\chapter{Treatment planning study for irradiation of pulmonary veins under influence of heartbeat motion in human data}

\minitoc

% \section{Introduction}

The PVs move on one hand due to the heartbeat and on the other hand due to respiration of the patient.

Both motion types are independent from each other and can hence be studied individually. While the influence of respiration is analyzed in

chapter XXX, the effect of heartbeat motion will be discussed in this chapter.

CTs gated to the complete cardiac cycle in end-expiration of five AF patients were acquired at Mayo Clinic (Minnesota, USA).

Motion influences on accuracy and homogeneity of the dose delivery in the PVs were studied.

The resulting interplay pattern for all patients as well as

rescanning as possible motion mitigation technique have been studied and the results will be presented in this chapter.

\section{Material and methods}

Details on the used input data as well as the used treatment planning parameters will be given. Afterwards an overview over all

studies will be given. Finally, the analysis proceeding will be described.

\subsection{Treatment planning input data}

For treatment planning studies with the in-house treatment planning software TRiP4D \cite{Ric13}, 4DCT data sets, target and OAR contours as

well as a deformable image registration for motion assessment in-between the different motion phases are needed.

\subsubsection{4DCT}

In order to assess the motion of the PV under influence of heartbeat motion ECG gated 4DCTs in end exhale (breath hold) were studied.

Five AF patient data sets (four male patients and one female) were recorded and anonymized at Mayo Clinic (Minnesota, USA).

The CT scans were acquired on a Sensation 64 CT scanner (Siemens). The 4DCT data set each consisted of twenty cardiac motion phases, the

reference phase was motion phase zero. In order to distinguish structures within the heart the CT scans were contrast enhanced.

The radiopaque material was administered intravenously (150cc Omnipaque 350 at 4cc/sec).

\subsubsection{Segmentation}

Segmentation of the target volumes as well as the OAR were carried out by a collaborating cardiologist at Mayo Clinic with Eclipse\texttrademark

(Varian Medical Systems). The volumes of the contours for the ablation sited for LPV and RPV are presented for each patient

in table \ref{tab:volume:mayo}.

\begin{table}[htbp]

\centering

\caption{Target volume for LPV and RPV for all investigated patients.}

\begin{tabular}{|c|c|c|}

\hline\hline

patient no\rule{0pt}{2.6ex}\rule[-1.2ex]{0pt}{0pt} & LPV [cm$^{3}$] & RPV [cm$^{3}$]\\

\hline

1 & 2.03 & 2.39 \\

2 & 2.62 & 5.16 \\

3 & 1.45 & 4.16 \\

4 & 1.66 & 2.07 \\

5 & 2.06 & 1.90 \\

\hline\hline

\end{tabular}

\label{tab:volume:mayo}

\end{table}

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\subsubsection{Image registration}

Non-rigid image registration have been performed with Plastimatch \cite{Sharp07} \cite{Shack10}.

The quality of registration was validated with visualization techniques: false color images \cite{Bro07}, checker board images

\cite{Bro07} as well as a qualitative check of the vector field regularization. These tests were carried out between motion phase 3

(which is the motion phase of the maximal displacement of the ventricle) and the reference phase (motion phase zero) or motion

phase 18 (the motion phase of the maximal displacement of the atria) and the reference phase.

\subsection{Treatment planning parameters}

Treatment plans without motion (3D, static) as well as with motion (4D) were generated.

For the dose optimization process, 3D treatment plans were generated to homogenously cover the CTVs, 4D treatment plans covered the ITV. Both

CTV and ITV were studied with additional safety margins (see section \grqq Margin\grqq). The grid spacing was chosen to 1 $\mathrm{mm}$ in $x$

and $y$ direction, respectively. The spacing between the IESs were chosen to 3 mm$\_{H2O}$. A maximal contour extension of 1.1 times the focal

spot size of 4mm was chosen as well as a distal contour fall off of 4 mm$\_{H2O}$. TRiP's 'all points divergent beam' algorithm was used to

calculate the absorbed dose. Intensity modulated particle therapy (IMPT) including the esophagus as critical structure have been used in part

of the study. Thereby a maximum dose fraction of 70\% was chosen and the weightfactor for the structure was set to 75\%. All other

treatment plans were generated as single field uniform dose (SFUD). In all simulations a physical dose of 25 Gy was applied in one fraction.\newline

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The generation of treatment plans is furthermore also dependent on the theoretically possible

beam application. Spill lenght, shape and particle density are thus important factors. For the here presented simulations GSI accelerator

parameters have been used. Thereby a spill length of 2.2s is assumed. The pause inbetween spills is either 2.2s, when no energy change is

required afterwards, or 3.2s when a energy change is needed. The spill shape is approximated by a Gaussian function. The particle intensities

feasible at GSI vary between 2x10$^{6}$ particles per spill and 2x10$^{8}$ particles per spill. Inbetween these two extreme intensity levels,

fifteen different intensity levels can be used. In the resulting treatment plan, the intensity steps are automatically chosen.

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\subsubsection{Field number and beam directions}

The field number and directions were systematically investigated and are listed in table \ref{tab:fields}. Four different field numbers

(one to four) were studied. While for one field the gantry angle was kept constant to 0$^{\circ}$ and only the couch angle was

changed, for higher field numbers different gantry angles were used. These angles are illustrated in figure \ref{gantrydirection}.

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\begin{table}[H]

\centering

\small

\caption{Studied field number and beam channel directions}

\begin{tabular}{|c|c|c|}

\hline\hline

Field number & Couch angle [$^{\circ}$] & Gantry angle [$^{\circ}$]\\

\hline

1 field & -90 & 0 \\

& -45 & 0 \\

& -135 & 0 \\

\hline

2 fields & 90 & -60/120 \\

& 90 & -60/135 \\

& 90 & -60/0 \\

& 90 & -45/135 \\

& 90 & -45/150 \\

& 90 & -45/0 \\

\hline

3 fields & 90 & -60/120/150 \\

& 90 & -60/120/0 \\

& 90 & -45/135/150 \\

& 90 & -45/135/0 \\

\hline

4 fields & 90 & -60/120/-45/135 \\

& 90 & -60/120/0/180 \\

& 90 & -45/135/0/180 \\

& 90 & -160/90/-60/145 \\

\hline\hline

\end{tabular}

\label{tab:fields}

\end{table}

\vspace\*{-0.6cm}

\begin{figure}[H]

\begin{center}

\includegraphics[scale=0.4]{GantryDirection.png}

\caption{Entry channels for different gantry directions for a couch angle of 90$^{\circ}$.}

\label{gantrydirection}

\end{center}

\end{figure}

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\subsubsection{Motion trajectories}

As the reconstruction of the 4DCTs was based on the time scale a phase-based motion state detection was employed. A sinus motion was

chosen for the motion trajectories. In order to consider possible divergence in the heartbeat motion pattern of patients,

different periods (1 s and 0.7 s) as well as different starting phases (0$^{\circ}$ and 90$^{\circ}$) were used.

\subsubsection{Margins}

Besides the original volume of the CTV safety margins have been added to the volumes of the treatment planning study. These margins were applied

in order to account for theoretically possible deviations in between treatment planning and delivery, like slight positioning errors, changes

between CT acquisition and treatment delivery etc. Isotropic safety margins of 3mm, 5mm and 7mm have been chosen. The ITV volumes used as the

final target were generated from the original CTV contour as well as the CTVs with margin, so that potential range variations were considered

in the margins.

% By studying the dose to OAR when depositing dose in the so increased target, possible limitations on the needed accuracy were analyzed.

\subsection{Treatment planning studies}

3D treatment plans were produced on one hand as reference values to the 4D cases, as it represents the ideal but not deliverable dose

distribution. On the other hand they were also generated in order to study the best suited combinations of beam entry channels

as well as to study possible safety margin limitations. In order to find a suitable field number and beam direction for the treatment planning

studies, static simulations on the original CTV volume (LPV together with RPV) with the above mentioned treatment planning parameters were

carried out for all five patients. 17 different beam channel combinations were studied (see table \ref{tab:fields}). As a criteria for the

best possible solution the dose to OAR were assessed. Furthermore, different ITV margins (original, an increased with 3mm, 5mm and 7mm margin)

were studied in 3D treatment plans for all patients. The resulting dose depositions were compared to IMPT dose deliveries (where the esophagus

was included in the optimization process). Possible limitations were again analyzed according to the dose deposition in the OARs. In order to

prepare for the 4D simulations, the motion of the PVs due to heartbeat was than assessed.

