = 0$. Hence, using

$$\nabla\mathcal{L}(\theta) \approx \nabla\mathcal{L}(\hat{\theta}) + \nabla^2\mathcal{L}(\hat{\theta}) \underbrace{(\theta - \hat{\theta})}_{=p}$$

we get that

$$-\nabla\mathcal{L}(\hat{\theta}) \approx \nabla^2\mathcal{L}(\hat{\theta})p \,. \tag{2.14}$$

Solving Equation 2.14 and updating θ iteratively gives us the Newton-Method [90]. However, the Hessian matrix $\nabla^2\mathcal{L}(\theta)$ can be very cumbersome to calculate and expensive to compute. The GN method approximates the Hessian matrix $\nabla^2\mathcal{L}(\theta)$ with the Jacobian matrix of $G(t^{obs}, \theta)$

$$J_G(\theta) = \begin{bmatrix} \nabla d_1(\theta)^T \\ \vdots \\ \nabla d_N(\theta)^T \end{bmatrix} = \begin{bmatrix} \dfrac{\partial g(t_1^{obs}, \theta)}{\partial \theta_1} & \cdots & \dfrac{\partial g(t_1^{obs}, \theta)}{\partial \theta_M} \\ \vdots & \ddots & \vdots \\ \dfrac{\partial g(t_N^{obs}, \theta)}{\partial \theta_1} & \cdots & \dfrac{\partial g(t_N^{obs}, \theta)}{\partial \theta_M} \end{bmatrix}$$

as follows

$$\nabla^2\mathcal{L}(\theta) \approx J_G(\theta)^T J_G(\theta) \,. \tag{2.15}$$

The Hessian matrix can be approximated in that way because the gradient of Equation 2.13 is

$$\nabla\mathcal{L}(\theta) = \sum_{n=1}^{N} d_n(\theta)\nabla d_n(\theta) = J_G(\theta)^T d(\theta) = J_G(\theta)^T \left(G(t^{obs}, \theta) - Y^{obs} \right) , \tag{2.16}$$

and therefore, the Hessian matrix is

$$\begin{aligned} \nabla^2\mathcal{L}(\theta) &= \sum_{n=1}^{N} \nabla d_n(\theta)\nabla d_n(\theta)^T + \sum_{n=1}^{N} d_n(\theta)\nabla^2 d_n(\theta) \\ &= J_G(\theta)^T J_G(\theta) + \sum_{n=1}^{N} d_n(\theta)\nabla^2 d_n(\theta) \end{aligned} \tag{2.17}$$

In most cases, the first term of Equation 2.17 dominates the second part (for θ close enough to the minimum of $\mathcal{L}(\theta)$); hence, the convergence is similar to Newton's method. The first term is dominant if the $|d_n(\theta)| \left\|\nabla^2 d_n(\theta)\right\|$ terms are significantly smaller than the eigenvalues of $J_G(\theta)^T J_G(\theta)$. This happens either if the residuals $d_n(\theta)$ are small, or if the residuals $d_n(\theta)$ are nearly affine, hence $\left\|\nabla^2 d_n(\theta)\right\|$ are small. This leads to a rapid local convergence of the GN algorithm [90].

We note that according to Levenberg-Marquardt [90], the GN method finds a solution with

$$(J_G(\theta)^T J_G(\theta) + \lambda E)p = -\nabla\mathcal{L}(\theta_n) \tag{2.18}$$

for an appropriate λ and the unity matrix E.

In Algorithm 4, the GN algorithm is explained. First, an initial guess $\theta^{(0)}$ is defined. Then, while the breaking condition is not fulfilled: First, the Jacobian matrix is computed, second the Hessian matrix H is approximated either with Equation 2.15 or Equation 2.18, and third, the equation

$$Hp = -\nabla\mathcal{L}(\theta^{(n)}) \tag{2.19}$$

is solved. Solving Equation 2.19 with the CG method using a maximal number of c iterations (e.g. $c = 2$), is called the CqN algorithm. For large-scale matrices, the advantage of solving Equation 2.19 with CqN is that it speeds up the algorithm (reducing the computational cost when solving the inverse problem) and still gives a good approximation.

2.5.5 Examples

This subsection will show examples of how to solve a *linear* and a *non-linear* model.

Linear Model

Here, we will give a simple example of how to solve a linear model and explain how to transform the function

$$l(t,\theta) = -t^2 + \theta_1 t + \theta_2 \,, \tag{2.20}$$

with the experimental condition t and the unknown condition θ, into a linear model. First, we bring all the unknowns θ onto one side and all the parameters independent of θ onto the other side

$$g(t,\theta) = l(t,\theta) + t^2 = \theta_1 t + \theta_2 \,. \tag{2.21}$$

We can deduce from the right side of Equation 2.21 and Equation 2.6, that

$$y^{obs} \approx f(t^{obs})^T\theta = \begin{bmatrix} t^{obs} \\ 1 \end{bmatrix}^T \begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix} \,. \tag{2.22}$$

We assume, that we have N measurements, and hence, with the help of Equation 2.7, Equation 2.8, and Equation 2.21 we get

$$F\left(t^{obs}\right) = \begin{bmatrix} t_1^{obs} & \cdots & t_N^{obs} \\ 1 & \cdots & 1 \end{bmatrix} \,.$$

We note that in [72] some methods are described to solve linear equations, but in this thesis, we focus solely on the CG Algorithm [34], which is described in more detail in Section 2.5.1. In our example, the equation can easily be solved analytically. The CG method is generally used to solve large linear systems.

We assume, that we have N independent measurements, and $l(t, \theta)$ has an error distribution of $\mathcal{N}(0, 1)$. Further, we assume that the ground truth is $\theta = [\theta_1, \theta_2]^T = [3, 10]^T$, as shown in Table 2.2. We would like to find θ using y^{obs} from Table 2.2 with N observations.

t^{obs}	-5	-3	-1	1	3	5
$l(t^{obs}, \theta)$	-30	-8	6	12	10	0
$l(t^{obs}, \theta) + \varepsilon$	-29.4623	-6.1661	3.7412	12.8622	10.3188	-1.3077
$y^{obs} = g(t^{obs}, \theta) + \varepsilon$	-4.4623	2.8339	4.7412	13.8622	19.3188	23.6923

Table 2.2: We assume that we have N measurements of $l(t^{obs}, \theta)$ where ε is drawn from a $\mathcal{N}(0, 1)$ distribution.

Case 1, $N = 2$

In the first case $N = 2$, with the known experimental condition $t^{obs} = [-5, -3]$, we have

$$Y^{obs} = \begin{bmatrix} -4.4623 \\ 2.8339 \end{bmatrix} = \begin{bmatrix} -5 & -3 \\ 1 & 1 \end{bmatrix}^T \begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix} = F(t^{obs})^T \theta$$

a linear system with two equations and two unknowns can be solved analytically, and we thus get

$$\begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix} = \begin{bmatrix} 3.6481 \\ 10.4009 \end{bmatrix}$$

as shown in Figure 2.3. We note that it has an error of $||\theta^{true} - \theta||_2 = 0.7621$.

Case 2, $N > 2$

Now we assume that we have more measurements than unknowns, e.g., $N = 6$. To be more precise, we assume that we have measurements at $t^{obs} = [-5, -3, -1, 1, 3, 5]$, see Table 2.2. Hence, we have

$$Y^{obs} = \begin{bmatrix} -4.4623 \\ 2.8339 \\ 4.7412 \\ 13.8622 \\ 19.3188 \\ 23.6923 \end{bmatrix} = \begin{bmatrix} -5 & 1 \\ -3 & 1 \\ -1 & 1 \\ 1 & 1 \\ 3 & 1 \\ 5 & 1 \end{bmatrix} \begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix} = F(t^{obs})^T \theta \, .$$

As we can see, we have more equations than unknowns. We cannot get an analytical solution assuming all the equations are linearly independent. However, there exists a simple trick to

t^{obs}	-5	-3	-1	1	3	5
$g(t^{obs}, \theta)$	-30	-8	6	12	10	0
$g(t^{obs}, \theta) + \varepsilon$	-29.4623	-6.1661	3.7412	12.8622	10.3188	-1.3077

Table 2.3: We assume that we have N measurements of $g(t^{obs}, \theta)$ where ε is drawn from a $\mathcal{N}(0, 1)$ distribution.

get the same amount of equations and unknown parameters, namely multiplying both sides by $F(t^{obs})$,

$$F(t^{obs})Y^{obs} = \begin{bmatrix} 199.3489 \\ 59.9860 \end{bmatrix} = \begin{bmatrix} 70 & 0 \\ 0 & 6 \end{bmatrix} \begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix} = F(t^{obs})F(t^{obs})^T \theta \,.$$

Now, we have only two linear equations with two unknowns, and they can be easily solved. We get a very good approximation of

$$\begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix} = \begin{bmatrix} 2.8478 \\ 9.9977 \end{bmatrix} \,,$$

as shown in Figure 2.3. It has an error of $||\theta^{true} - \theta||_2 = 0.1522$.

We note that for a large-scale linear problem (a lot of unknowns), the CG method described in Subsection 2.5.1 is a good and inexpensive approximator since only matrix-vector multiplications are needed.

Case 3, $N < 2$

Assuming now that we have fewer equations than unknowns, e.g., $N = 1$, with $t^{obs} = -1$, hence, we have

$$Y^{obs} = \begin{bmatrix} 4.7412 \end{bmatrix} = \begin{bmatrix} -1 \\ 1 \end{bmatrix}^T \begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix} = F\left(t^{obs}\right)^T \theta \,.$$

We have one equation with two unknowns; therefore, we have infinitely many solutions. Two of them are

$$\begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix} = \begin{bmatrix} -4.7412 \\ 0 \end{bmatrix} \quad \text{and} \quad \begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix} = \begin{bmatrix} -2.3706 \\ 2.3706 \end{bmatrix} \,,$$

as shown in Figure 2.3. In such a case, additional boundary conditions can improve the results.

Non-linear Model

We give an easy example of a non-linear function $f : \mathbb{R} \longrightarrow \mathbb{R}$

$$g(t, \theta) = (\theta_1 - t)(\theta_2 + t) \quad \text{with} \quad \begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix} = \begin{bmatrix} 5 \\ 2 \end{bmatrix} \,.$$

In fact, it is the same function as $l(t, \theta)$ in Equation 2.20 as visualized in Figure 2.3. We will use the same values as in Table 2.2, and display the values of the function $g(t^{ob}, \theta)$ in Table 2.3. We
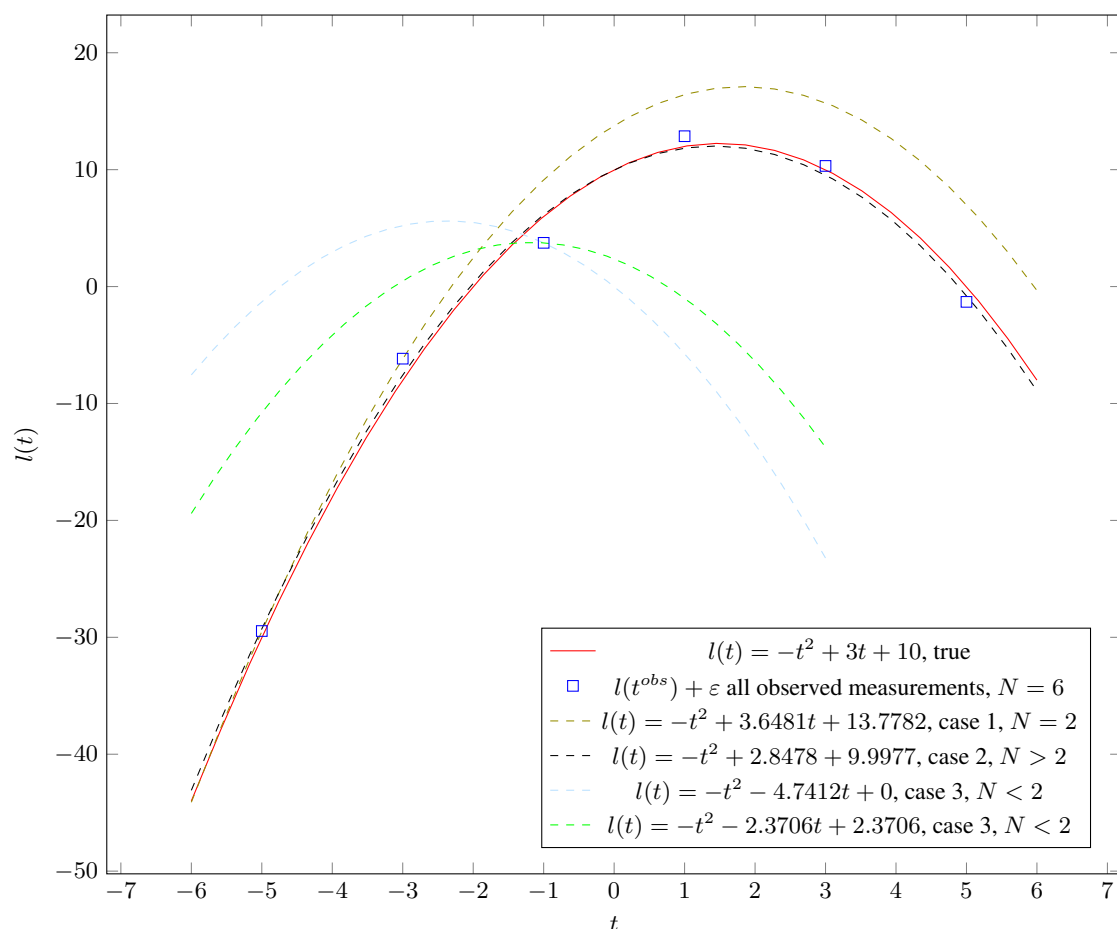
Figure 2.3: A visualization of the function $l(t, \theta)$ of Equation 2.20, and the resulting reconstruction of the model, assuming that θ is unknown, and only N measurements at the points of Table 2.2 are known.

define the gradient $\nabla \mathcal{L}(\theta)$ and the Hessian matrix $\nabla^2 \mathcal{L}(\theta)$ as follows

$$
\nabla \mathcal{L}(\theta) = \begin{bmatrix} \dfrac{\partial \mathcal{L}(\theta)}{\partial \theta_1} \\ \vdots \\ \dfrac{\partial \mathcal{L}(\theta)}{\partial \theta_k} \end{bmatrix} \quad \text{and} \quad \nabla^2 \mathcal{L}(\theta) = \begin{bmatrix} \dfrac{\partial^2 \mathcal{L}(\theta)}{\partial \theta_1 \partial \theta_1} & \cdots & \dfrac{\partial^2 \mathcal{L}(\theta)}{\partial \theta_k \partial \theta_1} \\ \vdots & \ddots & \vdots \\ \dfrac{\partial^2 \mathcal{L}(\theta)}{\partial \theta_1 \partial \theta_k} & \cdots & \dfrac{\partial^2 \mathcal{L}(\theta)}{\partial \theta_k \partial \theta_k} \end{bmatrix}.
$$

We minimize the function $\mathcal{L}(\theta)$ in Equation 2.10 using the GD, GN, and CqN (see Subsection 2.5.2 and Subsection 2.5.4). For these optimizations, we need to calculate the gradient $\nabla \mathcal{L}(\theta)$ and approximate the Hessian matrix $\nabla^2 \mathcal{L}(\theta)$. Because of Equation 2.16 and Equation 2.15, it is sufficient to calculate the Jacobian matrix $J_G(\theta)$ of $G(t^{obs}, \theta)$. Hence using

Equation 2.16, we calculate

$$J_G(\theta) = \begin{bmatrix} \theta_2 + t_1^{obs} & \theta_1 - t_1^{obs} \\ \vdots & \vdots \\ \theta_2 + t_N^{obs} & \theta_1 - t_N^{obs} \end{bmatrix}$$

and therefore get

$$\nabla\mathcal{L}(\theta) = J_G(\theta)^T \left(G(t^{obs}, \theta) - Y^{obs} \right) . \tag{2.23}$$

Then with Equation 2.15 the approximation for the Hessian matrix of $\mathcal{L}(\theta)$ is

$$\nabla^2\mathcal{L}(\theta) \approx J_G(\theta)^T J_G(\theta) .$$

The resulting θ from all the algorithms are similar. In Figure 2.4 we show the value of the MSELoss $\mathcal{L}(\theta)$ after each iteration, and in Figure 2.5 we show the development of θ_1 and θ_2 after each iteration with the initial guess of $\theta = [0, 0]^T$. We note that it is essential that the GD have a good step size. Otherwise, it may converge very slowly or not at all. Therefore, using the Armijo-Goldstein condition can drastically improve the performance of the GD. In general, finding the step size with the Armijo-Goldstein condition improves the number of iterations needed to find a good approximation of θ.
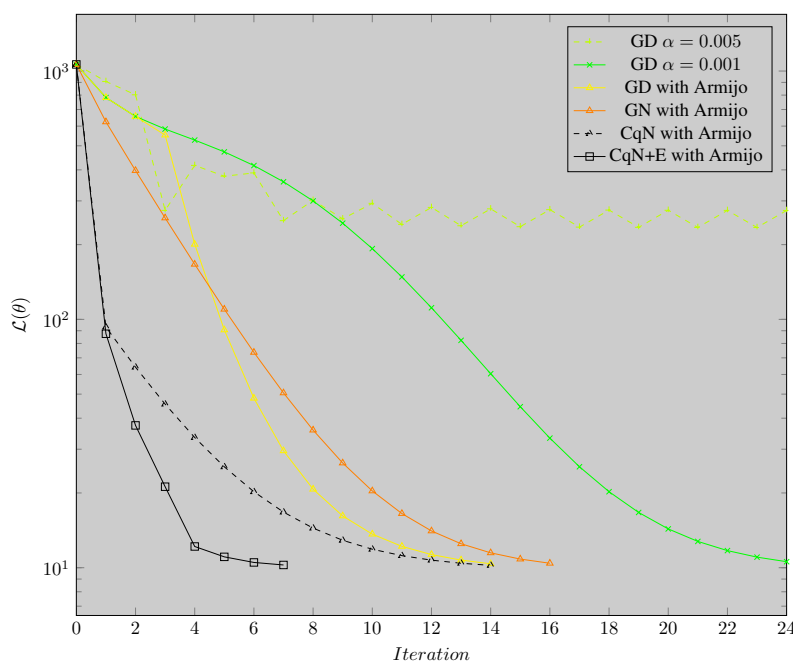

Figure 2.4: Comparing the $\mathcal{L}(\theta)$ value of Equation 2.10 using GD with step size $\alpha = 0.005$, $\alpha = 0.001$, and Armijo-Goldstein condition. In addition, we solve the minimization problem with GN, CqN, and add the unity matrix to the Hessian approximation (CqN+E).
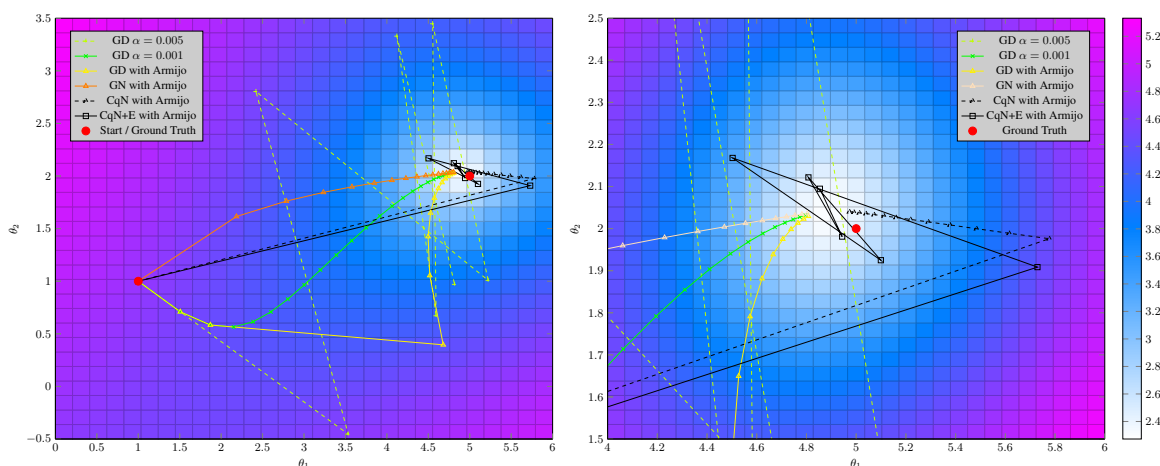
Figure 2.5: The background of the figure shows the value (colorbar) of the loss function $\mathcal{L}(\theta)$. The lines visualize the minimization process of $\mathcal{L}(\theta)$ of Equation 2.10 resulting θ_1 and θ_2 after each iteration with GD using the step size $\alpha = 0.005$, $\alpha = 0.001$, and Armijo-Goldstein condition. In addition, the GN, CqN, and adding the unity matrix to the Hessian approximation using CqN (CqN+E) are shown. On the left, we see the optimization process from the start to end, and on the right just a limited area of the optimization process towards the end. The initial guess is $\theta^{(0)} = (1, 1)$ and the ground truth is $\theta = (5, 2)$.

2.6 Partial Differential Equation (PDE)

Sine, cosine, and ln are at a party. Sine approaches cosine and says, "Hey, what's ln doing over in the corner by themself?". Cosine responds, "You see, ln doesn't integrate very well.".
– unknown

A PDE is a relation between a multi-variable function with various partial derivatives [88]. These are not only used in the pure mathematical field but also in fields like physics and engineering. In this thesis, we use PDEs for a more fundamental understanding of the propagation of the acoustic waves in the tissues. With the help of the PDE of the wave equation, we aim to reconstruct the structure and the medium velocity of different tissues. This section uses [63] as a basis to explain the transformation of the PDE from the wave equation to the Helmholtz equation and the description of FD and FE. The PDE of the wave equation is

$$-\nabla \cdot (u(x)\nabla \bar{y}(x,t)) + \bar{y}_{tt}(x,t) = \bar{f}(x,t) \,, \tag{2.24}$$

where $u(x) > 0$ is the squared medium velocity, $\bar{f}(x,t)$ the source function and $\bar{y}(x,t)$ the pressure variation. We note, that $x \in \mathbb{R}^n$ is the n dimensional space domain and $t \in \mathbb{R}_{\geq 0}$ the time domain. From this PDE, the Helmholtz equation can be derived. A time-harmonic wave can express the source and the wave field; hence, we can use the Fourier transform of the time variable and separate time and space dimensions to write $\bar{f}$ and $\bar{y}$ as:

$$\bar{y}(x,t) = y(x)e^{-i\omega t} \quad \text{and} \quad \bar{f}(x,t) = f(x)e^{-i\omega t} \,, \tag{2.25}$$

where ω is the angular frequency, $f(x)$ the source function and $y(x)$ the pressure variation. By substituting Equation 2.25 into the wave Equation 2.24, we get the frequency dependent form of the wave equation; namely, the Helmholtz equation

$$-\nabla \cdot (u(x)\nabla y(x)) - \omega^2 y(x) = f(x) \,.$$

In our approach, we use the Sommerfeld boundary condition, which is an absorbing boundary condition [10, 11, 21]

$$
\begin{cases}
-\nabla \cdot (u(x)\nabla y(x)) \;-\; \omega^2 y(x) \;=\; f(x), & \text{in } \Omega^o = \Omega \setminus \partial\Omega \\[2mm]
\dfrac{\partial y(x)}{\partial \mathbf{n}} \;-\; ik(x)y(x) \;=\; 0, & \text{on } \Gamma = \partial\Omega
\end{cases}
, \qquad (2.26)
$$

where $k(x) = \dfrac{\omega}{\sqrt{u(x)}}$ is the wave-number at time-frequency ω and

$$\frac{\partial y(x)}{\partial \mathbf{n}} := \mathbf{n} \cdot \nabla y(x)$$

is the normal derivative, where $\mathbf{n}$ denotes the normal on the boundary $\Gamma = \partial\Omega$.

It is generally challenging to solve a PDE analytically, and sometimes an analytical solution does not even exist. Therefore, we solve it numerically by discretizing the PDE using either FD or FE [63].

