# Elastic Registration of Multiphase CT Images of Liver

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# ABSTRACT

In this work we present a novel approach for elastic image registration of multi-phase contrast enhanced CT images of liver. A problem in registration of multiphase CT is that the images contain similar but complementary structures. In our application each image shows a different part of the vessel system, e.g., portal/hepatic venous/arterial, or biliary vessels. Portal, arterial and biliary vessels run in parallel and abut on each other forming the so called portal triad, while hepatic veins run independent. Naive registration will tend to align complementary vessel.

Our new approach is based on minimizing a cost function consisting of a distance measure and a regularizer. For the distance we use the recently proposed normalized gradient field measure that focuses on the alignment of edges. For the regularizer we use the linear elastic potential. The key feature of our approach is an additional penalty term using segmentations of the different vessel systems in the images to avoid overlaps of complementary structures. We successfully demonstrate our new method by real data examples.

## 1. INTRODUCTION

Liver tumors belong to the worldwide most common malignancies. Particularly due to the filter function of liver, tumors from other sites as, e.g., the colon, are very likely to spread metastasis to here. The only known curative therapy is surgical intervention to remove a tumor. Such a so-called R0-resection is a difficult task and requires extensive planning. Liver consist of quite homogeneous tissue and vessels which makes it difficult for the surgeon to navigate. In particular, the surgeon needs to be careful not to cut vessels supporting functional tissue unintentionally. However, few days before an intervention multi-phase CT images are generated for planning to exactly localize vessels and tumors. Then, from this data a 3D model is generated for planning the surgical path, doing risk analysis, etc.

The multiphase CT images are contrast enhanced images each showing different parts of the vessel system. Before we can fuse the information from all images to reconstruct the whole vessel system we have to do registration. There have been proposed several methods for rigid and non-rigid registration of multi-phase CT of liver<sup>1-4</sup> reporting reasonable results. The methods are mainly based on mutual information as similarity measure for images and in the case of non-rigid registration typically a B-spline or Thin-Plate-spline deformation model is used.

However, state-of-the-art methods are purely based on multi-modal image registration not taking into account the presence and absence of complimentary structure, i.e., different parts of the vessel system. In particular in liver, vessels run in parallel and abut on each other. In our experiments we found that plain multi-modal image registration, rigid or non-rigid, is likely to match complementary vessel. To avoid this phenomena, in our new approach we do segmentations of the vessels for each phase before registration. Then we use this additional information to avoid matching and overlaps of complementary vessel parts.

Similar to existing methods, in our new approach we use volumetric elastic image registration. To this end, we compute a deformation field by minimizing a suitable cost function made up from a distance measure that quantifies similarity of two images and a regularizer that forces smoothness of the deformation. For the distance measure we use the recently proposed normalized gradient fields<sup>5</sup> that focus on the alignment of edges. The reason for this choice is twofold. First, due to the contrast enhancement of the CT we cannot compare two images directly such that we have to deal with a multi modal setting. Second, due to the homogeneous structure of liver

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tissue, here the dominant structures in the images are edges of vessels and liver boundary. We also restrict the distance measure to the region occupied by  $liver^{1-4}$  to avoid mis-alignments resulting from matching non-target structures such as, e.g., ribs.

The new feature of our approach is an additional penalty term to avoid matching complementary structures. Therefore, we use segmentations of the vessels for the different phases and penalize intersections during registration.

The paper is organized as follows. In section 2 we describe our approach that builds on a variational setting. We start with the continuous formulation of the problem and subsequent describe our discretization. Next we consider a numerical scheme for finding a non-linear deformation. To this end, we propose a limited memory BFGS quasi Newton optimization strategy. Finally, in section 5 we present some results that demonstrates the effectiveness of our method.

## 2. METHOD

In the following we describe the framework for the registration of contrast enhanced biphasic CT images, e.g., images with contrast agent timed for arterial, venous, or biliary vessels, respectively. We use a variational formulation of the registration problem and minimize a suitable cost function for finding a non-linear deformation field. Therefore, we adapt a standard variational approach made up from a so-called distance measure that quantifies the similarity of the images and a regularizer term forcing smoothness properties of the deformation. Furthermore we extend the standard setting by a constraint to avoid mis-alignments of complementary vessels.

We start with the continuous model.

For the registration we are given two images, a reference R and template T. The images are modeled as d-dimensional intensity mappings  $R, T : \mathbb{R}^d \to \mathbb{R}$ . Here, we particularly considering the three-dimensional case, i.e., d = 3. In a addition to the images we assume we have three segmentations available. These are:

- $\Sigma_{R}^{\text{Liver}} \subset \mathbb{R}^{d}$ , the area occupied by liver in the reference R,
- $\Sigma_{R}^{\text{Vessel}} \subset \mathbb{R}^{d}$ , the vessels in R, and
- $\Sigma_T^{\text{Vessel}} \subset \mathbb{R}^d$ , the vessels in the template image T that shall not be matched to the vessels  $\Sigma_R^{\text{Vessel}}$ .

The goal of the registration is to find a deformation  $y : \mathbb{R}^d \to \mathbb{R}^d$  of the template such that R and T(y) are aligned. Note that here T(y) means the composition of functions, i.e,  $T(y) = T \circ y$ . Furthermore, in our new approach we have additional knowledge about vessels that do not coincide. Thus, a point x in the set  $\Sigma_R^{\text{Vessels}}$  shall not be matched to a point y(x) in  $\Sigma_T^{\text{Vessels}}$ , i.e., we require  $y(\Sigma_R^{\text{Vessels}}) \cap \Sigma_T^{\text{Vessels}} = \emptyset$ . Next, we first describe the standard variational setting and following its extension to our novel approach.