4D plans were distinguished between an underlying motion without any compensation, resulting in interplay patterns, and with the application of

rescanning as motion mitigation technique. For rescanning different rescan numbers (5, 10, 15 and 20) were compared.

Static, interplay as well as rescanning treatment plans for all patients where carried out with one beam channel combination, all four safety

margins, the stated treatment planning parameters and the four stated motion trajectories.

\subsection{Analysis}

Both the dose deposition in OAR as well as dose homogeneity in the target volume were studied. For the OAR dose-volume restriction in

esophagus, trachea, aorta and the whole heart were compared to values from RTOG study protocols (see next paragraph).

As further OAR cardiac substructures (ventricles and coronary arteries) were studied. Here the mean dose into the structures as well as the

maximum point dose and the maximal irradiated volume (thus sum over all voxels of the organ which receive dose) were analyzed. In general, the

median values of these parameters over all patients were further calculated. Besides the second quartile (median, 50th percentile) also the

third quartile (75th percentile) was assessed. For comparison of the resulting dose coverage in the target region dose-volume-histograms

(DVHs) were studied. Furthermore motion-volume-histograms (MVHs) \cite{Ric13} were generated displaying the relative displacement of every

voxel of the investigated volume to the reference phase in all three motion directions. With these the resulting motion of the PV due to

heartbeat could be assessed.

\subsubsection{Dose-volume constraints for organs at risk}

The dose deposition in the OAR is an important limitation and selection criteria when studying the field number and beam channel

direction as well as the possible safety margin limitations. Since a single fraction of 25 Gy or higher is assumed to be used in the

presented, non-invasive treatment modality, dose tolerance limits used in stereotactic body radiotherapy (SBRT) are highly related. An

extensive collection of dose-volume-limits for SBRT are presented in Grimm et al. \cite{Gri11} and the AAPM Task Group Report \cite{AAPM10}.

Both are literature reviews of limits utilized and reported in existing publications. For the OAR in the here presented

treatment planning study (esophagus, trachea, heart and aorta) the dose-volume-limits in both literature reviews were taken from the

Radiation Therapy Oncology Group (RTOG). The RTOG is a national clinical cooperative group of over 360 institutions across the United

States and Canada, which was funded by the National Cancer Institute (NCI) \cite{RTOG}. In their study protocols RTOG 0631

(a phase II/III trial of SBRT for localized spine metastasis) \cite{RTOG0631} and RTOG 0915 (a randomized phase II trial of SBRT for

medically inoperable patients with stage I peripheral non-small cell lunger cancer) \cite{RTOG0915} the following dose-volume-limits

were stated (see table \ref{tab:RTOG}).

\vspace\*{-0.8cm}

\begin{table}[H]

\centering

\caption{Dose-volume limits for OAR.}

\begin{tabular}{|c|c|c|c|}

\hline\hline

OAR & Volume [cc] & Dose [Gy] & endpoint \\

\hline

Aorta / great vessels & 10 & 31 & Aneurysm \\

Esophagus & 5 & 11.9 & Stenosis / fistula \\

Heart & 15 & 16 & Pericarditis \\

Trachea & 4 & 10.5 & Stenosis / fistula \\

\hline\hline

\end{tabular}

\label{tab:RTOG}

\end{table}

Since the heart is not only a critical organ but also the target site in this treatment modality, further differentiation of

limits depending on the substructures of the heart are needed. Unfortunately, data herefore is scarce and

literature on cardiac disease resulting from radiation exposure mostly reliant on patient data treated with cancer radiotherapy

(in particular breast cancer and Hodgkin's lymphoma) or atomic bomb survivors. Besides

the stated dose-volume limitation, the mean dose and maximum point dose to the whole heart was studied.

Furthermore the maximal irradiated heart volume (each voxel which received a dose deposition) was examined.

Concerning substructures the left and right ventricle as well as the coronary arteries were analyzed

for mean and maximum dose deposition and maximal irradiated volume contribution.

\subsubsection{Dose deposition in target volume and motion of PVs}

The V95 (measure of dose coverage) and V107 (measure

of over dosage) of the CTVs were analyzed. As an indicator for the dose homogeneity, the width of the dose fall off was determined by analyzing

the difference D5-D95. The stated values have been evaluated for all beam applications (static, interplay, rescanning). Static thereby means that

no motion was included, resulting in a 3D case. This is only used as a reference value for the 4D cases interplay and rescanning, as the static

case represents the ideal, but not deliverable dose distribution.

\section{Results}

In the following the results of the beam direction and safety margin study, PV motion assessment as well as the treatment planning studies

will be discussed. As a criteria for an adequate field number and beam channel direction as well as safety margin limitation the dose to OAR

will be presented in detail.

The motion is shown as the relative displacement to the reference motion phase.

For the treatment planning study different dose analysis parameters will be presented and compared for different cases (static, interplay and rescanning).

\subsection{Beam direction}

In figure \ref{beamdirection} the resulting dose to the pertinent OARs is shown for all studied beam directions and patients.

The corresponding volumes result from the dose volume limits (e.g. 5 cm$^{3}$ for esophagus, see table

\ref{tab:RTOG}). The stated, recommended dose limit is represented by a dashed line in the plots. In all studied cases, the

difference between different beam directions for a certain patient is rather small, resulting in no obvious preferable beam direction for

the five studied patient. For the four studied OAR it becomes furthermore obvious, that while some organs, like trachea and aorta, are well

spared for almost all beam directions in all patients, esophagus and in particular the heart are much more critical.

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\begin{figure}[H]

\subfigure[Esophagus]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_ESO.png}

}

\subfigure[Trachea]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_TRACHEA.png}

}

\subfigure[Heart]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_HEARTwoOverlap.png}

}

\subfigure[Aorta]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_AORTA.png}

}

\caption{Dose-volume data of different OAR when irradiating the LPV and RPV as ITV in the five patient data sets with different field numbers

(1 field, 2 fields, 3 fields, 4 fields) and different beam directions. The dose-volume-limit for each critical organ is indicated with a dashed line in

each plot, respectively.}

\label{beamdirection}

\end{figure}

In the esophagus the median dose over all patients is 7.75Gy (75th percentile: 9.00Gy) for one field, 10.50Gy (75th percentile: 13.94Gy) for

two fields, 11.00Gy (75th percentile: 13.94Gy) for three fields and 9.13Gy (75th percentile: 12.81Gy) for four fields.

The result is dependent on the underlying patient anatomy.

While the majority of the beam directions for patient 1, 4 and 5 remain under the

respective dose-volume limit, patient 2 and 3 result in many dose-volume exceeding depositions. For these patients a dose deposition

of 11.9 Gy or less are achieved in only about 2\% and 65\% of studied cases, for patient 2 and 3, respectively. While a single field yields

very small dose deposition in the esophaghus, these beam channels result in higher dose depositions in the heart and cardiac substructures like

the coronary arteries (see figure \ref{beamdirection\_dose\_ca}) and are thus inapplicable. For patient 2 higher field numbers and thus more beam

directions result in dose limit exceeding depositions. Due to this result a different treatment delivery (intensity modulated particle

therapy, IMPT) was additionally studied in comparison to a simple ITV irradiation in further dose deposition studies (see section \ref{safetymarginlimitation}).\newline

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The dose volume limit for the heart is exceeded in all patients for all beam directions. As the heart is not only an

OAR in this treatment modality, but some of its substructure are also the target itself, a closer analysis of the dose deposition in the heart

is required. In figure \ref{beamdirection\_dose\_heart} the mean and maximal dose deposition in the whole heart as well as the maximal

irradiated volume are shown. The mean dose over all patients

and beam directions is found to have a median of 1.26Gy (75th percentile: 1.48Gy).

The median over the maximum point dose is found to 26.60Gy (75th percentile: 27.12Gy).

Cocerning the maximal irradiated volume it can be seen that expect of one result less than 30\% of the heart is irradiated in all other cases.