2.6.1 Finite Difference (FD)

The FD grid is a uniformly staggered mesh, as visualized in Figure 2.6. The PDE is solved numerically on the grid points. We will explain how to solve the Helmholtz Equation 2.26 using FD in a 2D space. It can be generalized to higher dimensions as well. First, we separate the functions $y = y(x)$ and $f = f(x)$ into the real (r) and imaginary (i) parts,

$$y = y^{(r)} + iy^{(i)} \,, \quad f = f^{(r)} + if^{(i)} \,,$$

therefore obtaining a double real-valued system instead of a singly complex-valued system. Since the real part, $y^{(r)}$ and the imaginary part $y^{(i)}$ are only coupled on the boundary Γ; they can be computed separately on Ω^o. Hence, the discretized real part of the Equation 2.26 at the grid point (i, j) can be written as

$$-\frac{\partial}{\partial x^{(1)}}\left(u_{i+\frac{1}{2},j}\frac{y^{(r)}_{i+1,j} - y^{(r)}_{i,j}}{h}\right) - \frac{\partial}{\partial x^{(2)}}\left(u_{i,j+\frac{1}{2}}\frac{y^{(r)}_{i,j+1} - y^{(r)}_{i,j}}{h}\right) - \omega^2 y^{(r)}_{i,j} = f^{(r)}_{i,j} \,, \quad (2.27)$$

where the second order approximation of the first derivative is

$$\frac{\partial}{\partial x^{(1)}}y^{(r)}\bigg|_{x=x_{i+\frac{1}{2},j}} = \frac{y^{(r)}_{i+1,j} - y^{(r)}_{i,j}}{h} \quad \text{and} \quad \frac{\partial}{\partial x^{(2)}}y^{(r)}\bigg|_{x=x_{i,j+\frac{1}{2}}} = \frac{y^{(r)}_{i,j+1} - y^{(r)}_{i,j}}{h} \,.$$

We note that

$$\frac{\partial}{\partial x^{(i)}}\left(u(x)\frac{\partial y(x)}{\partial x^{(i)}}\right) = \frac{\partial}{\partial x^{(i)}}u(x)\frac{\partial}{\partial x^{(i)}}y(x) + u(x)\frac{\partial^2}{\partial^2 x^{(i)}}y(x)\,.$$

Further, we assume that $u(x)$ is a piecewise constant function in the area

$$\begin{array}{l} x_{i,j}^{(1)} < x^{(1)} < x_{i+1,j}^{(1)} \\ x_{i,j}^{(2)} < x^{(2)} < x_{i,j+1}^{(2)} \end{array} \quad \text{for all } i \text{ and } j\,,$$

hence,

$$\frac{\partial}{\partial x^{(i)}}u(x) = 0 \quad \text{for all} \quad \begin{array}{l} x_{i,j} < x^{(1)} < x_{i+1,j}^{(1)} \\ x_{i,j} < x^{(2)} < x_{i,j+1}^{(2)} \end{array}\,.$$

We discretize Equation 2.27 to

$$-\left(u_{i+\frac{1}{2},j}\frac{y_{i+1,j}^{(r)} - y_{i,j}^{(r)}}{h^2} - u_{i-\frac{1}{2},j}\frac{y_{i,j}^{(r)} - y_{i-1,j}^{(r)}}{h^2}\right)$$

$$-\left(u_{i,j+\frac{1}{2}}\frac{y_{i,j+1}^{(r)} - y_{i,j}^{(r)}}{h^2} - u_{i,j-\frac{1}{2}}\frac{y_{i,j}^{(r)} - y_{i,j-1}^{(r)}}{h^2}\right) - \omega^2 y_{i,j}^{(r)} = f_{i,j}^{(r)}$$

or

$$-\frac{1}{h^2}\left[u_{i+\frac{1}{2},j}y_{i+1,j}^{(r)} + u_{i-\frac{1}{2},j}y_{i-1,j}^{(r)} + u_{i,j+\frac{1}{2}}y_{i,j+1}^{(r)} + u_{i,j-\frac{1}{2}}y_{i,j-1}^{(r)}\right]$$

$$+\frac{1}{h^2}\left[u_{i+\frac{1}{2},j} + u_{i-\frac{1}{2},j} + u_{i,j+\frac{1}{2}} + u_{i,j-\frac{1}{2}}\right]y_{i,j}^{(r)} - \omega^2 y_{i,j}^{(r)} = f_{i,j}^{(r)}\,.$$

The system for the imaginary part $y^{(i)}$ is similarly determined. In the final step, we look at the Sommerfeld boundary condition using the second order of FD. The boundary condition is

$$\frac{\partial y(x)}{\partial \mathbf{n}} - ik(x)y(x) = 0 \quad \text{on} \quad \Gamma,$$

and is discretized on the upper boundary of Γ by

$$\frac{y_{N+1,j} - y_{N,j}}{h} - i\frac{\omega}{\sqrt{u}_{N+\frac{1}{2},j}}y_{N,j} = 0 \quad \text{on} \quad \Gamma\,.$$

Now, by separating the real and the imaginary part of y on the boundary, we get

$$\begin{cases} y_{N+1,j}^{(r)} = y_{N,j}^{(r)} - \dfrac{\omega h}{\sqrt{u}_{N+\frac{1}{2},j}}y_{N,j}^{(i)} \\ y_{N+1,j}^{(i)} = y_{N,j}^{(i)} + \dfrac{\omega h}{\sqrt{u}_{N+\frac{1}{2},j}}y_{N,j}^{(r)} \end{cases} \quad \text{on} \quad \Gamma$$

The other boundaries are similarly calculated.
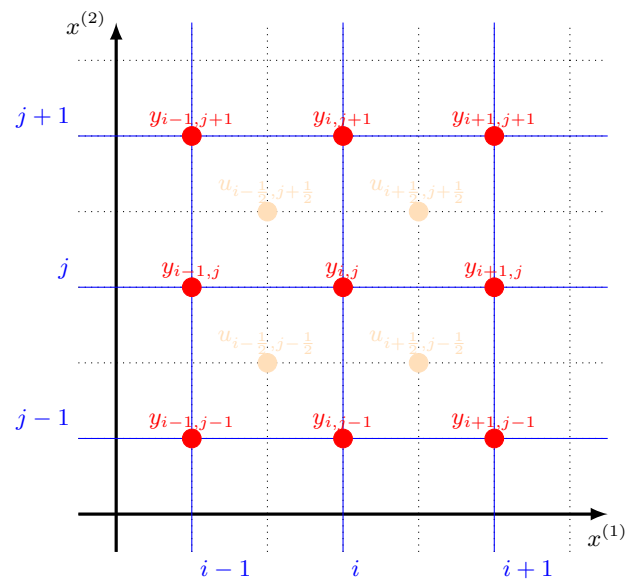
Figure 2.6: Visualization of a staggered grid used in the FD method.
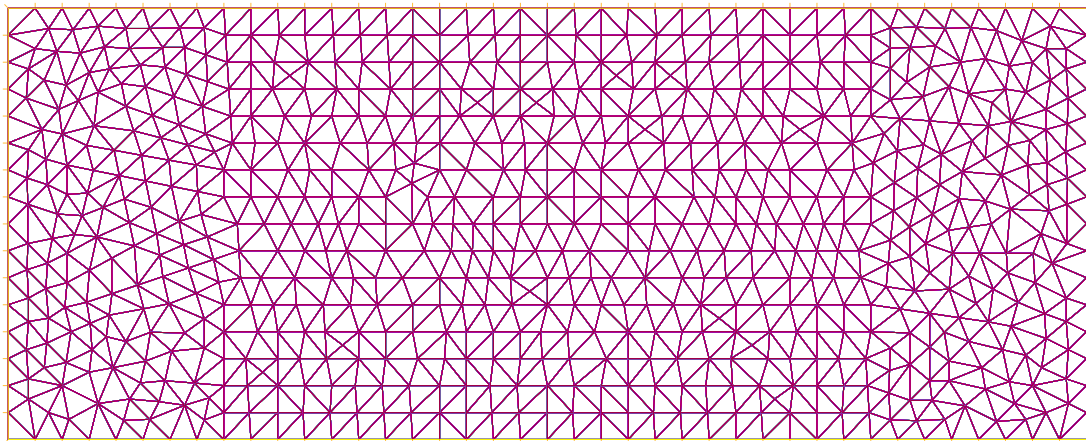
Figure 2.7: Visualization of a 2D FE mesh using triangle.

2.6.2   Finite Elements (FE)

One of the main advantages of FE compared to the FD method is that the mesh is more flexible. Hence, for complex geometries and mesh adaptation, FE is recommended [40]. To solve PDEs with the help of the FE method, a subspace has to be divided into smaller subparts called finite elements. The finite elements are triangular or quadrilateral in a 2D subspace, see Figure 2.7 as an example. The PDE is solved with an equivalent variations formulation of the problem. This allows a formulation of a piecewise polynomial function in each FE represented in a large linear system. To do so, we use the weak form. As described in [83], the weak form is the observation

that two finite-dimensional vectors u, $v \in \mathbb{R}^d$ are equal, if and only if their inner product with any vector $\varphi \in \mathbb{R}^d$ are equal:

$$u = v \in \mathbb{R}^d \iff \forall \varphi \in \mathbb{R}^d, \, u \cdot \varphi = v \cdot \varphi \,. \tag{2.28}$$

To find the semi-discrete problem of the PDE in Equation 2.28, we multiply it by the complex conjugate $\bar{v}$ of a test function $v \in H^1(\Omega)$. Then, we integrate it over Ω and get the following variational formulation: We search for the unique solution $y \in H^1(\Omega)$ [23, 61] where

$$a(y, v) - \omega^2 (y, v)_{L^2} - i\omega b(y, v) = (f, v)_{L^2} \,, \quad \forall \, v \in H^1(\Omega)$$

where $(\cdot \,, \cdot)_{L^2}$ is the $L^2(\Omega)$ hermitian product, and the sesquilinear forms are given by

$$a(y, v) = \int_\Omega u(x) \nabla y(x) \nabla \bar{v}(x) dx$$

and

$$b(y, v) = \int_\Gamma \sqrt{u(x)} y(x) \bar{v}(x) dx \,.$$

We now look at a finite element of our mesh; in other words, we look at a finite dimension subspace $V_h \subset H^1(\Omega)$ of a piecewise polynomial function of degree p. This leads to the semi-discrete Galerkin formulation, where we find $y_h \in V_h$ such that

$$a(y_h, v) - \omega(y_h, v)_{L^2} - i\omega b(y_h, v) = (f, v)_{L^2} \,, \quad \forall v \in V_h \,. \tag{2.29}$$

Let $\{\varphi_i\}_{i=1}^N$ denote a nodal Lagrangian basis [89] of V_h. We can then write, for all $v_h \in V_h$,

$$y_h = \sum_{j=1}^N Y_j \varphi_j \,, \quad \text{with} \quad (\varphi_i, \varphi_j)_{L^2} = \left\{ \begin{array}{ll} 0 & , \quad i \neq j \\ 1 & , \quad i = j \end{array} \right. \,.$$

Hence, the semi-discrete formulation of Equation 2.29 is equivalent to

$$\sum_{j=1}^N Y_i a(\varphi_j, \varphi_i) - \omega^2 \sum_{j=1}^N Y_j (\varphi_j, \varphi_i)_{L^2} - i\omega \sum_{j=1}^N Y_j b(\varphi_j, \varphi_i) = (f, \varphi_i)_L^2$$

for all $i = 1 \,, \cdots , N$. Finally, we can write it as a matrix-vector multiplication: $Y = [Y_1, \cdots, Y_N]^T \in \mathbb{R}^{N \times 1}$ is the unknown discretized pressure variation, solved by the equation

$$KY - \omega^2 MY - i\omega BY = R \,,$$

where $R \in \mathbb{R}^{N \times 1}$ and M, N, $B \in \mathbb{R}^{N \times N}$ are given by

$$R_i = (f, \varphi_i)_{L^2} \,, \quad M_{i,j} = (\varphi_j, \varphi_i)_{L^2} \,, \quad K_{i,j} = a(\varphi_j, \varphi_i) \,, \quad B_{i,j} = b(\varphi_j, \varphi_i) \,,$$

for $i, j = 1 \,, \cdots , N$. We note that the matrices M and K are sparse, symmetric, and positive semi-definite and that the matrix B is sparse, symmetric, and has a low rank.

2.7 Neural Networks (NN)

> *The world is a very strange place, and the dice are always rolling.*
> *– Tom Robbins*

NN [12] are well established in medical imaging [18, 49, 53, 75], speech and signal processing [32, 42, 48, 62]. The fundamental principle of a NN is to interpret an input and compute the desired output. In medical imaging, an input may be a CT data set, and the output will be segmented bones. In speech recognition, an audio recording is used as an input and results in a word classification, respectively word recognition as an output. Another example, discussed in more detail in Chapter 5, predicts the depth of the cut during bone ablation. There the NN uses an acoustic wave emitted during the bone ablation to predict the depth of the cut. In this case, the NN solves the forward problem, which maps the acoustic waves (the subset $\mathcal{A}$) to the depth of the cut (the subset $\mathcal{B}$).

The simplest explanation of a NN is that it is a combination of derivable functions f_i that map a set $\mathcal{A}$ onto another set $\mathcal{B}$

$$f = f_K \circ \cdots \circ f_0 : \mathcal{A} \longrightarrow \mathcal{B}.$$

The NN we use is called a feed-forward neural network [2]. This means that the function f maps the set $\mathcal{A}$ directly on the set $\mathcal{B}$ without using any loops or recurrent connections. The functions f_i are usually fully connected layers, convolution layers, Maxpool layers, activation functions, and some normalization. These functions have different weights, and depending on the structure and the weights, the NN will perform better or worse. To get a well-performing network, we need to optimize the weights. Therefore, we first need to solve the following inverse problem: For *a given acoustic wave* (known initial condition), what are the unknown parameters θ (here, *what are the weights*), so that we can get *the desired depth* (observation). Hence, when we solve the inverse problem, we find the unknown parameters θ; thus, we find the weights, which we will use to solve the forward problem.

Solving the inverse problem of a NN is referred to as training the network. To train the network, we first need to separate our measured data (initial condition) and its corresponding label (observation). In most cases, the data is divided into three disjoint subsets: Training, validating, and testing data. The training data is used to find the unknown parameters by solving the inverse problem, and the validating data is used to validate the performance of the forward problem of the network. The best-performing parameters on the validation data are then used to test the network's performance on previously unseen data, namely, the testing data. This strategy helps to find suitable parameters and avoids over-optimizing on the training data.

We use a Convolutional Neural Network (CNN), where, first, we have several convolutional layers (see Subsection 2.7.2). A Maxpool layer follows each convolutional layer (see Subsection 2.7.3). After multiple convolutional layers, the output is flattened to a one-dimensional vector. This is then used as input for the fully connected layers. A dropout may be applied onto the fully connected layer (see Subsection 2.7.1). In the final step, the output of the fully connected layer is the desired output. We note that after each layer, a batch normalization can be applied. The loss function is minimized using the optimizer Adam [47]. We will not show
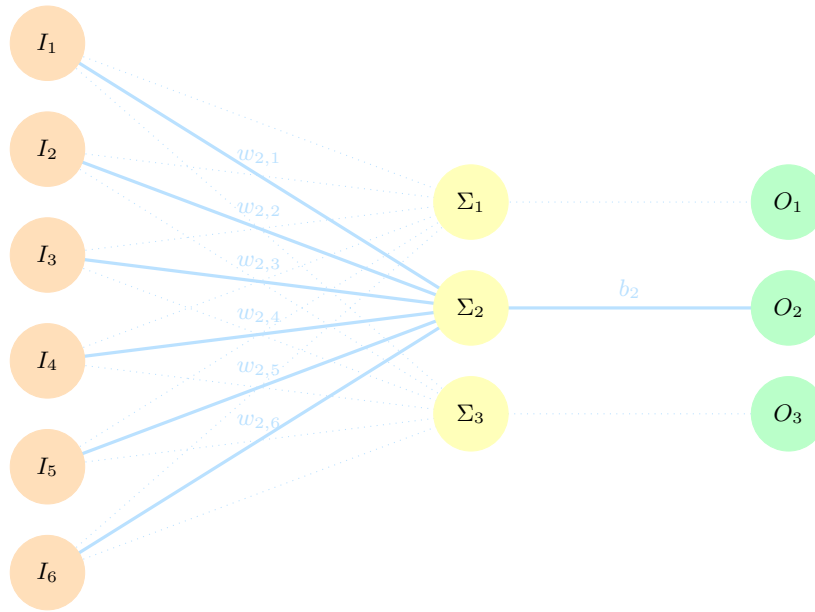
Figure 2.8: Visualization of a fully connected layer. Each element (neuron) of the input layer I is multiplied by the weight $w_{j,i}$. Σ_j represents the sum of the weighted I. Then the bias b is added, and in a final step, the activation function σ is applied to map the input layer I to the output layer O.

how the gradient is calculated because this has been shown in great detail in the thesis of Andermatt [2].

2.7.1   Fully Connected Layers

A fully connected layer can be described as a matrix-vector multiplication. To better visualize the multiplication, we take a look at Figure 2.8. In our example, we have an input vector I of the size $N_I = 6$ and an output vector O of the size $M_O = 3$. Each element of I and O are called neurons. As the word fully connected indicates, each neuron of I is connected with each neuron of O. We describe the mapping of the input layer I to the neuron O_j as follows

$$\sigma\left([w_{j,1}I_1] + \cdots + [w_{j,N_I}I_{N_I}] + b_j\right) = \sigma\left(\sum_{i=1}^{N_I}[w_{j,i}I_i] + b_j\right) = O_j\,.$$

In the mapping from I to O_j, each neuron I_i of the input is multiplied by the weight $w_{j,i}$. Then we take the sum over all $i = 1, \cdots, N_I$ and add the bias b_j. In the final step, an activation function σ is applied, as described in Subsection 2.7.4. To generalize the mapping between the neurons I and O we write it as a matrix-vector multiplication:

$$\sigma(W \cdot I + b) = \sigma\left(\begin{bmatrix} w_{1,1} & \cdots & w_{1,N_I} \\ \vdots & \ddots & \vdots \\ w_{M_O,1} & \cdots & w_{M_O,N_I} \end{bmatrix} \cdot \begin{bmatrix} I_1 \\ \vdots \\ I_{N_I} \end{bmatrix} + \begin{bmatrix} b_1 \\ \vdots \\ b_{M_O} \end{bmatrix}\right) = \begin{bmatrix} O_1 \\ \vdots \\ O_{M_O} \end{bmatrix} = O\,,$$

with the weight matrix $W \in \mathbb{R}^{M_O \times N_I}$, the input vector $I \in \mathbb{R}^{N_I \times 1}$, the bias $b \in \mathbb{R}^{M_O \times 1}$, and the output vector $O \in \mathbb{R}^{M_O \times 1}$. We note that the input and output sizes can be chosen arbitrarily. If multiple fully connected layers follow each other, then the output size of the previous layer has to be the same as the input size of the current layer. The final layer has the same output size as the desired output of the network, or in our case, the dimension of $\mathcal{B}$. We note that the weights have a linear dependency; hence, the derivative function exists. Therefore, the gradient can be found for each layer and used for the backpropagation. A dropout can be applied on the fully connected layers during the training. A dropout randomly omits weights. This improves the robustness and, therefore, avoids over-optimization of the network.

2.7.2 Convolutional Layers
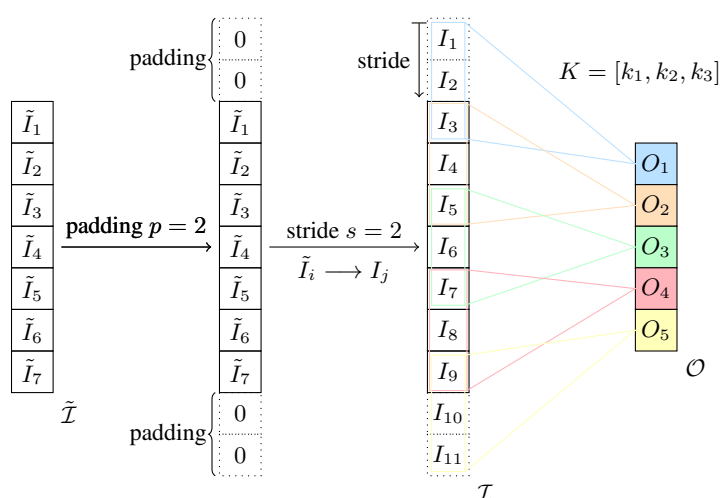
Figure 2.9: A convolution of an array $\tilde{\mathcal{I}} = [\tilde{I}_1, \cdots, \tilde{I}_7]$ with a kernel $K = [k_1, k_2, k_3]$, with padding size $p = 2$ (two zeros are added on each boundary which we will refer to as $\mathcal{I} = [I_1, \cdots, I_{11}]$), and stride set to $s = 2$ (the kernel K moves two entries, e.g., $O_1 = I_1 \cdot k_1 + I_2 \cdot k_2 + I_3 \cdot k_3$ and $O_2 = I_3 \cdot k_1 + I_4 \cdot k_2 + I_5 \cdot k_3$), leads to an output vector $\mathcal{O} = [O_1, \cdots, O_5]$.

Another common layer used for NN are convolutional layers. For simplification, we show the convolution in the 1D case. However, it will work similarly for multidimensional cases. First, we will explain what a convolution is, then how the neural network uses the convolutional layers.

We explain how convolution works with the variables padding p, stride s, and kernel size k. In our example, we set the input array $\tilde{\mathcal{I}}$ to $\tilde{N}_I = 7$. The padding $p = 2$ indicates the number of zeros added to the boundaries, as shown in Figure 2.9. In our case, it will add two zeros on the top and bottom of the array. We define the resulting array of the size $N_I = 11$ as $\mathcal{I}$. A convolution with the kernel $K = [k_1, k_2, k_3]$, with stride $s = 2$, on the array $\mathcal{I} = [I_1, \cdots, I_{N_L}]$

$$\mathcal{I} * K = \mathcal{O} \,,$$

is calculated as follows: The first entry O_1 of the output array $\mathcal{O} = [O_1, \cdots, O_{M_O}]$ is

$$O_1 = k_1 I_1 + k_2 I_2 + k_3 I_3 \,,$$

as visualized in Figure 2.9 with the blue triangle. The stride indicates how far the kernel shifts to calculate the next output O_2, as visualized with the orange triangle. In our case, we have stride $s = 2$; hence, the kernel shifts two indices to calculate the next output. Therefore, we get

$$O_2 = k_1 I_3 + k_2 I_4 + k_3 I_5 \,.$$

We can generalize the equation to calculate the output O_j for an arbitrary kernel size k, and an arbitrary stride size of s

$$O_j = k_1 I_{s(j-1)+1} + k_2 I_{s(j-1)+2} + \cdots + k_k I_{s(j-1)+k} = \sum_{i=1}^{k} k_i I_{s(j-1)+i} \,.$$

The length M of the output array $\mathcal{O}$ depends on the length $\tilde{N}_I$ of the input array $\tilde{\mathcal{I}}$, the kernel size k, the stride s, and the padding p. It can be calculated with the formula

$$M_O = \left\lfloor \frac{\tilde{N}_I + 2p - k}{s} + 1 \right\rfloor \,, \tag{2.30}$$

which, in our case, is $M_O = 5$.

The 1D convolutional layer used in PyTorch [71] has some additional properties. In the previous example, the number of input and output channels is one. However, in PyTorch, the number of channels can vary. In Figure 2.10, we give an example of $N_L = 4$ input channels and $M_L = 3$ output channels. For simplification, we use stride $s = 1$ and padding $p = 0$. One of the major differences between single and multiple input and output channels are the number of weights of the kernel. In the previous example, the kernel K had $k = 3$ weights, and only one kernel existed. In Figure 2.10, we see that the kernel K of the size k now has more than k weights. The number of total weights of a kernel is the number of input channels N_L times the size of the kernel; here, it is $N_L \cdot k = 4 \cdot 3 = 12$. In addition, instead of a single kernel, we now have M_L kernels, one for each output channel. Therefore, in our example the output $O_{i,2}$, with $i \in \{1, \cdots, M_L\}$ can be formulated as follows

$$
\begin{aligned}
O_{i,2} &= I_{1,2} k_{1,1}^i + I_{1,3} k_{1,2}^i + I_{1,4} k_{1,3}^i + \cdots \\
&\qquad \cdots + I_{N_L,2} k_{N_L,1}^i + I_{N_L,3} k_{N_L,2}^i + I_{N_L,4} k_{N_L,3}^i \\
&= \left[I_{1,2} k_{1,1}^i + I_{1,3} k_{1,2}^i + I_{1,4} k_{1,3}^i \right] + \cdots \\
&\qquad \cdots + \left[I_{N_L,2} k_{N_L,1}^i + I_{N_L,3} k_{N_L,2}^i + I_{N_L,4} k_{N_L,3}^i \right] \\
&= \sum_{n=1}^{N_L} \left[I_{n,2} k_{n,1}^i + I_{n,3} k_{n,2}^i + I_{n,4} k_{n,3}^i \right]
\end{aligned}
\tag{2.31}
$$

We generalize the equation by assuming that the input has N_L channels, and each channel has the length $\tilde{N}_I$. Therefore, the input can be represented as a matrix $\tilde{\mathcal{I}} \in \mathbb{R}^{N_L \times \tilde{N}_I}$. The padding size increases each channel's boundary, as visualized in Figure 2.9. Therefore, after padding, we get a matrix of the size $\mathcal{I} \in \mathbb{R}^{N_L \times N_I}$, with $N_I = \tilde{N}_I + 2p$. Since the stride is s and the kernel size is k, we can deduce the length of the output M_O of each layer with the Equation 2.30

$$M_O = \left\lfloor \frac{\tilde{N}_I + 2p - k}{s} + 1 \right\rfloor .$$

When we have M_L output channels, we can represent the output as a matrix $\mathcal{O} \in \mathbb{R}^{M_L \times M_O}$. We note that each output channel $\mathcal{O}_i$ has its own kernel K^i. We generalize Equation 2.31 and write for each entry $O_{i,j}$ in the matrix $\mathcal{O}$ the following

$$
\begin{aligned}
O_{i,j} &= I_{1,s(j-1)+1}k^i_{1,1} + \cdots + I_{1,s(j-1)+k}k^i_{1,k} + \cdots \\
&\qquad \cdots + I_{N_I,s(j-1)+1}k^i_{N_I,1} + \cdots + I_{N_I,s(j-1)+k}k^i_{N_I,k} \\
&= \left[I_{1,s(j-1)+1}k^i_{1,1} + \cdots + I_{1,s(j-1)+k}k^i_{1,k} \right] + \cdots \\
&\qquad \cdots + \left[I_{N_I,s(j-1)+1}k^i_{N_I,1} + \cdots + I_{N_I,s(j-1)+k}k^i_{N_I,k} \right] \\
&= \sum_{n=1}^{N_L} \left[I_{n,s(j-1)+1}k^i_{n,1} + \cdots + I_{n,s(j-1)+k}k^i_{n,k} \right] \\
&= \sum_{n=1}^{N_L} \left[\sum_{m=1}^{k} I_{n,s(j-1)+m}k^i_{n,m} \right] \\
&= \sum_{n=1}^{N_L} \sum_{m=1}^{k} I_{n,s(j-1)+m}k^i_{n,m} .
\end{aligned}
$$

