Simulation and quantification of the interplay effect in treatment of lung tumors with IMPT

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“In the debate of photons versus protons one should not take the matter lightly, but positively”
TU DELFT

Abstract

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Simulation and quantification of the interplay effect in treatment of lung tumors with IMPT

by Dominique Reijtenbagh

In spot scanning irradiation techniques the application to moving tumors can cause interplay effects that can severely deteriorate the tumor coverage. In this thesis a model is presented with which IMPT treatment deliveries can be simulated for moving lung tumors. Two different respiratory motion models are analyzed for interplay effects and three patients are planned with different methods to analyze their robustness against interplay. For the planning four methods are used, of which three use robust optimization. One of the methods is robust multi CT optimization, a novel technique proposed by Erasmus MC. This type of optimization is used for the analysis of the respiratory models, and it was found that the different respiratory models result in different interplay effects. The robust multi CT optimization was found to be the most robust planning method against interplay effects in comparison with the other optimization types such as ITV planning, especially after fractionation. It was the only method that would converge towards the planned V95% and V107% value, as more fractions were simulated. Other optimization techniques and hypofractionation require interplay mitigation methods to improve the tumor coverage. The model has shown the capability to simulate the interplay effect for IMPT in lung tumors and analyze the 4D robustness of planning methods.
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Chapter 1

Introduction

Cancer has been a problem of all times, but was still responsible for one in every four deaths in the US in 2012. Lung cancer was responsible for one fourth of those cancer deaths (Siegel, Miller, and Jemal, 2016). The ultimate cure for cancer does therefore not appear to be found. Radiotherapy has however developed significantly over the past years. New treatment modalities have been developed and new types of planning have been implemented.

One of these novel techniques is discussed in this thesis. The technique, IMPT (Intensity Modulated Proton Therapy), delivers high energy protons to the patient while spot scanning the target. Protons possess features that make them a more interesting treatment modality over photons in some cases. IMPT is promising as it has shown the capability to spare OARs (Organs At Risk) better than IMRT, while maintaining excellent tumor coverage (Zhang et al., 2010). An exemplary dose distribution of a single spot is depicted in Figure 1.1a. When all spots are applied, a dose distribution looking as shown in Figure 1.1b arises. It is visible that the separate spots with protons are fully stopped in the body, in contrast with photon based modalities.

![Exemplary IMPT dose distribution of a single spot](image1.png)

![Exemplary IMPT dose distribution of combined spots](image2.png)

Figure 1.1: Visual depiction of an exemplary IMPT dose distribution of a single spot and of combined spots. In red the target is delineated. As can be seen in Figure 1.1a the spot does not exit the body.

Applying a spot scanning technique such as IMPT to moving tumors (e.g. the lung) on the other hand, might give rise to distortions in the dose distributions, also called interplay effects. The interplay effects are mostly large inhomogeneities in the target, leading to local under- and overdosage. Conclusions in literature differ in final verdict, mostly due to different planning techniques and evaluation methods (Li et al., 2014, Knopf, Hong, and Lomax, 2011, Grassberger et al., 2015). The aim of this study is to simulate the interplay effect in a moving tumor in order to quantify the effect as a function of different treatment parameters. With the
opening of new proton treatment facilities in The Netherlands, the wish is there to find better understanding and possibly a solution for the effect, such that high treatment quality can be established for moving tumors.

In this thesis an interplay model is presented for the lung, capable of predicting the magnitude of the interplay effect as a function of different (possibly influential) factors. These factors include planning techniques, (ir)regularity of breathing motion, and magnitude of tumor movement. A practical background to give more understanding about certain aspects of the model is given in Chapter 2. The aim of the study is to use the model to give a prediction about the magnitude of the interplay effect and the capability of the planning methods to cope with the effect. In Chapter 3 an elaborate explanation of the model is given. The model uses 4DCT sequences of three actual lung cancer patients with contours on the reference phase, of which the CT scans are used to determine the deformable image registrations. With the help of these registrations contours are warped from the reference phase to the other respiratory phases. Four types of planning are used on the contour sets, robust single CT, robust multi CT, ITV and robust ITV planning, of which the reference CT scan is used for planning for all but the second planning method. In Chapter 4 the results are laid out, after all planning methods of all three patients are tested for robustness against interplay. The robust multi CT results of one patient are also used to find the difference of the impact of breathing motion on the dose distribution due to interplay. Finally, a comparison with literature is made. In Chapter 5 recommendations are given for future research, both directly and indirectly related to this thesis.
Chapter 2

Movement of targets in proton therapy

2.1 Proton therapy

2.1.1 Impact of radiation

In contemporary cancer treatment multiple options are available, in which chemotherapy and irradiation play a big role. Irradiation is performed to induce DNA damage in the tumor cells, inhibiting cell division and ultimately causing cell death. Tumor cells have a lower capability of regeneration mechanisms to repair double strand DNA breaks in comparison with normal tissue cells, indicating a fundamental application of irradiation.

Over the years different techniques have been developed, with photon irradiation being the most widely applied. However, there are other options, some being more or less beneficial. Based on the tumor characteristics and combinations with other treatment forms such as chemotherapy, it will be determined which irradiation method is most promising to control the tumor growth and hopefully cure the patient from cancer. The question is why a particular irradiation method is sometimes more beneficial for the patient than another.

The first and primary difference between photon based methods and others is based on the nature of the radiation. There are multiple possibilities, such as electron, neutron or ion based. Ion based radiation has some subcategories, given by the Z-number of the ion used for irradiation, and does therefore also include proton therapy. The difference in nature of the particle, is best shown in the energy deposition as a function of the traveled path of the particle. This is visualized in Figure 2.1. As one can see, the shape of the dose deposition curve can differ a lot based on weight, energy and charge of the particle. Ions and photons have different dose deposition characteristics, that can be exploited when treating a patient. From now on only proton and photon therapy shall be discussed, since these are most clinically applied and will be the most relevant for the thesis. Other techniques, such as carbon ion therapy, also show promising results, but are considered beyond the scope of this research. In this thesis only external beam radiotherapy is discussed.

Now the difference between the dose deposition curves of protons and photons shall be further elaborated. When looking at Figure 2.1 one can see that photons have a relatively early and broad peak, with a gradual dose fall-off. This is in contrast with protons, that have a later and sharper peak, with a very sharp dose fall-off (Bragg peak). Combining multiple of these Bragg peaks in one beam can create a dose deposition curve having a plateau in the tumor only. An example of such a
Chapter 2. Movement of targets in proton therapy

Figure 2.1: Relative dose deposition as a function of depth in water for different particles. It is visible that depending on the type of particle, the dose deposition is different. The heavier ions show a shallow and late peak, while photons and neutrons show a broad and early peak. Depending on the energy of a particle the deposition curve changes. As is also shown, ions are more easily stopped in the body than gammas and neutrons. Taken from Paganetti, 2012.

Figure 2.2: Spread out Bragg peak (SOBP) composed of protons with different energies. Their dose deposition curves combined (with each their distinct Bragg peak) compose a plateau, which is ideally covering only the tumor. Taken from Paganetti, 2012.

Naturally, both techniques have their disadvantages. Photons have energies that make them fully traverse the body, and they deposit dose along their entire path. This dose deposition is unwanted, as it harms healthy tissue unnecessarily. The dose deposition behind the tumor could be circumvented with protons, but they have on the other hand a high sensitivity to placement errors and movement. This is a particular problem for tumor sites, or tumor sites close to organs, undergoing anatomical changes, e.g., bowel and bladder filling. The density changes cause overshoot or undershoot of the proton beam, meaning that due to a higher difference in density along the path the beam is stopped earlier (undershoot), or due to a lower difference along the path is stopped later (overshoot). Machine range uncertainties
2.1. Proton therapy

also contribute to this problem. One can imagine that the latter could pose significant problems. If proton therapy is chosen to avoid an OAR, overdosage in the OAR due to overshoot is definitely undesired.

The problem described above is visualized in Figure 2.3. The figure shows that in the nominal scenario, in which one assumes the treated anatomy is exactly as expected, the SOBP perfectly covers the tumor. The heart, an organ that should get a dose as low as possible, receives a negligible dose when protons are used. In the case of photons a higher dose is seen, which is an indication to switch to protons. However, when one turns to a more realistic scenario, an 'uncertain' situation, in which only the approximate anatomy with respect to the beams is known, it becomes clear that this potentially has a big effect on the heart dose. This is in contrast with the photon dose, in which it has little to no effect.

There are multiple ways to account for the effect, but it is obvious that the differences in nature of dose deposition also imply a different approach in treatment planning. Therefore optimal proton plans will have to be found in a different way than photon plans. This will be discussed in the sections below.

2.1.2 Proton treatment facilities

In photon therapy the treatment techniques are numerous. The principle is the same for all, as changing the energy of the beam is done quite easily in contrast with protons. Having taken this hurdle, there is room for more flexibility in time and position. This category of treatment is IMRT (Intensity Modulated Radiation Therapy), which basically means that the beam can be shaped in form and in energy. There are different types in this category, such as the aforementioned LINAC, CyberKnife and VMAT. The most basic technique of the three is the LINAC (LINEar ACcelerator), that can shape the beam and allows a 360 degree rotation around the patient. VMAT (Volumetric Modulated Arc Therapy) is one step more sophisticated. VMAT, contrary to conventional LINAC, can be applied continuously as the beam rotates around the patient, reducing treatment time. More flexibility in

---

Figure 2.3: Differences in effect in the case of range uncertainties for photons and protons when treating a lung tumor. A bigger impact for a proton path is seen, causing a higher unwanted dose in the heart. Taken from Knopf and Lomax, 2013.
position can be obtained with the CyberKnife, which has the strength in its accurate and quick robotic arm. This allows the tracking of the tumor when coupled to a movement detector.

In proton therapy two major modalities can be considered, passive scattering and IMPT (Intensity Modulated Proton Therapy). It is quite difficult to find direct parallels with photon therapy, as the principles of the techniques are quite different. Passive scattering is the first technique discussed here, and has its principle as described in the name. With the use of collimators and scattering in compensators the beam is shaped to give a 3D dose distribution with an appropriate SOBP. The major disadvantage of this type of proton therapy is the necessity for patient-specific collimators and compensators, and the lack of flexibility when the anatomy of the patient changes (Paganetti, 2012).