In the case of couch position 90$^{\circ}$ and gantry angles of -160$^{\circ}$, -90$^{\circ}$, -60$^{\circ}$ and 145$^{\circ}$ these maximal

volume is drastically increased, and reaches up to 49.93\% for patient 2. Hence this beam channel case (beam channel case 17) will be

stated separately in the following analysis.

The median of the maximal irradiated volume over all patients results to 17.43\% (75th percentile: 20.75\%), excluding beam channel case 17

and to 16.75\% (75th percentile: 20.48\%) including this case.\newline

\newline

For results for the dose deposition in the cardiac substructures are presented in figure \ref{beamdirection\_dose\_ventricle} -

figure \ref{beamdirection\_volume\_ca}. For the ventricles, the mean dose to both LV and RV is negligible.

The maximal point dose on the other hand varies dependent on beam direction and patient. Single beam directions yield a high maximal dose

deposition in the LV as in the case of a couch angle of -90$^{\circ}$ or -135$^{\circ}$ the beam traverses the LV.

Thus for these beam directions the maximal dose to the RV is smaller. The overall maximal dose deposition results to a median of

1.35Gy (75th percentile: 7.40Gy) for LV and 1.33Gy (75th percentile: 5.03Gy) for RV.

Besides the single beam direction no maximal point dose exceeds 11.2 Gy in case of LV and in case of RV all maximal point doses are smaller

than 10.1 Gy. Concerning the maximal irradiated volume of the ventricles, it can be stated that the results differ depending on the studied

patient. In case of the LV patient 2 has a higher irradiated volume compared to the other patients, while for this patient on the contrary

the RV is better spared than in other patients. Over all patients the LV is irradiated to a higher extend than the RV. The maximal

irradiated volume over all beam directions and patients results to a median of 1.17\% (75th percentile: 6.02\%) for LV, excluding the case of

beam channel 17 and to 1.91\% (75th percentile: 6.39\%) including this case. For RV it results to 0.19\% (75th percentile: 7.64\%) excluding

the beam channel case and to 0.20\% (75th percentile: 8.25\%) including it.

For the coronary arteries the beam channel 17 also results in the highest irradiated volume.

Even though the coronary arteries are found on the surface of the whole heart and hence also on the ventricles, the irradiated volume of

these structures differ from the result of the ventricles. Here the RCA are irradiated to a higher extend than the LCA.

The median maximal value for the LCA results to 15.70\% (75th percentile: 28.03\%) including the stated beam channel case 17 and to 15.23\%

(75th percentile: 27.35\%) excluding it. For the RCA the median over the maximal value is much higher and found to 27.86\% (75th percentile:

42.44\%) including the beam channel case and to 24.81\% (75th percentile: 42.10\%) excluding it.

For the mean dose deposited in the LCA one and four beam directions result in an increased dose deposition, while three fields

yield in general a low mean dose for all studied beam directions and patients. The same is true for the maximum point dose in the LCA. In the

case of RCA, the result seem to be independent of field number and beam direction. Overall the median over the mean dose results to 0.41Gy

(75th percentile: 1.02Gy) for LCA and 0.57Gy (75th percentile: 1.60Gy) for RCA.

For the maximal point dose the median dose deposition over all beam directions and patients results to 6.82Gy (75th percentile: 10.85Gy) for LCA.

For the RCA it is found to 5.35Gy (75th percentile: 7.95Gy). \newline

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While it was not expected to find one beam direction feasible for all five patients, it is striking that no beam position results in a clear

benefit for the OAR of the individual patients. This is due to the challenging position of the PV target site, which is in direct proximity

to the esophagus and due to the fact that the heart is not only an OAR in this treatment modality, but also the target site itself.

Nevertheless for the analyzed cardiac substructure, especially the radiosensitive LCA, it can be concluded that three beam channels seem to be

beneficial for all patients. Regarding the mean dose deposition in the LCA as well as the maximal irradiated heart volume, combined with the

requirement of a robust treatment and hence the benefit of large gantry angles in between different beam channels, a couch angle of

-90$^{\circ}$ was chosen together with gantry angles of -45$^{\circ}$, 135$^{\circ}$ and 0$^{\circ}$. These beam channel directions were used

for a closer analysis of safety margin limitation as well as for the treatment planning studies for all patients.

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%%%%%%%%%%%%%%%%%%%%%%%%%

%%%%%%%% DOSE TO THE HEART

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\begin{figure}[H]

\begin{center}

\subfigure[Heart: mean dose]{

\includegraphics[scale=0.17]{Mayo\_Human\_BeamDirection\_HEARTwoOverlap\_MeanDose.png}

}

\subfigure[Heart: maximum point dose]{

\includegraphics[scale=0.17]{Mayo\_Human\_BeamDirection\_HEARTwoOverlap\_MaxDose.png}

}

\subfigure[Heart: maximum volume]{

\includegraphics[scale=0.17]{Mayo\_Human\_BeamDirection\_HEARTwoOverlap\_MaxVolume.png}

}

\caption{Mean and maximum dose to the heart and maximal irradiatied heart volume when irradiating the LPV and RPV in the five patient data

sets with different field numbers and beam directions.}

\label{beamdirection\_dose\_heart}

\end{center}

\end{figure}

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\begin{figure}[H]

\subfigure[Mean dose: LV]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_LV\_MeanDose.png}

}

\subfigure[Mean dose: RV]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_RV\_MeanDose.png}

}

\subfigure[Maximum point dose: LV]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_LV\_MaxDose.png}

}

\subfigure[Maximum point dose: RV]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_RV\_MaxDose.png}

}

\caption{Mean dose with standard deviation and maximal point dose of left ventricle (LV) and right ventricle (RV), respectively, when

irradiating the LPV and RPV in the five patient data sets with different field numbers and beam directions.}

\label{beamdirection\_dose\_ventricle}

\end{figure}

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\begin{figure}[H]

\subfigure[Maximum volume: LV]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_LV\_MaxVolume.png}

}

\subfigure[Maximum volume: RV]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_RV\_MaxVolume.png}

}

\caption{Maximal irradiated volume of left ventricle (LV) and right ventricle (RV), respectively, when

irradiating the LPV and RPV in the five patient data sets with different field numbers and beam directions.}

\label{beamdirection\_volume\_ventricle}

\end{figure}

\begin{figure}[H]

\subfigure[Maximum volume: LCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_LCA\_MaxVolume.png}

}

\subfigure[Maximum volume: RCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_RCA\_MaxVolume.png}

}

\caption{Maximal irradiated volume of left coronary artery (LCA) and right coronary artery (RCA), respectively, when

irradiating the LPV and RPV in the five patient data sets with different field numbers and beam directions.}

\label{beamdirection\_volume\_ca}

\end{figure}

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\vspace\*{1cm}

\begin{figure}[H]

\subfigure[Mean dose: LCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_LCA\_MeanDose.png}

}

\subfigure[Mean dose: RCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_RCA\_MeanDose.png}

}

\subfigure[Maximum point dose: LCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_LCA\_MaxDose.png}

}

\subfigure[Maximum point dose: RCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_BeamDirection\_RCA\_MaxDose.png}

}

\caption{Mean dose with standard deviation and maximal point dose of left coronary artery (LCA) and right coronary artery (RCA), respectively,

when irradiating the LPV and RPV in the five patient data sets with different field numbers and beam directions.}

\label{beamdirection\_dose\_ca}

\end{figure}

\subsection{Safety margin limitations}

\label{safetymarginlimitation}

Figure \ref{static\_margin} shows the dose results for the main OAR when irradiating the PVs with no safety margin (0mm) and different additional,

isotropic safety margins (3mm, 5mm or 7mm). The dose-volume-limits were studied according to the recommendation of RTOG (see table \ref{tab:RTOG})

and the limit for each organ is indicated by a dashed line in the plots. Besides an ITV treatment, IMPT deliveries were also studied. Thereby

the esophagus was implemented as a critical structure in the optimization process and it was stated that this structure should not receive

more than 70\% of the physical dose of 25 Gy. The results of these two treatment delivery techniques, ITV irradiation and IMPT, are both shown

in each plot.\newline

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As expected, the dose to the enclosed OAR increases with increasing safety margin for all patients. This is the case both for ITV and IMPT

delivery. Nevertheless the IMPT delivery does lead to a reduced dose deposition in the esophagus. For no safety margin, the median dose over a

all patients is found to 8.50Gy (75th percentile: 12.38Gy), which decreases to 7.00Gy (75th percentile: 9.00Gy) with IMPT delivery.

