

A Diffeomorphic MLR Framework for Surrogate-based Motion Estimation and Situation-adapted Dose Accumulation

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Abstract. Respiratory motion is a major source of uncertainty in radiotherapy. Current approaches to cope with it – like gating or tracking techniques – usually make use of external breathing signals, interpreted as surrogates of internal motion patterns. Due to the complex nature of internal motion, a trend exists toward the application of multi-dimensional surrogates. This requires the development and evaluation of appropriate correspondence models between the surrogate data and internal motion patterns. We suggest using a multi-linear regression (MLR) and exploit the Log-Euclidean Framework to embed the MLR within a correspondence model yielding diffeomorphic estimates of motion fields of internal structures. The framework is evaluated using 4D CT data of lung tumor patients and different surrogates (spirometry, diaphragm tracking, monitoring chest wall motion). Further, the application of the framework for incorporating surrogate-based information about breathing variations into the process of dose accumulation is illustrated.

Keywords: radiation therapy, breathing signals, motion estimation, multivariate statistics, diffeomorphic registration, Log-Euclidean framework

1 Introduction

Respiratory motion is a major source of error in conventional radiation therapy (RT) of thoracic and abdominal tumors. Current approaches to cope with it usually rely on the use of external breathing signals that are easy and fast to acquire. This holds on the one hand for 4D CT imaging, during which image or projection data are sorted (“binned”) to different breathing states based on breathing signals like spirometry records or abdominal belt measurements; for dose delivery, on the other hand, analogue technical devices are reported to be used to steer gated dose delivery or tumor tracking techniques [1, 2].

These breathing signals usually provide only a surrogate of the object of interest, which is the respiratory motion of internal structures (tumor/clinical target, organs at risk); they are therefore also referred to as surrogates (of the internal motion). Due to the three-dimensional nature of internal motion patterns, intra-

and inter-cycle motion variability like, e.g., phase shifts between movements of different structures, the reliability of simple one-dimensional breathing signals is, however, more and more considered to be problematic, and a trend toward the use of multi-dimensional surrogates can be observed [3]. This requires the development and evaluation of correspondence models between the breathing signals and internal motion patterns that especially take advantage of the multi-dimensional structure of the surrogates.

The use of multi-dimensional signals and the complexity of motion patterns of internal structures, usually described by non-linear transformations or displacement fields, naturally suggests the use of multi-variate statistics. A straightforward approach for defining a correspondence model would therefore be a multi-linear regression (MLR); a patient-specific correspondence between surrogate data and internal motion patterns could then be trained using, e.g., a 4D CT image sequence of the patient and information about internal motion extracted from them on the one hand and surrogate measurements corresponding to the individual image frames on the other hand. In this case, the needed representation of the internal motion information would usually be given by transformations or displacement fields estimated by non-linear registration of the image frames of the 4D CT data [4].

In the context of motion estimation of internal structures it is, however, considered to be a natural choice to restrict the transformations to diffeomorphisms, as these ensure that “connected sets remain connected, disjoint sets remain disjoint, smoothness of anatomical features [...] is preserved, and coordinates are transformed consistently” [5]. This cannot be guaranteed when applying a standard MLR correspondence model – neither for interpolating internal motion fields from a surrogate measurement being in the range of the surrogate data available for the MLR training phase, nor for extrapolation purposes. Now, being placed in that context, the motivation of our contribution is three-fold. First, we propose to exploit the Log-Euclidean framework, which in the last years has been proven to be an efficient way for performing statistics on diffeomorphic transformation [6, 7], for definition of a diffeomorphic MLR-based correspondence model. Second, we present a first evaluation of the diffeomorphic MLR framework, including a comparison of the capabilities of three different but typical types of breathing signals when applied as regressors/surrogates: spirometry, tracking the motion of the diaphragm, and tracking chest wall motion. Third, we demonstrate the use of such a framework in the context of 4D dose calculation. The last part aims at incorporation of information about motion variations as provided by breathing signals into the process of dose accumulation during RT treatment planning.