Intensity Modulated Proton Therapy (IMPT), a form of pencil beam scanning, allows a more dynamic treatment of patients. In making the plan each spot is optimized together with the other spots, to deliver a good treatment. The beams are therefore not uniform separately, but the combination of the beams gives a uniform dose to the tumor. This is in contrast with Single Field Uniform Dose (SFUD), in which fields are optimized separately to be uniform. With the use of bending magnets the IMPT treatment is delivered to the patient spot by spot. The beam scans the tumor according to an afore-calculated treatment plan, easily allowing small or big changes. The delivery of a single spot is in the order of milliseconds, followed by a spot-off time in which no dose delivery is possible (also in the order of milliseconds). Switching to different proton energies can take up to seconds.

In both IMPT and passive scattering, it becomes clear that the delivery of the proton beam is prone to less flexibility than photon based delivery. The need for a cyclotron or synchrotron with a big gantry for accuracy severely deteriorates the possibilities of developing a CyberKnife-like robotic delivery. Only IMPT shall now be discussed in the remainder of this thesis.

2.2 Moving targets in proton therapy

In this section a more in-depth explanation will be given about a specific problem in radiotherapy, which is on how to deal with moving targets. In contrast with stationary targets, additional measures have to be taken to deal with moving targets with all types of treatment modalities. However, in proton therapy the consequences are more severe, and therefore the solutions more complicated. The main focus is on lung tumors, as this type of tumor was the main focus of this thesis. First an explanation is given on how tumor movement is described in order to incorporate this in planning or analysis, then the key problem of this thesis, the so-called interplay effect, is be explained. Finally, literature is discussed in which possible solutions for the interplay effect are given.

2.2.1 Lung tumors

Lung cancer has been the most common cancer for decades, globally speaking. The most frequent type of lung cancer is non-small cell lung cancer (NSCLC), accounting for 85% of the cases, after that comes small cell lung cancer (SCLC) (Navada et al., 2006). The survival rate for these types is generally low; the ratio of mortality is as high as 87%, depicted in Figure 2.4. In addition to that, lung cancer is responsible for one out of five cancer deaths in the US (WHO, 2012). The most common treatment for lung cancer is combination of chemotherapy and irradiation, but surgical
resection appears to be the most successful option. However, most patients cannot be treated this way (Nesbitt et al., 1995). One limitation of lung tumor irradiation is the incidence of radiation pneumonitis due to irradiation of healthy lung tissue. When applying a regular fractionation scheme there is a risk of pneumonitis, but this risk gets bigger when hypofractionation (delivering the treatment in only a few fractions, instead of 20+ fractions) is applied (Seppenwoolde et al., 2003). An overview of other risk organs (tumors with intrafractional movement) is given by Langen et al. (Langen and Jones, 2001).

![Figure 2.4: Mortality of NSCLC and SCLC, grouped by years after diagnosis. The dashed line is for small cell lung cancer (SCLC), the solid line is for non-small cell lung cancer (NSCLC). Made from data from IKNL, 2017.](image)

When treating lung tumors, there are multiple organs at risk to take into account when planning the treatment. In Table 2.1 a short overview is given of the organs with the possible toxicities that might arise.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>Pulmonary fibrosis and radiation pneumonitis (Mehta, 2005)</td>
</tr>
<tr>
<td>Heart</td>
<td>Coronary artery disease (CAD), valvular disease, chronic pericardial disease, arrhythmias and conduction disturbances, cardiomyopathy, or carotid artery stenosis (Carver et al., 2007)</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>Radiation myelopathy (Kadir et al., 2012)</td>
</tr>
<tr>
<td>Plexus Brachialis</td>
<td>Transient neuropathy, acute ischemic plexopathy (Delanian, Lefaix, and Pradat, 2012)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Radiation esophagitis (Kwint et al., 2012)</td>
</tr>
<tr>
<td>Trachea</td>
<td>Tracheitis (Levy et al., 2013)</td>
</tr>
<tr>
<td>Proximal bronchial trees</td>
<td>Bronchial stricture, bronchial necrosis, and fatal hemoptysis (Guckenberger et al., 2007)</td>
</tr>
</tbody>
</table>
The toxicities can become quite serious, and might even be a cause to stop treatment if the patient suffers too much from them. When creating a treatment plan for the patients used in this study, the optimization takes into account the OARs and tries to get a feasible treatment plan while keeping the dose to the OARs as low as achievable. Considering the 'actual' OAR dose delivered in treatment is therefore important to see if these toxicities will arise. Depending on the type of planning the dose to the OARs can be a limiting factor in the treatment.

2.2.2 Describing tumor movement

Tumor movement can have complex shapes, depending on the tumor site and specific patient. This section explains different scenarios to describe tumor movement.

Ideal scenario

One can approximate respiratory motion by describing tumor motion with a perfect cosine based on literature studies, as shown in Figure 2.5. Here the y-direction could be for example the caudal-cranial direction and the x-direction the anterior-posterior direction. If \( x \) and \( y \) are in phase, Figure 2.5.b takes place. If they are not, Figure 2.5.d is applicable, which means there is hysteresis in the movement of the tumor. This means that the tumor location is different in 50% exhale position from the 50% inhale position. In this thesis hysteresis is not accounted for. This means that only the motion curves of Figure 2.5.a and 2.5.b are implemented in the thesis.

![Figure 2.5: Approximating respiratory motion with cosines in two normal directions. In a both directions are in phase, in c they are not, causing hysteresis. In b and d the resulting motion trajectory is shown. Taken from Ehrhardt, Lorenz, et al., 2013.](image)

When a patient shows breathing similar to this ideal scenario, the tumor location does not obey a Gaussian distribution due to its sinusoidal movement. The tumor will spend more time in full exhale and full inhale position than it will mid-exhale or mid-inhale position, which is shown in Figure 2.6. This way of evaluating motion is considered less accurate than actual patient’s breathing motion. Dowdell et al. reasons that using an ideal scenario will result in a worst case scenario (Dowdell et al., 2013). Since fewer averaging effects take place in perfect motion, less favorable dose distributions are created. In a real treatment the effect of breathing on the
2.2. Moving targets in proton therapy

dose deposition will be less visible. Whether this is actually the case is discussed in Chapter 4.

![Figure 2.6](image)

**Figure 2.6:** A few (raw data) breathing periods are analyzed to find the probability density function of the tumor movement. As can be seen, the tumor is more likely to be found at full exhale and full inhale. Taken from Bortfeld, Jiang, and Rietzel, 2004

**Binning scenario**

Another option is to use raw signal of patients, which could be obtained with a breathing monitor. An example of this kind of signal is shown in Figure 2.7.

![Figure 2.7](image)

**Figure 2.7:** Exemplary signal from CyberKnife respiratory motion tracking system, position of the tracker as a function of time. Baseline shifts are visible and big variations in amplitude, as well as gaps without data.

By defining the relative positions of the phases, the signal can be 'binned'. This is shown in Figure 2.8, in which it is visible that the motion is approximated with discrete steps in time instead of continuous ones. Binning was considered too difficult for the breathing signal used in this thesis, as the signal was deemed to be too irregular.
Chapter 2. Movement of targets in proton therapy

Figure 2.8: Binning a breathing signal. In this example is visualized an example of amplitude binning. Half a breathing period can be binned in 10 regions, of which the regions are linked to a position of the tumor. Taken from Lujan et al., 1999.

Hybrid scenario
The final scenario that is considered in this thesis is the hybrid scenario. In this scenario a raw breathing signal is analyzed to find the probability density distribution of the breathing period of the patient. In Figure 2.9 the fitted probability density function of the signal of Figure 2.7 is depicted, together with the breathing periods found in the signal. Then, to simulate the motion of the tumor, different periods are sampled in accordance with this probability density function and are consecutively placed behind each other in time.

Figure 2.9: The signal from Figure 2.7 is filtered and processed to find the breathing phases and their distribution. A Gaussian distribution is assumed and fitted to the data, which is used for sampling later on. Periods below 2.5 s and above 5.5 s were considered noise and discarded. The Gaussian fit is scaled for visibility.

The idea is that this scenario is more realistic than the ideal scenario, but less realistic than the binning scenario. The hybrid scenario is also easier to apply than the binning. According to a study performed by Quirk et al. the periodicity of a signal is more stable than the amplitude (Quirk, Becker, and Smith, 2013). This means that statistical modeling would be easier to do with the periodicity as it is
easier to predict. In their study volunteers were compared to patients, and it was found that patients have more irregular breathing and smaller amplitudes.

### 2.2.3 Treatment plans for moving targets

The nature of the irradiation method and the nature of the tumor determine the approach to treat the patient. In treatment planning, the clear tumor boundaries are drawn and named the GTV (Gross Tumor Volume). To account for microscopic spread of the tumor, a margin is added to the GTV, to form the CTV (Clinical Target Volume). So far the methodology for proton and photon therapy is the same. The last step, however, tends to be different. To account for set-up errors and inter-fractional tumor movement in photon therapy, an extra margin is added around the CTV. This extra margin is the planning target volume (PTV) and is due to the slow, approximately linear, dose fall-off for photons, a mostly uniform expansion of the CTV. An extra difficulty is introduced when a patient has a tumor that moves intra-fractionally due to, for example, breathing motion. In this case the patient needs a 4D CT scan (4DCT), which records the patient while breathing to find the positions of the tumor in different breathing phases. The most extreme positions can then be found and are then delineated and combined, to form the ITV (internal target volume) (Kang et al., 2007). The PTV can also be applied to compensate for motion, by expanding the contour non-uniformly more in the direction of the motion (Paganetti, 2012). This does not necessarily require a 4DCT.

For protons the PTV expansion is more complicated, as the sensitivity of the proton dose does not allow a similar reasoning. The existence of the Bragg peak and the potential under-/overshoot problem causes a non-linear change in dose deposition when the anatomy is not according to plan. This makes the definition of the PTV more difficult to determine.

![Diagram of different volumes used in radiotherapy](image)

**Figure 2.10:** Depiction of the different volumes used in radiotherapy. The visible tumor is the GTV (Gross Tumor Volume). This volume does not incorporate microscopic expansions of the tumor, to compensate for these the CTV (Clinical Target Volume) is created. Depending on the uncertainties in delivering the treatment the physician might decide to expand this contour a little more to assure a good tumor coverage, resulting in the PTV (Planning Target Volume). This is only truly applicable for photons, as they are less sensitive to density differences in the body. Specifically for moving tumors an ITV (Internal Target Volume) is often used. Creating a contour that encompasses all positions of the tumor can help increase tumor coverage.