For 3mm safety margin an ITV irradiation results to 13.00Gy (75th percentile: 18.63Gy) and reduces to 9.25Gy (75th percentile: 12.13Gy) for

IMPT. With 5mm safety margin the RTOG limit of 11.9 Gy starts to be exceeded even for IMPT deliveries as it

results to 11.75Gy (75th percentile: 15.13Gy) (compared to 19.00Gy (75th percentile: 22.75Gy) with ITV). For 7mm margin this result further

increases to 14.25Gy (75th percentile: 17.13Gy) (ITV irradiation: 23.25Gy (75th percentile: 24.63Gy)).

Even though only the esophagus is included in the IMPT optimization process, also other OAR profit from this irradiation mode. This can be

understood as the beam stopping in front of the esophagus (gantry angle of -45$^{\circ}$) is optimized into having less raster points in the

IMPT delivery compared to an ITV irradiation and hence a reduced dose contribution to the total dose delivery. The other beam

channels (gantry angles of 135$^{\circ}$ and 0$^{\circ}$) are hence optimized into having more raster points compared to the ITV delivery,

contributing more to the dose deposition. Adjacent OAR to the esophagus, like trachea and aorta, are thus also receiving a smaller dose

deposition from the beam channel stopping in proximity to them. As only an IMPT treatment leads to acceptable dose depositions in the esophagus,

the median dose to the other organs will only be stated for this delivery type. Over all patients the trachea is receiving a median dose of 0Gy

in all cases, since only patient 2 and 3 are yielding a dose in this critical structure. The 75th percentile is found to 0.38Gy with no safety

margin and 1.13Gy, 3.00Gy, 6.63Gy for 3mm, 5mm and 7mm, respectively.

All of these dose deposition are under the recommended dose-volume-limit for the trachea (10.5Gy for 4cm$^{3}$).

For the aorta an irradiation with no safety margin leads to a median dose deposition of 6.50Gy (75th percentile: 8.50Gy), while 8.25Gy (75th percentile: 10.63Gy),

9.75Gy (75th percentile: 12.25Gy) and 11.25Gy (75th percentile: 14.00Gy) are deposited with 3mm, 5mm and 7mm margin.

% (7.25 $\pm$ 1.51)Gy, while (8.90 $\pm$ 1.86)Gy, (10.30 $\pm$ 2.08)Gy and (11.90 $\pm$ 2.38)Gy are deposited with 3mm, 5mm and 7mm margin.

All these results are far under the critical dose-volume limit of 31Gy for 10cm$^{3}$. It can thus be concluded that trachea and aorta do not

receive a critical dose deposition while treating the PVs with a dose of 25 Gy. For the heart the dose-volume limits are much more critical.

% An average of (76.60 $\pm$ 12.78)Gy was yielded for no safety margin and (89.60 $\pm$ 9.52)Gy, (92.60 $\pm$ 7.94)Gy and (94.20 $\pm$ 6.82)Gy

% for 3mm, 5mm and 7mm margin, respectively.

A mean of 18.25Gy (75th percentile: 22.75Gy) was yielded for no safety margin and 23.00Gy (75th percentile: 24.88Gy), 24.25Gy (75th

percentile: 25.00Gy) and 24.75Gy (75th percentile: 25Gy) for 3mm, 5mm and 7mm margin, respectively.

Hence all studied irradiations by far exceed the dose-volume limit of 16Gy for 15cm$^{3}$. A close analysis of the radiosensitive cardiac

substructures is presented in figure \ref{static\_margin\_dose\_heart} - figure \ref{static\_margin\_dose\_coronary\_arteries}.

%%%%%%%% DOSE TO OAR

% \vspace\*{-0.4cm}

\begin{figure}[H]

\subfigure[Esophagus]{

\includegraphics[scale=0.18]{Mayo\_Human\_ESO\_alternativeLimit\_diffIMPT.png}

}

\subfigure[Trachea]{

\includegraphics[scale=0.18]{Mayo\_Human\_TRACHEA.png}

}

\subfigure[Heart]{

\includegraphics[scale=0.18]{Mayo\_Human\_HEARTwoOverlap.png}

}

\subfigure[Aorta]{

\includegraphics[scale=0.18]{Mayo\_Human\_AORTA.png}

}

% \subfigure[Left coronary artery]{

% \includegraphics[scale=0.18]{Mayo\_Human\_LCA.png}

% }

% \subfigure[Right coronary artery]{

% \includegraphics[scale=0.18]{Mayo\_Human\_RCA.png}

% }

\caption{Dose-volume data of different OAR when irradiating the PVs in five patient data sets with different margins and two

different delivery techniques (ITV and IMPT).

The dose-volume-limit for each critical organ is indicated with a dashed line in each plot, respectively.}

\label{static\_margin}

\end{figure}

It should further be noted that another IMPT parameter set was studied for the esophagus of patient 2 with 3mm Margin. While the other four

patients are within the dose-volume limit with this safety margin this patient exceeds the limit

by 1.6Gy. The result could be improved by using another parameter set (maximum dose fraction of 30\% and a weighting factor of two), which

is represented as a triangle in plot \ref{static\_margin}. The dose can be drastically reduced to 5.75Gy for 5cm$^{3}$ esophagus.

% Nevertheless, this leads to an increased dose deposition in the other OAR so that e.g. the aorta receives a slightly higher dose (13 Gy

% compared to 12.5Gy in 10cm$^{3}$).

It can thus be concluded that patient individual optimization can further improve the stated results.

However, as the majority of the patients did not exceed the limit for 3mm margin, the previously stated parameters for IMPT treatment were

used in further analysis.\newline

\newline

Closer analysis of the dose deposition in the heart can be seen in figure \ref{static\_margin\_dose\_heart}. The mean deposited dose in the

heart does not increase with the size of the safety margins. Furthermore only a small difference in between ITV and IMPT irradiation can be observed.

The median value of the mean dose over all patients for an IMPT irradiation with no safety margin is found to 0.97Gy (75th percentile: 1.12Gy).

For the irradiation of the PVs with safety margin it results to 1.26Gy (75th percentile: 1.48Gy) for 3mm, 1.43Gy (75th percentile: 1.59Gy) for

5mm and 1.54Gy (75th percentile: 1.63Gy) for 7mm, respectively.

% % The median value of the mean dose over all patients for an ITV irradiation with no safety margin is found to 1.02Gy (75th percentile: 1.27Gy)

% % compared to 0.97Gy (75th percentile: 1.12Gy) with IMPT. For the irradiation of the PVs with safety margin it results to 1.34Gy (75th

% % percentile: 1.69Gy) versus 1.26Gy (75th percentile: 1.48Gy), 1.51Gy (75th percentile: 1.84Gy) versus 1.43Gy (75th percentile: 1.59Gy) and

% % 1.64Gy (75th percentile: 1.90Gy) versus 1.54Gy (75th percentile: 1.63Gy) for 3mm, 5mm and 7mm, respectively.

While also the maximum point dose does not increase with added safety margin, it can be seen that IMPT treatment does lead to a higher point

dose compared to an ITV irradiation. A comparison of the median maximum point dose and the 75th percentile over all patients and for all

margin cases is presented in table \ref{tab:maxdose\_heart}.

\vspace\*{-0.3cm}

\begin{table}[H]

\centering

\caption{Mean of maximum point dose to the heart.}

\begin{tabular}{|c||c|c||c|c|}

\hline\hline

Margin & ITV: median [Gy] & ITV: 75th [Gy] & IMPT: median [Gy] & IMPT: 75th [Gy] \\

\hline

0 mm & 26.90 & 26.92 & 27.58 & 29.42 \\

3 mm & 26.23 & 26.55 & 28.35 & 29.00 \\

5 mm & 26.50 & 26.58 & 28.00 & 28.80 \\

7 mm & 26.20 & 27.70 & 26.80 & 27.70 \\

\hline\hline

\end{tabular}

\label{tab:maxdose\_heart}

\end{table}

The highest maximum point dose (30.30Gy) was deposited in the heart of patient 3 with a margin of 3mm. In comparison, the ITV result for this

case is 26.55Gy. As esophagus and the other adjacent OAR (trachea, aorta) receive in general less dose with IMPT due to the intensity reduction

in one beam channel direction, the other beam channels have to deposit more particles. Especially gantry angle 0$^{\circ}$, which traverses

the heart, is hence leading to an increased dose deposition in the heart. Since this beam channel direction has to penetrate only a small

volume of the heart, the maximal irradiated volume shows a slight improvement in IMPT delivery compared to ITV irradiation. The results are

presented in table \ref{tab:maxvolume\_heart}.