Finally, similarly to the previous Subsection 2.7.1, a bias $b_{i,j}$ is added, and a non-linear activation function σ is applied. Hence, we get the final output of the convolutional layer for each entry in $\tilde{O}$

$$\tilde{O}_{i,j} = \sigma\left(O_{i,j} + b_{i,j}\right) = \sigma\left(\sum_{n=1}^{N} \sum_{m=1}^{k} I_{n,s(j-1)+m}k^i_{n,m} + b_{i,j}\right),$$

or simpler

$$\tilde{\mathcal{O}} = \sigma\left(\mathcal{O} + b\right),$$

with the final output $\tilde{\mathcal{O}} \in \mathbb{R}^{M_L \times M_O}$ and the bias $b \in \mathbb{R}^{M_L \times M_O}$ having the same dimensions as $\mathcal{O}$. Again, similarly to the previous Subsection 2.7.1, the parameters which are determined during the training of the network, namely $k^i_{n,m}$ and $b_{i,j}$ are a linear combination, apart from the non-linear activation function. Therefore, the gradient can be computed easily.
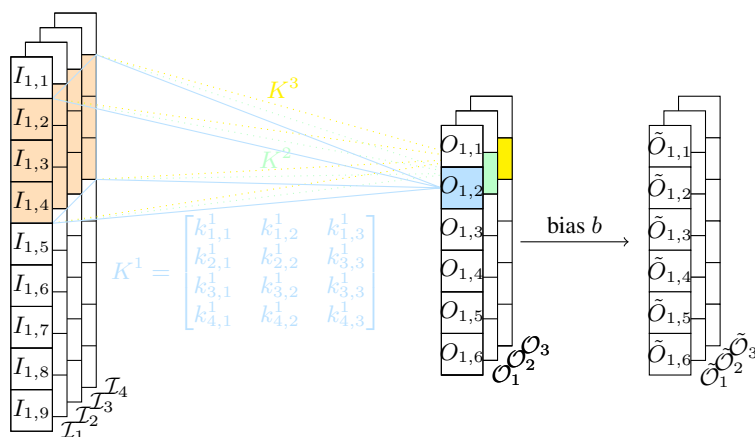
Figure 2.10: An example of a convolution in a NN using $N_L = 4$ channels as input $\mathcal{I} = [\mathcal{I}_1, \cdots, \mathcal{I}_{N_L}]$ and $M_L = 3$ channels as output $\mathcal{O} = [\mathcal{O}_1, \cdots, \mathcal{O}_{M_L}]$. In this case, we have no padding $(p = 0)$, and the stride is set to one $(s = 1)$. The kernel of the size $k = 3$ has the dimensions of the input channel; hence, it is of the form $K^i \in \mathbb{R}^{N_L \times k}$ and each output channel has its own kernel, implying, $i = 1, \cdots, M_L$. The entry $O_{1,2}$ of the output array is calculated as follows $O_{1,2} = I_{1,2}k_{1,1}^1 + I_{1,3}k_{1,2}^1 + I_{1,4}k_{1,3}^1 + \cdots + I_{4,2}k_{4,1}^1 + I_{4,3}k_{4,2}^1 + I_{4,4}k_{4,3}^1$. A bias b is added, and an activation function is applied to get the output $\tilde{\mathcal{O}}$ of the convolutional layer.
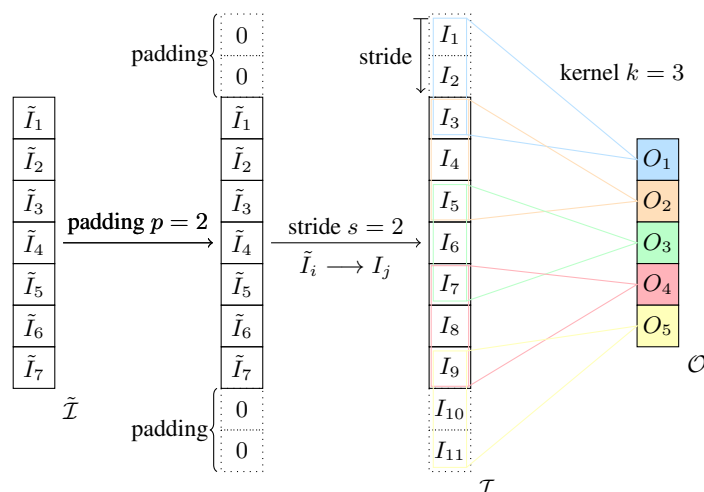
Figure 2.11: Maxpool layer on an input array $\tilde{\mathcal{I}} = [\tilde{I}_1, \cdots, \tilde{I}_7]$ of the size $N_I = 7$ with a kernel of the size $k = 3$, with padding size $p = 2$, and stride set to $s = 2$ This leads to an output vector $\mathcal{O} = [O_1, \cdots, O_5]$ of the size $M_O = 5$.

2.7.3 Maxpool Layer

As the name indicates, the Maxpool layer calculates the maximum values of the input in a certain way. Similarly to the convolutional layer in the previous Section 2.7.2, a padding of size p adds p zero values on the boundary of the array, as visualized in Figure 2.11. Hence, we get the array

$\mathcal{I} = [0, \cdots, 0, \tilde{\mathcal{I}}, 0, \cdots, 0] = [I_1, \cdots, I_N]$ of the size $N = \tilde{N} + 2 \cdot p$. The kernel of the size k takes k consecutive entries of the array $\mathcal{I}$ and calculates its maximum for the output. That is, the entry O_1 of the output array $\mathcal{O}$ is

$$O_1 = \max\{I_1, \cdots, I_k\},$$

or concretely $O_1 = \max\{I_1, I_2, I_3\}$ in the example illustrated in Figure 2.11. As before, the stride s skips the next s entries of the array to calculate the next maximum. Therefore, we can generalize the equation to

$$O_j = \max\{I_{s(j-1)+1}, \cdots, I_{s(j-1)+k}\},$$

yielding, for instance, $O_3 = \max\{I_5, I_6, I_7\}$ in the above. The output size can be calculated similarly to the convolutional layers given in Equation 2.30. We note that this layer is used to downsample, resp. pool features and highlights the most present feature in the patch. It has no weights and therefore does not change during the training of the network.

2.7.4 Activation Function: ReLU

An activation function is generally placed after a fully-connected or convolutional layer. According to [35, 52, 54], a feed-forward network can approximate any continuous function, which is compact in $\mathbb{R}^n$ under a mild assumption of the activation function. It is further generalized in [52], where the only condition of the activation function $\sigma : \mathbb{R} \longrightarrow \mathbb{R}$ is that it shall not be a polynomial. A common and well-performing activation function is the ReLU activation function

$$\sigma(x) = ReLU(x) = \max\{0, x\} = \begin{cases} x, & x > 0 \\ 0, & x < 0 \end{cases}$$

which is continuously differentiable in $\mathbb{R} \backslash \{0\}$ and results in the unit step function

$$\sigma'(x) = \frac{\partial}{\partial x} ReLU(x) = \begin{cases} 1, & x > 0 \\ 0, & x < 0 \end{cases},$$

as visualized in Figure 2.12.
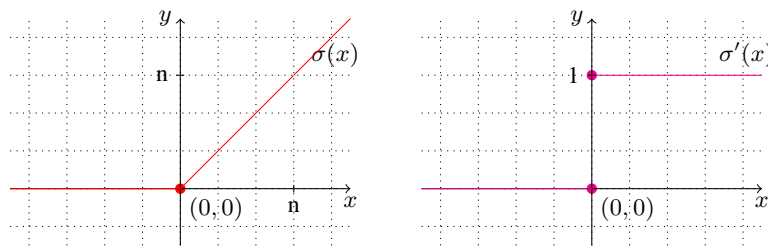
Figure 2.12: On the left side is the ReLU activation function $\sigma(x) = \max\{0, x\}$ which is undefined at position 0 and on the right side its derivation $\sigma'(x)$.

Chapter 3

Sentinel Lymph Node Fingerprinting

This publication is a continuation of the work of [79, 84]. To know if a cancer has spread, a biopsy of the SLN is done [81, 82]. This is done by injecting the patient with Tc^{99m} around the tumor, whereupon the Tc^{99m} accumulates in the SLN. Using a γ detector, these SLN can be found and removed. We aim to accurately pinpoint these SLNs so that the surgeon can operate minimally invasively.

In our previous work [79, 84], we used a multiple pinhole collimator, in which all pinholes were separated with septum walls, to detect the Tc^{99m} sources *ex-vivo*. One of the drawbacks was that the computation time was long and not applicable in real-case scenarios. In addition, the accuracy was limited. In this paper, we introduce the Sentinel Lymph Node Fingerprinting (SLNF) algorithm, increases the reconstruction's accuracy and speed. In addition, we use the optimal design method proposed in [31] to give mathematical reasoning as to why the reconstruction improves when removing the septum walls. With the optimal design method, we found new positions of the pinholes, that provides us with a better reconstruction of the Tc^{99m} sources.

In this paper, we are solving two inverse problems. The first one is finding the position of the Tc^{99m} sources or, in other words, for which position of the Tc^{99m} sources (condition) we get the image on the detector (measurement). The second one is what pinhole designs are a good condition to find the position of the Tc^{99m} sources.

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Sentinel lymph node fingerprinting

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Abstract

Background. When locating the sentinel lymph node (SLN), surgeons use state-of-the-art imaging devices, such as a 1D gamma probe or less widely spread a 2D gamma camera. These devices project the 3D subspace onto a 1D respectively 2D space, hence loosing accuracy and the depth of the SLN which is very important, especially in the head and neck area with many critical structures in close vicinity. Recent methods which use a multi-pinhole collimator and a single gamma detector image try to gain a depth estimation of the SLN. The low intensity of the sources together with the computational cost of the optimization process make the reconstruction in real-time, however, very challenging.

Results. In this paper, we use an optimal design approach to improve the classical pinhole design, resulting in a non-symmetric distribution of the pinholes of the collimator. This new design shows a great improvement of the accuracy when reconstructing the position and depth of the radioactive tracer. Then, we introduce our Sentinel lymph node fingerprinting (SLNF) algorithm, inspired by MR-fingerprinting, for fast and accurate reconstruction of the tracer distribution in 3D space using a single gamma detector image. As a further advantage, the method requires no pre-processing, i.e. filtering of the detector image. The method is very stable in its performance even for low exposure times. In our *ex vivo* experiments, we successfully located multiple Technetium 99m (Tc-99m) sources with an exposure time of only one second and still, with a very small L^2-error.

Conclusion. These promising results under short exposure time are very encouraging for SLN biopsy. Although, this device has not been tested on patients yet, we believe: that this approach will give the surgeon accurate 3D positions of the SLN and hence, can potentially reduce the trauma for the patient.

1. Background

Among the types of cancer in the head and neck area, oral and oropharyngeal squamous cell carcinoma are very typical. If initial staging cannot rule out an extensive spreading of the cancer, the standard of care includes the complete surgical removal of the lymph nodes in the vicinity. Post-resection analysis has shown, however, that this invasive intervention was only warranted in about 30% of the patients (Byers *et al* 1988, van den Brekel *et al* 1996). A biopsy of the SLN, i.e. the first draining lymph node(s) after the tumor, has shown to be a good indicator whether the tumor already spread through the lymphatics (Shoaib *et al* 2001, Stoeckli *et al* 2001) and complete removal of the lymphnodes is warranted. To identify these SLN, radioactive tracer (Tc-99m) is injected around the tumor. After some hours, the highest concentration of the radio-active tracer is found in the SLN and hence can be located using a gamma detector. Surgeons either use a 1D gamma probe (Sullivan *et al* 2001, Hayashi *et al* 2003, Povoski *et al* 2009, Civantos *et al* 2010) or a 2D gamma camera (Gerbaudo *et al* 2002, Vermeeren *et al* 2010, Ozkan and Eroglu 2015, Hellingman *et al* 2015), to locate the SLN. These types of detectors have no depth perception in finding the SLN, or need preoperative imaging aid, an additional tracking device or multiple detectors to get a depth perception. An alternative is the freehand SPECT device, which is introduced in Mandapathil *et al* (2014) and Hellingman *et al* (2015). Although (Mandapathil *et al* 2014) is able to give a 3D approximation of the SLN,

an optical tracking device is needed with multiple images from the detector, while in Hellingman *et al* (2015) the pinhole collimator is only used to increase the resolution. In Jaszczak *et al* (1994), the authors proposed on using a SPECT camera with a pinhole collimator instead of a parallel hole collimator to measure the tracer distribution. Furthermore, by increasing the number of pinholes (resulting in a multi-pinhole collimator), the sensitivity is improved, hence allowing a reduction of the Tc-99m activity (dosage) injected.

Quantification of radioactive tracer distribution for SLN detection has proven itself as a useful approach (Alex and Krag 1993, Britten 1999, Warncke *et al* 2007). Nevertheless, the state-of-the-art approaches suffer from a host of challenges such as a long exposure time of the detector to the radioactive source(s), pre-processing of the gamma detector image, images from several angles are needed for the depth reconstruction, long computation-time of an ill-posed optimization method, poor depth control, lack of sensitivity for two sources located behind each other and the results may suffer from a post-processing step or a reader bias in locating the position of the source(s).

In this publication, we propose a novel multi-pinhole based collimator together with a processing algorithm that overcomes the above mentioned drawbacks. In contrast to our previous work (von Niederhäusern *et al* 2016, Seppi *et al* 2017), we introduce here a fast and accurate processing approach, inspired by MR-fingerprinting. Fingerprinting for MR images became very popular in the last years. Using a unique fingerprint for the data, pattern recognition algorithms are used to find the fingerprint in a predefined dictionary, see for example (Allen and Stott 2003, Zhang *et al* 2003). Instead of using an optimization method or huge dictionaries with complex optimization methods, the proposed approach uses a reduced dictionary and inquires low memory and a short run-time. The detection algorithm can be performed in a few seconds, even on a standard laptop, and gives results which are very close to the true position of the source(s). Our *ex vivo* experiments using multiple Tc-99m sources underpin the accuracy and precision of our approach.

This paper is organized as follows: first, we show how to improve our multi-pinhole collimator, inspired by the optimal design approach (Haber *et al* 2008), resulting in a non-symmetric distribution of the pinholes. Second, we introduce the SLNF algorithm for the detection of the radioactive tracer positions. Then, we perform experiments with different exposure times and different dictionaries. At last, we demonstrate the superiority of our new collimator design (non-symmetric distribution of the pinholes) in a comparative study with the previous collimator design (regular distributed pinholes with septum walls).

2. Method

In our experiments, we use a PILATUS3 gamma detector produced by DECTRIS Ltd. (5405 Baden-Dättwil, Switzerland). The detector features 487×195 pixels, with each pixel having a size of 172×172 μm. The gamma detector's CMOS readout ASICs uses cadmium telluride as the sensor-material. This technology allows direct detection of the gamma rays, where each signal generated by the pixel of the sensor is amplified, discriminated and counted. Our custom design collimator was manufactured by an external company. It is composed of 3D printed and machined tungsten parts, with a density of 19.25 g cm^{-3} and the dimension of $86.9 \times 36 \times 36$ mm^3. Further, the cylindrical shaped pinholes, with a diameter of 1 mm, are drilled through the 1 mm thick front plate.

In front of the detector/collimator, we place one or more sources in several known positions, see figure 2. In our experiments, we use Tc-99m samples as radioactive sources. The photons are propagating through the pinholes of the collimator and hit the detector in a randomly distributed way.

Let u be a three-dimensional subspace of $\mathbb{R}^3$ in front of the collimator which contains radioactive tracers. The relationship between u and the detector image d can be described by the linear system

$$Au = d. \tag{1}$$

The *projection matrix* $A \in \mathbb{R}^{N_d \times N_u}$, which is dependent on the design of the collimator and its pinholes, is built to translate the sources to their detector image. The numbers N_u and N_d represent the number of discretization points of u and the number of pixels on the detector, respectively.

2.1. Optimal design of the pinhole distribution

In previous experiments (von Niederhäusern *et al* 2016, Seppi *et al* 2017) the collimator in figure 3 was used. Although, Seppi *et al* (2017) achieved a good localization in the *xy*-plane, its depth accuracy (*z*-axis) was limited. Here, we aim to find a good pattern for the pinholes on the collimator front plate such that 3D estimations are improved, hence the approximation of the depth (*z*-axis) improved.

To improve the depth estimation, the sources must be seen on the detector from multiple angles. This can be done by removing the septum walls in the collimator, see figures 1 and 6.

In Haber *et al* (2008), an optimal design for large-scale linear ill-posed inverse problems was introduced. Adapting this approach for our experiments, we find an optimal collimator design, i.e. an optimal distribution of the collimator's pinholes for improved 3D localization of the sources. Here, we examine $N_p = 200$ possible

Figure 1. Side view of the collimator: left collimator with compartment, right collimator without septum walls (a) Front plate of the collimator (1 mm thick), (b) Cylindrical shaped pinhole (diameter of 1 mm), (c) Pinhole compartment of symmetric collimator (10.9 × 9.5 mm), (d) Detector (83.76 × 33.54 mm), (e) Septum walls of the compartments from the symmetric collimator (0.6 mm thick), (f) symmetric collimator: angle depends on the walls of the compartment (16.6–22.7°), (g) collimator with no septum walls, hence the angle is i.e. 90°.

pinholes for some given subspace u containing radioactive tracer(s). In figure 4, we illustrate the 200 possible pinholes marked with white dots.

For each pinhole p_m, $m = 1, \ldots, N_p$, we build a projection matrix A_m. The matrix A_m projects the component of u through the *single pinhole p_m* onto the detector image d_m. The photons hit the detector in a stochastic process, which numerical simulation cannot precisely imitate. Therefore, we write

$$d_m = A_m u + \varepsilon_m. \tag{2}$$

Here, ε_m represents the noise (e.g. intrinsic spatial resolution of the detector, scattered photons, photons penetrating the collimator walls) in the experiment, which has different probabilities for each detector pixel. Hence, the variable ε_m must be in the same dimension as the image of the detector d_m and we write for each $\varepsilon_m = [\varepsilon_{m,i}]_{i=1}^{N_d}$. We assume that each $\varepsilon_{m,i}$ is independent and identically distributed (i.i.d) random variable with a mean value of 0 and variance of σ^2 (here, σ depends on the number of photon reaching the detector).

For each pinhole p_m, we define a weight w_m, $m = 1, \ldots, N_p$, where the weights w_m are the solution of

$$\arg \min_w \sum_{m=1}^{N_p} w_m \|d_m - A_m u\|_{L^2}^2, \quad \text{s.t. } w_m \geqslant 0 \tag{3}$$

where $w = [w_1, w_2, \ldots, w_{N_p}]^T$. Note, that the L^2-norm is defined as

$$\|v\|_{L^2} = \left(\sum_i^{N_v} v_i^2 \right)^{1/2} \quad \text{for} \quad v = [v_1, \cdots, v_{N_v}] \in \mathbb{R}^{N_v}.$$

We write (3) in matrix form:

$$\arg \min_w (d - Au)^T W (d - Au), \tag{4}$$

where

$$A = \begin{pmatrix} A_1 \\ A_2 \\ \vdots \\ A_{N_p} \end{pmatrix}, \quad d = \begin{pmatrix} d_1 \\ d_2 \\ \vdots \\ d_{N_p} \end{pmatrix} \quad \text{and} \quad W = \begin{pmatrix} W_1 & & \\ & \ddots & \\ & & W_{N_p} \end{pmatrix},$$

with $W_m = \text{diag}(w_m, w_m, \ldots, w_m) \in \mathbb{R}^{N_d \times N_d}, w_m \geqslant 0$, for $m = 1, \ldots, N_p$. Note that, A is not a square matrix, hence, A is not invertible. Following (Haber *et al* 2008), we find a solution of (4) by minimizing the equivalent equation

$$\arg \min_w \mathcal{J}(w) = \arg \min_w \left(\sigma^2 \mathcal{V}(w) + \beta \sum_{m=1}^{N_p} w_m \right), \quad \text{s.t. } w_m \geqslant 0, m = 1, \ldots, N_p, \tag{5}$$

with

$$\mathcal{V}(w) = \text{trace}(WAC(w)^{-2} A^T W) \quad \text{and} \quad C(w) = A^T W A \tag{6}$$

and β has typically a small value (here, we choose $\beta = 10^{-2}$). To reduce computation cost we approximate the trace (Golub and Von Matt 0000, Hutchinson 1990) in (6) as

$$\text{trace}(H) \approx v^T H v,$$

where v is a random vector of i.i.d. entries of values ± 1 with the probability of $1/2$. Hence, we approximate $\mathcal{V}(w)$ through $\hat{\mathcal{V}}(w)$

$$\hat{\mathcal{V}}(w) = v^T WAC(w)^{-2} A^T W v = w^T V(w)^T V(w) w, \quad \text{with} \quad V(w) = C(w)^{-1} A^T \text{diag}(v).$$

We replace $\mathcal{V}(w)$ in (5) with $\hat{\mathcal{V}}(w)$ and get

$$\arg\min_w \hat{\mathcal{J}}(w) = \arg\min_w \left(\sigma^2 \hat{\mathcal{V}}(w) + \beta \sum_{m=1}^{N_p} w_m \right), \quad \text{s.t. } w_m \geqslant 0, m = 1, \ldots, N_p. \tag{7}$$

To optimize (7), we compute the gradient and the Gauss–Newton (G–N) approximation of the Hessian of $\hat{\mathcal{V}}(w)$ with respect to w. First, we compute the gradient

$$\nabla \hat{\mathcal{V}}(w) = \nabla [w^T V(w)^T V(w) w] = 2 J_v(w)^T V(w) w$$

where

$$J_v(w) = \frac{\partial [V(w)w]}{\partial w} = V(w) - C(w)^{-1} A^T \text{diag}(Ar_v) \quad \text{with} \quad r_v = V(w) w_{\text{fixed}} \tag{8}$$

and w_{fixed} is a fixed w.

Remark 1. We omit the long description of technical details. The steps (4)–(8) serve as referencing point to understand the detailed explanation in Haber *et al* (2008).

Next, we compute the G–N approximation of the Hessian

$$\Delta \hat{\mathcal{J}} \approx \sigma^2 J_v^T J_v.$$

To find a search direction for the optimization, we solve in each G–N iteration the system

$$\Delta \hat{\mathcal{J}} p = -\nabla \hat{\mathcal{J}}. \tag{9}$$

For an efficient solution of (9) we opt for the inexact Newton method, where we solve the inner iteration using the conjugate gradient (CG) method (Haber *et al* 2000, Grote *et al* 2017). We iterate in both G–N and CG iterations until a relative residuum of 0.1 is reached. Starting with equal weights for all $w_m = 1$ for $m = 1, \ldots, N_p$, we optimize (7) and find the weights w_m with the highest values. The pinholes p_m corresponding to those highest weights are the most essential pinholes for the reconstruction.

Remark 2. To compare different collimator designs we fix the number and the position of the pinholes and solve (6). Further, the collimator with the smallest $\mathcal{V}(\mathbf{1})$ value, with $\mathbf{1} = [1, \ldots, 1]$, is the collimator of choice.

2.2. Optimal design for known sources

To conclude how the holes are distributed on the collimator, we solve (7) for four different sub-spaces u: with one, two, three and four sources with a diameter of 5 mm (approximated size of the lymph node). We start with 200 possible pinholes (all of them have a diameter of 1 mm), shown in figure 4. In figure 5, the 24 white dots correspond to the resulting 24 pinholes with the highest weight (the number 24 is taken from Seppi *et al* (2017), to compare the results with the symmetric collimator discussed in this paper) and the big red dots corresponding to the (x, y) position of the source(s) (they were located at a distance of 100–150 mm from the collimator front plate respectively).

Although the process gives a clear suggestion for each experiment, in reality the positions of the sources are not known and the optimization selects each time a different pinhole combination with respect to the position of the source(s). In all of the experiments performed, there were, however, two common properties:

(i)   The pinholes are spread over the entire collimator front plate.
(ii) The pinholes are spread non-symmetrically.

Actually, if we initiate the optimal design process with symmetrically distributed pinholes (see right side of figure 6), the optimal design optimization breaks the symmetry. A major drawback of the examples given above, is that they show only one possible design for a single subspace u and neglect all other sub-spaces. We built a collimator with the properties mentioned above and introduce it on the left of figure 6. To ensure, the superiority of the new collimator we compare it to the symmetric collimator (with and without septum walls). We solve $\mathcal{V}(\mathbf{1})$ in equation (6) (with $\mathbf{1} = [1, \cdots, 1]$) for 100 randomly chosen subspaces with one, two, three and four sources. The mean value of (6) from the collimators without septum walls (figure 6) are at least three times smaller than for the symmetric collimator with septum walls (figure 3). Additionally, all the mean values of the symmetric

Table 1. Comparison between the symmetric collimator (with and without septum walls) and the non-symmetric collimator for optimal design: mean value of $\mathcal{V}(\mathbf{1})$ in equation (6) (with $\mathbf{1} = [1, \cdots, 1]$) for 100 randomly chosen subspace with one, two, three and four sources.

Number of sources	1	2	3	4
$\mathcal{V}(\mathbf{1})$ value of symmetric-collimator (with septum walls)	5.44	10.70	15.95	22.37
$\mathcal{V}(\mathbf{1})$ value of symmetric-collimator (no septum walls)	1.41	2.14	3.41	4.82
$\mathcal{V}(\mathbf{1})$ value of non symmetric-collimator	0.98	2.01	3.32	4.00

breaking collimator are lower than the one with symmetric pinholes. Hence, the new non-symmetric collimator proves itself as a good choice in our optimal design process (see table 1). Clearly, this design is not a perfect optimal design for all combination of sources, and yet, we show in our *ex vivo* experiments the superiority of the new symmetry breaking design, in comparison to the symmetric designs.