2 Theoretical Background

During definition of the MLR-based correspondence model we assume the patient’s anatomy to be represented by a 4D CT image sequence $(I_j)_{j \in \{1, \dots, n_{ph}\}}$, $I_j : \Omega \subset \mathbb{R}^3 \rightarrow \mathbb{R}$, with j denoting the breathing states. Designating w.l.o.g. the state $j = 1$ as a reference breathing state, the motion of the anatomical and patholog-

ical structures will then be described by transformations $\varphi_j = id + u_j : \Omega \rightarrow \Omega$, which – in the sense of image registration – maximize similarity/minimize dissimilarity of I_1 and $(I_j \circ \varphi_j)$ with respect to additional smoothness requirements for the transformations. Being interested in a general diffeomorphic motion estimation framework, we choose a diffeomorphic registration scheme to compute the transformations φ_j ; the scheme is described in Section 2.1. Following, the theory behind the MLR framework is explained in Section 2.2. Finally, in Section 2.3, the integration of the MLR-based correspondence model into the process of dose accumulation is detailed.

2.1 Diffeomorphic Registration and the Log-Euclidean Framework

Diffeomorphic transformations can be modeled as endpoints of the evolution equation over unit time $t \in [0, 1]$,

$$\frac{\partial}{\partial t} \phi_t(x) = v(\phi_t(x), t) \quad \text{with } \phi_0(x) = x, \quad (1)$$

with $v : \Omega \times [0, 1] \rightarrow \mathbb{R}^3$ being sufficiently smooth velocity fields parameterizing the flow $\phi : \Omega \times [0, 1] \rightarrow \Omega$. Thus, a diffeomorphic transformation $\varphi : \Omega \rightarrow \Omega$ can be computed by

$$\varphi(x) = \phi_1(x) = \phi_0(x, 0) + \int_0^1 v(\phi_t(x), t) dt \quad (2)$$

[8]. The time-dependence of the velocity fields leads, however, to time and memory consuming algorithms in the context of image registration [5]. To avoid these problems, stationary velocity fields can be considered instead. Then, as part of the Log-Euclidean Framework, it can be exploited that the set of diffeomorphisms $\text{Diff}(\Omega)$, together with the function composition, exhibits a Lie group structure. For a diffeomorphism parameterized by a stationary velocity field v , v is part of the tangential space $\mathcal{T}_{\text{id}}\text{Diff}(\Omega)$ at the neutral element of $\text{Diff}(\Omega)$ [6]. Further, $\mathcal{T}_{\text{id}}\text{Diff}(\Omega)$ and $\text{Diff}(\Omega)$ are connected by the so-called group exponential $\exp : \mathcal{T}_{\text{id}}\text{Diff}(\Omega) \rightarrow \text{Diff}(\Omega)$, with the paths $\phi_t = \exp(tv)$ being one parameter subgroups of $\text{Diff}(\Omega)$. Based thereon, Arsigny et al. proposed to rephrase the transformation of (2) by

$$\varphi(x) = \phi_1(x) = \exp(v(x)), \quad (3)$$

with the group exponential being efficiently computed using the scaling-and-squaring algorithm [6].

The parameterization (3) also states the basis of the PDE-driven non-linear registration framework applied in the work at hand to compute the sought transformations φ_j describing the respiratory motion of internal structures in the 4D image sequences. Let therefore I_1 serve as reference image and I_j with j being an arbitrary breathing state denoting the target image, we search for the transformation $\varphi_j = \exp(v_j)$ that minimizes the energy functional

$$\mathcal{J}[v_j] = \mathcal{D}[I_1, I_j \circ \varphi_j] + \alpha \mathcal{S}[v_j]; \quad (4)$$

\mathcal{D} represents a dissimilarity measure and \mathcal{S} a smoothness term/regularizer. The Euler Lagrange equations can then be formulated as

$$f(x, \varphi_j(x)) + \alpha \mathcal{A}[v_j](x) = 0, \quad x \in \Omega, \quad (5)$$

with f being a force-term corresponding to the dissimilarity measure and \mathcal{A} as a linear differential operator associated to \mathcal{S} . Here, a diffusion regularization approach (i.e. $\mathcal{A} = \Delta$) and the so-called active Thirion forces, also referred to as normalized SSD forces, are applied; for details see, e.g., [9].