\vspace\*{-0.3cm}

\begin{table}[H]

\centering

\caption{Mean and 75th percentile of maximum irradiated volume of the heart.}

\begin{tabular}{|c||c|c||c|c|}

\hline\hline

Margin & ITV: median [\%] & ITV: 75th [\%] & IMPT: median [\%] & IMPT: 75th [\%]\\

\hline

0 mm & 17.18 & 20.04 & 15.65 & 18.88 \\

3 mm & 19.40 & 22.61 & 17.42 & 21.23 \\

5 mm & 20.66 & 24.94 & 18.49 & 23.22 \\

7 mm & 21.82 & 26.37 & 19.94 & 24.44 \\

\hline\hline

\end{tabular}

\label{tab:maxvolume\_heart}

\end{table}

%%%%%%%% DOSE TO THE HEART

\newpage

\begin{figure}[H]

\begin{center}

\subfigure[Heart: mean dose]{

\includegraphics[scale=0.18]{Mayo\_Human\_HEARTwoOverlap\_MeanDose.png}

}

\subfigure[Heart: maximum point dose]{

\includegraphics[scale=0.18]{Mayo\_Human\_HEARTwoOverlap\_MaxDose.png}

}

\subfigure[Heart: maximum volume]{

\includegraphics[scale=0.18]{Mayo\_Human\_HEARTwoOverlap\_MaxVolume.png}

}

\caption{Mean and maximum dose to the heart and maximal irradiated heart volume when irradiating the LPV and RPV in the five patient data sets with

different margins (0 mm, 3 mm, 5 mm, 7mm) and two different delivery techniques (ITV irradiation and IMPT).}

\label{static\_margin\_dose\_heart}

\end{center}

\end{figure}

\newpage

%%%%%%%% DOSE TO THE VENTRICLES

The results for the analysis of the affected cardiac substructures can be found in figures \ref{static\_margin\_dose\_ventricle} and

\ref{static\_margin\_dose\_coronary\_arteries}.

Concerning the ventricles it can be seen that the mean dose is negligible (see figure \ref{static\_margin\_dose\_ventricle}).

The result for the maximal point dose is patient anatomy dependent. While patient 2 receives

a higher LV maximal point dose than all the other patients (about 5Gy), no dose is deposited in the RV of this patient for any added margin.

For an IMPT irradiation the median and 75th percentile of the maximal dose to the LV and RV over all patients and for all safety margin

cases is shown in table \ref{tab:maxdose\_ventricle}. For both ventricles the dose is increasing with the size of the safety margin. The left

ventricle is receiving a higher maximum point dose than the right ventricle in all cases. Concerning the maximal irradiated volume

it can also be stated that the LV is irradiated to a higher extend than the RV, and that also the affected volume is increasing with the

underlying safety margin size (see table \ref{tab:maxvolume\_ventricle}).

\begin{table}[H]

\centering

\caption{Median and 75th percentile of maximum point dose to the ventricles.}

\begin{tabular}{|c|c|c|}

\hline\hline

Margin & LV: Median [Gy] & LV: 75th [Gy] \\

\hline

0 mm & 0.93 & 1.30 \\

3 mm & 1.45 & 2.40 \\

5 mm & 1.80 & 4.47 \\

7 mm & 3.17 & 5.95 \\

\hline\hline

Margin & RV: Median [Gy] & RV: 75th [Gy] \\

\hline

0 mm & 0.03 & 0.12 \\

3 mm & 0.88 & 1.33 \\

5 mm & 2.47 & 3.17 \\

7 mm & 4.12 & 4.80 \\

\hline\hline

\end{tabular}

\label{tab:maxdose\_ventricle}

\end{table}

\vspace\*{-0.6cm}

\begin{table}[H]

\centering

\caption{Median and 75th percentile of maximum irradiated volume of ventricles.}

\begin{tabular}{|c|c|c|}

\hline\hline

Margin & LV: Median [\%] & LV: 75th [\%] \\

\hline

0 mm & 4.65 & 5.14 \\

3 mm & 6.08 & 7.32 \\

5 mm & 7.31 & 9.12 \\

7 mm & 8.86 & 10.72 \\

\hline\hline

Margin & RV: Median [\%] & RV: 75th [\%] \\

\hline

0 mm & 0.01 & 0.08 \\

3 mm & 0.52 & 0.62 \\

5 mm & 1.05 & 1.19 \\

7 mm & 1.81 & 2.14 \\

\hline\hline

\end{tabular}

\label{tab:maxvolume\_ventricle}

\end{table}

%%%%%%%% DOSE TO THE VENTRICLES

\newpage

\begin{figure}[H]

\subfigure[Mean dose: LV]{

\includegraphics[scale=0.18]{Mayo\_Human\_LV\_MeanDose.png}

}

\subfigure[Mean dose: RV]{

\includegraphics[scale=0.18]{Mayo\_Human\_RV\_MeanDose.png}

}

\subfigure[Maximum point dose: LV]{

\includegraphics[scale=0.18]{Mayo\_Human\_LV\_MaxDose.png}

}

\subfigure[Maximum point dose: RV]{

\includegraphics[scale=0.18]{Mayo\_Human\_RV\_MaxDose.png}

}

\subfigure[Maximum volume: LV]{

\includegraphics[scale=0.18]{Mayo\_Human\_LV\_MaxVolume.png}

}

\subfigure[Maximum volume: RV]{

\includegraphics[scale=0.18]{Mayo\_Human\_RV\_MaxVolume.png}

}

\caption{Mean dose, maximal point dose and maximal irradiated volume of left ventricle (LV) and right ventricle (RV), respectively, when irradiating the LPV

and RPV in the five patient data sets with different margins (0 mm, 3 mm, 5 mm, 7mm) and two different delivery techniques (ITV irradiation and IMPT).}

\label{static\_margin\_dose\_ventricle}

\end{figure}

%%%%%%%% DOSE TO THE CA

Concerning the coronary arteries, it can be seen that the LCA and RCA are receiving a comparable mean dose. The maximum point dose on the other

hand is higher for the LCA. The same is valid for the maximum irradiated volume. This is due to the proximity of the upper LCA branches

to the LPV target site (see figure XXX). Due to the small vessel size of the coronary arteries this also results in a relatively high

maximal irradiated volume. Nevertheless, a median dose of less than 1Gy in most studied cases yields good results compared to the data

known from heart irradiation with photons (see Discussion XXX).

\vspace\*{-0.4cm}

\begin{table}[H]

\centering

\caption{Median and 75th percentile of mean dose to the coronary arteries.}

\begin{tabular}{|c|c|c|}

\hline\hline

Margin & LCA: median [Gy] & LCA: 75th [Gy] \\

\hline

0 mm & 0.22 & 0.54 \\

3 mm & 0.46 & 0.86 \\

5 mm & 0.69 & 1.13 \\

7 mm & 1.45 & 1.58 \\

\hline\hline

Margin & RCA: median [Gy] & RCA: 75th [Gy] \\

\hline

0 mm & 0.28 & 0.36 \\

3 mm & 0.51 & 0.84 \\

5 mm & 0.72 & 1.30 \\

7 mm & 0.98 & 1.72 \\

\hline\hline

\end{tabular}

\label{tab:meandose\_ca}

\end{table}

\vspace\*{-0.5cm}

\begin{table}[H]

\centering

\caption{Median and 75th percentile of maximum point dose to the coronary arteries.}

\begin{tabular}{|c|c|c|}

\hline\hline

Margin & LCA: median [Gy] & LCA: 75th [Gy] \\

\hline

0 mm & 6.00 & 6.25 \\

3 mm & 7.35 & 7.62 \\

5 mm & 8.70 & 13.18 \\

7 mm & 20.05 & 21.30 \\

\hline\hline

Margin & RCA: median [Gy] & RCA: 75th [Gy] \\

\hline

0 mm & 3.08 & 4.70 \\

3 mm & 3.83 & 6.45 \\

5 mm & 4.25 & 7.22 \\

7 mm & 5.85 & 7.90 \\

\hline\hline

\end{tabular}

\label{tab:maxdose\_ca}

\end{table}

\vspace\*{-0.5cm}

\begin{table}[H]