2.3. Dictionary

Let u be a subspace containing a single source at the position $(20, 50, 140)$ mm. We use (1) to compute the corresponding detector image d_1 as shown on the top left of figure 7. Next, we consider a slightly different position of the source: $(21, 50, 140)$ mm (i.e. we change the position of the x coordinate by 1 mm). The computed corresponding detector image d_2 for this source is shown on the top right of figure 7. Even though we changed the position of the source by just 1 mm in the horizontal direction x, the changes on the resulting detector image are evident, as can be seen on the bottom of figure 7, where we show the difference $d_1 - d_2$ between the detector images. Similar results can be seen when changing the position slightly in the y and z directions. In the following, we take advantage of this sensitivity of the detector image to small changes in the source position to get a very fast and robust reconstruction of the position of the sources.

Here, we build a dictionary of computed detector images, which holds all the projections of all source positions in our 3D subspace onto the detector. When performing an experiment, a detector image d^{true} is produced. Then, we use a coherency functional

$$\mathcal{C} : \mathbb{R}^{N_d} \to \mathbb{R},$$

to find the image in the dictionary with the highest coherency to d^{true}. The detected source is the one corresponding to the image where $\mathcal{C}$ gets its global maximum (for the choice of $\mathcal{C}$ we refer to section 2.4). In an optimal situation, we would like to have a dictionary containing all detector images for all numbers of sources and their combinations. This is, unfortunately, impossible. Even if we restrict the reconstruction to a maximum number of three sources, in a subspace of $30 \times 80 \times 100 \text{ mm}^3$, with a coarse grid of 3 mm between the sources. The following number of matrices with the size of 487×195 would have to be stored:

$$\binom{8580}{1} + \binom{8580}{2} + \binom{8580}{3} = 105,271,459,150.$$

Since this is impossible on a standard computer, we reduce the dictionary only to images corresponding to a single source. In the example described above, we reduce the number of entries of the dictionary to 8580. In the following (section 2.4), we show how it is still possible to find multiple sources using this reduced dictionary. This is done in an iterative process. Since the images for a single source in the dictionary are sparse (see figure 7, for example) we can store them easily without any special memory requirements.

Note, that we locate the center of the Tc-99m source (diameter 5–7 mm). Hence, even a small error can still be within the diameter of the source.

2.4. SLNF algorithm

Here, we want to define the requirements of the functional $\mathcal{C}$. Let u_1 respectively u_2 be two 3D subspaces containing a single radioactive tracer s_1 respectively s_2, and let s be one of the sources in the true subspace u. The radioactive sources s_1 and s_2 assumed to be within Euclidean space distances, $\text{dist}(s_1, s)$ and $\text{dist}(s_2, s)$, which are not too large. Let d_1 respectively d_2 be the detector images in the dictionary representing the projection of the source s_1 respectively s_2 (using (1)). We seek for a functional $\mathcal{C}$, s.t.

$$\mathcal{C}(d_1) > \mathcal{C}(d_2), \quad \text{if } \text{dist}(s_1, s) < \text{dist}(s_2, s). \tag{10}$$

Having such a functional $\mathcal{C}$, we apply it on each detector image in the dictionary D and find the index in the dictionary where the coherency functional finds its maximum. Several functionals can be applied here and fulfill the above mentioned requirement. To get fast and reliable results, we follow (Ma *et al* 2013) and choose

$$\mathcal{C}(d) = \|d \circ d^{\text{true}}\|_{\mathbb{F}} = \sqrt{\sum_{i,j} \left(d_{ij} \cdot d_{ij}^{\text{true}} \right)^2}. \tag{11}$$

Here, the operator $\circ$ denotes the Hadamard product and $\mathbb{F}$ denotes the Frobenius norm. In other words: the higher the value of $\mathcal{C}(d)$, the more similar are d^{true} and d.

In figure 8, we visualize the principle of the coherency functional $\mathcal{C}(d)$ on a simplified example. In figure 8(a), we have the measured image d^{true} with noise (e.g. photons penetrating the collimator walls) and in the center the measured projection of the source (yellow). In the left column of figures 8(b)–(d) we have three simulated detector images d^1, d^2 and d^3. These correspond to three different source positions P^1, P^2 and P^3. Each value of the pixel of d^{true} is represented as d_{ij}^{true} and each pixel of the images d^{ℓ} is represented as d_{ij}^{ℓ} for $\ell = 1, 2, 3$, respectively. For this simplified example, we only choose the three aforementioned images d^1, d^2, d^3 for the dictionary D, hence we have $D = \{d^1, d^2, d^3\}$. In the right column of figures 8(b)–(d) we show the Hadamard multiplication, i.e. a pixel-wise multiplication, of d^{ℓ} and d^{true} (for all pixel entries we compute $d_{ij}^{\ell} \cdot d_{ij}^{\text{true}}$). The coherency functional $\mathcal{C}(d^{\ell})$ in (11) is the quadratic sum of all the pixel from the resulting image. We observe, that d^1 covers the whole projection of the source, d^2 does not intersect with the projection and only the noise is observed. In the case of d^3 the projection is partially covered. As mentioned, the coherency functional $\mathcal{C}(d)$ in equation (11), compares the simulated detector images d from the dictionary D to the true detector image d^{true}. The more similar the images are, the higher is the value of $\mathcal{C}(d)$. We have the highest value from d^1 with $\mathcal{C}(d^1) = 216$ (where the whole projection is observed), the lowest value from d^2 with $\mathcal{C}(d^2) = 125$ (where only noise is observed) and the value for d^3 with $\mathcal{C}(d^3) = 167$. In conclusion, the the dictionary entry d^1, corresponding to the source P^1, is the most similar to the measured image d^{true}, since it's coherency value is the highest. Hence, we assume that the true source position corresponds to P^1.

The dictionary D contains images corresponding only to a single source. However, u may contain more than one source and hence we find all sources in an iterative process:

Algorithm 1.   **SLNF**: Finding the position of the radioactive sources using a predefined dictionary.

Input: a detector image d^{true}, dictionary of corresponding detector images D for all possible locations of sources p.

  Output: position of sources L.

1. Evaluate $\mathcal{C}(d_i)$, $\forall d_i \in D$ and set m as the median of all $\mathcal{C}(d_i)$
2. repeat until $\max(\mathcal{C}(d_i)) < \delta \cdot \log(m)$
  2.1.   set $i^{\star}$ as the index i of the global maximum of $\mathcal{C}$
  2.2.   add to $L \leftarrow p_{i^{\star}}$
      % the $i^{\star}$'s index of p is the approximation of the source
      % with the highest intensity.
  2.3.   Set d^{true} to zero where $d_{i^{\star}} > 0$
      % delete the values in the true detector image
      % corresponding to $i^{\star}$ to reveal another
      % possible source.
  2.4.   update $\mathcal{C}$ with the modified d^{true}
3. return L

In the first step of the algorithm, we evaluate $\mathcal{C}$ on all the detector images in the dictionary and compute the median m for the stop criteria of the algorithm. If the maximum of $\mathcal{C}$ is significantly higher than m, there is another source to be found (step 2). After saving the information of the source (step 2.1), we delete its corresponding information from the true detector image d^{true} (step 2.3). In the last step of the loop we update $\mathcal{C}$ with the modified d^{true} (step 2.4). If the maximal value of $\mathcal{C}$ is still significantly higher than m, there is another source to be found and the process is repeated. The loop finally breaks when the maximal value of $\mathcal{C}$ is close to m, i.e. there is no significant activity on the detector, that correlates to a source. Hence, all sources are found.

Remark 3.

- The images d_i in the dictionary D are highly sparse. On average, more than 97% of the entries in d_i are zero. Hence, the computation can be run very fast without any special memory requirements.
- The sequence in which we find the sources is a non-increasing sequence of intensities, i.e. the algorithm finds the sources from the strongest to the weakest intensity.
- With the non-symmetric collimator the parameter δ was experimentally chosen for every exposure time.
- Another possibility for automatic detection of the number of sources is using deep neural network. First results on simulated detectors images has shown very good results, and in the future, we plan on refining this approach using real patient data.
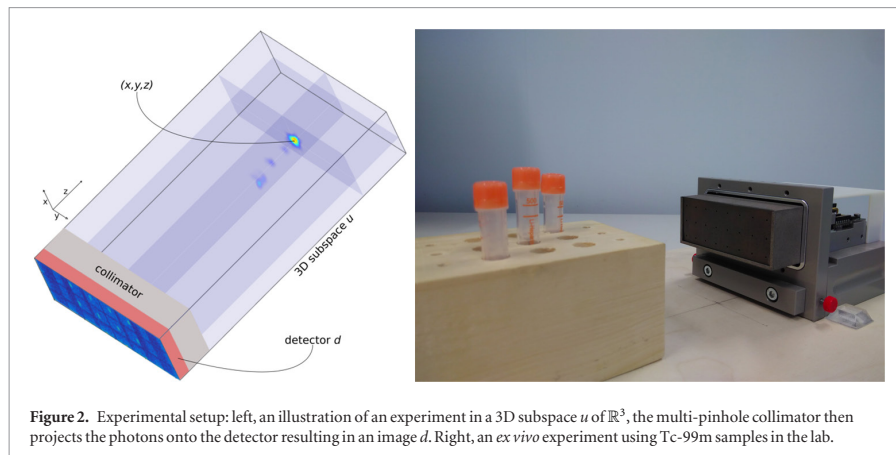
Figure 2. Experimental setup: left, an illustration of an experiment in a 3D subspace u of $\mathbb{R}^3$, the multi-pinhole collimator then projects the photons onto the detector resulting in an image d. Right, an *ex vivo* experiment using Tc-99m samples in the lab.

Table 2. Seven different experiments with Tc-99m in the lab and reconstruction of the source positions using a detector which was exposed for one resp. 16 s to the sources using the new non-symmetric collimator.

#	True position(s) in mm	Reconstruction with 1 s in mm	L^2-error in mm	Mean in mm	Reconstruction with 16 s in mm	L^2-error in mm	Mean in mm
1	(21, 41, 130)	(20, 42, 128)	2.4	2.4	(20, 42, 130)	1.4	1.4
2	(21, 41, 130)	(20, 42, 130)	1.4	5.3	(20, 42, 130)	1.4	2.2
	(26, 21, 110)	(26, 22, 101)	9.1		(26, 21, 107)	3	
3	(21, 41, 130)	(20, 41, 131)	1.4	9.6	(20, 41, 127)	3.2	3.2
	(16, 21, 130)	(14, 22, 130)	2.2		(15, 22, 127)	3.3	
	(26, 61, 150)	(24, 63, 175)	25.2		(24, 63, 149)	3	
4	(21, 41, 130)	(20, 42, 130)	1.4	1.8	(20, 42, 130)	1.4	2.4
	(16, 21, 130)	(15, 21, 132)	2.2		(15, 22, 127)	3.3	
5	(16, 21, 130)	(15, 22, 127)	3.3	4	(15, 22, 127)	3.3	4
	(26, 61, 130)	(25, 63, 134)	4.6		(25, 63, 134)	4.6	
6	(21, 41, 110)	(21, 41, 108)	2	4	(21, 41, 111)	1	2.2
	(21, 41, 150)	(18, 42, 145)	5.9		(18, 42, 149)	3.3	
7	(16, 21, 130)	(16, 22, 126)	4.1	—	(15, 21, 129)	1.4	5.3
	(21, 41, 150)	(20, 43, 153)	3.7		(19, 42, 144)	6.4	
	(26, 21, 110)	—	—		(26, 22, 102)	8.1	
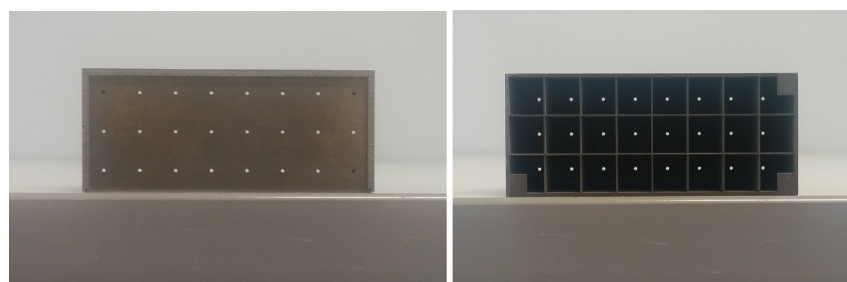
Figure 3. Symmetric collimator: a pinhole collimator with 24 compartments and 24 pinholes matching the centers of the compartment. Front view (left) and rear view (right).
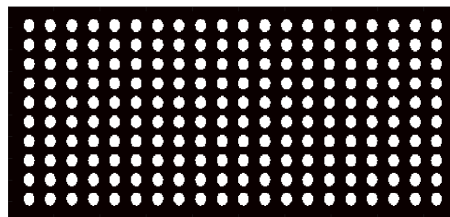
Figure 4. Optimal collimator design: 200 possible pinholes marked in white.
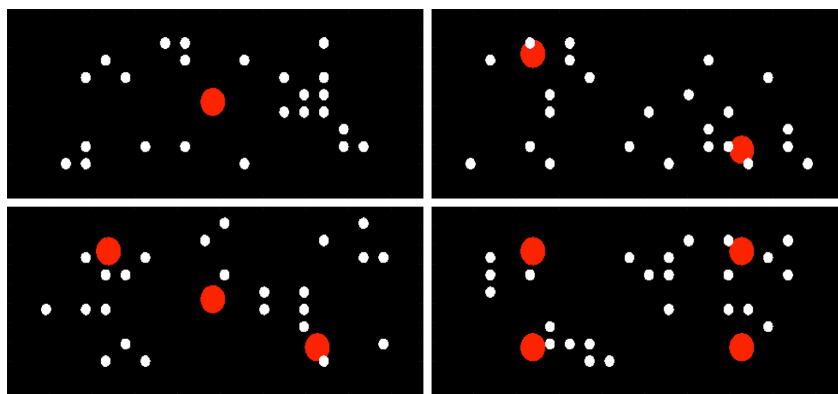
Figure 5. Optimal design: white circles represent the pinholes with the highest weights, given by solving (7) and red circles represents the (x, y) position of the source(s).
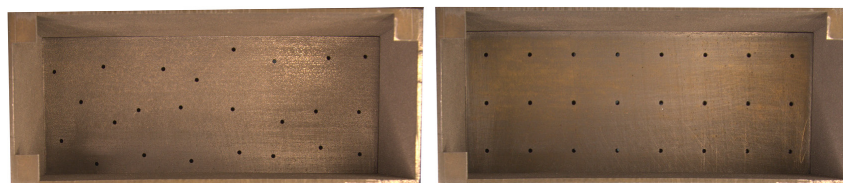
Figure 6. New collimator without septum walls: 24 pinhole collimator with non-symmetric pinholes (left) and the collimator with symmetric pinholes (right).

3. Results

In this section, we reconstruct the 3D position of the radioactive sources using a single 2D image of the detector. The image is received from the detector after placing up to three sources in different positions in front of the collimator and the detector (see figure 2). All veils are filled with a fluid of 19 ml with different strength of Tc-99m.

For the illustration of algorithm 1, we use a dictionary, that includes all detector images corresponding to all single sources in a subspace u of $30 \times 80 \times 180 \, \text{mm}^3$ with a grid spacing of 1 mm in each direction. Moreover, we use detector images, produced by exposing the detector for 16 s to the sources. After illustrating the algorithm and its functionality, we compare the results with images received after an exposure time of one second to the sources, see section 3.4.

Remark 4. Four rectangular areas can be seen on the corners of the detector image, see for example on the right of figure 10. The big empty rectangle on the bottom right is due to a faulty sensor area of the detector. The other three rectangles are used to geometrically align the collimator to the detector. Despite these non-sensitive areas, the positional estimations of the detector are very accurate proving the robustness of the developed design and processing.

Figure 7. Two computed detector images and their difference: top, the detector image d_1 corresponding to a source located at $(20, 50, 140)$ mm (left), the detector image d_2 corresponding to a source located at $(21, 50, 140)$ mm (right). Bottom: the difference between the images $d_1 - d_2$.

Figure 8. Simplified example to visualize the functional $\mathcal{C}(d)$: (a) noisy measured image d^{true} and the projection of the source in the center (yellow). Left column: simulated detector image d^{ℓ} in dictionary corresponding to position P^{ℓ} for $\ell = 1, 2, 3$ (from top to bottom). Right column: pixel-wise multiplication of d^{ℓ} and d^{true} for $\ell = 1, 2, 3$. The coherency functional $\mathcal{C}(d)$ has the maximum at $\mathcal{C}(d^1)$, hence the measured image d^{true} corresponds to the position P^i.

Figure 9. Illustration of the center of the source positions in four different experiments: one to three Tc-99m sources in a three-dimensional subspace u. (a) 60 MBq source at $(21, 41, 130)$ (b) 60 MBq source at $(21, 41, 130)$ mm (red) and 30 MBq source at $(26, 21, 110)$ mm (green) (c) 60 MBq source at $(21, 41, 130)$ mm (red), 30 MBq source at $(16, 21, 130)$ mm (gray) and 15 MBq source at $(26, 61, 150)$ mm (green) (d) 60 MBq source at $(21, 41, 110)$ mm (red) and 30 MBq source at $(21, 41, 150)$ mm (green).

3.1. One source experiment

First, we consider a single Tc-99m source with an intensity of 60 MBq, located at the position $(21, 41, 130)$ mm, as illustrated in figure 9(a) (the lines in the figure visualize the axes in the 3D subspace).

On the right of figure 10(a), we plot the functional $\mathcal{C}$ evaluated on all detector images in the dictionary D. We remind the reader that the more similar the true detector image is to the detector image of the dictionary, the higher is the value of the functional $\mathcal{C}$. We find its maximum on the 172 159th entry of the dictionary. This entry corresponds to the point $(20, 42, 130)$ mm. This yields a very small L^2-error of 1.4 mm. Next, we delete the information corresponding to the source found from d^{true}, as described in step 2.3 of algorithm 1 and shown on the left of figure 10(b). Then, we update the functional $\mathcal{C}$ with the modified detector image as in step 2.3 of algorithm 1 and plotted on the right of figure 10(b). Now, there is no significant activity left, i.e. the maximum of the functional $\mathcal{C}$ is not significantly larger than its median m. Hence, all sources have been found and the algorithm terminates (see, algorithm 1, step 2).

Figure 10. Single source: illustrating the steps of algorithm 1 for the single source experiment. (a) Left: initial image d^{true}. Right: graph of the functional $\mathcal{C}$ on all detector images in the dictionary with a global maximum corresponds to $(20, 43, 133)$ mm (step 2.2). (b) Deleting the corresponding information of the first source in algorithm 1 from the initial image d^{true}. Left: the detector image, which is received at the step 2.3 with no significant activity left. Right: updated functional $\mathcal{C}$ with no significant global maximum.

Remark 5. Note that the other clear local maxima of $\mathcal{C}$, shown on the right of figure 10(a), correspond to sources in the close neighborhood of the located point.

3.2. Two sources experiment

Now, we consider a subspace u with two sources at $(21, 41, 130)$ mm and $(26, 21, 110)$ mm with intensities of 60 MBq and 30 MBq, respectively. In figure 9(b), we plot the sources, where the red color represents a source with higher intensity and the green color a weaker one.

On the right of figure 11(a), we plot the functional $\mathcal{C}$ applied on the dictionary. The functional $\mathcal{C}$ finds its global maximum at the 172 159th entry of the dictionary, which corresponds to a source located at $(20, 42, 130)$ mm. We follow algorithm 1 and delete the corresponding information of the source found from d^{true} (see step 2.3 of algorithm 1 and figure 11(b), left). On the left of figure 11(b), we see that there is still significant activity left after deleting the corresponding information of the last source found. We update the functional $\mathcal{C}$, with the modified detector image (step 2.4) and evaluate it for all images of the dictionary (see figure 11(b), right). Indeed, the remaining activity is translated to a new clear global maximum of $\mathcal{C}$. The maximum is on the 220 606th entry of the dictionary, which corresponds to the source located at $(26, 21, 107)$ mm. Following algorithm 1, we repeat the process until no significant activity remains (see figure 11(c)). The algorithm finds two sources with a remarkable mean L^2-error of 2.2 mm.

3.3. Three sources experiment

Next, we consider a subspace u with three sources at the positions $(21, 41, 130)$ mm, $(26, 61, 150)$ mm and $(16, 21, 130)$ mm with intensities of 60 MBq, 30 MBq and 15 MBq, respectively. In figure 9(c), we plot the sources and mark different intensities with different colors: from strongest to weakest: red, green and gray.

In figure 12, we plot the four different detector images, during the algorithm (we omit the graphs of $\mathcal{C}$, since they are similar to the ones showed in the previous examples). In the first three images a significant activity exists, which corresponds to an additional source. On the fourth detector image (bottom right of figure 12) there is no such activity left. Hence, the loop breaks in step 2 of algorithm 1. The algorithm finds three sources at the following positions: $(20, 41, 127)$ mm, $(15, 22, 127)$ mm and $(24, 63, 149)$ mm. Again, the mean L^2-error is very small and equal to 3.2 mm.
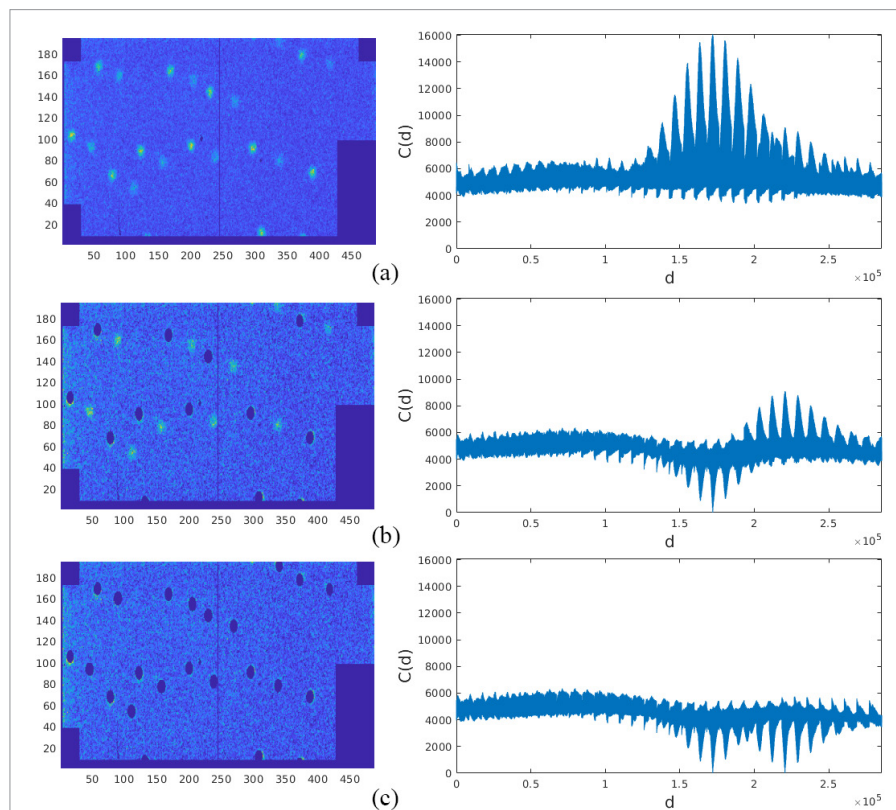
Figure 11. Illustrating the steps of algorithm 1 for two sources experiment. (a) Left: initial image d^{true}. Right: the functional $\mathcal{C}$ evaluated on all detector images in D with a global maximum corresponding to $(20, 42, 130)$ mm (step 2.2). (b) Deleting the corresponding information of the first source from the initial image d^{true}. Left: detector image received in step 2.3 with significant activity left. Right: updated functional $\mathcal{C}$ in step 2.4, with a global maximum corresponds to $(26, 21, 107)$ mm. (c) Deleting the corresponding information of the second source. Left: detector image received in step 2.3 with no significant activity left. Right: updated functional $\mathcal{C}$ in step 2.4, with no significant global maximum.
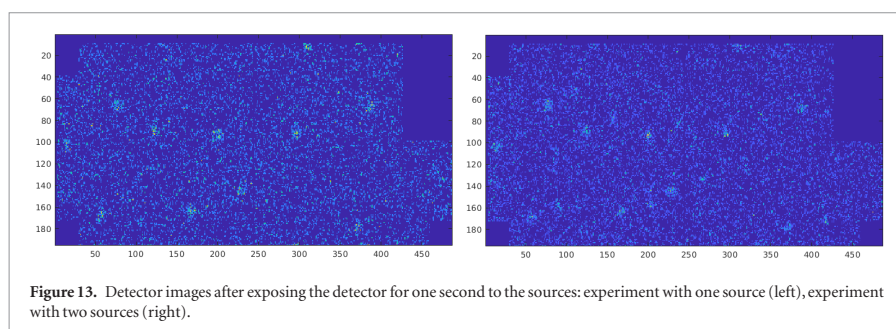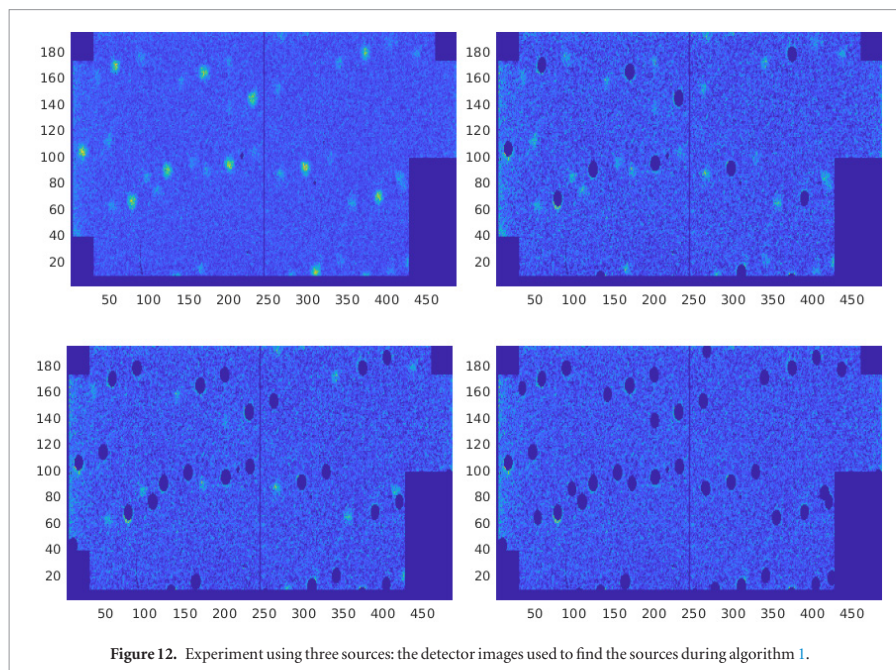
3.4. One second exposure of the detector to the sources

In this experiment we repeat the tests described above, but this time we expose the detector only for one second. 60 MBq is a higher dosage then generally measured in the SLN. Hence, it is utmost important to be able to reconstruct the images with a low exposure time. This enables us to use slightly longer exposure times to detect weaker radiant sources.