Solving the problem of the PTV for protons is not trivial, and the way to deal with this differs per institution (Li et al., 2015, Graeff, Durante, and Bert, 2012).
Erasmus MC tries to account for this problem (in research) by planning robustly to account for set-up uncertainties and inter fraction motion, and in the case of intrafractional motion, on multiple CT scans simultaneously. The optimization is performed by not simply implementing a bigger margin, but instead by considering multiple CT scans, as shown in Figure 2.11. By using multiple CT scans a change in surrounding anatomy during respiratory motion is included as well, which is not the case with ITV or PTV planning. The scans are loaded into the optimization, while sharing information about the spatial position of the organs and tumor (in order to determine the respective locations to the beam). This makes it possible to investigate the outcome of each spot on all phases simultaneously, and even include robustness scenarios.

![Figure 2.11: When applying multi-CT optimization, the 0% inhale, 50% exhale and 100% inhale CT scans are used for optimization simultaneously. The spatial position of the tumor is known in all three cases, which makes simultaneous optimization possible. The nine robustness scenarios that are used in robust optimization are applied to all three phases separately, resulting in a total of 27 scenarios to be optimized.](image)

If robustness is included, which means that patient shifts and uncertainty in spot delivery are anticipated, there is a new scenario to optimize for each patient shift or uncertainty. Normally, this would mean 9 scenarios for a phase, as shown in Figure 2.12. In this case, where 3 phases are used, this adds up to 27 scenarios. Robust optimization is therefore more time-consuming and intensive than ITV or PTV optimization, and requires more computational power. On the other hand, it is meant to give better robustness to set-up errors in patient positioning and uncertainties in beam delivery (Stoel, 2016). The plan that is constructed will therefore not only show good coverage in the 9 scenarios, but also in all other breathing phases and their scenarios.

![Figure 2.12: The nine robustness scenarios taken into account in the robust optimization. Five are displayed, but the patient shift is for the 3 dimensions separately (x, y and z) and therefore includes 4 extra scenarios. The plan is made to not only cover the nominal scenario, but the error scenarios as well. Courtesy of M. Hoogeman.](image)
2.2.4 The interplay effect

Lung tumors are different from many other types of tumors in the sense that they are not static. Movement of the tumor may cause under- or overdosage of the tumor or OARs, possibly reducing the tumor control probability and increasing risks of complications. But how does this happen?

Again, protons are very sensitive to density changes they find along the way, a proton can travel 1000 times further in air than in water (Suple, 2009). Therefore it is intrinsically important for the success of a treatment that the anatomy of the patient is similar to the planning anatomy. This is a problem even without movement of the tumor. Air cavities in the beam path cause overshooting of protons in tumors near these organs. This is an issue for lung tumors, as the tissue thickness and composition around the lungs depends highly on the position in the lung. The differences in anatomy can be accounted for by using multiple CTs of breathing phases in the optimization. Accounting for these differences in anatomy can be called a 3D robust plan, which means that if the tumor were static in a breathing position, the coverage would be sufficient in each of these breathing positions. This does however not necessarily mean that a plan is 4D robust.

The 4D robustness of a plan can be investigated by evaluating the movement of the tumor during a treatment. Not only might the tumor surpass the boundaries of the planning volume (although this can be fixed by increasing the margin), the tumor accumulates spots during irradiation that do not necessarily end up in the planned position. In this case the total dose to the tumor might be according to plan, but the final (dynamic) dose distribution is almost certainly not. This problem is depicted in Figure 2.13 and shows the arising of hot- and coldspots in the tumor. Therefore the interplay effect can be described as the dose degradation due to unplanned hot- and coldspots because of interfractional anatomical movement. The interplay effects causes possible inhomogeneities in target coverage and dose blurring along the edges of the targeted structures (Zhang et al., 2012). Therefore, even when the anatomy is taken into account, which could be considered a 3D robust plan, a robust 4D plan is not guaranteed. Interplay is not only an issue for IMPT, but also affects IMRT and other forms of treatments that involve spot scanning.

![Figure 2.13: Consequences of the interplay effect. A spot sequence for a tumor is applied to the moving tumor. One can see that, due to respiratory motion as displayed in the graph, the tumor receives spots in places different from the spot sequence in the most left picture. One should take into account that the figure has a plan that is based on a static condition with small margins, but the interplay effect will affect plans with bigger margins too.](image)

* Taken from Rietzel and Bert, 2010.
In literature the opinions on the consequences of the interplay effect differ. According to Kraus et al. the interplay effect will be reduced significantly after fractionation, but the effect will remain visible. Irregular breathing motion will also help this reduction (Kraus, Heath, and Oelfke, 2011). Grassberger et al. found that the spot size used during treatment has an effect on the magnitude of the interplay effect, as well as the motion amplitude. On the other hand they also found that motion amplitude is not a good predictor of the magnitude of the interplay effect (Grassberger et al., 2013). Bert et al. performed a phantom study and also agree on fractionation to mitigate the effect, and expect a residual difference from the static case as well. They also express their concerns on hypofractionation in these case, and predict that the use of extra mitigation techniques (as will be discussed in the next section) will be crucial (Bert, Grözinger, and Rietzel, 2008). To conclude, Inoue et al. found that increasing the robustness settings from 5 to 7 mm when applying minimax robust optimization did not mitigate the interplay effects, yet including fractionation and rescanning did (Inoue et al., 2016).

A factor that has not been taken into account in the above mentioned studies is changing anatomy during treatment. According to Hoffmann et al. 61% of the NSCLC patients they investigated would have needed re-planning if they had been treated with IMPT (Hoffmann et al., 2017). This means that, on top of the predicted residual effect of the interplay, the dose deposition is also distorted by change in anatomy by an unquantified amount. Another factor influencing the magnitude, as demonstrated by Knopf et al., is the choice of the field geometry and the number of fields (Knopf, Hong, and Lomax, 2011). Even if a beam angle is beneficial to mitigate interplay, however, it might not be beneficial with respect to OARs.

### 2.2.5 Mitigating the interplay effect

The interplay effect occurs with all tumors that move intra fractionally, meaning it will not only influence lung, but also e.g. liver and pancreas tumors. There are multiple ways to get a supposed reduction of the effect, according to literature. The principle of mitigation is either focused on controlling the movement, controlling the beam-on time, or a combination of both. A visual depiction of some methods is shown in Figure 2.14.

**Rescanning**

The first technique is rather easy to implement, as no extra equipment is needed, and only has its disadvantage in longer treatment times. By lowering the intensity of irradiation, but irradiating the tumor multiple times during a fraction, the coverage of the tumor will be enhanced. The principle is based on the assumption amongst many researchers that the interplay effects will average out over the course of many fractions. Therefore, if the patient is treated according to the ITV principle hot- and coldspots will arise, but by ‘simulating’ more fractions in the form of rescanning, chances are that they are canceled out. One can distinguish volumetric or layered rescanning. With the first approach the target is scanned entirely, and this is repeated. With the latter an energy layer is scanned, and then rescanned a fixed number times, after which the beam continues to the next layer (Rietzel and Bert, 2010). Layered rescanning is faster than volumetric rescanning, as fewer beam energy switches have to be executed (Grassberger et al., 2015).

**Breath hold**

The principle of this method, although being rather intuitive, is to place the patient in a position in which he or she can hold his or her breath. This can either be done voluntarily, or with the help of extra equipment that allows longer breath holds. By holding breath, the tumor gets an approximately fixed position, which makes it a static target. This reduces the chances of hot- and coldspots. However, multiple
breath holds are necessary to complete the fraction and the fixed position of the tumor may vary per breath hold. Therefore there is still an uncertainty in dose delivery, but the benefit might be big enough (Dueck et al., 2016).

**Gating**

Gating basically holds the same principle as breath hold, but in this technique (controlled) free breathing is allowed. Although this sounds contradictory, in both techniques the tumor is irradiated in only one phase of the breathing motion. Additional techniques are used to determine the position of the tumor, and the beam is only switched on when the patient is in the pre-determined irradiation phase (Rietzel and Bert, 2010). This is usually end-expiration, as this appears to be the most stable phase (Song et al., 2008).

**Tracking**

The technologically most challenging technique of this list is tracking. Tracking allows a faster treatment than gating, as gating only allows a fraction of the breathing cycle to be used, thus requiring a lot of cycles. By tracking the tumor throughout treatment it can be made sure that all dose ends up in the tumor homogeneously, mitigating interplay effects. The technique requires a perfect detection of tumor motion and a fast switching time. Nevertheless, it cannot compensate for differences in anatomy during scanning (Water et al., 2009).

---

**Figure 2.14:** Different techniques to compensate for the movement of tumors, some of them being more robust to interplay than others. In rescanning the total dose is the same, but instead of delivering it in one scanning sequence, it is delivered in multiple. Practically this means the fraction is delivered multiple times, but with smaller intensity. Gating focuses on tracking the patient’s breathing, and when the breathing enters a predetermined breathing phase, the dose is delivered. It is relatively slow, as only a small part of the breathing of the patient can effectively be used. Third is tracking, which allows constant dose deposition as the tumor is tracked with breathing monitoring. It is technologically the most challenging one, yet does not guarantee perfect irradiation. Lastly is breath hold, which is quite similar to gating. The patient is only irradiated in one breathing phase, but the delivery will be faster as the patient spends more time in the particular phase. As the patient is irradiated during multiple breath holds, the position of the tumor might not always be the same.
Chapter 3

Simulation of the interplay effect

The goal of this thesis is to demonstrate a model, that can accurately predict the influence of the interplay effect on the dose delivery of IMPT in the lung. In this chapter the design of the model is explained.

3.1 Building an interplay model

To simulate the interplay effect a similar approach is taken that has been described in literature before. Examples are Kardar et al. (Kardar et al., 2014), and Dowdell et al. (Dowdell et al., 2013). There are some differences, as Kardar et al. use a synchrotron, which affects treatment times, and Dowdell et al. only analyze perfect and periodic breathing motion, which would not be the case in a real treatment scenario. The implementation of the model is depicted in a flowchart, which is shown with its components in Figure 3.1. The model is explained step by step.

3.1.1 Simulating the patients and their breathing

The basis of the simulation is formed by 4DCT sequences of the lung cancer patients described above, all having the reference breathing phase (50% exhale) contoured. The phases available always included the extremities and the in-between phases; 0%, 25%, 75%, 100% inhale and reference phase 50% exhale. For the thesis no hysteresis in breathing motion was considered, which caused the assumption that the 25% inhale is equal to the 75% exhale and so forth. The assumption is that this 4DCT sequence is representative for the patient’s motion throughout the treatment. According to Guckenberger et al. this is a valid assumption when the patient has tumors that are not located in the lower lobe (Guckenberger et al., 2007). Therefore, by describing the respiratory movement, the tumor motion is also found. For this thesis five respiratory phases are included in the simulation (0% inhale, 25% inhale, 50% exhale, 75% inhale and 100% inhale). By sequencing these phases in accordance with the chosen breathing scenario, a CT time line is constructed.