\centering

\caption{Median and 75th percentile of maximum irradiated volume of coronary arteries.}

\begin{tabular}{|c|c|c|}

\hline\hline

Margin & LCA: median [\%] & LCA: 75th [\%] \\

\hline

0 mm & 26.68 & 39.17 \\

3 mm & 28.48 & 41.52 \\

5 mm & 29.60 & 44.58 \\

7 mm & 31.44 & 49.64 \\

\hline\hline

Margin & RCA: Median [\%] & RCA: 75th [\%] \\

\hline

0 mm & 19.24 & 26.48 \\

3 mm & 25.09 & 29.80 \\

5 mm & 33.21 & 35.57 \\

7 mm & 39.58 & 39.69 \\

\hline\hline

\end{tabular}

\label{tab:maxvolume\_ventricle}

\end{table}

%%%%%%%% DOSE TO THE CA

\begin{figure}[H]

\subfigure[Mean dose: LCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_LCA\_MeanDose.png}

}

\subfigure[Mean dose: RCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_RCA\_MeanDose.png}

}

\subfigure[Maximum point dose: LCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_LCA\_MaxDose.png}

}

\subfigure[Maximum point dose: RCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_RCA\_MaxDose.png}

}

\subfigure[Maximum volume: LCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_LCA\_MaxVolume.png}

}

\subfigure[Maximum volume: RCA]{

\includegraphics[scale=0.18]{Mayo\_Human\_RCA\_MaxVolume.png}

}

\caption{Mean dose, maximal point dose and maximal irradiated volume of left coronary artery (LCA) and right coronary artery (RCA), respectively,

when irradiating the LPV and RPV in the five patient data sets with different margins (0 mm, 3 mm, 5 mm, 7mm) and two different delivery

techniques (ITV irradiation and IMPT).}

\label{static\_margin\_dose\_coronary\_arteries}

\end{figure}

\newpage

\subsection{Motion assessment of heartbeat}

% \vspace\*{-0.7cm}

Using the resulting deformation maps from deformable image registration the motion of the ablation sites of LPV and RPV was assessed. Motion

volume histograms (MVHs) \cite{Ric13} displaying the relative displacement of every voxel of the investigated volume to the reference phase in

all three motion directions were generated. The mean and standard deviation of these displacement values in each motion phase of LPV and RPV

are plotted for all patients and motion directions in figure \ref{fig:motion\_hb\_lpv} and \ref{fig:motion\_hb\_rpv}, respectively.\newline

\newline

The mean and standard deviation of each patient over all motion phases are stated in table \ref{tab:motion\_pv}.

From the five studied patients patient 4 is displaying the highest absolute displacement, both in LPV and RPV.

Furthermore it can be seen that none of the motion directions can be determined as the largest contribution to the absolute displacement,

neither in LPV or RPV motion.

% While the largest contribution to the LPV displacement in patient 1 is e.g. in the AP direction, patient 4 on

% the other hand shows the largest displacement in SI direction.

In table \ref{tab:maxabs\_pv} the maximal absolute displacement for each patient is presented together with the corresponding motion

phase. While motion phase six is the motion phase with the biggest displacement in 30\% of all cases, no evident maximal motion phase can be

assessed. On average, the absolute amplitude over all motion phases and patients is found to (2.71 $\pm$ 1.57)mm for LPV and

(2.62 $\pm$ 1.41)mm for RPV. In SI direction, the mean amplitude is (-0.60 $\pm$ 1.36)mm for LPV and (-0.17 $\pm$ 1.57)mm for RPV. In AP

direction it is (0.77 $\pm$ 0.96)mm for LPV and (1.00 $\pm$ 1.58)mm for RPV, while in LR direction it is found to (0.36 $\pm$ 0.92)mm for LPV

and (-1.00 $\pm$ 1.48)mm for RPV. Hence, averaged over all patients it can be stated that the PVs are moving mostly in AP direction.

Nevertheless the contribution of the other motion directions are in the same order of magnitude.\newline

\newline

The motion phases of the heartbeat gated CT scan are based on the ECG trace and result in a division of a single heartbeat. The

motion phases can hence be directly assigned to the contraction (systole) and dilatation (diastole) of both atria and ventricles.

Contraction of the atria (atrial systole) is occurring in between motion phase four and nineteen, in the same time as the ventricular relaxation

(ventricular diastole). The ventricular systole and at the same time atria diastole are hence much shorter, occurring in the

remaining motion phases twenty to three. The maximal displacement of the atria should thus be observed in motion phase eighteen, while the

maximal amplitude of the ventricle should be observed in motion phase three. The motion of the PVs on the other hand result in a much more chaotic displacement.

No motion phase can be assessed to a maximal displacement in all patient cases and no dominant motion direction is

observed. The underlying heartbeat motion which causes the PVs to move should hence be much more complex.

\newpage

\begin{figure}[H]

\begin{center}

\includegraphics[scale=0.25]{MAYO\_allPatients\_HB\_LPV.png}

\caption{Motion amplitude of LPV under influence of heartbeat for all patients. (Patient 1: black, Patient 2: red, Patient 3: green,

Patient 4: blue, Patient 5: turquois) }

\label{fig:motion\_hb\_lpv}

\end{center}

\end{figure}

\vspace\*{-1.3cm}

\begin{figure}[H]

\begin{center}

\includegraphics[scale=0.25]{MAYO\_allPatients\_HB\_RPV.png}

\caption{Motion amplitude of RPV under influence of heartbeat for all patients. (Patient 1: black, Patient 2: red, Patient 3: green,

Patient 4: blue, Patient 5: turquois) }

\label{fig:motion\_hb\_rpv}

\end{center}

\end{figure}

\newpage

\vspace\*{1cm}

\begin{table}[H]

\centering

\caption{Mean displacement of PVs over all motion phases (MP) in all patients and motion directions.}

\begin{tabular}{|c|c|c|c|c|}

\hline\hline

Patient & LPV: ABS [mm] & LPV: SI [mm] & LPV: AP [mm] & LPV: LR [mm] \\

\hline

1 & 2.71 $\pm$ 1.18 & -1.17 $\pm$ 0.91 & 1.35 $\pm$ 1.08 & -0.89 $\pm$ 0.75 \\

2 & 2.31 $\pm$ 1.14 & 1.16 $\pm$ 1.10 & 0.63 $\pm$ 0.53 & -1.38 $\pm$ 0.90 \\

3 & 2.48 $\pm$ 1.75 & -0.36 $\pm$ 1.07 & 0.54 $\pm$ 0.78 & -1.18 $\pm$ 1.95 \\

4 & 4.27 $\pm$ 2.54 & -3.07 $\pm$ 2.49 & 0.34 $\pm$ 1.43 & -0.78 $\pm$ 2.47 \\

5 & 2.15 $\pm$ 1.23 & -0.75 $\pm$ 1.44 & 0.67 $\pm$ 1.10 & -0.18 $\pm$ 0.94 \\

\hline\hline

Patient & RPV: ABS [mm] & RPV: SI [mm] & RPV: AP [mm] & RPV: LR [mm] \\

\hline

1 & 2.12 $\pm$ 0.71 & -0.88 $\pm$ 0.65 & 1.11 $\pm$ 0.87 & 0.60 $\pm$ 0.60 \\

2 & 2.25 $\pm$ 1.28 & 0.70 $\pm$ 1.15 & 0.96 $\pm$ 1.07 & -1.19 $\pm$ 1.01 \\

3 & 2.22 $\pm$ 1.19 & 0.23 $\pm$ 1.25 & 0.50 $\pm$ 1.77 & 0.39 $\pm$ 0.70 \\

4 & 4.62 $\pm$ 2.33 & -1.68 $\pm$ 3.12 & 1.67 $\pm$ 2.82 & 1.84 $\pm$ 0.94 \\

5 & 2.77 $\pm$ 1.72 & 0.22 $\pm$ 1.77 & 1.03 $\pm$ 1.25 & 1.40 $\pm$ 1.40 \\

\hline\hline

\end{tabular}

\label{tab:motion\_pv}

\end{table}

\begin{table}[H]