The number of photons detected when exposing the detector to the sources for one second decreases and the signal to noise ratio is drastically increased. In figure 13, we plot such images for the source combination described in sections 3.1 (left) and 3.2 (right). Although it seems that these images contain very limited data, the SLNF is able to extract all source positions with a small L^2-error.

In table 2, we show seven different source combinations, with an exposure time of one second resp. 16 s. In experiments 1–3 in table 2, we use the same source positions and source intensities described in sections 3.1–3.3. In experiments 4 and 5, we present another two source combinations and their successful position detection.

The SLN in the body might be located in such way, that one SLN with a weak intensity is hidden behind another one with a higher intensity. We consider this case as a very challenging one. In experiment 6, we consider this case in the lab when we locate a weaker source exactly behind a stronger one. In this experiment, the subspace u contains two sources at the positions $(21, 41, 110)$ mm and $(21, 41, 150)$ mm with intensities of 60 MBq and 30 MBq, respectively. In figure 9(d), we illustrate the position of these sources. Again, the red color represents a source with higher intensity and the green color a weaker one. The robustness of the SLNF is again demonstrated in this experiment, when the results hold a small L^2-error of less than 4 mm. In the case of twin SLN (two SLN very close to each other), the SLNF algorithm might detect them as a single source. This should not be a major problem, since the medical doctor will take them both out. Finally, we investigate in experiment 7a different

Figure 12. Experiment using three sources: the detector images used to find the sources during algorithm 1.

Figure 13. Detector images after exposing the detector for one second to the sources: experiment with one source (left), experiment with two sources (right).

combinations of three sources. Although it does not find all the sources with one second exposure time, it still manages to find all the sources with an exposure time of 16 s with a mean L^2-error of 5.3 mm.

Remark 6. If we reduce the dictionary from $30 \times 80 \times 180\,\text{mm}^3$ to $30 \times 80 \times 170\,\text{mm}^3$ we get a remarkable reduction of the error in experiment 3 for 1 s exposure time: the third source is now at (24, 63, 154), which reduces the mean error from 9.6 mm to 2.8 mm.

3.5. Error estimation

At last, we compare our choice of the non-symmetrical collimator, shown on the right of figure 6, with a symmetric distributed pinhole pattern, shown in figure 3. In figure 14, we compare the L^2-error of the two collimators for up to three sources (the source combinations are those shown in sections 3.1–3.3). This time we expose the sources for different times: 1, 2, 4, 8 and 16 s. The advantage of the non-symmetrical distributed pinhole collimator is clear: the accuracy is very high, even for multiple sources with exposure time as low as one second. When using the symmetric collimator this is, unfortunately, not the case. In some experiments, especially in multiple sources, exposing the detector to the sources through the symmetric collimator for 16 s yields a higher L^2-error with compare to the non-symmetric collimator for a single second. The comparison was repeated for some other source positions and similar results were shown.
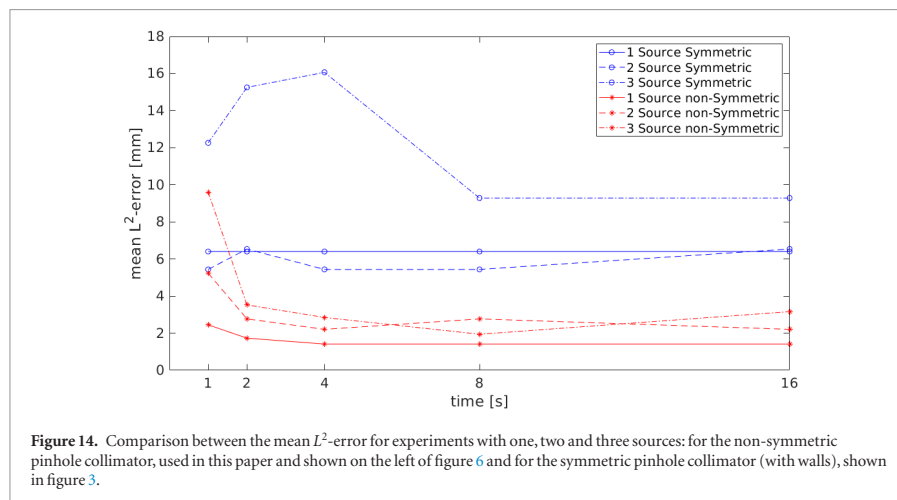
Figure 14. Comparison between the mean L^2-error for experiments with one, two and three sources: for the non-symmetric pinhole collimator, used in this paper and shown on the left of figure 6 and for the symmetric pinhole collimator (with walls), shown in figure 3.

Remark 7. The symmetric collimator without septum walls, shown on the right of figure 6, provides often similar results to the non-symmetric collimator. However, In the case when two sources are located behind each other, which is very relevant in the detection of sentinel lymph-nodes, only the non-symmetric collimator is able to locate both of them. Actually, we discover in the experiment setup shown in figure 9(d) (with an exposure time of 16 s), that the symmetric collimator has a high mean L^2-error of 18.3 mm and the non-symmetric collimator provides a remarkable low error of 2.2 mm. This experiment supports as well the superiority of the non-symmetrical collimator.

4. Discussion

We introduce a new approach using a single gamma detector image. The method improves accuracy and reduces the run time dramatically with respect to former methods using, for example, non-linear optimization. Using a single gamma detector image, can be a drawback, especially when two sources are located very close and exactly behind each other. In our experiments, the method had difficulties when two sources are under 20 mm away from each other in depth, but share the same horizontal and vertical values. In this situation, the methods show a single source, which is positioned exactly between the sources. The medical doctor will remove all lymph nodes around the detected position, and hence, will remove both sentinel lymph nodes in this case.

In head and neck melanoma, we may find an intensity which can be at least twenty times smaller than the one we used in this paper. Since we used a very short exposure time, we can increase it to more than 20 s to get similar results. In addition, we aim to improve our *ex vivo* experiment into a more realistic model, by adding a hot background.

We use a non-symmetric collimator without septum walls. Although this collimator is not a fully optimal design (an other random distribution of pinholes might be marginally more optimal) it proofs itself as a good choice. Not only in our optimal design process, but also in our *ex vivo* experiments it exceeds the symmetric designs and gives good results even under low exposure time.

Our device is still limited with regards to the field of view to solely the front of the collimator. However, due to the pinholes, we can measure activity of sources on the side of the collimator, but still in the field-of-view of the pinholes. This can be improved, by taking in account the whole field of view of all the pinholes and not solely the area directly in front of the collimator. Furthermore, a bigger, stationary device, e.g. built-in under the patient bed, can increase it further. Alternatively, a surgeon could use it as a portable device to receive live updates of the area of interest.

5. Conclusions

We introduce a new approach, the SLNF, for sentinel lymph node detection using a single gamma detector image. Furthermore, we show that our new non-symmetric collimator not only improves the accuracy of the reconstruction in comparison to the previous one (symmetric), but also enables very short exposure times. In

ex vivo experiments the method is able to find the 3D position of multiple Tc-99m sources. SLNF needs only a few seconds of computational time to locate the position of the sources and without any pre-processing of the gamma detector image.

The results of the algorithm are robust for multiple sources and its reliability is demonstrated. The robustness of our approach (also in depth) is a very critical aspect for SLN detection in the head and neck area, where important blood vessels and nerves are located.

In the future, we will test our approach on patients, where the radioactive intensity in the sentinel lymph nodes might be lower. Further, we will increase the the measurable subspace to the field of view of the pinholes instead of solely in front of the collimator. This can ensure that the dictionary will cover all the possible positions of the measurement from the detector. Our promising results for one second exposure time and the remarkable robustness of our algorithm for different source positions and exposure times are, however, very encouraging.

Acknowledgments

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Chapter 4

Joint Inverse Medium and Optimal Control Problem

The main goal of the MIRACLE project is to cut bones with laser light. To improve navigation and avoid cutting sensitive tissue, it is essential to have an accurate feedback system. The first approach was made in the work [67], where they were able to reconstruct the bone's structure and the ablation's position in a 2D simulation using only two transducers. They assumed that the source is precisely known, presupposing, the source's form and frequency composition. However, this cannot be assumed. For example, when ablating with an Er:YAG laser, the acoustic wave may change depending on the kind of tissue and its water content. Hence, we cannot assume that the form and the generated frequencies are known during the ablation process.

This paper investigates the challenge when the source form and the medium surrounding the source are unknown. We can reconstruct the medium velocity and the source by solving the Helmholtz equation with the Adaptive Eigenspace introduced in [63]. Here, we solve the following inverse problem in a 2D simulation: What are the form of the source and the medium velocity for the measured acoustic wave?

There is one major limitation. The computation time was too long for the 2D simulation to be suitable for a real-time application. Furthermore, the number of transducers required is not feasible, and generalizing everything in 3D space is not realistic.

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Joint Inverse Medium and Optimal Control Problem for Acoustic Waves

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ABSTRACT

Background: Ever since endoscopes were invented, surgeons try to widen their field of usage by developing novel surgical approaches. An obvious advantage of the endoscope is the minimal invasiveness, but this comes at a price of reduced dexterity, loss of tactile feedback and difficulty in orientation. One of the challenges is to acquire the data of the neighborhood to find the relative position of the endoscope to the surrounding tissues.

Methods & Results: In this paper, we present a mathematical approach to reconstruct unknown source(s) position(s) (e.g. endoscope, which produces a signal in different frequencies) and a medium (e.g. tissue surrounding the endoscope). We solve the joint Inverse Medium and Optimal Control on the Helmholtz equation, where both source(s) and medium velocity are unknown. The use of the Adaptive Eigenspace Inversion (AEI) in combination with frequency stepping, proofs itself to be a good solution. We underline our claim, with two-dimensional numerical experiments.

Conclusion: The application of this method together with its promising results can potentially aid to navigate an endoscope through the body while collecting information on the surrounding tissue. These results may also find their application in geophysics.

CCS CONCEPTS

• **Mathematics of computing → Partial differential equations**; **Discrete optimization**; *Discrete mathematics*; *Nonlinear equations*; Solvers; Numerical differentiation; • **Computing methodologies → Optimization algorithms**.

KEYWORDS

Inverse medium problem, unknown source term, optimal control, Helmholtz equation, full waveform inversion, PDE constrained optimization, frequency stepping, multi-parameter problems, Adaptive Eigenspace Inversion.

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1 INTRODUCTION

Minimally invasive surgery reduces the trauma of patients [20, 25]. The method of choice is to insert the endoscopes through small ports into the body. Multiple methods have been introduced to track the position of the endoscope [1, 7, 22–24, 35], but it is also important to know the surrounding tissues, to collect information or to perform a surgery [29]. Here, we have multiple unknown parameters (the surrounding tissue and the position of the endoscope) and hence, we have a joint inverse medium and optimal control problem.

To solve the joint inverse medium and optimal control problem, a multi-parameter inverse problem must be solved, which has been a challenging area of research since more than three decades [38]. In recent years, this problem has been addressed extensively in geophysics [10, 13, 31, 34, 39], e.g. for exploring gas and oil occurrence two distinct parameters are crucial: density and bulk-modulus. This paper deals with a different multi-parameter problem: the two parameters are the unknown medium (e.g. position and wave velocity of the tissue) and the position of the source (e.g. wave sources in the endoscope).

Multi-parameter inverse problems pose various challenges [27]:

(1) Cross-talk – one of the consequences of optimizing several parameters simultaneously within the same equation manifests itself as unwanted artifacts, resulting from the parameters influencing each other [31]. For instance, when the gradients are coupled regularization problems can occur [33].

(2) Ill-posedness – in addition, the multi-parameter inverse problem is ill-posed [34], i.e. there is no admissible solution, the solution is not unique or the solution does not depend continuously on the input data.

Different methods have been introduced to address the multi-parameter inverse medium problem. In [34] the full-Newton method and the data-driven strategy are presented. Here, the expected decrease is defined in the misfit functional and combined with a separate Tikhonov (TV) regularization term for each parameter to reduce the Cross-talk between them. Moreover, for the penalty formulation, a sparse version of the Gauss-Newton Hessian is used with prior information of the parameters with respect to the similarity of the

structures [10, 33]. In addition [39] proposed the use of random successive sources (hence, multiple right hand sides) to solve the multi-parameter inversion.

Acoustic waves travel through different tissues with different velocities. Knowledge of these velocity profiles can assist the classification of tissue and structure while the medium velocity is reconstructed. In some cases, the position of the endoscope within the body is unknown. To improve the navigation through the body, not only the velocity profile is important but also the position of the sources. The optimal control problem is then affected by the medium, and hence the resulting combined optimal and inverse medium problem must be solved. The Adaptive Eigenspace (AE) representation of the time-dependent scattering problems, was proposed by [5, 6] and has been extended to a fix frequency for electromagnetic inverse medium problems [5]. It was also used for image processing [28] and strongly relates to nonlinear spectral representation [11]. In [15, 16, 27] the AEI for a single and multi-parameter inverse medium problems was investigated and the eigenspace of the TV regularization gradient was used. The problem was well regularized by slowly increasing the number of eigenfunctions with the time-frequency.

Several approaches have been introduced, where both medium and source are unknown, see for example [12, 29, 32, 36]. In a similar approach to the solution of the multi-parameter inverse problem, which has been introduced in [16], we solve the inverse medium and optimal control problems – where we not only reconstruct the medium velocity (helpful for tissue classification), but also the form and position of the source(s) using the Adaptive Eigenspace Inversion (AEI).

2 THE MEDIUM-CONTROL INVERSE HELMHOLTZ PROBLEM

We begin by introducing the time dependent propagation of a wave through a medium. This can be described with the acoustic wave equation

$$\bar{y}_{tt}(x,t) - \nabla \cdot (u(x)\nabla \bar{y}(x,t)) = \bar{f}(x,t). \tag{1}$$

Herein, $u > 0$ represents the squared medium velocity, $\bar{f}$ resp. f is the source function, $\bar{y}$ resp. y the pressure variation – i.e. the wave field – and ω the time-frequency. Using the Fourier transform of the time variable, we write

$$\bar{y}(x,t) = y(x)e^{-i\omega t} \quad \text{and} \quad \bar{f}(x,t) = f(x)e^{-i\omega t}. \tag{2}$$

In our simulation, we use unbounded domains. Hence, we need artificial boundaries to mimic the unbounded exterior. One possible approach are perfectly matched layers [4, 17, 37]. Another one is the use of absorbing boundary conditions [2, 3, 9], e.g. Sommerfeld boundary condition. In our case, we use the Sommerfeld boundary condition for the Helmholtz equation:

$$\begin{cases} -\omega^2 y - \nabla \cdot (u\nabla y) = f, & \text{in } \Omega^o = \Omega \setminus \partial\Omega, \\ \dfrac{\partial y}{\partial \mathbf{n}} - iky = 0, & \text{on } \Gamma = \partial\Omega, \end{cases} \tag{3}$$

where $k(x) = \dfrac{\omega}{\sqrt{u(x)}}$ is the wave-number at time-frequency ω and

$$\frac{\partial y(x)}{\partial \mathbf{n}} := \mathbf{n} \cdot \nabla y(x)$$

is the normal derivative, where $\mathbf{n}$ denotes the normal on the boundary $\Gamma = \partial\Omega$.

In the following, we introduce the reduced-space approach [14, 18, 21]. This takes advantage of the adjoint and state variables on the control variable u and f, by reducing the search space. The state variable $y = [y_1, \cdots, y_{N_s}]$ can be expressed as a function of the squared medium velocity u and the source(s) $f = [f_1, \cdots, f_{N_s}]$ (where N_s are the number of sources):

$$y_\ell(u,f) = A(u)^{-1} f_\ell, \quad \text{for } \ell = 1, \cdots, N_s. \tag{4}$$

Here, $A(u)$ denotes the forward Helmholtz problem operator in equation (3). By eliminating y_ℓ the optimization problem for the reduced-space approach reads

$$\arg\min_{u,f} \mathcal{F}(u,f), \quad \text{where} \quad \mathcal{F}(u,f) = \frac{1}{2} \sum_{\ell=1}^{N_s} \|\hat{y}_\ell(u,f)\|_2^2 \tag{5}$$

with

$$\hat{y}_\ell(u,f) = y_\ell(u,f) - y_\ell^{obs}$$
$$= PA(u)^{-1} f_\ell - y_\ell^{obs}.$$

The observed pressure variation by the microphones is denoted by $y^{obs} = [y_1^{obs}, \cdots, y_{N_s}^{obs}]$ and P projects the computed pressure variation $y_\ell(u,f) = A(u)^{-1} f_\ell$ onto the microphones. The regularization functionals $\mathcal{R}_1(u)$ and $\mathcal{R}_2(f)$ can be added to the misfit functional.

Through the choice of $\mathcal{R}_1(u)$ and $\mathcal{R}_2(f)$, each parameter can be regularized separately according to a priory information on each parameter. Sometimes an additional constraint is added to the optimization [10] to penalize the difference between the structures of two parameters and thus avoid Cross-talk.

We will apply the Adaptive Eigenspace Inversion (AEI), where we can omit the regularization functionals $\mathcal{R}_1(u)$ and $\mathcal{R}_2(f)$, by using the Eigenspace Expansion of u and f (see Sec. 2.1). This will not only improve the reconstruction but also the stability of the reconstruction significantly. For the optimization of the medium u and f, we use the inexact quasi-Newton (Gauss-Newton) method with the Eisenstat-Walker stopping criteria [18, 26, 27] for the internal conjugate gradient (CG) iteration.

2.1 Adaptive Eigenspace (AE) Expansion

We apply the AEI from [15, 16, 27] for the Helmholtz inversion to the joint inverse medium and optimal control problem: in addition to the unknown squared medium velocity u, the sources f are unknown as well. Hence, we use the AE of the squared medium velocity u and of all the sources f_ℓ for $\ell = 1, \cdots, N_s$.

As in [16], instead of using a standard nodal basis, such as Finite Difference (FD) or Finite Elements (FE) grid-based discretization, we shall use bases of global eigenfunctions $\{\phi_m\}_{m\geq 1}$ and $\{\varphi_l^\ell\}_{l\geq 1}$ for each parameter, to represent the squared medium velocity $u(x)$ and the source $f_\ell(x)$ as

$$\begin{aligned} u(x) &\approx u^{AE}(x,\beta) &= u_0(x) &+ \sum_{m=1}^{K_1} \beta_m \phi_m(x), \\ f_\ell(x) &\approx f_\ell^{AE}(x,\gamma) &= f_0^\ell(x) &+ \sum_{l=1}^{K_2} \gamma_l^\ell \varphi_l^\ell(x). \end{aligned} \tag{6}$$

In [15], the values of K_1 and K_2 are linearly depend on the time-frequency ω. This reduces the number of unknowns drastically in

comparison to the standard nodal basis approach. Further, we use the eigenspace of the TV regularization gradient

$$\mu(x) = \frac{1}{\sqrt{|\nabla u(x)|^2 + \varepsilon^2}} \tag{7}$$

for the AEI ($\varepsilon > 0$ is a small value, e.g. $\varepsilon = 10^{-6}$). Hence, the eigenfunctions ϕ_m are given by the following eigenspace problem

$$\begin{cases} -\nabla \cdot (\mu(x)\nabla\phi_m(x)) &=& \lambda_m \phi_m(x), \quad \forall\, x \in \Omega^o \\ \phi_m(x) &=& 0, \qquad\qquad \forall\, x \in \Gamma \end{cases}, \tag{8}$$

Following [15], we set the "background" $u_0(x) \in H^1(\Omega)$ as the eigenfunction of the zero eigenvalue with the boundary condition u_∞ on the exterior of u, namely

$$\begin{cases} -\nabla \cdot (\mu(x)\nabla u_0(x)) &=& 0, \qquad\quad \forall\, x \in \Omega^o \\ u_0(x) &=& u_\infty(x), \quad \forall\, x \in \Gamma \end{cases}, \tag{9}$$

Similarly, we find the eigenfunctions φ_l^ℓ and the "background" f_0^ℓ of the source f_ℓ, by replacing in equation (7), (8), and (9): ∇u, $\nabla\phi_m(x)$, $\phi_m(x)$, ∇u_0, u_0, and u_∞ with ∇f_ℓ, $\nabla\varphi_l^\ell(x)$, $\varphi_l^\ell(x)$, ∇f_0^ℓ, f_0^ℓ, and f_∞^ℓ, respectively.

2.2 Adaptive Eigenspace Inversion (AEI) Algorithm

We transform our optimization problem (5) to account for the AEI basis. Instead of using the standard nodal basis, we expand u and f using the AE (see Sec. 2.1). To simplify the algorithm, we only use a single source $f = f_1$ (hence, $f^{AE} = f_1^{AE}$, $f_0 = f_0^1$, $\varphi_l = \varphi_l^1$, $\gamma_l = \gamma_l^1$, and $y^{obs} = y_1^{obs}$). However, it can easily be expanded to multiple sources. Our new reduced-space objective reads

$$\underset{\beta,\gamma}{\arg\min}\, \mathcal{F}\left(u^{AE}(\beta), f^{AE}(\gamma)\right), \tag{10}$$

where

$$\mathcal{F}\left(u^{AE}(\beta), f^{AE}(\gamma)\right) = \frac{1}{2}\left\|\hat{y}\left(u^{AE}(\beta), f^{AE}(\gamma)\right)\right\|_2^2, \tag{11}$$

with

$$\begin{aligned} \hat{y}\left(u^{AE}(\beta), f^{AE}(\gamma)\right) &= y\left(u^{AE}(\beta), f^{AE}(\gamma)\right) - y^{obs} \\ &= P\left[A\left(u^{AE}(\beta)\right)\right]^{-1} f^{AE}(\gamma) - y^{obs}, \end{aligned}$$

We set the gradient of $\mathcal{F}\left(u^{AE}(\beta), f^{AE}(\gamma)\right)$ as

$$\nabla\mathcal{F} = \begin{bmatrix} \nabla_\beta \mathcal{F} \\ \nabla_\gamma \mathcal{F} \end{bmatrix}, \tag{12}$$

where

$$\begin{aligned} \nabla_\beta \mathcal{F} &=& \left[\nabla_\beta u^{AE}(\beta)\right]^\top \nabla_{u^{AE}}\mathcal{F} \\ \nabla_\gamma \mathcal{F} &=& \left[\nabla_\gamma f^{AE}(\gamma)\right]^\top \nabla_{f^{AE}}\mathcal{F} \end{aligned}, \tag{13}$$

with

$$\begin{aligned} \nabla_{u^{AE}}\mathcal{F} &=& \left(\frac{\partial y\left(u^{AE}, f^{AE}\right)}{\partial u^{AE}}\right)^\top P^\top \hat{y}\left(u^{AE}, f^{AE}\right) \\[2ex] \nabla_{f^{AE}}\mathcal{F} &=& \left(\frac{\partial y\left(u^{AE}, f^{AE}\right)}{\partial f^{AE}}\right)^\top P^\top \hat{y}\left(u^{AE}, f^{AE}\right) \\[2ex] &=& \left[A\left(u^{AE}\right)\right]^{-\top} P^\top \hat{y}\left(u^{AE}, f^{AE}\right). \end{aligned} \tag{14}$$

To minimize the objective function (10), we use conjugate quasi-Newton method, with the Gauss-Newton approximation of the Hessian [18, 26]. We use the Eisenstat-Walker criteria [8] and the safeguards of *Nash* [30] to terminate the inner CG method.

For this, we need the Jacobi-Matrix $\mathcal{J}$, hence equation (12) reads

$$\nabla\mathcal{F} = \mathcal{J}^\top \hat{y}\left(u^{AE}, f^{AE}\right) \tag{15}$$

where

$$\mathcal{J} = [\,\mathcal{J}_\beta\,,\,\mathcal{J}_\gamma\,]. \tag{16}$$

From (13) and (14) we deduce

$$\begin{aligned} \mathcal{J}_\beta &= P\left[\frac{\partial y\left(u^{AE}, f^{AE}\right)}{\partial u^{AE}}\right]\nabla_\beta u^{AE}(\beta) \\[2ex] \mathcal{J}_\gamma &= P\left[A\left(u^{AE}\right)\right]^{-1}\nabla_\gamma f^{AE}(\gamma). \end{aligned}$$

Finally, we adapt the inexact Newton algorithm of [16] in Algorithm 1 so that we can apply AEI for the joint problem. We note that we do not store the the full Jacobi-Matrix, rather all the operations can be reduced to Matrix-Vector multiplication [18]. This is essential for the success of the inversion. Further, we use frequency stepping: starting at ω_1 and slowly increase the frequency up to ω_N.