The CT time line is dependent on the type of breathing input. As an input three scenarios are implemented, a hybrid (or sampled) scenario, in which the breathing is approximated as sequences of random periods with perfect shape, sampled from a fitted Gaussian (mean of $3.8 \text{ s}$) to raw data. The other two scenarios are ideal, in which the first one has a single breathing period that is fixed throughout all fractionation schemes, the second being a combination of two fixed breathing periods. These scenarios are visualized in Figure 3.2.
Figure 3.1: Flowchart of the interplay model used in this thesis. The blue boxes represent processes to be performed, the white boxes include available or calculated data. The dotted line encloses the steps for which Erasmus MC RTStudio is used, all other processes are performed in separate MATLAB codes.
3.1. Building an interplay model

Figure 3.2: A visual representation of the different breathing scenarios used for simulation. The first scenario is the ideal scenario, with one fixed $T$ throughout treatment. In the middle is the ideal scenario with two alternating breathing periods during treatment. Lastly there is the hybrid scenario, with Gaussian distributed breathing periods. The starting point of treatment is chosen randomly, and can be anywhere on these time lines.

Depending on whether the ideal or hybrid scenario is chosen, this time line is repetitive. For this thesis the ideal motion is described as $\cos^4(\frac{\pi}{T} + \varphi)$. The power of the cosine is based on information from George et al., and the starting ideal breathing period is chosen to be $T = 4.2$ s, in accordance with Lujan et al. and Kardar et al. (George et al., 2005, Lujan et al., 1999, Kardar et al., 2014). When a fixed combination of two alternating periods was applied the chosen times were $T = 3.8$ s and $T = 4.2$ s. The 4DCTs are also used to determine the deformable image registrations (DIRs) between the reference phase and all other phases, discussed in the next section.

3.1.2 Obtaining the deformable image registrations

To find the movement of the tumor, deformable image registration (DIR) was performed on all 4DCT phases and the reference phase (which was set to 50% exhale, as mentioned before). The method for the DIR is the Grey-Scale Mean Squares method, as it gave good results on the patients and uses the functionalities of Erasmus MC RTStudio. The image registration can then provide a more natural transition. The work flow to determine the DIRs is depicted in Figure 3.3.
The choice of a type of image registration, instead of contour registration was decided based on phantom studies. Both have their advantages and disadvantages, but the main reason to go for the image registration is to keep a reliable dose distribution around the tumor. As shown in Figures 3.4a and 3.4b, the contour registration only focuses on the contours used for registration.
Outside these contours strange results may occur, especially when there is an extreme deformation.

![Image](image1.png) ![Image](image2.png)

(A) A dose distribution with four beams optimized for a phantom. (B) A dose distribution with four beams optimized for a phantom with half the dimensions as in Figure 3.4a, which is then deformed.

Figure 3.4: An example of contour registration problems. On the left a phantom is shown, with a dose distribution that is optimized for the phantom. On the right a dose plan was optimized for a phantom with half the dimensions of the left image, then a contour registration was performed from the small to the big phantom, which was used to deform the dose distribution to the bigger phantom. This deformed dose distribution is displayed on the right. The dose distribution inside the target is still uniform, but outside the target a clear blurring and smearing of the dose is visible due to the deformation. A deformable image registration would have been more suitable in this case.

Starting with the CT scans of both the reference phase and phase of interest, the first step to undertake is to assign the phase of interest with a new frame of reference. As both CT scans originate from the same 4DCT sequence, a new frame of reference is necessary to distinguish between the two. When this is assigned, the region of interest is chosen. The key here is to choose a region of interest that is big enough to follow the most important organs (lungs, OARs), but small enough to ensure good resolution. After setting the region of interest, parameters concerning the DIR routine are chosen and the DIR routine is started. These are empirically found, after trying multiple rounds with different settings. The tuned parameters included increases in grid size, number of pixels and number of iterations. In all cases, the modification of three parameters would work. The number of pixels per resolution level was set to 200 and 1000, the vector field grid size per resolution level was set to 15 and 30, and the number of optimization iterations per resolution level was set to 10.

When the routine is finished, inspection of the DIR is possible in RTStudio. The reference phase and transformed phase of interest are overlapped, which makes it possible to spot differences and inspect quality. This type of inspection is arbitrary in the sense that it requires a trained eye, but is good enough as a first inspection. This transformation is then used to propagate the contours, after which plan optimization or recomputation can be executed. The DIR is tested more elaborately after the plan optimization or recomputation is finished, and when the dose distributions on the phase of interest are available. With these dose distributions, the DVHs (Dose Volume Histograms) can be computed. As these curves have to be
the same after transformation, the distribution is transformed with the DIR to the reference phase to be checked. If the DVH curve does not deviate too significantly, the DIR and thus transformation is considered good enough. The DIR can then be used to transform all dose per spot distributions to the reference phase. An example of the DVH curve comparison is shown in Figure 3.5.

Figure 3.5: Dose volume histogram of the recomputed dose distributions on other phases than the reference phase and the DVHs after transformation from the other phases to the reference phase.

A good match indicates a reliable transformation.

The transformation is not perfect, but is considered to be reliable enough to show interplay effects. The differences can be explained by interpolation differences after dose transformation around the edges of the target structures, or by small modifications to the propagated contours due to transformation mistakes. Multiple settings were tried, but a perfect overlap was unfortunately not found. Good enough is hereby defined as 'could not be improved with more computational power'. The quality assurance of the DIR may seem like an overkill, but is very important. To investigate the deterioration in dose delivery it is crucial to have absolute certainty about the origin of the effect. By assuring that the quality of the transformation is good enough, inhomogeneities in dose distribution are certainly not caused by errors in transformation, and are therefore a direct consequence of the interplay effect.

3.1.3 Generation of treatment plans

Single robust optimization

For this thesis four planning methods are used, of which the single robust optimization is the first. In the case of the single robust optimization the 50% exhale (mid-exhalation) position was chosen, as was assumed this was the position mid-extremities. Then a robust optimization was performed on these contours, which means that multiple error scenarios are taken into account during the planning. These error scenarios are shifts of patient location in the ±x-, ±y- and ±z-direction, and an uncertainty in proton range, which results in a total of 9 scenarios (including the nominal scenario without errors). This hopefully leads to a better tumor coverage in real life, as limited shifts or uncertainty in tumor location will not deteriorate
the quality of the plan. As mentioned before, an 8 mm set-up uncertainty and a range uncertainty of 3.5% and 1 mm were used. This margin is based on the work of Van der Voort et al. (Voort et al., 2016).

<table>
<thead>
<tr>
<th>Scenario</th>
<th>$x$ [mm]</th>
<th>$y$ [mm]</th>
<th>$z$ [mm]</th>
<th>$\rho_{perc}$ [%]</th>
<th>$\rho_{abs}$ [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>-8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>-8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>-8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3.5</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-3.5</td>
<td>-1</td>
</tr>
</tbody>
</table>

**Multi CT robust optimization**

The multi-phase part of the optimization is specific for moving tumors, or lung tumors in this case. Multiple CT images were obtained from a 4DCT sequence and used. The most extreme positions are chosen (0% inhale and 100% inhale), together with the 50% exhale phase, and on these three a treatment plan is calculated with the robust multi-criteria dose optimization (this is then a 27-scenario optimization). The multi CT optimization takes into account the changing anatomy in the other phases, which could pose a major advantage over other techniques.

**ITV (robust) optimization**

For the ITV planning a slightly different approach was used. Using the functionalities of Erasmus MC RTStudio an ITV (Internal Target Volume) was constructed using the contours of the 0% inhale, 50% exhale and 100% inhale phases. As the optimization is only performed on the 50% exhale CT scan with the ITV contour, the change in surrounding anatomy when moving is not taken into account. This gives the technique ab initio a disadvantage over multi CT optimization. A plan was made with and without using robustness settings. When robustness settings were used, they were the same as in the single phase optimization.

For the dose planning Erasmus MC’s in-house developed system Erasmus MC iCycle is used. The optimization is based on multi-criteria optimization with the help of a wish list. This wish list is in this case predetermined, and contains not only the beam information, but also the constraints on OARs and dose values prescribed to the tumor region. The system strives towards satisfaction of these constraints or minimizing or maximizing towards desired values. For this thesis a wish list was used that was developed by Stoel et al. as shown in Table 3.2.

All dose plans are delivered by three beams, depending on the location of the tumor. The number of beam angles and angle choice for the planning are mostly based on Stoel’s work (Stoel, 2016). This work was performed at Erasmus MC and provides advice on how the beam angles should be chosen in order to give optimal results. The resulting plans from optimization were evaluated for target coverage, and the results can be found in the appendix.
Table 3.2: Wish list used for this thesis. This wish list was composed by Stoel (Stoel, 2016) and is used together with robustness settings. In the case an ITV was used for planning, the CTV total (which includes the CTV and nodes) was replaced with the ITV. The rings around the CTV then become rings around the ITV.

The term ‘Min./Max.’ stands for minimize or maximize value.