2.2 Multi-linear Regression for Surrogate-based Motion Estimation

With the transformations $(\varphi_j)_{j \in \{1, \dots, n_{ph}\}}$ and velocity fields $(v_j)_{j \in \{1, \dots, n_{ph}\}}$ being computed by diffeomorphic registration, we further assume that surrogate measurements $(\xi_j)_{j \in \{1, \dots, n_{ph}\}}$, $\xi_j \in \mathbb{R}^{n_{sur}}$ have been acquired simultaneously to the CT image data (or subsequently simulated). Then, the idea of the diffeomorphic MLR-based correspondence model is to apply a regression to estimate the relationship between the surrogate-signals ξ_j (regressors) and the velocity fields v_j (regressands) instead of the motion fields u_j or transformations φ_j . Interpret the velocity fields v_j and the surrogate data ξ_j as random variables \mathbf{V}_j and \mathbf{Z}_j , for which the motion information is written in a single column. Let the individual random variables further be combined within the matrices $\mathbf{V} := (\mathbf{V}_1^c, \dots, \mathbf{V}_{n_{ph}}^c)$ and $\mathbf{Z} := (\mathbf{Z}_1^c, \dots, \mathbf{Z}_{n_{ph}}^c)$ with $\mathbf{V}_j^c = \mathbf{V}_j - \bar{\mathbf{V}}$ and $\mathbf{Z}_j^c = \mathbf{Z}_j - \bar{\mathbf{Z}}$ as the centered versions of \mathbf{V}_j and \mathbf{Z}_j . The multi-variate multi-linear regression can then be phrased as the estimation of the relationship

$$\mathbf{V} = \mathbf{B}\mathbf{Z} \quad (6)$$

by

$$\mathbf{B} = \arg \min_{\mathbf{B}'} \text{tr} \left[(\mathbf{V} - \mathbf{B}'\mathbf{Z})(\mathbf{V} - \mathbf{B}'\mathbf{Z})^T \right] = \mathbf{V}\mathbf{Z}^T \left(\mathbf{Z}\mathbf{Z}^T \right)^{-1}. \quad (7)$$

Thus, \mathbf{B} represents an ordinary least squares (OLS) estimator between the surrogate data $\xi_j \equiv \mathbf{Z}_j$ and the velocity fields v_j and \mathbf{V}_j , respectively.

With the OLS estimator \mathbf{B} computed, for any measurement $\hat{\xi} \equiv \hat{\mathbf{Z}}$ a corresponding velocity field \hat{v} can be derived by $\hat{\mathbf{V}} = \bar{\mathbf{V}} + \mathbf{B} \left(\hat{\mathbf{Z}} - \bar{\mathbf{Z}} \right)$ and resorting the entries of $\hat{\mathbf{V}}$ wrt. the structure of \hat{v} . Exploiting the Log-Euclidean framework, the sought diffeomorphic transformation is finally to be calculated by $\hat{\varphi} = \exp(\hat{v}_j)$.

2.3 Application of the MLR-based Correspondence Model to Situation-adapted Dose Accumulation

In the context of 4D dose calculation, dose accumulation aims at assessing dosimetric effects of respiratory motion for a generated (3D) treatment plan. Given a

4D image sequence $(I_j)_{j \in \{1, \dots, n_{ph}\}}$ of the patient, a standard dose accumulation for voxels $x \in \Omega$ of the reference image reads

$$D^{4D}(x) = \sum_{j=1}^{n_{ph}} w_j (D_j \circ \varphi_j)(x) \quad (8)$$

with $D^{4D} : \Omega \rightarrow \mathbb{R}_+$ being the sought accumulated dose; in that, the dose contributions $D_j : \Omega \rightarrow \mathbb{R}_+$ (3D dose calculated as resulting for the given treatment plan and the CT image I_j) are often equally weighted, i.e. $w_j = 1/n_{ph}$.

It is obvious that neither motion variations nor effects due to the interplay of organ motion and short delivery times of single irradiation fields can be assessed by (8) [10]. Thus, going one step further toward accurate dose accumulation, in this contribution we propose to start the dose accumulation process with a patient-specific surrogate signal measurement and the corresponding OLS estimator \mathbf{B} as computed by (7). Additionally, we assume the beginning time and the duration of each irradiation field of the treatment plan to be known and denoted by $t_{k,0}$ and $t_{k,end}$ ($k = 1, \dots, n_{fields}$). Then, instead of a weighted summation over the dose distributions D_j , we now sample the surrogate signal equidistantly in time and rephrase the dose accumulation problem as follows:

$$\begin{aligned} D^{4D}(x) &= \sum_{k=1}^{n_{fields}} \int_{t_{k,0}}^{t_{k,end}} \dot{D}_k(x(t), t) dt \\ &\approx \sum_{k=1}^{n_{fields}} \sum_l \dot{D}_k(\hat{\varphi}_l(x), t_l) \Delta t \\ &\approx \sum_{k=1}^{n_{fields}} \frac{\Delta t}{t_{k,end} - t_{k,0}} \sum_l D_k(\hat{\varphi}_l(x), t_l). \end{aligned} \quad (9)$$