\centering

\caption{Biggest absolute displacement of PVs with corresponding motion phase (MP) in all patients.}

\begin{tabular}{|c|c|c|}

\hline\hline

Patient & LPV: max. ABS [mm] & MP \\

\hline

1 & 4.50 $\pm$ 1.72 & 06 \\

2 & 5.26 $\pm$ 1.92 & 06 \\

3 & 3.39 $\pm$ 2.24 & 08 \\

4 & 5.52 $\pm$ 3.06 & 11 \\

5 & 2.92 $\pm$ 1.54 & 16 \\

\hline\hline

Patient & RPV: max. ABS [mm] & MP \\

\hline

1 & 3.99 $\pm$ 1.40 & 06 \\

2 & 5.20 $\pm$ 1.80 & 04 \\

3 & 2.93 $\pm$ 1.35 & 11 \\

4 & 6.49 $\pm$ 3.00 & 10 \\

5 & 3.95 $\pm$ 3.95 & 15 \\

\hline\hline

\end{tabular}

\label{tab:maxabs\_pv}

\end{table}

\newpage

The overall displacement field between the extreme states of the ventricular displacement (motion phase three) and atrial displacement

(motion phase eightteen) for two exemplary patients with a small motion amplitude (patient 5) and a large motion amplitude (patient 4) are

shown in figure \ref{contour\_plot\_hb}. In order to visualize the location of the displacement, an axial cut of the reference state CT is

underlayed. The absolute values of the displacement vectors are shown as contour plots.

\begin{figure}[H]

\subfigure[Patient 4: max motion ventricle]{

\includegraphics[scale=0.18]{Contour\_z\_abs\_HB\_Pat08\_03\_gedreht.png}

}

\subfigure[Patient 5: max motion ventricle]{

\includegraphics[scale=0.18]{Contour\_z\_abs\_HB\_Pat10\_03\_gedreht.png}

}

\subfigure[Patient 4: max motion atria]{

\includegraphics[scale=0.18]{Contour\_z\_abs\_HB\_Pat08\_18\_gedreht.png}

}

\subfigure[Patient 5: max motion atria]{

\includegraphics[scale=0.18]{Contour\_z\_abs\_HB\_Pat10\_18\_gedreht.png}

}

\caption{Axial slices of the reference state of the CT overlayed with the absolute values of the displacement field (obtained from

deformable image registration) in the corresponding slice for heartbeat motion. In the top row the displacement from the motion phase with the

maximal ventricle motion to the reference phase is shown, in the lower row the displacement from the motion phase with the maximal

atrial motion, for Patient 4 and Patient 5, respectively.}

\label{contour\_plot\_hb}

\end{figure}

\newpage

\subsection{Motion mitigation techniques for heartbeat}

The absolute motion amplitudes of up to 5mm due to heartbeat are expected to yield dose inhomogeneities when not compensated for. The

resulting Interplay effect and dose deposition was studied for every patient for different motion patterns and different margins to the target

volumes. The dose analysis values V95, V107 and D5-D95 were assessed and plotted. For comparison also the corresponding

values for the 3D case (static) are shown. Due to the small motion amplitude, rescanning was studied as motion mitigation technique.

The results of the stated dose values in case of rescanning with different rescan numbers will also be presented.

\subsubsection{Dose deposition}

A representative dose deposition for all studied techniques (static, interplay and rescanning with ten rescans) is shown exemplary for patient

4 (as this is the patient with the largest PV motion amplitude both in LPV and RPV) in figure \ref{dose\_pat08}. Rescanning and interplay are

shown for a sinus motion with a period of 0.7s and a starting phase of 0$^{\circ}$. The target volumes LPV and RPV were irradiated

simultaneously and a margin of 3mm was added. It can already been seen from this dose cut figures that rescanning with only ten rescans drastically

improves the outcome compared to interplay and yields a result which is comparable to the static case.\newline

\newline

For patient 4, the different motion patterns DVHs of ten rescans compared to the interplay results as well as a static irradiation are

displayed in figure \ref{dvhs\_pat08} for 3mm safety margin.

In order to assess the dose information of all patients the DVHs were analyzed and compared for dose steepness, dose coverage as well as over dosage. The average results

over all patients with the resulting standard deviation can be seen in figure \ref{static\_interplay\_rescanning\_ALL}. A more detailed analysis

can be found in appendix XXX, where the values are plotted for each patient (figures \ref{static\_interplay\_rescanning\_Pat01} -

\ref{static\_interplay\_rescanning\_Pat05}) and all corresponding numerical values are shown (tables \ref{tab:Pat02\_LPV} - \ref{tab:Pat10\_RPV}).\newline

\newline

For interplay it can be seen that the results are dependent on the used motion period and starting phase. This can be seen in the mean values

of dose parameter value results for different, underlying motion patterns. E.g. for the RPV, the mean value of the dose coverage parameter

over all patients is V95=(88.82 $\pm$ 12.76)\% for a sinus motion with 1s period and a starting phase of 90$^{\circ}$ and

(98.01 $\pm$ 1.36)\% for a sinus motion with 0.7s period and a starting phase of 90$^{\circ}$, while for a sinus motion with 0.7s period

and a starting phase of 0$^{\circ}$ the dose coverage is found to (92.14 $\pm$ 12.67)\%. The resulting high standard deviation over all patient

cases shows that the result is also dependent on the studied patient case. Furthermore the result is also dependent on the studied safety

margin, so that e.g. the dose coverage for a sinus motion with 1s period and a starting phase of 90$^{\circ}$ results to (95.88 $\pm$ 2.40)\%

with 3mm safety margin. All these dependencies are also valid for the other studied dose analysis parameters, dose homogeneity and over dosage.\newline

\newline

The underlying deformation map with its motion amplitude does not enable a prediction of the magnitude of the

interplay effect. This was studied in more detail for the dose coverage parameter V95. Here, the correlation between the maximal absolute

motion amplitude of the left and right PV (see table \ref{tab:maxabs\_pv}) and the resulting V95 value for 3 mm Margin were assessed for all

studied motion patterns (sinus motion with period of 1s or 0.7s and starting phase of 0$^{\circ}$ and 90$^{\circ}$) and patients. The results

can be seen in figure \ref{corr\_maxabs\_V95\_interplay}. A moderate correlation between the dose coverage and maximal amplitude resulted only

in the case of RPV where a motion period of 0.7s with a starting phase of 90$^{\circ}$ was chosen (r=0.49; p<0.05). Nevertheless these results

could not be verified in the other motion cases and in the irradiation of the LPV and hence no dependence between target volume displacement

and dose coverage in case of interplay was found.\newline

\newline

As can be seen in figure \ref{static\_interplay\_rescanning\_ALL} (as well as in more detail for all patients in appendix XXX)

rescanning yields improved results compared to interplay in all studied cases. This is valid for dose steepness, dose

coverage as well as over dosage. Especially dose coverage and over dosage are comparable to the static results for all patient and motion patterns.

Exemplary, the dose coverage of patient 4 (with the largest absolute displacement) will be discussed. V95 for a static irradiation of the LPV

of patient 4 with 3mm safety margin is found to 99.75\%. With a motion of 0.7s period length and a starting phase of 0$^{\circ}$ the value

decreases to 90.02\%. With rescanning, V95 can be improved to 99.75\% with only five rescans. Also for RPV the static dose coverage

with 3mm margin is found to 100\% for this patient. With the stated motion and safety margin the dose coverage decreases to 97\%

in the case of interplay. With five rescans the value improves again to 100\%. The improvement of dose coverage and over dosage

compared to interplay is valid for all studied rescan numbers, starting from the smallest studied rescan number of five, as shown here.

Nevertheless, in some studied cases five rescans is not enought to yield results comparable to the static irradiation. For example for the LPV

irradiation with five rescans in patient 1 with a motion period of 1s and 90$^{\circ}$ starting phase (3mm safety margin) V95 results in a

smaller dose coverage (93.18\%) than the static case (100\%). Even though this result is improved compared to interplay (86.88\%), a much

better result can be gained with higher rescan numbers, starting with ten rescans (99.21\%). Also the results for dose homogeneity improves

with higher rescan numbers. For a motion pattern of 0.7s period and 0$^{\circ}$ starting phase (3mm safety margin) in patient 4, the dose

homogeneity in case of interplay is found to 9.86\%. With five rescans a dose homogeneity of 5.52\% is yielded, which further decreases to

4.62\% with ten rescans, 4.44\% with fifteen rescans and 3.93\% with twenty rescans (compared to 3.92\% in the static irradiation).