<table>
<thead>
<tr>
<th>Priority</th>
<th>Organ</th>
<th>Type</th>
<th>Min./Max.</th>
<th>Goal [Gy]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constraint</td>
<td>CTV total</td>
<td>Linear</td>
<td>Max.</td>
<td>0.99*66</td>
</tr>
<tr>
<td>1</td>
<td>CTV total</td>
<td>Linear</td>
<td>Min.</td>
<td>1.06*66</td>
</tr>
<tr>
<td>2</td>
<td>CTV ring 0-10 mm</td>
<td>Linear</td>
<td>Min.</td>
<td>1.06*66</td>
</tr>
<tr>
<td>3</td>
<td>CTV ring 10-15 mm</td>
<td>Linear</td>
<td>Min.</td>
<td>0.90*66</td>
</tr>
<tr>
<td>4</td>
<td>Lungs-GTV</td>
<td>Mean</td>
<td>Min.</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>Spinal Cord</td>
<td>Linear</td>
<td>Min.</td>
<td>20.0</td>
</tr>
<tr>
<td>6</td>
<td>Plexus Brachialis</td>
<td>Linear</td>
<td>Min.</td>
<td>20.0</td>
</tr>
<tr>
<td>7</td>
<td>Oesophagus</td>
<td>Mean</td>
<td>Min.</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>Trachea</td>
<td>Mean</td>
<td>Min.</td>
<td>1.0</td>
</tr>
<tr>
<td>9</td>
<td>Left Bronchial Tree</td>
<td>Mean</td>
<td>Min.</td>
<td>1.0</td>
</tr>
<tr>
<td>10</td>
<td>Right Bronchial Tree</td>
<td>Mean</td>
<td>Min.</td>
<td>1.0</td>
</tr>
<tr>
<td>11</td>
<td>CTV ring 15-25 mm</td>
<td>Linear</td>
<td>Min.</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>CTV ring 25-35 mm</td>
<td>Linear</td>
<td>Min.</td>
<td>1.0</td>
</tr>
<tr>
<td>13</td>
<td>MU</td>
<td>Linear</td>
<td>Min.</td>
<td>1.0</td>
</tr>
</tbody>
</table>

3.1.4 Processing the plan optimization output

The output of the plan optimization is used to construct the treatment time line, as step by step depicted in Figure 3.6. In this output the spot list is defined, with the composition of the beams (which spots make up the beams). This includes the spots’ energy, number of monitor units (MUs), which is a measure for the amount of energy leaving the machine, and dose deposition matrix on the phase(s) used for planning. With this information a treatment time line can be composed, with a simulated time stamp for each spot. For this, multiple parameters have to be taken into account. Depending on the number of MUs, a spot has an on-time, in which the machine is irradiating the patient. After delivering the single spot, the machine needs time to switch to the next position, which is the off-time. Both are in the order of milliseconds, but the on-time is calculated with the machine specifications and the number of MUs given by the optimization. When the machine has to switch to a different energy layer or a different beam angle there is an extra delay in the delivery of the next spot, which is called the energy switching time and the beam switching time. This is also machine specific, the energy switching time is set to the order of hundreds of milliseconds, the beam switching time is depending on the size of the rotation (but in the order of several seconds).

By analyzing the output file of the optimization this can be included in putting together the treatment time line. One final possible delay in delivery is if the patient has to be treated with a range shifter, in which case an extra component has to be inserted in the system. This can add an additional time of tens of seconds. Having all time parameters combined, the time line is constructed. This is the foundation of the interplay simulation. One element that has not been taken into account is a possible gantry switching time, in which case the treatment time is depending on the number of gantries used for irradiation. As this is highly unpredictable it is not taken into account.

By analyzing the output file of the optimization this can be included in putting together the treatment time line. One final possible delay in delivery is if the patient has to be treated with a range shifter, in which case an extra component has to be inserted in the system. This can add an additional time of tens of seconds. Having all time parameters combined, the time line is constructed. This is the foundation of the interplay simulation. One element that has not been taken into account is a
possible gantry switching time, in which case the treatment time is depending on the number of gantries used for irradiation. As this is highly unpredictable it is not taken into account.

Now the dose deposition matrices of all separate spots of the treatment are available, but only of phases used in optimization. To also get the matrices on the other
(intermediate) phases, the plan is recomputed on these phases. All dose depositions matrices are transformed to the 50% exhale reference phase (with the same transformations used to warp the contours as described above), for final dose accumulation. Therefore, if \( n \) is the number of phases used for evaluation, there will be \( n \) different scenarios for each spot of the treatment. To summarize, out of the plan a number of \( y \) spots are found, meaning a timeline with \( y \) timestamps, of which the first spot is delivered at time \( t = 0 \). These spots are recomputed on the other \( n-1 \) phases, resulting in \( y \) times \( n \) dose deposition matrices, as shown below. Each \( d_{i,y} \) represents the dose deposition matrix of spot \( y \) on phase \( i \). A combination of \( y \) dose deposition matrices forms an interplay dose.

\[
\begin{pmatrix}
    d_{0\%inhale,1} & d_{25\%inhale,1} & d_{50\%inhale,1} & d_{75\%inhale,1} & d_{100\%inhale,1} \\
    \vdots & \vdots & \vdots & \vdots & \vdots \\
    d_{0\%inhale,y} & d_{25\%inhale,y} & d_{50\%inhale,y} & d_{75\%inhale,y} & d_{100\%inhale,y} \\
\end{pmatrix}
\]

(3.1)

### 3.1.5 Calculating the interplay dose

Having all information about the movement of the tumor throughout the treatment is enough to actually start the interplay simulation. By choosing a random (virtual) starting point in time for the patient to breathe (which is a sample, different starting points and timelines therefore form different samples), the CT timeline is defined. This timeline can be compared to the treatment timeline, to find which spots are delivered in which phases. A visual representation of the process is shown in Figure 3.7.

If it is known in which point in time the spot is delivered, it can be compared to the CT timeline as shown above. First however has to be decided which phase this corresponds to, which is depicted in Figure 3.8.
3.1 Building an interplay model

By varying the starting point (and thus taking a sample), the breathing signal or breathing scenario, this dose distribution will change as spots end up in different phases than before (Table 3.3 shows a possible configuration of a spot division). Consequently, there will be a wide array of possible interplay dose distributions.

Table 3.3: After assigning \( y \) spots to the respiratory phases, it becomes clear what the spread of the spots looks like. An example of this spread is given in this table. With this information the appropriate dose matrices of the spots can be summed to compose the interplay dose. Note that each spot is only delivered to one phase.

<table>
<thead>
<tr>
<th>Spot number</th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
<th>6.</th>
<th>7.</th>
<th>...</th>
<th>y</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% inhale</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25% inhale</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% exhale</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75% inhale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% inhale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Representing this in vector form results in Equation 3.2. The final vector shows in which phase each spot is delivered, e.g. the first spot is delivered in the 0% inhale phase, and the dose deposition matrix belonging to this spot and phase. As all dose deposition matrices are already transformed to the reference phase, they can be summed to get the final dose distribution. This can be referred to as the 'interplay dose'.

\[
\begin{pmatrix}
  d_{0\%}, 1 \\
  d_{0\%}, 2 \\
  d_{25\%}, 3 \\
  d_{50\%}, 4 \\
  d_{25\%}, 5 \\
  d_{50\%}, 6 \\
  \vdots \\
  d_{0\%}, y \\
\end{pmatrix}
= \begin{pmatrix}
  0 \\
  d_{25\%} \\
  d_{50\%} \\
  0 \\
  d_{25\%} \\
  d_{50\%} \\
  \vdots \\
  d_{0\%} \\
\end{pmatrix}
+ \begin{pmatrix}
  0 \\
  d_{25\%} \\
  d_{50\%} \\
  0 \\
  d_{25\%} \\
  d_{50\%} \\
  \vdots \\
  d_{0\%} \\
\end{pmatrix}
+ \begin{pmatrix}
  0 \\
  0 \\
  0 \\
  0 \\
  0 \\
  0 \\
  \vdots \\
  0 \\
\end{pmatrix}
+ \begin{pmatrix}
  0 \\
  0 \\
  0 \\
  0 \\
  0 \\
  0 \\
  \vdots \\
  0 \\
\end{pmatrix}
= \begin{pmatrix}
  d_{0\%}, 1 \\
  d_{0\%}, 2 \\
  d_{25\%}, 3 \\
  d_{50\%}, 4 \\
  d_{25\%}, 5 \\
  d_{50\%}, 6 \\
  \vdots \\
  d_{0\%}, y \\
\end{pmatrix}
\] (3.2)
The interplay simulation is sampled many times to find these dose distributions to examine the spread in results in dose parameters. In this case the sampling is defined as calculating the interplay dose for different starting treatment times (the treatment will start in a different phase each fraction). After the interplay dose is composed of the different spots, dose parameters are calculated to quantify the interplay effect. The dose parameters to be found include the V95% (volume receiving more than 95% of the prescribed dose), the V107% (volume receiving more than 107% of the prescribed dose) and the V70% (in this thesis described as volume receiving less than 70% of the prescribed dose).

The interplay (or dynamic) dose is not a linear combination of the full dose distribution (all spots summed) on the separate phases, resulting in nontrivial results. The V95% value of the interplay dose of a selected optimization method can thus be lower than the lowest value found in the recomputation of the same optimization method on all phases, which is not intuitive.

### 3.2 Processing the output of the interplay model

The MATLAB script that facilitates the calculation of the interplay model saves its output in a structure containing all input and output information. The input information includes the optimization results as given by the plan optimization, the chosen breathing scenario, the number of samples, the dose distributions of all spots before and after transformation, the treatment time line and the CT time line. In the output information is stored which spots end up in which phase, as shown in Table 3.3, the dose parameters before fractionation and after fractionation. The results of the model are discussed in Chapter 4.

### 3.3 Application of the interplay model

With the interplay model being built, we investigate two issues. First in literature, as mentioned in Chapter 2, an interplay model is often presented with an ideal breathing motion with the argumentation that this is a worst-case scenario. This means that calculating the interplay dose with the ideal scenario gives an upper limit to the effect of the interplay effect, as in real life the patient’s irregular breathing will average out the effect, according to the papers. It is worth finding out if this is actually the case.

Second is to investigate the 4D robustness of plans made for the patients. A plan can be considered 3D robust if its coverage is sufficient in all breathing phases and error scenarios, but this does not necessarily guarantee a sufficient tumor coverage after movement. By investigating the 4D robustness the actual quality of the plan can be better determined, predicting the success of the planned treatment more accurately. This is done by examining the four plans made for each patient (single CT robust, multi CT robust, ITV and ITV robust) and performing the interplay calculation on them.
Chapter 4

Results and discussion

4.1 Patients used in study

In this study three non small cell lung cancer (NSCLC) patients were included. The patients were taken from a previous study, performed by Stoel at Erasmus MC Daniel den Hoed (Stoel, 2016). All three patients had nodal infiltrations, and two of them also had a visible tumor. The volumes and locations of the tumors are given in Table 4.1.

<table>
<thead>
<tr>
<th>Volume tumor [cm$^3$]</th>
<th>Location tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>Lung</td>
</tr>
<tr>
<td>Patient 1</td>
<td>23</td>
</tr>
<tr>
<td>Patient 2*</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient 3</td>
<td>12</td>
</tr>
</tbody>
</table>

*This patient had no visible tumor, the numbers given here and later on are for both CTV nodes.

The movement of the tumors was also measured in the aforementioned study by Stoel et al., which is shown in Table 4.2. The movement is given in millimeters for both CTV and CTV nodes.

| Peak to peak amplitude of the tumor movement of the patients used in this study. The movement is defined in millimeter and in the $x$, $y$ and $z$ direction separately. |
|-------------------------------|-------------------|-----------------|-------------------|
|                               | CTV nodes         |                  |
|                               | $x$               | $y$             | $z$               |
| Patient 1                    | 1                 | 3               | -1               |
| Patient 2                    | -2                | 5               | -2               |
| Patient 3                    | 1                 | 9               | 0                |
All patients were planned with four planning methods, as described in Chapter 3. The beam angles were chosen according to Stoel's proposal, and are listed in Table 4.3. The results of these plans are given in Appendix A and are used for further processing. Only the multi CT optimization showed good results on all breathing phases.