$\dot{D}_k(\hat{\varphi}_l(x), t_l)$ is the dose rate for field k at time t_l belonging to the sampling point l , which is evaluated at the position of voxel $x \in \Omega$ of the reference CT at time t_l ; $D_k(\hat{\varphi}_l(x), t_l)$ is the corresponding dose with $\hat{\varphi}_l$ being estimated based on the surrogate measurement at t_l and the OLS estimator \mathbf{B} (cf. Section 2.2).

3 Experiments and Results

Our experiments were based on 4D CT images of 10 lung tumor patients (10-14 breathing states, spatial resolution $320 \times 320 \times 270$ voxels with an isotropic spacing of 1.5 mm). The image binning was grounded on spirometry records, which were also considered as a first example of a (one-dimensional) breathing surrogate during evaluation of the MLR correspondence model. For evaluation purposes we further identified the domes of the left and the right hemi-diaphragm and interpreted the corresponding displacements $\{u_1(x^{dia}), \dots, u_{n_{ph}}(x^{dia})\}$ as a second type of surrogate measurements ($n_{sur} = 2 \cdot 3$). As a third type of breathing signal we simulated a laser-based tracking of lifting/raising of chest wall points within

Table 1. Landmark-based target registration errors and tumor propagation errors (evaluated based on the tumors’ centers of mass, COM), obtained for the diffeomorphic MLR-based estimation of inner lung motion as part of the leave-out tests and listed for the different surrogate types (mean \pm standard deviation for the ten patients considered; EE/ME = end-/mid-expiration, EI/MI = end-/mid-inspiration).

Motion Estimation	Landmark-based Target-Registration-Error [mm]			Tumor COM distance [mm]
	EI \rightarrow EE	EI \rightarrow MI	EI \rightarrow ME	EI \rightarrow EE
No motion estimation	6.8 ± 1.8	4.9 ± 1.2	2.5 ± 0.6	6.9 ± 6.1
Intra-patient registration	1.6 ± 0.2	1.6 ± 0.1	1.5 ± 0.2	0.9 ± 0.5
<i>Diffeomorphic MLR framework; surrogate = ...</i>				
spirometry	2.0 ± 0.3	2.0 ± 0.3	1.8 ± 0.3	1.5 ± 0.9
diaphragm motion	2.1 ± 0.4	1.8 ± 0.2	1.7 ± 0.3	1.7 ± 0.9
chest wall motion, sternum	4.7 ± 1.4	2.6 ± 0.9	2.4 ± 0.7	4.7 ± 4.3
chest wall motion, line	2.1 ± 0.4	1.9 ± 0.2	1.8 ± 0.2	1.4 ± 1.0

the 4D CT images by a ray tracing approach (ray direction: anterior-posterior). In a first run, a point laser was simulated with the laser origin placed over the sternum; in the second run, we used several (≈ 150) points lying on line (direction: superior-inferior), aiming at simulating the use of a line laser. For each surrogate and the state of end-inspiration (EI) as reference state, we evaluated the accuracy of the MLR correspondence models in leave-out tests. For evaluating “extrapolation” capabilities, all breathing states but the states of and around end-expiration (EE), i.e. in total $(n_{ph} - 3)$ states, are used for training the OLS estimators; the surrogate values ξ_{EE} were then applied to estimate the transformation $\hat{\varphi}_{EE}$. The accuracy of the motion estimation was evaluated by determining a target registration error based on manually defined corresponding landmarks (70 landmarks per patient and breathing phase). Additionally, the accuracy of a model-based tumor segmentation propagation between EI and EE was quantified considering manual tumor segmentations as ground truth data. Interpolation capabilities were analogously analyzed for motion estimation between EI and mid-inspiration (MI) and mid-expiration (ME).