It can thus be conluded that rescan numbers higher than five yield better slightly results, while ten rescans show results comparable to the

static irradiation in all studied patient cases, for all studied safety margins and for all underlying motion patterns. As can be furthermore

seen in figure \ref{static\_interplay\_rescanning\_ALL}, the standard deviation of the dose analysis parameters over all patients is

rather small for ten and higher rescan numbers, proving the robustness of rescanning as a motion mitigation technique for a displacement of

the PVs due to heartbeat.

\vspace\*{-0.3cm}

\begin{figure}[H]

\begin{center}

\subfigure[LPV]{

\includegraphics[scale=0.24]{Pat08\_LPV\_allDVHs\_withLegend.png}

}

\subfigure[RPV]{

\includegraphics[scale=0.24]{Pat08\_RPV\_allDVHs\_withLegend.png}

}

\caption{Dose volume histograms for CTV of patient 4 for 3mm safety margin irradiation (LPV (a) as well as RPV (b)) in case of static

irradiation (black), interplay (dashed) and rescanning with ten rescans (solid). The motion patterns are shown in colors (sin1s0: sinus with motion period of 1s

and starting phase 0$^{\circ}$, sin1s90: sinus with motion period of 1s and starting phase 90$^{\circ}$, sin07s0: sinus with motion period of 0.7s

and starting phase 0$^{\circ}$, sin07s90: sinus with motion period of 0.7s and starting phase 90$^{\circ}$.}

\label{dvhs\_pat08}

\end{center}

\end{figure}

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\begin{figure}[H]

\begin{center}

\subfigure[static]{

\includegraphics[scale=0.36, angle=180]{Pat08\_static.png}

}

\subfigure[interplay]{

\includegraphics[scale=0.36, angle=180]{Pat08\_interplay.png}

}

\subfigure[rescanning (10x)]{

\includegraphics[scale=0.36, angle=180]{Pat08\_10rescans.png}

}

\caption{Dose distribution of patient 4 for static (a) as well as interplay (b) and ten rescans (c) at motion period of 0.7s and a motion

starting phase of 0$^{\circ}$. The target volume has an added margin of 3mm. The improved outcome of rescanning compared to interplay

can already be seen in these dose cuts.}

\label{dose\_pat08}

\end{center}

\end{figure}

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% \vspace\*{-0.3cm}

\begin{figure}[H]

\subfigure[D5-D95: LPV]{

\includegraphics[scale=0.18]{MAYO\_CTV\_LPV\_D5D95\_ALL.png}

}

\subfigure[D5-D95: RPV]{

\includegraphics[scale=0.18]{MAYO\_CTV\_RPV\_D5D95\_ALL.png}

}

\subfigure[V95: LPV]{

\includegraphics[scale=0.18]{MAYO\_CTV\_LPV\_V95\_ALL.png}

}

\subfigure[V95: RPV]{

\includegraphics[scale=0.18]{MAYO\_CTV\_RPV\_V95\_ALL.png}

}

\subfigure[V107: LPV]{

\includegraphics[scale=0.18]{MAYO\_CTV\_LPV\_V107\_ALL.png}

}

\subfigure[V107: RPV]{

\includegraphics[scale=0.18]{MAYO\_CTV\_RPV\_V107\_ALL.png}

}

\caption{Mean and standard deviation of dose analysis parameters D5-D95 (first row), V95 (middle row) and V107 (last row) over all patients.

The LPV (left column) and RPV (right column) were studied seperately. Static (black) as well as interplay (red) and different rescanning

numbers (5 times: turquois, 10 times: blue, 15 times: light green, 20 times: dark green) were compared for different motion patterns and

safety margins. For a better visualization the rescanning data points for each motion pattern are shifted.}

\label{static\_interplay\_rescanning\_ALL}

\end{figure}

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\begin{figure}[H]

\centering

\subfigure[LPV: sinus, period 1s, phase 0$^{\circ}$]{

\includegraphics[scale=0.58]{Corr\_V95\_LPV\_sin1s0.png}

}

\subfigure[RPV: sinus, period 1s, phase 0$^{\circ}$]{

\includegraphics[scale=0.58]{Corr\_V95\_RPV\_sin1s0.png}

}

\subfigure[LPV: sinus, period 1s, phase 90$^{\circ}$]{

\includegraphics[scale=0.58]{Corr\_V95\_LPV\_sin1s90.png}

}

\subfigure[RPV: sinus, period 1s, phase 90$^{\circ}$]{

\includegraphics[scale=0.58]{Corr\_V95\_RPV\_sin1s90.png}

}

\subfigure[LPV: sinus, period 0.7s, phase 0$^{\circ}$]{

\includegraphics[scale=0.58]{Corr\_V95\_LPV\_sin07s0.png}

}

\subfigure[RPV: sinus, period 0.7s, phase 0$^{\circ}$]{

\includegraphics[scale=0.58]{Corr\_V95\_RPV\_sin07s0.png}

}

\subfigure[LPV: sinus, period 0.7s, phase 90$^{\circ}$]{

\includegraphics[scale=0.58]{Corr\_V95\_LPV\_sin07s90.png}

}

\subfigure[RPV: sinus, period 0.7s, phase 90$^{\circ}$]{

\includegraphics[scale=0.58]{Corr\_V95\_RPV\_sin07s90.png}

}

\caption{Interplay dose homogeneity of LPV (left column) and RPV (right column) in all patients in relation to the maximal absolute

displacement of the PVs and for different underlying motion patterns (first row: sinus with 1s period and starting phase of 0$^{\circ}$,

second row: 1s period and starting phase of 90$^{\circ}$, third row: 0.7s period and starting phase of 0$^{\circ}$, last row: 0.7s period

and starting phase of 90$^{\circ}$).}

\label{corr\_maxabs\_V95\_interplay}

\end{figure}

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\subsubsection{Irradiation time}

In figure \ref{irrTime\_all} the mean irradiation time over all patients for different rescanning irradiations of LPV and RPV are shown for

different safety margins and motion patterns. The duration for each beam entry channel (gantry angle of -45$^{\circ}$, 135$^{\circ}$ and 0$^{\circ}$)

is plotted individually. It can be seen that the needed irradiation time increases with the used safety margin as the to irradiated volume

increases. The irradiation time is independent of the motion pattern but varies depending on the used beam entry channel.

Concerning the used rescan number it can be seen that no treatment prolongation is expected for higher rescan numbers.

This can be understood as with higher rescans the intensity of each raster point in one iteration is reduced by a factor which is equal to

the rescanning number. Hence the time the beam has to spend in one raster position, depositing the predetermined intensity, is reduced

resulting in an overall treatment time which is constant for all rescan cases. The stated results were achieved with a low intensity irradiation

(minimal particle number of 5.000). For an irradiation with 3mm margin around LPV and RPV the overall treatment time results to (13.71 $\pm$

0.94)min (see table \ref{tab:rescan\_time}) with rescanning as motion mitigation technique for heartbeat motion.

\begin{figure}[H]

\begin{center}

\includegraphics[scale=0.2]{All\_irrTime.png}

\caption{Mean and standard deviation of the irradiation time over all patients for different rescan numbers, underlying motion patterns and beam entry

channels.}

\label{irrTime\_all}

\end{center}

\end{figure}

\begin{table}[H]

\centering

% \footnotesize

\caption{Mean irradiation time for LPV and RPV with a safety margin of 3mm over all patients.}

\begin{tabular}{|c|c|c|}

\hline\hline

Gantry angle [$^{\circ}$] & time [min] & total [min] \\

\hline

-45 & 4.73 $\pm$ 0.93 & \\

135 & 4.42 $\pm$ 0.94 & 13.71 $\pm$ 0.94\\

0 & 4.56 $\pm$ 0.96 & \\

\hline

\hline\hline

\end{tabular}

\label{tab:rescan\_time}

\end{table}