### Table 4.3: Treatment angles for the three patients. In this case the zero degree angle is defined as anterior, the 180 degree angle as posterior.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Beam 1</th>
<th>Beam 2</th>
<th>Beam 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0°</td>
<td>180°</td>
<td>210°</td>
</tr>
<tr>
<td>Patient 2</td>
<td>90°</td>
<td>150°</td>
<td>270°</td>
</tr>
<tr>
<td>Patient 3</td>
<td>90°</td>
<td>180°</td>
<td>210°</td>
</tr>
</tbody>
</table>

### 4.2 Tuning the model

**Choosing the number of evaluation phases**

Throughout the progress of this thesis the approach has changed several times. At first only the multi-CT optimization was applied, but without robustness settings. This made it easier to check the quality of the transformations. Furthermore, the interplay evaluation was only performed on three phases. After the interplay model proved to work, a switch was made to evaluation on five phases and inclusion of different planning methods. The necessity to evaluate on five phases instead of three becomes clear in Figure 4.1. Intuitively it is natural that an evaluation on phases not taken into account during optimization is more likely to to expose problems than only using optimized phases. How much more suboptimal becomes clear when looking at the figure. A shift in the mean of approximately 20% in the V95% for the non-robust case, and 10% for the robust case, shows that using three phases underestimate the interplay effect. Therefore, it was decided to continue with five-phase evaluation. The sections below all follow this principle.

**Choosing a CT registration method**

As mentioned in Chapter 3, an option for registering the deformation between to CT scans, is to use the contours as made by an MD. By using contour deformation a relation can be found between the CT scans. This technique was implemented and proved to only provide information about the contours used in the deformation, making it not widely applicable. Using all contours turned out to be much more computationally extensive than the most extreme settings of the DIR, and had the disadvantage of creating distorted dose distributions outside structures. Therefore, it was decided to choose the DIR instead.

**Choosing a breathing scenario**

In this part the impact of the choice of the breathing scenario on the outcome of the interplay dose is discussed. As mentioned in Chapter 3 this is done with a hybrid scenario (named ‘sampled’ in the figures), an ideal scenario with one fixed breathing period (named ‘ideal’) and two fixed breathing periods (named ‘fixed’). The single fraction treatments were sampled 2500 times per scenario for patient 1, and for each sample the V95% and V107% of the CTV and CTV nodes were calculated. Sampling is performed by varying the breathing pattern during treatment, meaning that the patient will start in a random breathing phase in a random breathing period (except when only one period is used). The start of treatment can simulated to be begin- and end-phase, or anywhere in between.
4.2. Tuning the model

Figure 4.1: Spread in V95% an V107% in CTV of patient 1 as a function of two different planning methods and number of evaluation phases. The red dashed line is the value found in the optimization on the reference phase (static case). Planning was done in both cases with the multi CT method (on 0% inhale, 50% exhale and 100% inhale), both non-robustly and robustly, and then evaluated for interplay. For the five-phase evaluation the plan was beforehand recalculated on the in between phases, 25% inhale and 75% inhale. The V95% and V107% values are calculated for each simulated single fraction treatment, 100 times per planning method and evaluation phases. Evaluation on five phases is more realistic, as phases are included that were not planned on, and shows major increase in the spread of the V95%. For the V107% there appears to be a smaller difference. Evaluating on three phases appears to give an underestimation of the interplay effect.

The main goal of the use of three different breathing scenarios was to determine what kind of influence this would have on the resulting interplay dose. Furthermore, literature has stated that using an ideal breathing scenario would give the worst case scenario results of an interplay simulation. Figure 4.2 shows the V95% of using the three different breathing scenarios. What stands out in general is the big spread in V95% values for all breathing scenarios, which goes up to 35%. When looking at the scenarios separately, it becomes clear that the sampled case has more extreme outliers, however the lower whisker of the ideal case stretches further down than the sample case. A possible explanation for this phenomenon is that in the ideal case averaging out is less likely, and the creation of a very unfavorable scenario (very low V95% and/or very high V107%) due to changes in breathing motion is not possible. Therefore, in the sampled case, averaging out takes place due to breathing motion, but also the creation of negative outliers, as visible in the graph. Finally, the fixed case is expected to be somewhere between the ideal and sampled case, due to the nature of the scenario. It is unfortunately impossible to draw this conclusion from the results.
Chapter 4. Results and discussion

Figure 4.2: Spread in V95% in CTV and CTV nodes of patient 1 as a function of three different breathing scenarios. The red dashed line is the value found in the optimization on the reference phase (static case). The V95% value is calculated for each simulated single fraction treatment, 2500 times per breathing scenario.

Figure 4.3 depicts the V107% of the same dataset. The results verify the conclusions drawn as for Figure 4.2. The main conclusion that can be drawn from this section is that the averaging effect of a hybrid breathing pattern is visible, yet the worst case scenarios are also found in this dataset. For further research the sampling scenario was chosen, not only for being more realistic, but also to include the most extreme cases.
4.3 Comparison of planning methods

When comparing the 4D robustness of the planning methods, all three patients were used in the evaluation. The patients were planned with the four methods described before: single robust, multi CT robust, ITV and ITV-robust, and then evaluated for interplay with a hybrid breathing scenario (‘sampled’). Per patient per planning method 2500 single fraction treatments were simulated, and then evaluated on V95% and V107% for the target. The sampling is performed by randomizing the CT time line for each fraction and randomizing the starting breathing phase. Starting begin-, mid- and end-phase were also a possibility. The results are shown in Figures 4.4 and 4.5. The figures are added in bigger size in Appendix B.

The expectation was that the multi CT robust optimization and ITV robust optimization would perform best considering the V95%, simply because a larger area is irradiated. This is clearly visible in the figure, as a higher V95 indicates a better tumor coverage. Investigating Table 4.2, there appears to be no strong dependence on amplitude of movement for the median and spread of the V95%. The multi CT robust optimization appears to perform best. This can be explained by the more elaborate planning procedure, as the multi CT optimization takes into account changes in anatomy in contrast with ITV based planning.
Figure 4.4: Comparing the 4D robustness of 4 different planning methods for three patients in the V95%. Each subplot contains 2500 samples per planning method of a simulated single fraction treatment, with a completely randomized hybrid breathing pattern each sample. The dashed line is the value found in the optimization on the static case of the reference phase. It is clear that the robust multi CT performs best for all patients, but is still heavily affected by interplay.

Figure 4.5: Comparing the 4D robustness of 4 different planning methods for three patients in the V107%. The same settings are used as discussed in Figure 4.4. The values are quite high compared to the value found in the optimization, but results are not consistent enough to draw a definitive conclusion.
The V107% values are less intuitively explained. An overdosage is understandable as parts can receive more spots than planned, but this should be correlated to a non-zero V70% (volume of the target receiving less than 70% of the prescribed dose) as well. This is due to the fact that local areas get more spots than planned (overdosage), with as a result that other local areas do not get enough spots (underdosage). The expectation is also that the V95% and V107% values will get more acceptable values after fractionation, and this shall be discussed in the next section together with the impact on the V70%.

### 4.4 Impact of fractionation

The results shown in the previous section lead to some preliminary conclusions, but are not realistic in the sense that single fraction treatments are not clinically relevant. As they will not actually be applied to patients, it is worth asking the question what is really happening to a patient. In a fractionated treatment the interplay effect should average out to a certain extent (according to literature), and to which extent shall be investigated in this section. For this calculation treatments are simulated for three fractionation schemes (1, 5 or 25 fractions) and for four different optimization methods. After the simulation the V70%, V95% and V107% are calculated for the CTV and CTV nodes. For the single fraction treatment results from Figures 4.4 and 4.5 were used, the other fractionation schemes and V70% values were simulated separately 250 times per optimization method per fractionation scheme. The results are depicted in Figures 4.6 and 4.7.

Figure 4.6: V95% after fractionation for Patient 1. For these results 250 samples were taken for each optimization method and fractionation scheme. The values converge for all optimization methods, with different outcomes. All methods benefit from fractionation, as the spread in values decreases significantly. However, only robust multi CT optimization reaches the value found in the static result of the optimization.
Chapter 4. Results and discussion

Figure 4.7: V107% after fractionation for Patient 1. The same sampling conditions were used as for Figure 4.6. The values for the V107% decreased towards the value found in the static result of the optimization as more fractions were applied, except for ITV planning. Remarkably enough, in the case of robust multi CT planning, the V107% value can drop below the optimized static value.

The effect of fractionation is clearly visible, as all planning modalities decrease their spread in the V95% and V107%, and their medians end up with better values in terms of tumor coverage. One important observation is nevertheless that even with 25 fractions the single robust optimization and ITV optimization find unacceptable values for tumor coverage. Robust multi CT optimization is the only planning modality that can be considered 4D robust after fractionation, and is therefore the most interesting for treatment planning. The explanation for the 4D robustness is most likely that the method shows the best 3D robustness to begin with (as can be seen in Appendix A), as it is the only planning method that has full coverage on all breathing phases without considering interplay. This guarantees a better starting point than the other planning methods. When one assumes that in the robust multi CT case the only concern is then local over- and underdosage, fractionation proves to give great benefit by averaging out the hot and cold spots.

In Figure 4.8 the V70% is displayed, as it gives a good view on underdosage of the tumor. It seems that only single fraction treatments show high values in V70%, and fractionation gets rid of the underdosage. This observation in combination with the relatively high values of the V107% in the single fraction treatments, creates the presumption of some kind of ‘ripple effect’. By depositing a large amount of dose in one part of the tumor, another part of the tumor is underdosed. By applying multiple fractions these ‘ripples’ start averaging out.
4.4. Impact of fractionation

Figure 4.8: V70% after fractionation for Patient 1, again from the same dataset of Figures 4.6 and 4.7. It is found that the values of the V70% are small, even in single fraction simulations. After this, they decrease even more rapidly, being practically zero for all optimization methods and both CTV and CTV nodes after 25 fractions. The non-zero values of the single fraction treatment nevertheless strengthen the hypothesis of the interplay effect as a 'ripple effect' in the dose delivery.

This ripple effect can be visualized with the dose distributions as found on the CT scan, which is depicted in Figures 4.9a and 4.9b.