The corresponding results are listed in Table 1. Referring to the accuracy of the breathing surrogates, no significant differences can be observed between spirometry, tracking diaphragm motion, and combining motion information of several chest wall points (i.e. simulating the line laser). In comparison thereto, the accuracy is significantly decreased when tracking the raising/lifting of only a single chest wall point (here: the sternum); this demonstrates the potential of combining motion information at least for tracking chest wall motion. The values listed in Table 1 were further compared with analogous results obtained by a standard non-diffeomorphic MLR framework (i.e. modeling correspondences directly between the motion fields u_j and the surrogate data ξ_j). It turned out that no significant differences were apparent wrt. the accuracy of the motion estima-

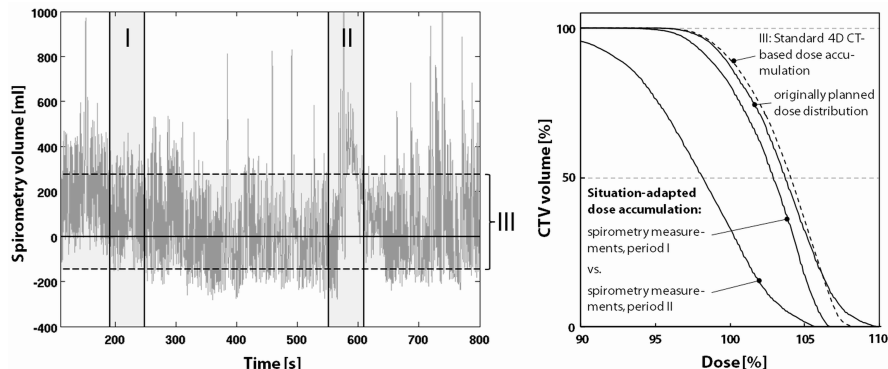


Fig. 1. Illustration of differences between the MLR-based situation-adapted and standard dose accumulation results. Left: spirometry record, acquired during 4D CT image acquisition. The interval III denotes the spirometry values represented by the 4D CT data. The periods I and II are the intervals considered for demonstration of the situation-adapted dose accumulation. Right: dose-volume-histograms for the dose accumulation approaches and the clinical target volume CTV.

tion. However, especially in the case of extrapolation, the motion fields obtained by non-diffeomorphic correspondence models featured a series of singularities – which were not existing for the diffeomorphic framework.

To further demonstrate the application of the diffeomorphic MLR-based correspondence model for dose accumulation purposes, a 3D IMRT treatment plan was generated for a patient with a clinically relevant tumor motion amplitude of 12 mm (10 mm isotropic margin between clinical and planning target volume CTV and PTV; planning phase: MI; treatment planning system: CMS XiO v.4.3.3). Accumulated dose distributions were computed using standard dose accumulation according to (8) and applying the surrogate-based accumulation scheme as derived in (9). The surrogate-based dose accumulation was based on the spirometry data recorded during the 4D CT image acquisition, see Figure 1 (left); we selected both a period of the record with little variance of the distribution of the local maxima (dose accumulation for a “regular breathing situation”; period I in the figure) and a period of high variance of the local maxima (“irregular breathing situation”, period II).

The dose-volume-histograms for the CTV and the different dose distributions are shown in Figure 1 (right). It becomes obvious that standard dose accumulation based on only the 4D CT image information underestimates the risk of CTV underdosages due to respiratory motion when compared with the surrogate-based dose accumulation and especially the “irregular breathing situation”. It should, however, be noted that for the case at hand the irregularities in the spirometry records are very pronounced compared to other patients. Further, the discrepancies between standard and situation-adapted dose accumulation are consequences of both breathing signal variations and the interplay effects mentioned in Section 2.3. The example case gives, nevertheless, an intuitive illustration of the principle and the idea behind the situation-adapted dose accumulation.

4 Conclusions

Current RT techniques to cope with respiratory motion usually rely on the use of breathing signals, also referred to as surrogates (of internal motion patterns). Taking into account a trend toward multi-dimensional surrogates, we applied the Log-Euclidean framework for defining a diffeomorphic MLR-based correspondence model and, considering different types of breathing signals, presented a first evaluation of its accuracy. Further, its use for incorporating surrogate-based information about breathing motion variations into 4D dose calculation has been illustrated. At this, the focus of the contribution lay on the theoretical concept of both the diffeomorphic MLR-based correspondence modeling and the surrogate-based dose accumulation with the results presented being a first proof-of-concept, which has to be approved in following evaluation studies. This addresses – as potential future work – the generation of suitable ground-truth data, perhaps by acquiring repeatedly 4D CT data of the patients or designing appropriate motion phantom studies.

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