3 CROSS-TALK

Cross-talk between the squared medium velocity u and the source(s) f can cause undesired artifacts. In this section, we visualize the challenges of Cross-talk, with the help of two numerical examples. To simplify these examples, we assume that we have Gaussian sources $\tilde{f}(x, \tilde{x}) = (\tilde{f}_1, \cdots, \tilde{f}_{N_s})$ with the centers at $\tilde{x} = (\tilde{x}^1, \cdots, \tilde{x}^{N_s})^\top$. Since the form of the sources are known, we can write the reduced-space approach as follow:

$$\underset{u,\tilde{x}}{\arg\min}\, \mathcal{F}(u, \tilde{f}), \quad\text{where}\quad \mathcal{F}(u, \tilde{f}) = \frac{1}{2}\sum_{\ell=1}^{N_s}\left\|\hat{y}_\ell(u, \tilde{f})\right\|_2^2 \tag{17}$$

with

$$\begin{aligned} \hat{y}_\ell(u, \tilde{f}) &= y_\ell(u, \tilde{f}) - y_\ell^{obs} \\ &= PA(u)^{-1}\tilde{f}_\ell - y_\ell^{obs}. \end{aligned}$$

3.1 The Gradients of the Multi-Parameter Inverse Problem

In the following, we are investigating the reduced-space gradient of two examples and we do not optimize or reconstruct either example.

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input :
- initial guess for squared medium velocity u
- initial guess for source f
- observed pressure variation y^{obs}

output:
- computed squared medium velocity u and source f

1 **for** $\omega \leftarrow \omega_1, \cdots, \omega_N$ **do**
2   // *Adaptive Eigenspace Expansion of u and f, see* (6);
3   Choose number of eigenfunctions K_1 and K_2;
4    $u^{AE} \leftarrow u_0 + \sum_{m=1}^{K_1} \beta_m \phi_m$;
5    $f^{AE} \leftarrow f_0 + \sum_{l=1}^{K_2} \gamma_l \varphi_l$;
6   // *Optimize*;
7   **while** $\|\nabla \mathcal{F}\|_2 < tolerance$ **do**
8   Update $A\left(u^{AE}\right)$;
9   Update Jacobi-Matrix $\mathcal{J}$;
10   Update $\nabla \mathcal{F}$;
11   // *Solve conjugate quasi-Newton (GN)*;
12   solve $\mathcal{J}^\top \mathcal{J} p = -\nabla \mathcal{F}$ for p;
13   // *p is divided for updating β and γ*;
14      $\begin{bmatrix} p_\beta \\ p_\gamma \end{bmatrix} \leftarrow p$
15   find step-size α using Armijo backtracking;
16   // *update β and γ*;
17      $\beta \leftarrow \beta + \alpha p_\beta$;
18      $\gamma \leftarrow \gamma + \alpha p_\gamma$;
19   // *update u^{AE} and f^{AE} with the new β and γ*;
20      $u^{AE} \leftarrow u_0 + \sum_{m=1}^{K_1} \beta_m \phi_m$;
21      $f^{AE} \leftarrow f_0 + \sum_{l=1}^{K_2} \gamma_l \varphi_l$;
22   **end**
23   *Update u and f*;
24    $u \leftarrow u^{AE}$;
25    $f \leftarrow f^{AE}$;
26 **end**
27 return u and f ;

Algorithm 1: Adaptive Eigenspace Inversion (AEI) using Adaptive Eigenspace (AE) Expansion and inexact quasi-Newton using the Gauss-Newton (GN) approximation of the Hessian and frequency stepping to solve equation (10).

Similar to (14) the multi-parameter gradients are coupled and are given in the directions of u and $\tilde{x}$ as

$$\nabla_u \mathcal{F}(u, \tilde{f}) = \sum_{\ell=1}^{N_s} \left(\frac{\partial y_\ell(u, \tilde{f})}{\partial u} \right)^\top P^\top \hat{y}_\ell(u) \qquad (18)$$

and

$$\begin{aligned}
\nabla_{\tilde{x}\ell} \mathcal{F}(u, \tilde{f}) &= \left(\nabla_{\tilde{x}\ell} \tilde{f}_\ell \right)^\top \nabla_{\tilde{f}\ell} \mathcal{F}(u, \tilde{f}) \\
&= \left(\nabla_{\tilde{x}\ell} \tilde{f}_\ell \right)^\top \left(\frac{\partial y_\ell(u, \tilde{f})}{\partial \tilde{f}_\ell} \right)^\top P^\top \hat{y}_\ell \left(u, \tilde{f} \right) \qquad (19) \\
&= \left(\nabla_{\tilde{x}\ell} \tilde{f}_\ell \right)^\top [A(u)]^{-\top} P^\top \hat{y}_\ell \left(u, \tilde{f} \right).
\end{aligned}$$

If u and $\tilde{x}$ are set to the true value, the gradients will read

$$\nabla_u \mathcal{F}(u, \tilde{f})_{|u=u^{\text{true}}, \tilde{x}=\tilde{x}^{\text{true}}} = 0$$
$$\nabla_{\tilde{x}\ell} \mathcal{F}(u, \tilde{f})_{|u=u^{\text{true}}, \tilde{x}=\tilde{x}^{\text{true}}} = 0.$$

for $\ell = 1, \cdots, N_s$. However, the parameters appear in both gradients, hence, a small change in one parameter can influence the gradient of the other [33]. In our case, it causes a non-zero gradient for both, even if one of the parameters already equals the true value.

We chose two slightly different examples to illustrate the issue of coupled gradients for the joint medium-control inverse problem. Both examples are chosen, such that one parameter is set to the true value while the other parameter is very close to the true value. In the first example, we modify the variable u slightly and assume, that we have a single source $\tilde{f} = \tilde{f}_1$ at the true position $\tilde{x} = \tilde{x}^1$. In the second example, we make a small modification to the position $\tilde{x}$ of the source $\tilde{f}$ and fix the parameter u at the true solution. Unlike when the gradients are independent – zero gradient in the direction of this parameter and non-zero gradient in the other – our gradient will be nonzero in both directions. Thus, we show that the squared medium velocity u and the source $\tilde{f}$ perturb each others gradient.

3.2 Numerical Examples for Cross-talk

Similar to [27], we visualize the Cross-talk between the squared medium velocity u and the source $\tilde{f}$. For this, we consider the following setup for the reduced-space gradient, we use

- a two-dimensional bounded region $\Omega = [0, 1] \times [0, 1]$,
- a Gaussian source $\tilde{f}(x, \tilde{x}) = \exp\left(-\frac{(x_1 - \tilde{x}_1)^2 + (x_2 - \tilde{x}_2)^2}{2R^2}\right)$ centered at $\tilde{x} = (\tilde{x}_1, \tilde{x}_2)$, where $x = (x_1, x_2) \in \Omega$ are the horizontal and vertical directions, respectively. Further, we use $\tilde{f}$ instead of f for the Helmholtz equation (3).
- the time-frequency $\omega = 8$,
- and a second order staggered FD method to discretize u and $\tilde{f}$ onto a 200×200 Cartesian grid.

In Fig. 1 we present a two-parameter profile in Ω. The squared medium velocity u is chosen as a piece-wise constant inside a circle O centered at $x = (0.5, 0.5)$ with a radius of 0.1 and we set the true values of the parameter u and the true position of the source $\tilde{x} = (\tilde{x}_1, \tilde{x}_2)$ as follows:

$$u(x) = \begin{cases} 1.2 & x \in O \\ 1 & x \in \Omega \backslash O \end{cases}, \qquad \tilde{x} = (0.5, 0.8). \qquad (20)$$

The profile u and the wave initiated by $\tilde{f}$ at $\tilde{x}$ with the time-frequency $\omega = 8$ are illustrated in Fig. 1.
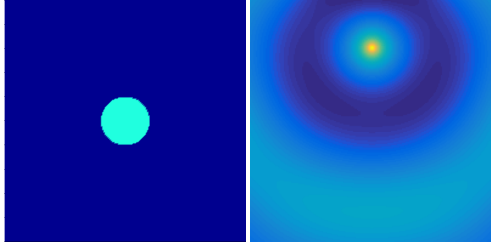
Figure 1: The true value of the squared medium velocity u (left) and the real part of the wave initiated at $\tilde{x} = (0.5, 0.8)$ propagating through the medium (right).

3.2.1 Example 1: For the initial guess, we slightly perturb the true value of u inside O by 0.01 but keep the position of $\tilde{f}$ at the true value:

$$u(x) = \begin{cases} 1.19 & x \in O \\ 1 & x \in \Omega \backslash O \end{cases}, \qquad \tilde{x} = (0.5, 0.8) \qquad (21)$$

On the left side of Fig. 2 we show the gradients for u and $\tilde{x}$. We note that both gradients are non-zero, although the source position $\tilde{x}$ (and the source $\tilde{f}$) are equal to the true value.

3.2.2 Example 2: For the second example, we slightly change the true position of $\tilde{x}$:

$$u(x) = \begin{cases} 1.2 & x \in O \\ 1 & x \in \Omega \backslash O \end{cases}, \qquad \tilde{x} = (0.49, 0.8), \qquad (22)$$

in particular, we shift the $\tilde{x}_1$ position of the source for 0.01 and keep the vertical position $\tilde{x}_2$ and the parameter u unchanged.

On the right side of Fig. 2 we show the gradients for u and $\tilde{x}$. Again, both gradients are non-zero although the squared medium velocity u is set to the true value.

3.2.3 The Reduced Gradient: In both examples, we get a non-zero gradient for all the parameters, even if we set one parameter to the optimal value and only perturb the other parameters slightly. However, a zero gradient at the optimal value of any parameter is essential for successful optimization.

In both examples shown in Fig. 2, a small modification in one parameter causes perturbations in the other parameter's gradient. This illustrates the Cross-talk between the parameters and the ill-posedness of the problem. We may have regularization problems and the gradients with an initial guess close to the true profile may point in a direction of a false solution.

4 NUMERICAL EXAMPLES

In the following, we show the challenges of the Cross-talk in the joint inverse medium and optimal control problem. Further, we propose the AE shown in Sec. 2.1 as a possible solution. We give three examples: in two examples the form of the source(s) are unknown, and one when the form of the sources are known.
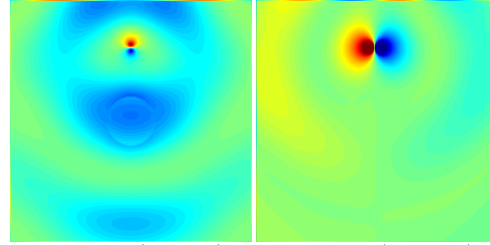
$$\nabla_{\tilde{x}} \mathcal{F}(u, \tilde{f}) = \begin{pmatrix} -0.197 \\ 0.0002 \end{pmatrix} \qquad \nabla_{\tilde{x}} \mathcal{F}(u, \tilde{f}) = \begin{pmatrix} -0.0001 \\ 0.7811 \end{pmatrix}$$

Figure 2: Reduced gradient $\mathcal{F}(u, \tilde{f})$ for the profile (20)**: the two images visualize $\nabla_u \mathcal{F}(u, \tilde{f})$ and beneath them we show the computed $\nabla_{\tilde{x}} \mathcal{F}(u, \tilde{f})$. Left: first example with the initial guess** (21)**. Right: second example with the initial guess** (22)**.**
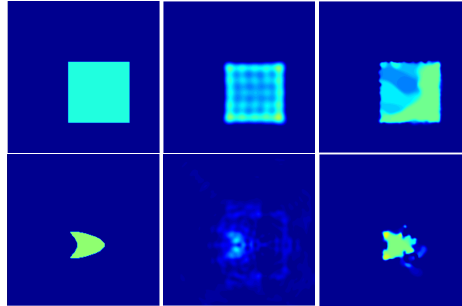
Figure 3: Top: source f. Bottom: squared medium velocity u. From left to right: True parameters u and f; illustrating Cross-talk using inexact Newton method; Adaptive Eigenspace Inversion (AEI) reduces Cross-talk.

4.1 Unknown Form of the Source

On the left side of Fig. 3, we show the target profiles of the source f (top) and for the squared medium velocity u (bottom). The parameters u and f are given by

$$u(x) = \begin{cases} 1.5 & x \in \mathcal{D} \\ 1 & x \in \Omega \backslash \mathcal{D} \end{cases} \qquad f(x) = \begin{cases} 0.4 & x \in Q \\ 0 & x \in \Omega \backslash Q \end{cases}, \qquad (23)$$

where $\mathcal{D}$ is a kite shaped object and Q is a square with a side length of 0.4 centered at $(0.45, 0.4)$. To reconstruct the squared medium velocity u and the form of the source f, we consider the Helmholtz equation (3) in the unit square $\Omega = [0, 1] \times [0, 1]$. The wave field y and the control variables u and f are discretized using second order FD.

We first illustrate the challenges of Cross-talk in the joint inverse medium and optimal control problem and apply the AEI to overcome them.

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4.1.1 Nodal-Basis. To illustrate the challenges of Cross-talk, we use the nodal basis approach to reconstruct the squared medium velocity u and the source f. We apply the inexact Newton (quasi-Newton) method using the Gauss-Newton approximation of the Hessian and frequency stepping at $\omega = 8, 10, \cdots, 78, 80$.

The reconstructed u and f for the nodal basis approach are shown in the middle column of Fig. 3. Both shapes of $\mathcal{D}$ and $\mathcal{Q}$ are reconstructed, but the values inside the shapes are poorly deduced. On the bottom – at the reconstructed squared medium velocity u – we see a trace of the source shaped structure, i.e. an undesired Cross-talk between the source f and the squared medium velocity u. The relative L^2-error of u, defined by

$$\frac{\|u^{\text{true}} - u\|_2}{\|u^{\text{true}}\|_2},$$

is 6.93%. The from of the source f holds a relative error, defined by

$$\frac{\|f^{\text{true}} - f\|_2}{\|f^{\text{true}}\|_2},$$

of 56.91%.

4.1.2 Adaptive Eigenspace Inversion (AEI). We apply the AEI approach for multi-parameter inverse problems [16] to tackle the Cross-talk. This time we use the AE for u and f (see Sec. 2.1) to solve the previous example. We solve equation (10) and use Algorithm 1 for the same observations as for the nodal basis at the same time-frequencies. On the right side of Fig. 3 we see, that the AE reduces Cross-talk and improves reconstruction of the squared medium velocity u. The results of the AE approach reduces the relative L^2-error of u to 3.03% and f is reduced to 40.17%. Still, the problem is severely ill-posed and the reconstruction here is not perfect, but the improvement with respect to the nodal basis is clear.

4.2 Unknown positions of the Sources

Now, we assume that we have multiple Gaussian sources with unknown positions. The true squared medium velocity u is composed of three layers and a kite-shaped obstacle $\mathcal{D}$ on the middle layer. For $x = (x_1, x_2) \in \Omega$ we have

$$u(x) = \begin{cases} 3 & x \in \mathcal{D} \\ 2.5 & 0.1 < x_2 \leq 0.3 \\ 2 & 0.3 < x_2 \leq 0.5 \quad \& \quad x \notin \mathcal{D} \\ 1.5 & 0.5 < x_2 \leq 0.9 \\ 1 & \text{else} \end{cases}$$

and for the Gaussian sources $\tilde{f} = [\tilde{f}_1, \tilde{f}_2, \tilde{f}_3]$. We consider three sources at the time-frequencies $\omega = 8, 10, \cdots, 118, 120$ initiated in

$$\tilde{x}^{\text{true}} = \begin{pmatrix} 0.2, 0.8 \\ 0.5, 0.8 \\ 0.7, 0.8 \end{pmatrix},$$

see left of Fig. 4. The wave field y and the variables u and $\tilde{f}$ are discretized with second order FD (200×200 equidistant grid for $\tilde{f}$ and y and y^{obs} on a finer non-coupled grid). The initial guess for u is $u = 1$ everywhere in Ω^o. Further, we assume that u is known on the boundary Γ ($u_\infty(x)$ is known in equation (9)) and since only the positions but not the form of the sources are unknown, we

just need to provide an initial value for $\tilde{x}$. For all three sources we choose the center of the domain:

$$\tilde{x} = \begin{pmatrix} 0.5, 0.5 \\ 0.5, 0.5 \\ 0.5, 0.5 \end{pmatrix}. \tag{24}$$

4.2.1 Nodal basis approach. We apply the nodal basis approach using the inexact Newton (quasi-Newton) method, to solve (17). The position of one of the sources was converging to a wrong position. Since this problem is severely ill-posed, a change in the initial guess can assist in finding the solution. Accordingly, we change the initial guess of the first source to (0.5, 0.6), instead of (0.5, 0.5):

$$\tilde{x} = \begin{pmatrix} 0.5, 0.6 \\ 0.5, 0.5 \\ 0.5, 0.5 \end{pmatrix}.$$

Now, all three sources are found with a small relative L^2-error, defined by

$$\frac{\|\tilde{x}^{\text{true}} - \tilde{x}\|_2}{\|\tilde{x}^{\text{true}}\|_2},$$

of 0.1%. The squared medium velocity u was reconstructed with a relative L^2-error close to 20%. Artifacts of the sources can be seen in the reconstruction of the medium velocity. Additionally, the bottom layer is poorly reconstructed.

4.2.2 Adaptive Eigenspace Inversion (AEI). Similar to (10) and (17) the reduced-space objective reads

$$\arg\min_{\beta, \tilde{x}} \mathcal{F}\left(u^{AE}(\beta), \tilde{f}(\tilde{x})\right) \tag{25}$$

with

$$\mathcal{F}\left(u^{AE}(\beta), \tilde{f}(\tilde{x})\right) = \frac{1}{2} \sum_{\ell=1}^{N_s} \left\| \hat{y}_\ell\left(u^{AE}(\beta), \tilde{f}(\tilde{x})\right) \right\|_2^2,$$

for $\ell = 1, \cdots, N_s$ and $N_s = 3$ the number of sources. The method is very similar to the one described in Sec. 2.2, however, we only apply the AE on $u(x)$. We define

$$\nabla \mathcal{F} = \begin{bmatrix} \nabla_\beta \mathcal{F} \\ \nabla_{\tilde{x}} \mathcal{F} \end{bmatrix}, \tag{26}$$

$$\tilde{x} = \begin{pmatrix} 0.2, 0.8 \\ 0.5, 0.8 \\ 0.7, 0.8 \end{pmatrix} \qquad \tilde{x} = \begin{pmatrix} 0.2011, 0.7993 \\ 0.4991, 0.7997 \\ 0.6997, 0.7998 \end{pmatrix} \qquad \tilde{x} = \begin{pmatrix} 0.2014, 0.8026 \\ 0.5000, 0.8033 \\ 0.6991, 0.8031 \end{pmatrix}$$
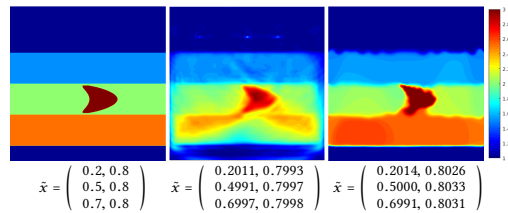
Figure 4: Left to right: the true value of the squared medium velocity u (top) and source positions $\tilde{x}$ of $\tilde{f}$ (bottom); Reconstructed parameters u (top) and $\tilde{x}$ (bottom) by solving equation (17); Adaptive Eigenspace Inversion (AEI) to solve equation (25), thus avoiding Cross-talk.

where similar to (19) we have

$$\nabla_{\tilde{x}^{\ell}} \mathcal{F}\left(u^{AE}, \tilde{f}\right) = \left(\nabla_{\tilde{x}^{\ell}} \tilde{f}_{\ell}\right)^{\top} \left[A\left(u^{AE}\right)\right]^{-\top} P^{\top} \hat{y}_{\ell}\left(u^{AE}, \tilde{f}\right), \quad (27)$$

and we use

$$\tilde{x} = \begin{pmatrix} \tilde{x}^1 \\ \vdots \\ \tilde{x}^{N_s} \end{pmatrix} \quad \text{and} \quad \nabla_{\tilde{x}} \mathcal{F} = \begin{pmatrix} \nabla_{\tilde{x}^1} \mathcal{F}\left(u^{AE}, \tilde{f}_1\right) \\ \vdots \\ \nabla_{\tilde{x}^{N_s}} \mathcal{F}\left(u^{AE}, \tilde{f}_{N_s}\right) \end{pmatrix}. \quad (28)$$

With a small modification of Algorithm 1 (increasing the number of sources and solving (25) instead of (10)), we are able to reconstruct the parameters u and $\tilde{x}$ using the initial guess (24).

The reconstructed u and $\tilde{x}$ are shown on the right of Fig. 4. We see, that the position of the sources are reconstructed with the small relative L^2-error of 0.34%. Further, all three layers combined with the kite-shaped obstacle $\mathcal{D}$ are fully reconstructed. The relative L^2-error for u is 6.28%, which is about three times smaller in comparison with the nodal approach.

4.3 Unknown Form of Multiple Sources

In this example, we have two unknown forms of the sources. Here, we apply the FE method (the success of the AE is not dependent in the underlying discretization [15]). First, we reconstruct the medium and the sources using a linearly increasing number of eigenfunctions (K_1 and K_2) dependent in the time-frequency ω. We tested different number of eigenfunction and show an example where we have an improvement of the reconstruction using different strategy. This shows that further research in the automation of choosing the number of eigenfunction must be done.

We extend the reduce space approach of (10) to multiple sources:

$$\mathcal{F}\left(u^{AE}(\beta), f^{AE}(\gamma)\right) = \frac{1}{2} \sum_{\ell=1}^{N_s} \left\| \hat{y}_{\ell}\left(u^{AE}(\beta), f^{AE}(\gamma)\right) \right\|_2^2, \quad (29)$$

with

$$\hat{y}_{\ell}\left(u^{AE}(\beta), f^{AE}(\gamma)\right) = y_{\ell}\left(u^{AE}(\beta), f^{AE}(\gamma)\right) - y_{\ell}^{obs}$$
$$= P\left[A\left(u^{AE}(\beta)\right)\right]^{-1} f_{\ell}^{AE}(\gamma) - y_{\ell}^{obs}.$$

We have a bounded region on $\Omega = [0,1] \times [0,1]$ and apply the AE of the squared medium velocity u and the sources f. Here, we use the FE approach on $\mathcal{P}^1$ elements (piece-wise linear continuous elements). Algorithm 1 is then computed with *Freefem* [19] as well as the FE approach of the Helmholtz equation. In this Example, the values on the boundary $\Gamma = \partial\Omega$ are known and the microphones are placed on it. Hence, $u = u_\infty$ and $y^{obs} = (y_1^{obs}, \cdots, y_{N_s}^{obs})$ is defined on $\Gamma = \partial\Omega$.

On the top of Fig. 5 we have the true parameters of u and $f = (f_1, f_2)$. The true squared medium velocity u has a layer $\mathcal{L}$ and on it an ellipse $\mathcal{E}$. The two squares sources ($\mathcal{S}_1$ and $\mathcal{S}_2$) are centered at $(0.75, 0.75)$ and $(0.35, 0.75)$ with a side length of 0.2. Hence, the parameters u and f are given by

$$u(x) = \begin{cases} \frac{3}{2} & x \in \mathcal{L} \\ 2 & x \in \mathcal{E} \\ 1 & \text{else} \end{cases}, \quad f_1(x) = \begin{cases} \frac{1}{2} & x \in \mathcal{S}_1 \\ 0 & \text{else} \end{cases}, \quad f_2(x) = \begin{cases} 1 & x \in \mathcal{S}_2 \\ 0 & \text{else} \end{cases}.$$
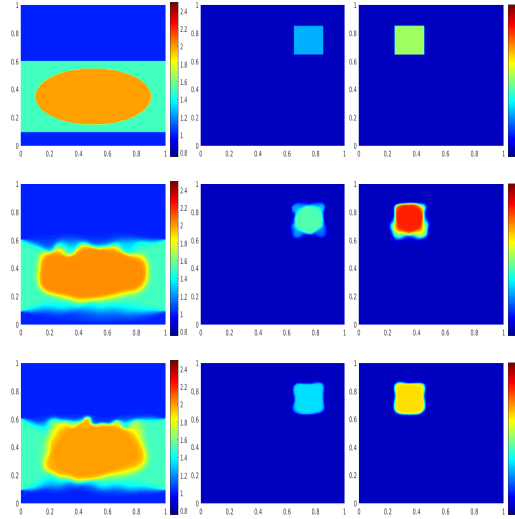

Figure 5: Left to right: squared medium velocity u, source f_1 and source f_2. From top to bottom: True parameters of u and $f = (f_1, f_2)$; reconstruction using AEI with $K_1 = K_2 = \omega$; reconstruction with $K_1 = \omega$ and $K_2 = 10$.

4.3.1 Adaptive Eigenspace Inversion (AEI). With a small modification of Algorithm 1, we solve (10) for multiple sources using (29). We computed the algorithm on an *Intel(R) Xeon(R) CPU E5-2680 v4 @ 2.40GHz* CPU with the initial guess $u = 1$ and $f = 0$ with frequency stepping at $\omega = 8, 10, \cdots, 48, 50$ on a grid with 101×101 points.

First, we solve the AEI with linear dependency of the eigenfunctions

$$K_1 = \omega \quad \text{and} \quad K_2 = \omega,$$

similar to [15, 16]. We get a good reconstruction for the squared medium velocity u, with a relative L^2-error of 7.92% (Fig. 6), but the amplitude of the sources are poorly deduce (see middle of Fig.5). The relative error of the sources f_1 and f_2 are 64% and 70%, respectively (see Fig. 6).