Figure 4.9: Optimized dose distribution from the robust multi CT optimization for patient 1, and the interplay dose distribution as found in the samples with the highest V107% value for a single fraction treatment. In both pictures the same patient with the same contour is displayed. The outer shape of the dose distribution does not change a lot due to interplay, but the inhomogeneity of the distribution due to interplay is clearly visible.
Chapter 4. Results and discussion

The figure displays the result of the robust multi CT optimization on patient 1. It is clear that good coverage is reached for the entire tumor in the static case, as shown in Figure 4.9a. A non-uniform margin is visible, resulting from the multi CT optimization, to compensate for good coverage in the other respiratory phases. In Figure 4.9b the interplay dose distribution belonging to the most extreme case of the V107% found in single fraction samples is displayed. The outer shape of the dose distribution is not precisely as the optimized dose distribution, but the shape can still be recognized easily. The strong inhomogeneity is more striking though, as clear hot and cold spots have arisen. The 'ripples' in the dose distribution are visible. The dose has been delivered to the tumor, but distributed in a way that there is serious underdosage in some parts and considerable overdosage in others.

When considering the effect of fractionation, it seems that even with dramatic inhomogeneities in dose delivery to the tumor in single fraction, robust multi CT optimization performs sufficiently well if enough fractions are applied. The good performance is not only found for this patient. In Figures 4.10, 4.11 and 4.12 the results are shown of fractionation being applied to all patients of this study, after being planned with the robust multi CT optimization. The figures can again be found full size in Appendix B. The sample size was again 250, with a hybrid breathing scenario. All show good coverage after 25 fractions, with a reduced V107% and approximate zero of the V70%.

![Figure 4.10: Impact of fractionation on the spread of the V95% for all patients. The planning method is robust multi CT optimization. All V95% values converge towards the optimization value as more fractions are applied.](image-url)
4.4. Impact of fractionation

Figure 4.11: Impact of fractionation on the spread of the V107% for all patients under the same conditions as Figure 4.10. The same conclusions can be drawn as for that figure. Remarkably enough, after 25 fractions values can be achieved lower than the optimized value.

Figure 4.12: Impact of fractionation on the spread of the V70% for all patients under the same conditions as Figures 4.10 and 4.11. The values are only non-zero in case of single fraction treatments, showing clear evidence that fractionation causes averaging out of these cold spots.
To conclude, interplay can severely deteriorate dose delivery, resulting in decreased V95% of up to 40% for a single fraction treatment of a robust multi CT plan. The magnitude of the effect cannot be directly correlated to size of the movement, as the largest movements do not match the biggest spread of V95% or the lowest median of the V95%. It might however be interesting to vary beam angle choice, to see to what extent this influences the dose delivery. Furthermore, it seems that for all optimization methods require additional interplay mitigation techniques as described in Chapter 2 when hypofractionation is desired. As only robust multi CT optimization appears to be capable to reach the optimization value after 25 fractions, it is advisable to investigate whether the use of the interplay mitigation techniques can benefit the other techniques to compete with the robust multi CT optimization.

4.5 Comparison results to literature

When comparing the results to literature, some interesting conclusions can be drawn. Kraus et al. performed a realistic simulation of the respiratory motion of lung tumors in IMPT. The planning strategy used was ITV planning. Multiple breathing variabilities were introduced, such as baseline shift, starting phase and breathing period. The evaluation was done on ten CT scans of the 4DCT sequences of three patients. Although it is difficult to compare the spread in results with the sampling and evaluation methods used by the group, they find that fractionation (30 fractions) greatly enhances tumor coverage (Kraus, Heath, and Oelfke, 2011). The planned value however was not found, but this is also the case with the ITV planning as used in this thesis. In the case of single fraction delivery the dose inhomogeneities showed comparable patterns to the ones found in this thesis.

Bert et al. performed an interplay evaluation on five ITV-planned patients, with 108 samples each (varying treatment period and starting time). The treatment was not IMPT, but carbon-ion scanning, and is therefore not entirely representative. For the five patients the found an average V95% of 71.0% ± 14.2% for a single fraction treatment, although the number of evaluation phases is not given (Bert, Grözinger, and Rietzel, 2008). The result is highly comparable to the patients and evaluation used in this study, but the comparison should be done cautiously as different irradiation techniques were used.

Grassberger et al. varied spot size, and investigated the dependency of interplay effects on motion amplitude (Grassberger et al., 2013). The spot size could not be varied in this thesis, but the motion amplitude correlation could not be found. The number of patients used in this study is not big enough to motivate the correlation either. More investigation on this part will have to be done, including more patients in the study.

Finally, Inoue et al. planned 10 patients on an ITV with a minimax robust multifield optimization technique, and evaluated for interplay on 8 phases with ideal breathing motion. The robustness settings were 5 and 7 mm. The breathing period was equal to $T = 4.5$ s. The interplay did not deteriorate the patients’ V95% to clinically unacceptable values. The reason for these different results is not clear. The movement of patients used in the study is equal or larger than the patients used for this thesis, such that at least comparable interplay effects are expected. The description of their interplay model is however quite short, such that differences with the model of this thesis are not easily found. Inoue et al. did find a big benefit for rescanning and fractionation, which is also one of the conclusions of this thesis.
The interplay model built in this study has shown the capability to predict 4D robustness of treatment plans. As the magnitude of the interplay effect cannot be directly correlated to tumor movement in this study, the model is a useful tool to predict the magnitude of the interplay effect. There are naturally more recommendations on how the model can be improved and fully exploited, which are discussed in the next chapter.
Chapter 5

Future research and recommendations

5.1 Improvement of the interplay model

In this section improvements for this thesis are discussed. These are mostly interesting when more use of this model is desired, but were not implemented before due to time constraints or lack of data.

5.1.1 Reduction of computation time

The major point of attention for the interplay model is the time it takes to gather samples. These samples, depending on the number of spots in one treatment, can take up to a few minutes. Since most of this time is spent in adding full dose matrices (one for each spot), it makes sense to invest in improving this part of the computation.

One of the methods to speed up this addition is to introduce a dose mask. A dose deposition matrix has the resolution of the CT scan it is matched to, and can therefore contain millions of voxels. Having a matrix this size for each spot, for each breathing phase, is therefore a memory intensive process. However, a big part of all these matrices will equal zero, as only the tumor and the trajectory before the tumor will be irradiated. By beforehand selecting the extremities of the CT scan where dose will be deposited (with the help of the available dose plans and recalculations on other phases), only a small part of the dose deposition matrix has to be selected and saved, which will form the dose mask. If this matrix is one third the size of the original matrix, the computation time goes down with a factor of three as well. A final, yet more trivial, suggestion to speed up computation time is to execute the samples in a computationally parallel way. However, the exact implementation is not clear yet.

5.1.2 Optimization of DIRs

A relatively weak point in building the interplay model is the need for qualitatively good deformable image registrations (DIRs). Some CT scans from the 4DCT sequences had artifacts due to problems in production of the 4DCT (merging issues), creating suboptimal registrations. Since this problem is unfortunately in the nature of the production of 4DCTs, it might be worth to look into 'combined' methods. By using a combination of the contours in the breathing phases and the CT scans themselves, a more reliable registration can be found. One of the advantages for this type of registration is that registrations are more accurate specifically for the
tumor and OARs. Dose that was accumulated in a CTV or an OAR voxel before transformation will also be contained in the same organ after transformation. This is particularly interesting as edges of the tumor, with the help of contour based registration, will no longer receive under dosage due to a rough transformation grid, yet outside the tumors and OARs transformations will remain accurate due the image based registration. By improving the quality of the registration it results become more reliable to be affected by interplay or transformation quality, and future calculations require less fine-tuning.

5.1.3 Inclusion of a realistic breathing scenario

Another point of improvement is the lack of use of a direct breathing signal. While this is the most reliable source of movement of the patient, it could unfortunately not be used for this thesis, making it lose some of its value. By using the signal directly, the model becomes more realistic, especially when data is available with which the patient’s breathing signal is actually directly connected to the patient’s 4DCT sequence. Hopefully it then becomes clear if this scenario is really patient dependent, and if the hybrid or ideal scenario prove to be worthy replacements. When using this methodology in combination with the better registrations, scenarios can be simulated in which the patient surpasses the most extreme positions found in the 4DCTs. Breathing motion is not constant during treatment, and assuming a patient always breathes a full and perfect cycle is therefore not always realistic. Deeper inhalation or exhalation can be located with the use of the breathing signal, and can be processed by creating a ‘virtual’ CT to investigate the dosimetric impact.

5.1.4 Inclusion of hysteresis

As shown by Seppenwoolde, hysteresis in tumor motion can be significant (Seppenwoolde et al., 2003). In this thesis hysteresis is not included, but significant hysteresis in patients will most definitely worsen tumor coverage. It is assumed that the 50% exhale of the patient is the intermediate position of the motion, but with hysteresis this might actually not be the case. Modification of the code and evaluation on this extra phase will give more clarity for patients that show problematic hysteresis. Optimizing on this extra 50% inhale phase might be then more 3D and 4D robust, as can be evaluated with the interplay model.

5.1.5 Inclusion of random and setup errors

While planning the patients, some of the planning methods included robust planning. The purpose of this planning method is to ensure good tumor coverage even when the patient or tumor is slightly shifted. In the interplay model made for this thesis it is assumed that the patient is always positioned in the nominal, error-free scenario. Naturally, this is not the case. It might be interesting to see if there is a difference in spread in V95, V107 etc. if random errors are introduced. Perhaps the convergence that is seen for multi CT robust planning will no longer hold, or will be beneficial for the other planning techniques, making them feasible alternatives.

5.1.6 Evaluation on more phases

In Chapter 4 it became clear that evaluation on five respiratory phases shows clearly different results from evaluation on three phases. One might wonder if switching
from five phases to even more phases shows different results for the magnitude of
the interplay effect. Due to limited resources of the 4DCTs and time constraints
this has not been done, but might also be worth investigating. The approaches in
literature differ: Kraus et al. and Li et al. use ten respiratory phases for evaluation
(Kraus, Heath, and Oelfke, 2011, Li et al., 2014), but Grassberger et al use four
(Grassberger et al., 2015). As more phases intuitively should display a more reliable
result (the discrete steps in time become smaller), the impact on the ultimate re-
sults will get smaller. More respiratory phases result in more dose recomputations
and are therefore more memory intensive. For the interplay model created in this
thesis a limited number of phases should therefore be used, but how many has yet
to be investigated.

