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Geometrical uncertainties

# A population based statistical model for daily geometric variations in the thorax

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ABSTRACT

*Purpose:* To develop a population based statistical model of the systematic interfraction geometric variations between the planning CT and first treatment week of lung cancer patients for inclusion as uncertainty term in future probabilistic planning.
*Materials and methods:* Deformable image registrations between the planning CT and first week CBCTs of 235 lung cancer patients were used to generate deformation vector fields (DVFs) representing the geometric variations of lung cancer patients. Using a second deformable registration step, the average DVF per patient was mapped to an average patient CT. Subsequently, the dominant modes of systematic geometric variations were extracted using Principal Component Analysis (PCA). For evaluation a leave-one-out cross-validation was performed.
*Results:* The first three PCA components mainly described cranial–caudal, anterior–posterior, and left–right variations, respectively. Fifty and 112 components were needed to describe correspondingly 75% and 90% of the variance. An overall systematic variation of 3.6 mm SD was observed and could be described with an accuracy of about 1.0 mm with the PCA model.
*Conclusions:* A PCA based model for systematic geometric variations in the thorax was developed, and its accuracy determined. Such a model can serve as a basis for probability based treatment planning in lung cancer patients.
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During the course of radiotherapy, the anatomy of a patient can change, representing a challenge for accurate patient irradiation. For photon therapy, most of these geometric uncertainties can be dealt with using margins [1,2] and adaption [3]. Several studies have shown that a simple geometric expansion of the target volume is not sufficient for proton treatments [4,5], as the dose can vary considerably when the anatomy in the beam path changes, causing tumor underdosage and/or hotspots in the Organs-At-Risk (OARs) [6–8]. Due to density heterogeneities [9] in the thorax, this effect is even more relevant for lung cancer patients, making it challenging to obtain robust proton treatment plans. Several methods have been proposed to replace the margin recipe for proton therapy, ranging from beam specific margins [10] to robust optimization [11–14]. These methods mainly take into account the range and rigid setup uncertainties. To mitigate the dose effect caused by respiration, the concept of Internal Gross Tumor Volume (IGTV) [15] has been introduced. Prediction of the respiratory motion has been studied using a statistical motion model [16–19]. To create robust treatment plans, we need to take into account other interfraction geometric variations during treatment as well, such as baseline shifts, differential motion, posture change, etc. However, this has not yet been extensively explored for the thorax. As in the case of respiratory motion, a statistical population-based model describing typical geometric variations [20] can be used to describe these variations and include them in robust treatment planning (e.g. generating multiple plausible instances of the geometric changes and convert these changes into probability distributions of range uncertainties to include in the probabilistic plan optimization). Large geometric changes and treatment response, such as resolution of atelectasis and tumor shrinkage, are beyond the scope of this paper and should be accounted for using adaptive plan modification.

This work describes the use of Principal Component Analysis (PCA) [21] to create a statistical deformation model for random and systematic variations in the thorax to be used in future probabilistic treatment planning techniques.

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## Method and materials

### Patient data

For the generation of the model we used the planning CT (pCT) and all available cone beam CTs (CBCTs) (1–5 scans) from the first treatment week of lung cancer patients (Table 1) treated with radical radiotherapy or chemo-radiotherapy (excluding stereotactic treatments). We selected patients with readily available data treated between 2010 and 2013. Patients treated prior to 2012 had a mid-ventilation (MidV) pCT [22], while the other patients had a mid-position (MidP) pCT [23] and motion compensated (MC) CBCTs [24]. The average difference between MidV and MidP is small (<0.5 mm in all directions) [23].

Due to the limitations of Deformable Image Registration (DIR) we excluded 128 out of 387 patients with synchronous tumors in both lungs or anatomical abnormality of lung tissues (pleural effusion, atelectasis, post-obstructive lung tissue infiltration, post-operative radiation) on the pCT or CBCTs from the first treatment week. In addition, 13 patients were excluded where visual inspection showed large tumor volume differences between the planning CT and the first week CBCTs (see Fig. A1), since the model is not intended to describe such variations.

As a common frame of reference we used an "average" patient $CT_{ref}$ developed in collaboration with Elekta AB (Stockholm, Sweden), using DIR from 109 early stage lung cancer patients (see Supplementary materials Fig. A2). Eleven of the selected patients were excluded as the DIR had difficulties in deforming the pCT to this $CT_{ref}$, because these patients were much larger than the reference template (see Fig. A3). In total 235 patients were eligible for inclusion.

### Deformable image registration

To collect the interfraction geometric variability in a common reference system, two separate DIR operations were performed with in-house software: CBCT to pCT, and pCT to $CT_{ref}$. Voxel sizes of CTs and CBCTs were $1 \times 1 \times 3\ mm^3$ and $1 \times 1 \times 1\ mm^3$, respectively.

Both methods used a cubic b-spline algorithm [25,26] based on a regular grid of control points, driven by correlation ratio [27] as cost function (more details below). It resulted in a 3D deformation vector field (DVF) describing the displacement of the source scan (e.g. pCT) to the target scan (e.g. CBCT). This DVF was defined on a regular grid in the source scan, thus allowing the deformation of the target scan to the grid of the source scan. Each DVF is associated to a transformation function **D**.