We can improve the reconstruction of the sources f by choosing a constant number of eigenfunction for the sources (see last row of Fig. 5):

$$K_1 = \omega \quad \text{and} \quad K_2 = 10.$$

The relative L^2-error of the squared medium velocity increased slightly, with 8.82%. However, the relative L^2-error of the sources improved drastically: f_1 and f_2 have an error of 31% and 34%, respectively. In addition, we save computational cost for the AE approach, as we compute less eigenfunctions at each time-frequency (see Fig. 6).

Here we see, that the choice of the number of eigenfunctions is critical for the success of the reconstruction. Further, we note
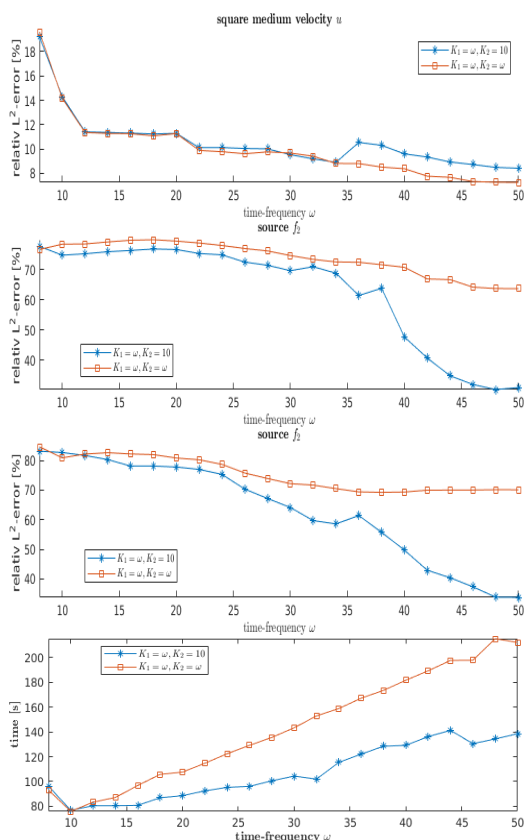
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Figure 6: Comparison of different numbers of eigenfunctions (K_1 for u, K_2 for f_1 and f_2) in the Adaptive Eigenspace (AE) expansion. From top to bottom: relative L^2-error of u, f_1 and f_2. Computation time for the AE Expansion of the squared medium velocity u and the sources $f = (f_1, f_2)$ for each time-frequency ω.

that finding an optimal number of eigenfunctions will improve the results. This may save computational time by computing a smaller number of eigenfunctions and by reducing dramatically the search space of the optimization.

5 CONCLUSION & DISCUSSION

We show in this paper the challenges that Cross-talk and ill-posedness bring in to the Helmholtz inversion when the source(s) f and the squared medium velocity u are unknown. Further, we apply the Adaptive Eigenspace Inversion (AEI) method for the joint inverse medium and optimal control problem and show in numerical experiments that this method can reduce these challenges. Although

we have an improvement of the Cross-talk with the Adaptive Eigenspace (AE) in comparison to the nodal presentation, the joint inverse medium and optimal control problem is severely ill-posed and a small change in the parameters might change the solution. Hence, an extended investigation for the optimal number of basis functions in the AE and further parameters has to be done.

We believe that this AEI approach will not only be a valuable contribution in medical applications, but also in geophysics. In the future, we plan to parallelize the Helmholtz inversion and investigate the challenges of Cross-talk on large scale modules and in three space dimensions. Further, we would like to attach several acoustic sources to an endoscope, and use this approach to collect information of its surrounding tissues and finding its exact position in the body.

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Chapter 5

Bone Ablation Depth Estimation from Er:YAG Laser-generated Acoustic Waves

The previous approach to reconstructing the bone with the acoustic wave using the FE method was too slow and not applicable for a real-time simulation. In addition, there are many unknown factors, and therefore we could not confirm our results (resp. the correctness of our forward problem simulation) in an *ex-vivo* experiment. Therefore, we simplify the problem and reduce the unknown factors as much as possible. In previous work, they could differentiate the different tissue being ablated [45]. We investigate the viability of predicting the depth of a cut in a bone resulting from the ablation process. In [14], they found that the ablation process is non-linear, so counting the number of ablations to predict the depth is insufficient. We analyze the prediction of the depth of the laser cut using the acoustic wave created during the ablation process with the help of a NN. We conclude that depth information is indeed embedded in the acoustic wave.

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GitHub code: https://gitlab.com/cian.unibas.ch/ablaiton-depth-estimation

RESEARCH ARTICLE

Bone Ablation Depth Estimation From Er:YAG Laser-Generated Acoustic Waves

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ABSTRACT Using a laser for cutting bones instead of the traditional saws improves a patient's healing process. Additionally, the laser has the potential to reduce the collateral damage to the surrounding tissue if appropriately applied. This can be achieved by building additional sensing elements besides the laser itself into an endoscope. To this end, we use a microsecond pulsed Erbium-doped Yttrium Aluminium Garnet (Er:YAG) laser to cut bones. During ablation, each pulse emits an acoustic shock wave that is captured by an air-coupled transducer. In our research, we use the data from these acoustic waves to predict the depth of the cut during the ablation process. We use a Neural Network (NN) to estimate the depth, where we use one or multiple consecutive measurements of acoustic waves. The NN outperforms the base-line method that assumes a constant ablation rate with each pulse to predict the depth. The results are evaluated and compared against the ground-truth depth measurements from Optical Coherence Tomography (OCT) images that measure the depth in real-time during the ablation process.

INDEX TERMS Acoustic feedback, depth control, laser ablation, neural network.

I. INTRODUCTION

Reducing the trauma of a patient during surgical procedures is paramount in improving the post-surgical standard of living. Consequently, minimally invasive alternatives to common interventions are a highly researched topic [1], [2]. One line of inquiry is the replacement of mechanical tools with laser-based ablation [3], [4], [5], [6], [7].

When the tissue is exposed to microsecond pulsed Er:YAG laser light, the water in the tissue heats up, vaporizes, and the expansion causes micro-explosions that ablate a small part of the tissue [8]. This process emits an acoustic wave that is captured by a transducer [9].

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In contrast to classical mechanical cutting tools, laser ablation does not provide direct haptic feedback on the progress of the cut to the surgeon. Furthermore, the laser system occludes the cutting location and impedes visual inspection. With the development of new tools that assist the surgeon in monitoring the depth of the cut, damaging sensitive tissue can be avoided.

A classical method to measure the cutting depth would be using an OCT [10], [11], [12], [13]. However, it can be challenging to integrate an OCT in combination with an Er:YAG laser for minimally invasive surgery. To this end, we propose an acoustic depth measurement technique that uses the acoustic wave created during the ablation process to determine the depth of the cut.

When the location of the ablation source is known, the depth of the cut can be estimated via various approaches. One

approach is to triangulate the source [14], [15], [16]. However, this approach requires multiple transducers to determine the source location. A different approach uses acoustic waves in a 2D simulation to detect the source position using just two transducers [17]. The main limitation of this approach is that the exact acoustic wave generator (form and the frequency composition of the source) has to be known. In another 2D simulation, the source position and its form were reconstructed in an unknown surrounding [18]. However, many transducers are required for the reconstruction, making this approach unsuitable for minimally invasive surgery.

There are several ways to determine the distance between an acoustic source and the transducer. One option is to estimate the time-of-flight (ToF). For example, in [19], the authors used auto-correlation between the transmitted and echoed signal. In [20], they exploited the phase shift between transmitting and measured signals. However, in our application, the source signal shape is unknown, and the signal may even change for different depths. In [21] and [22], the authors showed that the ToF correlates with the signal's distance and decay when ablating tissue with an Er:YAG laser and in [23], they used ToF to estimate the depth of the ablation with a Neodymium-doped Yttrium Aluminium Garnet (Nd:YAG) laser. However, the ToF option has a significant drawback. It requires the distance between the transducer and the bone surface to be constant, and the medium velocity of the ablated tissue must be known. As this can not be guaranteed in our envisioned application of robotic-guided laser osteotomy, we focus on different approaches to estimate the depth of the laser cut.

Since the use of Neural Networks [24] is well established in medical imaging [25], [26], [27], [28], speech, and signal processing [29], [30], [31], [32], we aim to estimate the ablation depth by interpreting the signal from one single air-coupled transducer with a neural network. We compare two approaches: The CA is used as a base-line approach, where we assume that the ablation rate per pulse is constant, and therefore, the depth is proportional to the number of ablation shots. The second approach uses one or multiple consecutive measurements of the acoustic waves during the ablation process. These acoustic waves are then used as input for an NN to predict the depth of the laser cut.

The goal of this work is to analyze the acoustic wave and to prove that there is depth information in the acoustic wave produced during the ablation process of the bone using the Er:YAG laser. In addition, we can show that one transducer is sufficient to measure the depth of the laser cut, simplifying the complexity of the setup in future work.

II. MATERIAL AND SETUP
An Er:YAG laser (Syneron Candela, litetouch LI-FG0001A) with an energy of 153 mJ, a wavelength of 2940 nm, with a repetition rate of 10 Hz, is used for ablating the bone. The ablation process emits an acoustic wave. A CaF_2 mirror diverts a small percentage of the laser beam to a PbSe photodiode (PbSe Fixed Gain Detector,

PDA20H, 1500 − 4800 nm), to trigger the acoustic measurement. The wideband transducer,[1] with a frequency range of 100 − 1000 kHz and a resonant frequency at 650 kHz, measures acoustic signals with a sample rate of 7.8125 MHz. It is placed at a distance of approximately 5 cm to the bone surface. The setup is displayed on the left of Fig. 1. We note that due to the limited acquisition rate of our setup, and the high repetition rate of the laser, we can only measure the acoustic wave of every second laser pulse.

A custom-made dichroic filter reflects the wavelength of the Er:YAG laser and transmits the OCT's wavelength, therefore, integrating the Er:YAG laser into the OCT system in a co-axial configuration. Consequently, we can monitor the ablation depth with a long-range Bessel-like beam OCT system [33] in real-time. The OCT has an imaging half-range of 22.21 mm in air and a field-of-view of 4.2 mm. The OCT system uses a swept-source laser (Insight Photonic Solution, Inc., Lafayette, Co, USA), with a scan rate of 104.17 kHz, a central wavelength of 1288.82 nm, and spectral bandwidth of 61.5 nm.

We used 13 cow femur bones as ablation material, bought in a local grocery store. The height of the bone varied between 2.4 cm to 2.9 cm. Muscle, fat, bone marrow, and tendons were carefully removed from the hard bone. To avoid dehydration of the bone, we submerged the samples in water between experiments.

We conducted our experiment by ablating a maximum of nine holes in each bone, each reaching a depth of up to 3.5 mm. The ablation process was stopped when we noticed that the cutting depth stagnated, i.e. if the bone started carbonizing. Bone carbonizes when insufficient water is in the tissue; hence, no micro-explosions remove the tissue, and the laser energy accumulates heating up the tissue. An exemplary bone is shown on the right of Fig. 1.

Since the frame rate of the OCT is 173.6167 Hz and the repetition rate of the laser is 10 Hz, we have a fixed number of OCT frames between the laser pulses. Therefore, we can align the OCT frames to the corresponding acoustic waves emitted during bone ablation. To generate a ground truth depth for each measured ablation wave, we locate the first pulse of the ablation in the OCT image stream. Then we labeled the 2443 OCT images by marking the bone's edge and the cut's end (see Fig. 2). We deduced the depth of the cut using the pixel resolution of the OCT of 10.86 μm.

III. METHOD
To assess the performance of our approaches, we divided our data into three mutually disjoint subgroups: training data, validation data, and testing data. Each bone was only part of one of these groups. Five-fold cross-validation was conducted to demonstrate the performance of the approach.

We investigated two approaches: (1) the first approach CA assumes that the ablation rate of the laser is constant, and

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[1] PHYSICAL ACOUSTICS WSα SNAK28
6.9.2022, physicalacoustics.com/content/literature/sensors/Model_WSa.pdf
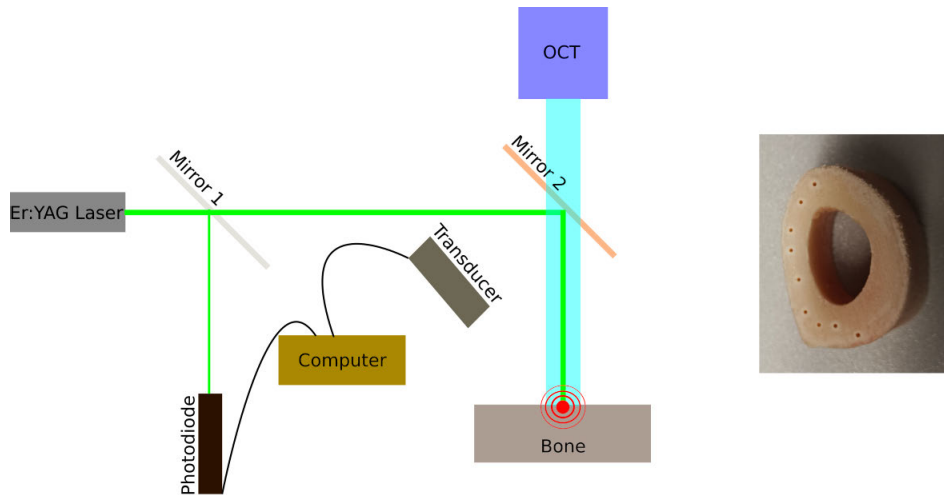
IEEE *Access*

FIGURE 1. (Left) the setup of our experiment. Laser light ablates the bone while the air-coupled transducer measures the acoustic wave. The laser beam gets split at mirror 1, and a small percentage of the laser beam is redirected to the photodiode. The photodiode triggers the acquisition of the acoustic wave with the transducer (distance to the bone: $5\,cm$ at a $45°$ angle to the ablation). Further, the laser light is diverted with mirror 2 (a custom-made dichroic filter that reflects the wavelength of the Er:YAG laser and transmits the OCT's wavelength) onto the bone for the ablation. At the same time, the OCT measures the depth of the ablation. (Right) an exemplary bone with nine holes after the ablation process.
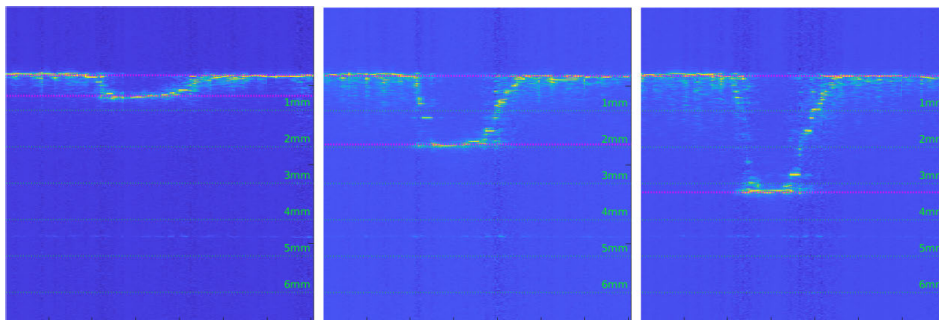

FIGURE 2. Exemplary OCT images, where we manually labeled the image after 10, 35, and 60 ablations. These corresponds to the depth of $0.5\,mm$, $1.9\,mm$, **and** $3.1\,mm$.

therefore when counting the number of shots, it can predict the depth of the laser cut. The ablation rate is estimated by the median value of the ablation rate of the training and validation data, and its performance is evaluated on the testing data. (2) In the second approach, we use a NN to predict the depth using the acoustic ablation waves.

A. NEURAL NETWORK (NN)

As the distance between the surface of the bone and the transducer can vary, all approaches using the ToF to estimate the cutting depth are of limited use. Furthermore, we wish to investigate if the depth information of a cut is embedded in other parts of the acoustic signal (excluding the ToF);

hence, we removed this information by cropping the signal as follows: First, we identified the maximum absolute value of the first 500 sample points (the time window of 64 μs). Then we used 1.5 times this value as a noise threshold to remove the first part of the signal that only contained noise and no signal from the ablation (see Fig. 3, top left): We removed all sample points before the absolute value of the acoustic wave that first exceeded this threshold (see Fig. 3, top right, red dot) and solely used the window after that point (see Fig. 3, bottom left). In the final step, we normalized the area of interest of the acoustic wave w with:

$$w = \frac{w^* - \bar{w}}{\sigma_w} \qquad (1)$$

where $\bar{w}$ is the mean value and σ_w is the standard deviation of the preprocessed acoustic wave w^* (see Fig. 3, bottom right).

To reduce over-optimization during training, we applied non-linear scaling of the wave amplitudes as data augmentation: Each sample point of the acoustic wave w was scaled by the formula

$$\hat{w} = w \cdot (1 + \lambda \cdot \exp[|w|]) \tag{2}$$

with λ a uniformly distributed random scaling factor.

As an input for the NN, we tried three different variants; namely, one, five, or ten consecutively measured acoustic signals as the input to the NN_1, NN_5, and NN_{10}, respectively. The Output of the NNs was a single value corresponding to the depth of the laser cut in [mm] from the latest measurement from the input. We trained the network using the *Mean Square Error Loss* (MSELoss):

$$\mathcal{L}_{MSE}(x, y) = \frac{1}{N_B} \sum_{i=1}^{N_B} (x_i - y_i)^2 \tag{3}$$

where $x = (x_1, \ldots, x_{N_B})$ is the output of the NN and $y = (y_1, \ldots, y_{N_B})$ is the label, that we labeled manually using the OCT images (see Section II and Fig. 2), and N_B is the batch size.

B. HYPERPARAMETER SEARCH

We use a hyperparameter search [34], [35] approach with five consecutive acoustic waves to find an initial network with the following search constraints, as visualized in Table 1. The input size, which correspond to the number of sample points, varies between $2000, 3000, \ldots, 7000$. The numbers of convolutional and fully connected layers vary between 1 and 9. The parameters of the convolution layers can get the following values: Each output channel can allocate a value of 2^n, where n varies between $n = 1, \ldots, 8$,, the kernel size varies between 2 and 5, and the stride is 1 or 2. In addition, the maxpool kernel is 2 or 3 with a stride of 1 or 2. Batch normalization is applied randomly before any layer, and dropout is randomly applied to the fully connected layers with a dropout rate between 0 and 1. The number of neurons of the fully connected layer is $\min(2^n, out_{CNN})$, where n varies between $n = 3, \ldots, 11$ and out_{CNN} is the number of neurons after the flattened output of the last convolutional layer. We use the Adam optimizer with a learning rate of 10^{-n}, where n varies between $n = 2, \ldots, 5$. The maximum value λ of (2), varies between $0, 0.1, \ldots, 1$.

C. IMPLEMENTATION DETAILS

We implemented the network using the PyTorch[2] [36] framework and trained the networks on an NVIDIA Tesla V100 DGXS 16 GB. As a result of the hyperparameter search, a well-performing architecture is shown in Fig. 4, which uses 2000 sample points as the input size, namely a time window of $256 \, \mu s$, for the NN. It has 5 convolutional layers followed

[2]May 2022, pytorch.org

TABLE 1. Overview of the parameter used in the hyperparameter search. Batch normalization is randomly applied before the convolutional and fully connected layers, and the dropout layers are randomly applied on the fully connected layers. out_{CNN} is the number of neurons after the flattened output of the last convolutional layer.

Input size (# of sample points):	$\{2000, 3000, \ldots, 7000\}$
Convolutional Layer	
Number of layers:	$\{1, \ldots, 9\}$
Output channels:	2^n, with $n \in \{1, \ldots, 8\}$
Kernel size:	$\{2, 3, 4, 5\}$
Stride:	$\{1, 2\}$
Maxpool layer	
Kernel size:	$\{2, 3\}$
Stride:	$\{1, 2\}$
Fully connected layer	
Number of layers:	$\{1, \ldots, 9\}$
Neurons:	$\min(2^n, out_{CNN})$, with $n \in \{3, \ldots, 11\}$
Dropout:	$p \in \mathcal{U}([0.1, 0.8])$
Optimizer:	Adam
learning rate:	10^{-n}, with $n \in \{2, 3, 4, 5\}$
Data augmentation:	$\max\|\lambda\| \in \{0, 0.1, \ldots, 1\}$

by 8 fully connected layers with 1024 neurons. The Adam optimizer had a learning rate of 10^{-3}, a batch size of $N_B = 32$, and the data augmentation parameter λ in (2) was a random value between -0.5 and 0.5. In addition, batch normalization uses a momentum of 0.1 and eps=1e-05, while the maxpool layer had a padding of 0 with dilation of 1. The Dropout layer had the parameter inplace=False, and the Linear layers bias was set to true. The code is published on our GitLab page.[3]

IV. RESULTS

We evaluated the accuracy of our models through five-fold cross-validation, which included splitting the data into five mutually disjoint subsets and omitting one subset during training for unseen forward passes during testing.

We assumed a constant ablation rate in the first approach CA. The median error over all the five-fold cross-validation sets was 0.13 mm and the distance $\mathcal{B}$ between the 25th percentile and the 75th percentile was 0.163 mm, as shown in Table 2. In Fig. 5, we visualize a box plot that shows the distribution of the deviating distance between the ground truth value and the output. As shown in Table 2, we see that the average box length was 0.271 mm with an average median value of -0.024 mm. At the interval between $\mathcal{I} = [3.25, 3.5]$mm the median value was -0.076 mm with a box length of 0.396 mm. We note that the number of shots was counted from the start of the ablation process to determine the depth of the cut.

In the second approach, we used one, five, or ten consecutively measured acoustic waves as the input for the NN. We trained the network on the training data and used the best-performing network on the validation data to test the performance of the testing data. In Table 2, we give a detailed description of the results. The median error was 0.174 mm, 0.130 mm, and 0.092 mm for NN_1, NN_5, and NN_{10}, respectively. In the box plots of Fig. 5, we visualize the difference

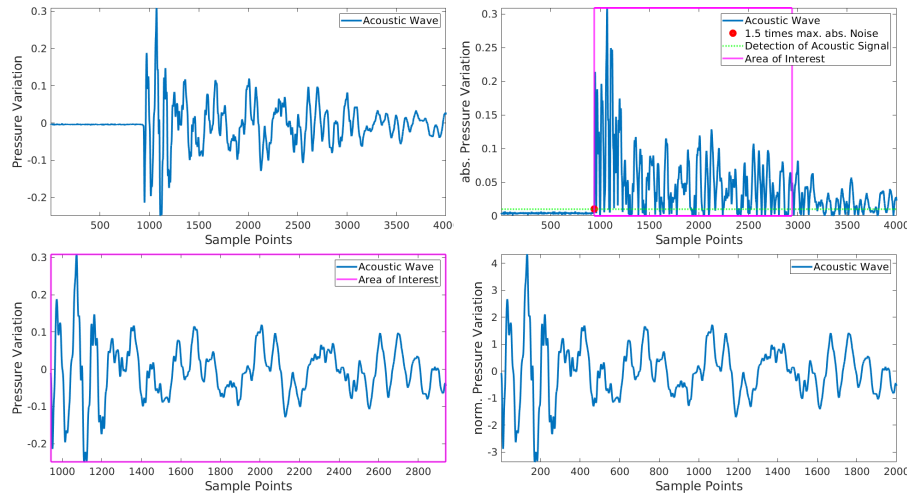[3]https://gitlab.com/cian.unibas.ch/ablaiton-depth-estimation

FIGURE 3. (Top left) measured acoustic wave with a sample rate of $7.8125\,\text{MHz}$. (Top right) multiply the maximum absolute value of the 500 first sample points (time window of $64\,\mu s$) by 1.5 (green). Remove all the data before the intersection between the green line and the acoustic signal from the ablation (redpoint). The 2000 sample points (time window of $256\,\mu s$) after the red dot are used for the further processing step (magenta). (Bottom left) the acoustic wave is visualized, where the time-of-flight is removed. (Bottom right) Normalized acoustic wave in the area of interest, which we use as input for the NN.