5.1.7 PCE analysis

The robust optimization method as applied in this thesis uses a set-up error of 8 mm
for optimization, based on the work by Stoel (Stoel, 2016), but set-up and random
errors have not been introduced in the simulation of the treatments. Based on the
results of the application of fractionation schemes, it appeared that 25 fractions are
sufficient to mitigate the interplay effect sufficiently without these errors. Smarter
robustness settings might however be desirable, either inhomogeneous (not a fixed
distance around the tumor) or simply homogeneously bigger or smaller, when the
actual treatment of the patient is considered with errors. Therefore, if the interplay
model is modified to take into account treatment uncertainties, a PCE (polynomial
chaos expansion) model can be built, as done by Van der Voort (Voort et al., 2016).
Hopefully, with this work, better margins can be created for moving tumors in
general to achieve better tumor control while sparing healthy tissue.

5.2 Interplay robust optimization

This section is more focused on research that is not directly linked to the interplay
model, but contains recommendations for research indirectly linked to 4D robust-
ness. To start, a proposal is described for a 4D optimization technique to compen-
sate for interplay effects. Contemporary techniques are capable of compensating for
movement, but lack tools to prevent hot and or cold spots and high dose delivery
in surrounding tissue and OARs. The technique described below has a better ca-

pability to prevent both situations and is therefore an interesting tool when one is
interested in applying hypo fractionation and/or making treatment plans for tumors
with serious intra-fractional movement.

5.2.1 iCycle optimization

Erasmus MC iCycle uses a multi-criteria plan optimization, and for a full explana-
tion it is advisable to read the work by Breedveld et al. (Breedveld et al., 2012).
On of the elements playing a role in the optimization is Equation 5.1, which will
be focused on now. In this equation three elements can be distinguished. $A$, which
is the dose deposition matrix, basically holding all information about the voxels of
the CT scans and their connection to the spots. Then $w$, which is the spot weight
vector and the element to be optimized. Then finally, there is the deposited dose
vector $d$, which describes the total dose that ends up in the voxels called in $A$ (thus
the voxels taken into account in the optimization).

$$Aw = d$$

(5.1)
In a matrix form this looks like Equation 5.2.

\[
\begin{pmatrix}
v_{\text{voxel},1} & \cdots & v_{\text{voxel},1} \\
\vdots & \ddots & \vdots \\
v_{\text{voxel},m} & \cdots & v_{\text{voxel},m}
\end{pmatrix}
\begin{pmatrix}
w_{\text{opt},1} \\
\vdots \\
w_{\text{opt},n}
\end{pmatrix}
= 
\begin{pmatrix}
d_{v_{\text{voxel},1}} \\
\vdots \\
d_{v_{\text{voxel},m}}
\end{pmatrix}
\]

(5.2)

When one wants to optimize robustly, thus include setup and range errors in the form of ±\(\delta x\), ±\(\delta y\), ±\(\delta z\) and ±\(\delta p\), nine equations in the shape of Equation 5.2 are optimized simultaneously.

In the multi CT optimization, as used in this thesis, a slightly different scenario is used. When \(n\) CT scans are used as input with \(m_n\) voxels used for optimization, dose deposition matrix is expanded for the other CT scans as well. This gives the following result:

\[
\begin{pmatrix}
v_{\text{voxel},CT_1,1} & \cdots & v_{\text{voxel},CT_1,1} \\
\vdots & \ddots & \vdots \\
v_{\text{voxel},CT_1,m_1} & \cdots & v_{\text{voxel},CT_1,m_1} \\
v_{\text{voxel},CT_n,1} & \cdots & v_{\text{voxel},CT_n,1} \\
\vdots & \ddots & \vdots \\
v_{\text{voxel},CT_n,m_n} & \cdots & v_{\text{voxel},CT_n,m_n}
\end{pmatrix}
\begin{pmatrix}
w_{\text{opt},1} \\
\vdots \\
w_{\text{opt},p}
\end{pmatrix}
= 
\begin{pmatrix}
d_{v_{\text{voxel},1}} \\
\vdots \\
d_{v_{\text{voxel},m_1+\ldots+m_n}}
\end{pmatrix}
\]

(5.3)

Again, in the case of robust optimization, nine of these equations are optimized simultaneously. One can expect that the computational time will increase when more CT scans are used for optimization.

Plans made with iCycle are Pareto-optimal, which means that the solution found (provided the optimization was executed successfully) is on the Pareto surface. A Pareto-optimal plan is described by Paganetti as: "Given a set of objectives and constraints, a plan is considered Pareto-optimal if it is feasible and if there does not exist another feasible plan that is strictly better with respect to one or more objectives and that is at least as good for the rest" (Paganetti, 2012). A Pareto-optimal plan is not a single solution, but part of a series of solutions: the Pareto surface. An example is given in Figure 5.1.
5.2. Interplay robust optimization

Figure 5.1: Visual example of a Pareto surface for three organs at risk (OARs). The Pareto surface is a collection of treatment plans that can be considered optimal solutions of an optimization. Improving the dose delivery in one OAR, while navigating on the Pareto surface and maintaining an optimal solution, results in a higher dose in a different OAR. Moving towards dose values lower than the Pareto surface is a possibility, but this has the consequence that constraints are not met and thus the plan is not clinically applicable.

5.2.2 Implementation in iCycle

As discussed before, movement of tumors can be accounted for by using margins for the movement or multiple CT scans for the change in anatomy, but not yet for the appearance of hot- and coldspots. Starting with Equation 5.3, a dose distribution for two phases resulting from this multi CT optimization would then look like Figure 5.2. A plan is made that satisfies both anatomies.

Figure 5.2: Multi CT optimization on two phases. Two phases are used in the optimization, guaranteeing good coverage when the tumor is in the upper and lower position. This is however a binary scenario, the tumor has to be in either one for the entire treatment. A combination of the two is not taken into account. The plan is 3D robust and covers therefore both positions, but not necessarily possible in-between positions and combinations of those.
When calculating the interplay dose, as described in Chapter 3, the spots of the treatment are assigned to a certain breathing phase. Then, for dose accumulation, the spots are also transformed to their reference phase, meaning that the voxels between phases are linked. Both principles are applied in the 4D optimization. Assigning spots to a breathing phase means they will not contribute to other breathing phases, resulting in a sparse dose deposition matrix. The key point of this new idea of optimization is that a switch is made from a binary scenario (tumor is either in one phase or the other) to a non-binary scenario, in which the tumor spends time in both phases. Spots are no longer projected on both phases, but will be projected only on one of the phases used for optimization.

In Equation 5.4 an example is shown in the case that 2 CT scans with 3 voxels are used for optimization. After the interplay simulation the spots are assigned, and in this case the spots alternately end up in the first and second CT scan. When looking at the scans separately, none of the dose objectives are met, as only approximately half of the dose is present on both scans.

\[
\begin{pmatrix}
v_{CT1,1} & 0 & v_{CT1,1} & 0 & v_{CT1,1} \\
v_{CT1,2} & 0 & v_{CT1,2} & 0 & v_{CT1,2} \\
v_{CT1,3} & 0 & v_{CT1,3} & 0 & v_{CT1,3} \\
0 & v_{CT2,1} & 0 & v_{CT2,1} & 0 \\
0 & v_{CT2,2} & 0 & v_{CT2,2} & 0 \\
0 & v_{CT2,3} & 0 & v_{CT2,3} & 0
\end{pmatrix}
\begin{pmatrix}
w_{opt,1} \\
\vdots \\
w_{opt,5}
\end{pmatrix}
= 
\begin{pmatrix}
d_1 \\
\vdots \\
d_6
\end{pmatrix}
\] (5.4)

Now the relation between the voxels can be used, since the CT scans depict the same tumor. This information is obtained with the help of deformable image registration (DIR) and creates a link between separate voxels. Using this information there can be a reduction of the dose deposition matrix of Equation 5.4, resulting in a simpler and more familiar matrix as shown in Equation 5.5. This transformed and merged matrix shows the ultimate dose on the tumor, the one that can fulfill the dose objectives.

\[
\begin{pmatrix}
v_{CTnew,1} & \cdots & v_{CTnew,1} \\
\vdots & \ddots & \vdots \\
v_{CTnew,mnew} & \cdots & v_{CTnew,mnew}
\end{pmatrix}
\begin{pmatrix}
w_{opt,1} \\
\vdots \\
w_{opt,p}
\end{pmatrix}
= 
\begin{pmatrix}
d_1 \\
\vdots \\
d_{mnew}
\end{pmatrix}
\] (5.5)

Without this reduction optimization is not possible. In the 'traditional' multi CT optimization both CT scans are treated as binary scenarios. The patient is assumed to be in either of the phases during a fraction of the treatment, and not in both. In normal practice, however, the patient switches between phases, and therefore has a combined dose depending on which spots are delivered in which phases. All phases contribute to the total accumulated dose, which is depicted in Figure 5.3. The sparse matrix in Equation 5.4 depicts this combination mathematically: the tumor no longer has good coverage in all phases separately. This makes sense, because treatment will be a combination and accumulation of all those phases, in contrast with the previous method. Therefore the phases have to be linked, in order to have the capability to optimize. Repetition of this simulation results in different distributions of spots, and therefore different scenarios that can be interpreted as robustness scenarios and optimized.
5.2. Interplay robust optimization

Figure 5.3: Visual explanation why DIR information is necessary for optimization. Delivering the plan of Figure 5.2 could result in two very extreme cases. In the top of the image, the lower part of the plan is deposited while the tumor is in the lower position, giving full coverage. The upper half is deposited while the tumor is in the upper position. The tumor receives good coverage, but is at risk of receiving a high V107%. The bottom of the picture shows the other possibility; the tumor is in the opposite position of where the dose is delivered. The tumor does not get full coverage and an unsuccessful treatment is given. The same plan, which was considered 3D robust, is not 4D robust.

The expected result of this technique is that static dose distributions per phase no longer give sufficient coverage and/or an inhomogeneous dose delivery. However, most of the 4D dose distributions (or interplay dose distributions) should give sufficient coverage and acceptable inhomogeneity levels in comparison with regular planning.
Appendix A

Coverage plans
### Appendix A. Coverage plans

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Appendix A. Coverage plans
Appendix B

Results
Figure B.1
Figure B.2
Figure B.3
Figure B.4
Figure B.5
Appendix B. Results

Figure B.6
Figure B.7
Figure B.8
Bibliography

Bert, Christoph, Sven O Grözinger, and Eike Rietzel (2008). “Quantification of interplay effects of scanned particle beams and moving targets”. In: *Physics in medicine and biology* 53.9, p. 2253.


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