Geometric variations between pCT and a treatment day of a patient were characterized by deforming the CBCT to the pCT, with $DVF_{CBCT \to pCT}$ as the result. Before deformation, a local rigid body registration of the bony anatomy was applied. In the optimization of the DIR, regularization terms (affine, orthonormality and properness [28]) were included due to limited CBCT quality to penalize undesired deformations. Furthermore, a 3 step coarse-to-fine multi-resolution optimization [29] was performed with a final control grid spacing of 1.0 cm. This CBCT-to-CT registration in lung cancer patients was previously validated by Abdoli et al. [30], and its accuracy was determined to be 1.5 ± 1 mm vector-length. As the cylindrical Field of View (FOV) of the CBCTs (Fig. A1b) was smaller ($\pi \times 12.5 \times 12.5 \times 25\ cm^3$) than the FOV of the pCT, we limited the deformation to the FOV of the CBCTs.

Each patient was mapped to the reference anatomy by deforming the pCT to the $CT_{ref}$ (see Fig. A4), producing $DVF_{pCT \to CT_{ref}}$. Unlike the previous DIR, an initial alignment was obtained by mapping the center of the pCT to the center of the $CT_{ref}$. As the $CT_{ref}$ had no tumor it was necessary to make an exclusion region around the primary tumor to prevent it from being deformed during the deformable registration procedure, while still allowing deformable registration of the surrounding tissues/organs (Fig. A5). For this DIR, no regularization terms were included and a 5 step coarse-to-fine multi-resolution optimization was performed with a final control grid spacing of 0.5 cm.

### Combining deformation vector fields

A DVF* (represented by transformation $\mathbf{D}^*$) describing geometric variations of a patient in the anatomy of the reference patient, can be obtained by combining its $DVF_{CBCT \to pCT}$ and $DVF_{pCT \to CT_{ref}}$:

$$\mathbf{D}^* = \mathbf{D}_{pCT \to CT_{ref}} \circ \mathbf{D}^{-1}_{CBCT \to pCT} \circ \mathbf{D}^{-1}_{pCT \to CT_{ref}}. \quad (1)$$

In radiotherapy, one generally distinguishes between systematic variations ($\Sigma$: between planned and treatment average) and random variations ($\sigma$: between treatment average and daily geometry). By averaging the $DVFs_{CBCT \to pCT}$ of the patient, we obtained the average DVF ($\langle DVF_{CBCT} \rangle$), describing the systematic variation in the anatomy of that patient

$$\langle DVF_{CBCT} \rangle = \frac{1}{F} \sum_{f=1}^{F} DVF^f_{CBCT \to pCT}, \quad (2)$$

where $F$ is the number of fractions with CBCT. The DVF describing the systematic geometric variation ($DVF_{SV}$) was then obtained by substituting $\langle DVF_{CBCT} \rangle$ into Eq. 1. The overall systematic variation was calculated by taking the root mean square (RMS) over all voxels of the standard deviations per voxel over all patients of these $DVF_{SV}$'s.

Random variations were calculated based on DVFs of all patients with more than one CBCT. First we calculated voxel-wise the standard deviation of the $DVF_{CBCT}$'s of each patient

$$\sigma = \sqrt{\frac{1}{F-1} \sum_{f=1}^{F} \left( DVF^f_{CBCT \to pCT} - \langle DVF_{CBCT} \rangle \right)^2}, \quad (3)$$

**Table 1**
Characteristics of the 246 patients included in the analysis.

| Characteristics | | |
|---|---|---|
| Gender *n (%)* | Male | 156 (63.4) |
| | Female | 90 (36.6) |
| Age [years] | mean (range) | 65.4 (32–88) |
| Tumor Location *n (%)* | Right Upper Lobe | 98 (38.9) |
| | Right Middle Lobe | 13 (5.3) |
| | Right Lower Lobe | 29 (11.8) |
| | Left Upper Lobe | 57 (23.2) |
| | Right Lower Lobe | 32 (13.0) |
| | Mediastinum | 17 (6.9) |
| Stage *n (%)* | IA | 5 (2.0) |
| | IB | 10 (4.1) |
| | IIA | 9 (3.7) |
| | IIB | 13 (5.3) |
| | IIIA | 101 (41.1) |
| | IIIB | 86 (35.0) |
| | IV | 18 (7.3) |
| | Unknown/Other | 4 (1.6) |
| Chemotherapy *n (%)* | Yes | 171 (69.5) |
| | No | 75 (30.5) |
| Tumor type *n (%)* | Non Small Lung Cancer | 220 (89.4) |
| | Small Lung Cancer | 20 (8.1) |
| | Unknown (no histology) | 6 (2.4) |
| Interval pCT – 1stCBCT [days] | median (range) | 10 (2–24) |
| Available CBCTs per patient *n* | 1 | 1 |
| | 2 | 5 |
| | 3 | 67 |
| | 4 | 25 |
| | 5 | 137 |