(0): $\text{Input}(\text{size}=\text{N}\times 2000),\ \text{BatchNorm1d}(\ )$

(1a): $\text{Conv1d}(\text{out\_c}=8,\ \text{k\_size}=4,\ \text{s}=1)$
(1b): $\text{MaxPool1d}(\text{k\_size}=3,\ \text{s}=2)$

(2a): $\text{Conv1d}(\text{out\_c}=32,\ \text{k\_size}=4,\ \text{s}=2)$
(2b): $\text{MaxPool1d}(\text{k\_size}=3,\ \text{s}=2)$

(3a): $\text{Conv1d}(\text{out\_c}=64,\ \text{k\_size}=4,\ \text{s}=1)$
(3b): $\text{MaxPool1d}(\text{k\_size}=2,\ \text{s}=1)$

(4a): $\text{Conv1d}(\text{out\_c}=256,\ \text{k\_size}=5,\ \text{s}=2)$
(4b): $\text{BatchNorm1d}(\ )$
(4c): $\text{MaxPool1d}(\text{k\_size}=3,\ \text{s}=2)$

(5a): $\text{Conv1d}(\text{out\_c}=256,\ \text{k\_size}=4,\ \text{s}=2)$
(5b): $\text{BatchNorm1d}(\ )$
(5c): $\text{MaxPool1d}(\text{k\_size}=2,\ \text{s}=1)$

(6): $\text{Flattening}(\text{size}=6912)$

(7a): $\text{Dropout}(p=0.48536),\ \text{Linear}(\text{out\_f}=1028)$
(7b): $\text{BatchNorm1d}(\ )$

(8a): $\text{Linear}(\text{out\_f}=1028)$
(8b): $\text{BatchNorm1d}(\ )$

(9a): $\text{Linear}(\text{out\_f}=1028)$
(9b): $\text{BatchNorm1d}(\ )$

(10): $\text{Dropout}(p=0.54307),\ \text{Linear}(\text{out\_f}=1028)$

(11a): $\text{Dropout}(p=0.43455),\ \text{Linear}(\text{out\_f}=1028)$
(11b): $\text{BatchNorm1d}(\ )$

(12a): $\text{Dropout}(p=0.56238),\ \text{Linear}(\text{out\_f}=1028)$
(12b): $\text{BatchNorm1d}(\ )$

(13a): $\text{Dropout}(p=0.19907),\ \text{Linear}(\text{out\_f}=1028)$
(13b): $\text{BatchNorm1d}(\ )$

(14): $\text{Dropout}(p=0.20917),\ \text{Linear}(\text{out\_f}=1028)$

(15): $\text{Linear}(\text{out\_f}=1)$
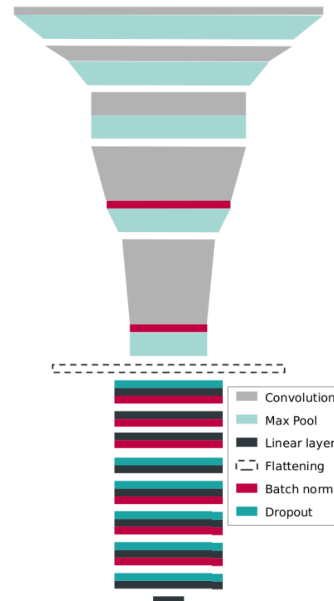
$\Rightarrow\ \text{Output for } MSELoss$

FIGURE 4. Detailed description of the neural network (left) and graphical visualization (right). It has 5 convolutional layers, followed by 8 fully connected layers. We chose a batch size of $N_B = 32$ and used the Adam optimizer. We note, that *k_size* represents the kernel size, *s* is the stride, *out_c* are the channel out, and *out_f* are the number output feature.

between the ground truth value and the label's output. Here, the mean length of the boxes $\mathcal{B}$ were $0.336\,\text{mm}$, $0.253\,\text{mm}$, and $0.200\,\text{mm}$ for NN_1, NN_5, and NN_{10}, with a mean median

value of $-0.010\,\text{mm}$, $-0.036\,\text{mm}$, and $-0.027\,\text{mm}$, respectively. The largest errors were located at the interval $\mathcal{I}$ (in the last box plot of each subfigure) with a median value of
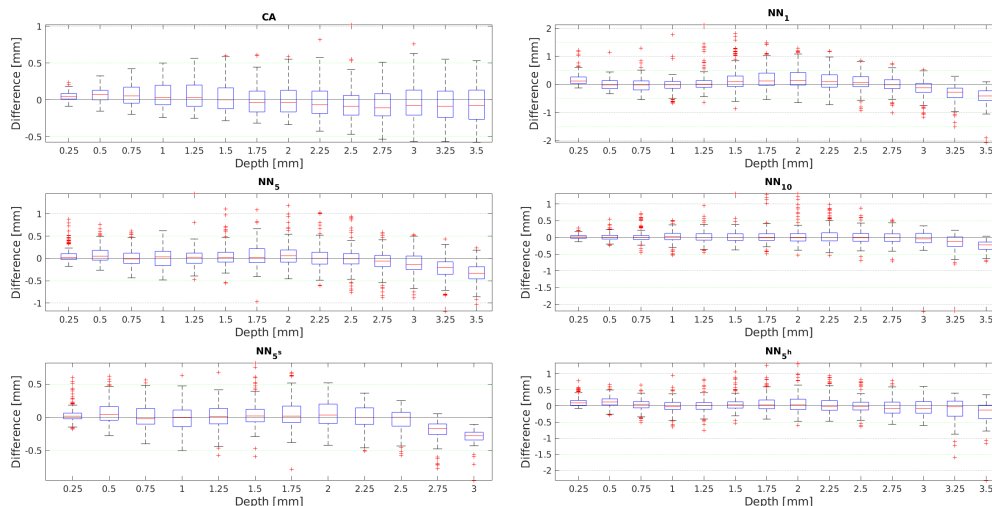
FIGURE 5. The box plots visualize the difference between the output and ground truth depth. CA is the method where we assume a constant ablation rate. NN_1, NN_5, and NN_{10} are the NN approaches with one, five, or ten consecutive acoustic measurements, respectively. NN_5s and NN_5h use five consecutive acoustic measurements as input. NN_5s data do not exceed the depth of $2.8\,mm$, and NN_5h uses some label augmentation. Each value on the x-axis corresponds to an interval, e.g., $0.25\,mm$ represents the interval between 0 and $0.25\,mm$.

$-0.407\,mm$, $-0.332\,mm$, and $-0.222\,mm$. The box length $\mathcal{B}$ was $0.349\,mm$, $0.275\,mm$, and $0.218\,mm$ for NN_1, NN_5, and NN_{10}, respectively.

V. DISCUSSION

We compared two approaches: CA, which assumes a linear estimation of the depth and a NN with either one (NN_1), five (NN_5), or ten (NN_{10}) consecutively measured acoustic waves as an input. In the box plots in Fig. 5, we observed that CA has fewer outliers than the NNs. The median value is close to 0 for all intervals, and even within the interval $\mathcal{I}$ ($Distance_I$), the median value was close to 0. The NNs had more outliers, and the median value between the distance of the output and the ground truth depth shifts into the negative with increasing depth. Hence, it underestimated the depth of the cut, especially in the interval $\mathcal{I}$, as can be seen in Table 2 and Fig. 5. However, the box length $\mathcal{B}$ was smaller for the NN than the CA for the interval $\mathcal{I}$. We further observed that CA outperforms the NN_1 and had a similar performance to NN_5. The best performing network was NN_{10}.

To further investigate the underestimation of the depth, we retrained the Network NN_5 with data that reaches a maximum depth of $2.8\,mm$ (NN_5s). We observe in Fig. 5 that both NN_5 and NN_5s had a significantly larger error in the reported interval $\mathcal{I}$ and $[2.75, 3]mm$, respectively. This is also reflected in Table 2, where the median value at $Distance_I$ were $-0.332\,mm$ and $-0.278\,mm$, with a box length of $0.275\,mm$ and $0.117\,mm$, respectively. Therefore, we assume that underestimating the depth at the end is due to the lack of training data.

TABLE 2. In the top row, the error, in the centre row, the mean distance over all intervals between the estimation and the label from the box-plots in Fig. 5, and in the bottom row, the distance of the last interval from the box-plots $Distance_I$ are described. We show the median, 25th percentile (PCTL), 75th PCTL value, and the distance $\mathcal{B}$, which is the difference between the 25th and 75th PCTL, of all the testing data from the cross-validation. CA is the method where we assume a constant ablation rate. NN_1, NN_5, and NN_{10} are the approach with the NN that uses one, five, or ten consecutive acoustic measurements. NN_5s and NN_5h use 5 consecutive acoustic signals as input. NN_5s data do not exceed $2.8\,mm$ depth, and therefore $Distance_I$ represents the interval $2.75\,mm - 3\,mm$, while all the others represent the interval of $\mathcal{I} = [3.25, 3.5]mm$. NN_5h was trained with some label augmentation.

mm	Median Value	25th PCTL	75th PCTL	distance $\mathcal{B}$
Error				
CA	0.130	0.065	0.228	0.163
NN_1	0.174	0.081	0.326	0.245
NN_5	0.130	0.060	0.252	0.192
NN_{10}	**0.092**	**0.040**	**0.189**	**0.149**
NN_5s	0.110	0.047	0.213	0.166
NN_5h	0.135	0.065	0.251	0.187
Distance				
CA	−0.024	−0.139	0.132	0.271
NN_1	−0.010	−0.1641	0.172	0.336
NN_5	−0.036	−0.158	0.096	0.253
NN_{10}	−0.027	**−0.120**	**0.080**	**0.200**
NN_5s	−0.026	−0.123	0.083	0.206
NN_5h	**0.003**	−0.136	0.143	0.278
Distance$_I$				
CA	**−0.076**	**−0.263**	0.133	0.396
NN_1	−0.407	−0.571	−0.222	0.349
NN_5	−0.332	−0.460	−0.185	0.275
NN_{10}	−0.222	−0.356	−0.138	0.218
NN_5s	−0.278	−0.340	−0.224	**0.117**
NN_5h	−0.127	−0.392	**0.023**	0.415

To this end, we retrained the network with label augmentation. Specifically, we added a random value r to the depth during the training of the network for all depths exceeding

3 mm. The value r is the absolute random number from the normal distribution $\mathcal{N}(0, 0.5)$, with the mean value of 0 mm and the standard deviation of 0.5 mm. We augmented the label as described above, leading to overestimating the depth during the network training. In Fig. 5 we can see that this strategy counteracts the general underestimation of the depth of the network at the last intervals. This is also reflected in Table 2, where the median value of $Distance_I$ was reduced from -0.332 mm to -0.127 mm. However, the box length $\mathcal{B}$ was increased to the value 0.275 mm to 0.415 mm. Therefore, augmenting the data improves the median accuracy but produces a higher output fluctuation.

VI. CONCLUSION

The experiments show that assuming a constant ablation rate already leads to good depth estimations of the cut by only counting the number of shots. This assumption, however, is limited to shallow cuts and does not hold for deep bone ablations that need a cooling system [37]. These cuts can reach a depth of up to 3 cm. Moreover, the number of shots must be maintained for a valid estimation. This is not stateless, meaning it needs all the information since the beginning of the ablation to estimate the depth. Therefore, it is not fail-safe since it may cause loss of depth information in case the number of the previous ablation gets lost.

It is essential for medical devices to continue working, even when a power failure occurs and all prior information is lost. Hence, we opt for a stateless method to ensure a fail-safe device. In this regard, the proposed approach with the NN is stateless (almost no prior information of previous ablations is needed) and, therefore, advantageous as it uses one or multiple consecutive acoustic waves as an input to predict the depth of the cut and does not need all information from the beginning of the ablation. Therefore, it is fail-safe and can predict the depth after only a few laser pulses. The NN approach has comparable accuracy but slightly more outliers due to its statelessness and sensitivity. The performance improved with an increasing number of consecutive acoustic waves used as input. Too many consecutive acoustic waves are disadvantageous because multiple acoustic waves are needed to estimate the depth accurately, increasing the risk of cutting the hole too deep and damaging sensitive tissue behind the bone.

In this work, we demonstrate the possibility of predicting the depth of a laser-ablated hole by analyzing the acoustic shock waves captured by a single transducer. The results encourage further investigations into the depth estimation during the laser ablation of tissue using acoustic waves. Our experiments were performed in a dry environment, and for future work, we plan depth estimation during a similar setup in wet conditions. Irrigation during laser ablation allows deeper cuts yet presents further challenges in combination with OCT systems. One of the challenges facing the irrigation system is that water accumulates in the hole, distorting depth measurement. In addition, the debris and water droplets pollute the OCT's protective window, reducing the image's contrast. An important factor may be the heterogeneity and the age of the bone influence the ablation process and the prediction of the depth using acoustic waves, which needs to be investigated.

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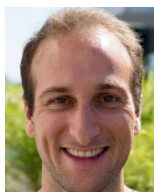
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Chapter 6

Discussion and Conclusion

"Life is like riding a bicycle. To keep your balance, you must keep moving."
– Albert Einstein

The objectives of this PhD thesis can be divided into two parts. In the first part, we reconstructed Tc^{99m} sources using measurements of γ-rays, and in the second part, we used acoustic waves to extract information of the surroundings.

6.1 Reconstruction of Tc^{99m} Sources

The first objective was to reconstruct Tc^{99m} sources from a single 2D measurement. One or multiple Tc^{99m} sources were placed in front of a detector. A multi-pinhole collimator was mounted between the detector and the sources. The γ-rays were emitted by the Tc^{99m} source and detected by the detector. From the resulting detector image, the source position was reconstructed.

6.1.1 Contribution

The main contribution of our work [66], was the improvement of the setup and the optimization of the algorithm from our previous work [79]. In [79] we used a Weighted Projected Gradient for ℓ_1-norm Minimization (WSPGL1) [60] to reconstruct the Tc^{99m} sources. To get a good reconstruction, a careful segmentation of the detector image and some post-processing of the reconstruction were needed. This is due to the fact that the forward problem does not take into account photons penetrating the collimator walls. One of our contributions to this thesis was that we developed a new algorithm. Our fingerprinting algorithm extracts the most dominant information on the detector and assigns it a position in the 3D subspace. Multiple sources are found when this method is applied recursively, without any pre-processing of the measurement and post-processing of the reconstruction. In addition, this method has a much lower computational time and is suitable for real-time implementation.

The second contribution of this work was the design of the collimator. In previous work, the authors of [69, 79] used a pinhole collimator where each pinhole was in the center of a

compartment. The main idea was that we could get depth information from a single measurement, as opposed to the parallel collimator, which requires multiple measurements at different angles to reconstruct the position of the Tc^{99m} source. The advantage of the septum walls is that they reduce the complexity of the forward problem. Depending on which compartment activity was measured, it is possible to limit the area of interest where the Tc^{99m} source is located. This reduces the complexity of the reconstruction. However, such a collimator design has some drawbacks. One of them is that information is lost due to the septum walls. In a regular pinhole pattern, there is no additional information from multiple holes due to the effect of symmetries, or even worse, it can lead to a reconstruction of positions that do not exist. In [66], discussed in Chapter 3, we addressed these challenges. The first step was to remove the septum walls, hence, increasing the complexity of the forward and inverse problem. This increased the computational time of the WSPGL1 algorithm. However, with our new fingerprinting algorithm, it was still feasible in an efficient way. To further improve the reconstruction, we created a new collimator design. We applied the algorithm described in [31] to find new pinhole distributions on the collimator and concluded that a random-looking distribution seems to be a good approach. We confirmed these assumptions in our research, by comparing the regular pinhole collimator with and without septum walls, and a collimator with a random distribution of pinholes.

6.1.2   Conclusion and Future Work

The results of this thesis are very promising. We were able to speed up the algorithm drastically and showed in an experimental and theoretical part that a random-like distribution improves the reconstructions of the Tc^{99m} sources. However, we still face some challenges. We managed to reconstruct multiple sources, but when two sources were located behind each other, it was still challenging. If the sources were located very closed behind each other, the fingerprinting algorithm failed to distinguish them. We believe that by measuring the Tc^{99m} sources from two different angles, the reconstruction can be improved drastically. Another possibility is that using other reconstruction methods, e.g. the CG algorithm in a recursive way, can detect if there are two sources behind each other. With additional constraints and regularization, it might be possible to reconstruct the shape of the Tc^{99m} source instead of just locating it. Another way to improve the results is with a better collimator design. To this end, we propose a different approach to finding the distribution of pinholes on the collimator. Instead of solving the tedious inverse problem to find the pinhole distributions, we can measure the performance of different collimators just by solving the forward problem of the algorithm described in [31]. To this end, we propose to use different distributions and numbers of pinholes and compare their performance. In addition, a realistic *ex-vivo* experiment should be designed that resembles the distribution of Tc^{99m} in the SLN of a patient.

6.2   Reconstruction using Acoustic Waves

The second objective was to extract information from an acoustic wave. To do so, we first used a purely mathematical approach, where we solved the Helmholtz equation to extract the shape, medium velocity, and position of the acoustic source of an area of interest. In the second method,

we used an experimental approach. Here, we ablated hard bone with an Er:YAG laser, and used the resulting acoustic waves to predict the depth of the cut using a NN.

6.2.1 Contribution

Previous work [63], showed that the Adaptive Eigenspace method works for reconstructing the medium velocity of objects using the Helmholtz equation. With the work of [64], the authors introduced a method, for given basis functions, to reconstruct the bone and the depth of the cut. This was done in a 2D simulation, and one of the challenges they faced was that the acoustic wave generator (the ablation point) was not well known. Our contribution of the work in [65], described in Chapter 4, was to reconstruct the medium velocity and the shape of the acoustic wave generator (source). We used the Adaptive Eigenspace method, which reduced the number of unknown parameters during the optimization process. However, the eigenfunction had to be computed after each iteration, and the number of transducers needed for a good reconstruction was not applicable in our setup. Another challenge was that the method used in a 3D simulation dramatically increased the computational cost and time, making it inapplicable for a real-time feedback system.

Therefore, we took a different approach in [78], described in Chapter 5, where we decided to focus only on the depth of the laser-cut. During the ablation process of the bone with the Er:YAG laser, we recorded the acoustic waves, and with the OCT image, the depth of the cut. We trained our NN using the acoustic measurement as an input to predict the depth of the cut. Our contribution was that we were able to find a correlation between the depth of the cut and the acoustic wave using only a single transducer during the ablation of the bone. A trained NN solves the forward problem (where the input is the acoustic wave and the output is the predicted depth of the cut) very quickly. Therefore, this approach can be implemented in a real-time matter during tissue ablation.

6.2.2 Conclusion and Future Work

I believe that real-time reconstruction of the shape of the bone and surrounding tissue during bone ablation with an Er:YAG laser by solving the Helmholtz equation with the Adaptive Eigenspace is not applicable. The required computational resources are too high. In addition, too many transducers are needed. However, I believe that the method can find another use in medical applications. One of them is to improve ultrasound imaging. In ultrasound, the wave generator is well known. Apart from that, the ultrasound image can be a good initial guess for the reconstruction with the Adaptive Eigenspace method. One of the challenges of this method is the computational cost. However, these reconstructed images can be used as a post-analysis, therefore the computational cost is not a limiting factor. Nevertheless, one of the major issues that still needs to be investigated is whether the forward problem of the Helmholtz equation holds up in the real world. Therefore, the 3D simulation should first be confirmed in an *ex-vivo* experiment before analyzing in which field it can be applied.

Using the NN to predict the depth of cut with the acoustic wave seems very promising and encourages further research. One of the main advantages is that a trained NN is very efficient in solving the forward problem. However, a disadvantage is that a lot of training data is needed

to have a good predictive NN. It needs to be investigated how realistic the *ex-vivo* experiments are compared to the *in-vivo* experiments. However, first the ablation should be performed in a wet condition to ensure that the acoustic wave correlates with the depth and not with the amount of water in the tissue. Another advantage of wet ablation is that the bone is not carbonized, and deep bone ablation is possible. One of the challenges will be to ensure exactly where the acoustic wave is generated. For example, if the hole is filled with water, then the ablation will not be at the bottom of the hole. Another approach that needs to be investigated is the position of the transducer and whether a contact transducer improves accuracy.

6.3 Final Thoughts

In this thesis, we investigated different approaches to solving inverse problems. One of the main challenges we faced was to find a mathematical model that would hold up in the real world. For this purpose, the NNs have a great advantage. These models require experimental data to work efficiently, so it is not necessary to understand the physics and mathematics behind the experiment to make an accurate prediction. However, this can also be a challenge and even a disadvantage. If the settings of the experiment change, a NN may suffer from inaccuracy due to previously unseen data. Therefore, we believe it is important to bring together the understanding of mathematical reconstruction, physical understanding, and the speed and efficiency of the NN. A closed collaboration between these topics can improve the reconstruction and make it more robust to unseen circumstances.

Chapter 7

Appendix

"True Beauty shines in many ways, and order is one of them."
– Friedrich Pukelsheim

Theorem 7.1. *The highest known prime number found in 2018* [1] *is*

$$p = 2^{82\,589\,933} - 1$$

(a Mersenne prime number) has the following property

$$p \pmod 5 \equiv 1 \,.$$

Proof. Let $n = 82\,589\,933$. Hence, we have

$$
\begin{aligned}
p \pmod 5 \quad &\equiv \quad 2^n - 1 \equiv 2^n + 4 \equiv 4(2^{n-2} + 1) \equiv -1(2^{n-2} + 1) \\
&\equiv \quad -1(2^{n-2} - 4) \equiv -4(2^{n-4} - 1) \equiv 1(2^{n-4} - 1) \\
&\equiv \quad 2^{n-4} - 1 \equiv \quad \cdots \quad \equiv 2^{n-4i} - 1 \equiv 2^{n \pmod 4} - 1 \\
&\equiv \quad 2^1 - 1 \equiv 1 \pmod 5
\end{aligned}
\,.
$$

$\square$

Theorem 7.2. *Let $A \in \mathbb{R}^{N \times M}$ be a matrix.*

$$H = A^T A \quad \Longrightarrow \quad H \text{ is a symmetric matrix}\,.$$

Proof. Let

$$
A = \begin{bmatrix} a_{1,1} & \cdots & a_{1,M} \\ \vdots & \ddots & \vdots \\ a_{N,1} & \cdots & a_{N,M} \end{bmatrix} = [a_{i,j}]_{1 \leq i \leq N, 1 \leq j \leq M} \ \in \mathbb{R}^{N \times M}\,.
$$

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[1] June 2022, https://primes.utm.edu/largest.html

Hence, we have

$$A^T A = \begin{bmatrix} a_{1,1} & \cdots & \cdots & \cdots & a_{N,1} \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ a_{1,i} & \cdots & a_{j,i} & \cdots & a_{N,i} \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ a_{1,M} & \cdots & \cdots & \cdots & a_{N,M} \end{bmatrix} \begin{bmatrix} a_{1,1} & \cdots & a_{1,j} & \cdots & a_{1,M} \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ \vdots & \ddots & a_{i,j} & \ddots & \vdots \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ a_{N,1} & \cdots & a_{N,j} & \cdots & a_{N,M} \end{bmatrix} = [\hat{a}_{i,j}]_{1 \leq i,j \leq M} \,.$$

Therefore, we can write for a given i, j in $1 \leq i, j \leq M$

$$\begin{aligned} [\hat{a}_{i,j}] &= a_{1,i} a_{1,j} + \cdots + a_{j,i} a_{i,j} + \cdots + \cdots + a_{N,i} a_{N,j} \\ &= \sum_{n=1}^{N} a_{n,i} a_{n,j} = \sum_{n=1}^{N} a_{n,j} a_{n,i} \\ &= a_{1,j} a_{1,i} + \cdots + a_{i,j} a_{j,i} + \cdots + \cdots + a_{N,j} a_{N,i} \\ &= [\hat{a}_{j,i}] \end{aligned} \,,$$

hence, it is clear that

$$\left(A^T A \right)^T = [\hat{a}_{i,j}]_{1 \leq i,j \leq M}^T = [\hat{a}_{i,j}]_{1 \leq i,j \leq M} = [\hat{a}_{j,i}]_{1 \leq i,j \leq M} = A^T A \,,$$

and therefore $H = A^T A$ is a symmetric matrix of the size $\mathbb{R}^{M \times M}$.

$\square$

Lemma 1. *Let $H = A^T A$ with $A \in \mathbb{R}^{N \times M}$,*

$$\text{if } H \text{ is invertible} \quad \Longrightarrow \quad \text{rank}(A) = M \leq N$$

Proof. It is clear, that $H \in \mathbb{R}^{M \times M}$ and therefore, if H is invertible, we know that

$$\text{rank}(H) = M \,.$$

Hence, we get

$$M = \text{rank}(H) = \text{rank}(A^T A) \leq \min(\text{rank}(A^T), \text{rank}(A)) \leq \min(N, M) \,.$$

This equation is only true, if $M \leq N$, and therefore we have

$$\text{rank}(A) = \text{rank}(A^T) = M \,.$$

$\square$

Theorem 7.3. *Let $H = A^T A$ with $A \in \mathbb{R}^{N \times M}$,*

$$\text{if } H \text{ is invertible} \quad \Rightarrow \quad H \text{ is positive-definite}$$

Proof. We remind the reader that H is positive-definite if and only if

$$x^T H x > 0 \quad \forall x \in \mathbb{R}^M \setminus \{0\}\,.$$

Since $H = A^T A$ we can write

$$x^T H x = x^T A^T A x = (Ax)^T A x = ||Ax||_2^2 \geq 0\,.$$

Case 1, $N = M$: Hence, we have $A \in \mathbb{R}^{M \times M}$ and with Lemma 1 it follows that

$$\mathrm{rank}(A) = M\,,$$

and therefore, A is invertible. Since A is invertible, we know there exists exactly one solution for

$$Ax = 0\,,$$

hence, $x = 0$. Therefore we get

$$x^T H x = ||Ax||_2^2 > 0 \quad \forall x \in \mathbb{R}^M \setminus \{0\}\,.$$

Case 2, $N > M$: Hence, we have $A \in \mathbb{R}^{N \times M}$ and with Lemma 1 it follows that

$$\mathrm{rank}(A) = M\,.$$

Since $N > M$, we can deduce that the linear system

$$Ax = y$$

with M unknowns ($x \in \mathbb{R}^M$) has more linear equations, namely N, than unknowns. Because $\mathrm{rank}(A) = M$, we know that there exists at most one solution x for a given y. Hence, we can deduce that $x = 0$ is the only solution for

$$Ax = 0\,.$$

Therefore we get

$$x^T H x = ||Ax||_2^2 > 0 \quad \forall x \in \mathbb{R}^M \setminus \{0\}\,.$$

Hence, we proved the theorem with *Case 1* and *Case 2*.

$\square$

Theorem 7.4. *If E is the identity matrix and $\lambda > 0$, then*

$$H = A^T A + \lambda E$$

is positive-definite for all $A \in \mathbb{R}^{N \times M}$.

Proof. For all $x \in \mathbb{R} \setminus \{0\}$ we have $||x||_2^2 > 0$ and therefore we can write

$$
\begin{aligned}
x^T H x &= x^T (A^T A + \lambda E)x = x^T A^T A x + x^T \lambda E x \\
&= (Ax)^T (Ax) + \lambda x^T x = ||Ax||_2^2 + \lambda ||x||_2^2 \geq \lambda ||x||_2^2 > 0
\end{aligned}
$$

,

and hence, H is positive-definite.

$\square$

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