In a standard variational setting without incorporating external knowledge we achieve the registration by minimize a joint functional such that

$$D(R, T(y)) + \alpha S(y - y_{\text{ref}}) = \min, \qquad (1)$$

where D is a distance measure that quantifies the similarity of the reference R and the deformed template T(y), S is a regularizer that forces smoothness of the deformation by penalizing derivatives,  $\alpha > 0$  is a fixed chosen parameter that weights the smoothness of the deformation versus similarity of the images, and  $y_{\text{ref}}$  is a reference deformation that allows for only penalizing changes from  $y_{\text{ref}}$ . A typical choice for  $y_{\text{ref}}$  is the identity, i.e.,  $y_{\text{ref}}(x) = x$ , such that only the displacement is penalized or  $y_{\text{ref}}$  is the resulting deformation from a pre-registration step. However, we will not discuss a particular choice for  $y_{\text{ref}}$  here.

For the distance measure we choose the normalized gradient field (NGF) distance measure<sup>5</sup> restricted to the segmentation of the liver in the reference  $\Sigma_{R}^{\text{Liver}}$ . Thus, the NGF distance measure is given by

$$D(R, T(y)) := \frac{1}{2} \int_{\Sigma_R^{\text{Liver}}} 1 - \left( \frac{\nabla R(x)^\top \nabla T(y(x))}{\|\nabla R(x)\| \|\nabla T(y(x))\|} \right)^2 dx.$$

Note that the integrand is the squared sine of the gray value gradients of the images. The reason for this choice is twofold. First, we are dealing with multi-modality, since the data stems from multi-phase contrast imaging. Thus, mono-modal measures such as the sum of squared differences will not work for us. A popular and suitable choice for a distance measure in multi-modal image registration is mutual-information. However, in our case we are dealing with images of liver where the dominant structures are vessels and liver boundary. On that account, we choose the NGF distance measure that focuses on edges. Furthermore, we restrict the integration domain to liver to avoid bad alignment of soft-tissue structures caused by aligning surrounding rigid non-target structures such as, e.g., ribs.

As second building block we use the popular elastic regularizer<sup>6</sup> given by

$$S(y) := \frac{1}{2} \int_{\Omega} \mu \|\nabla y(x)\|^2 + (\mu + \lambda) |\nabla \cdot y(x)|^2 dx$$

with the Lamé elasticity constants  $\mu$  and  $\lambda$ . A typical choice is  $\mu = 1$  and  $\lambda = 0$ . We do not restrict the integration domain to liver as for the distance measure. Here, we choose a rectangular domain  $\Omega \subset \mathbb{R}^d$  that covers the region of interest such that  $\Sigma_R^{\text{Liver}} \subset \Omega$  and  $\Sigma_R^{\text{Vessels}} \subset \Omega$ . Consequently, the registration outside  $\Sigma_R^{\text{Liver}}$  is not data driven and dominated by smoothness properties forced from the regularizer. This can be seen as smooth interpolation of the deformation to a larger domain. As a result, this strategy allows for computing the deformation as common on a rectangular domain and in particular we avoid technical problems and significantly simplify the treatment of the boundary.

Now we turn to our novel approach. Clearly, computing a solution of (1) will not guarantee that points in  $\Sigma_R^{\text{Vessels}}$  are not matched with points in  $\Sigma_T^{\text{Vessels}}$ . Even worse, since we do multi-modal registration matching non-corresponding but similar structures improves the distance measure such that it is likely this will happen. For that reason, we add the requirement  $y(\Sigma_R^{\text{Vessels}}) \cap \Sigma_T^{\text{Vessels}} = \emptyset$  as a constraint to problem (1).

Let C be any function that is supported on  $\Sigma_T^{\text{Vessel}}$ , i.e.,  $C(x) \neq 0$  for  $x \in \Sigma_T^{\text{Vessel}}$  and zero else. A natural choice would be  $C = \chi_{\Sigma_T^{\text{Vessel}}}$ , where  $\chi_{\Sigma_T^{\text{Vessel}}}$  is the indicator function of  $\Sigma_T^{\text{Vessel}}$  given by

$$\chi_{\Sigma_T^{\text{Vessel}}}(x) = \begin{cases} 1 & \text{if } x \in \Sigma_T^{\text{Vessel}} \\ 0 & \text{else.} \end{cases}$$

The reason for being quite general with the special choice of C is that we can use other functions than the indicator. In particular this allows to use smooth and differentiable functions. Later, we will apply derivative based optimization such that the smoothness of C becomes crucial.

However, with this formulation we can express the requirement  $y(\Sigma_R^{\text{Vessels}}) \cap \Sigma_T^{\text{Vessels}} = \emptyset$  as C(y) = 0 on  $\Sigma_R^{\text{Vessels}}$ . For our novel approach we add the constraint to problem (1) and aim to find a deformation  $y : \mathbb{R}^d \to \mathbb{R}^d$  such that

$$D(R, T(y)) + \alpha S(y - y_{ref}) = \min \quad \text{subject to} \quad C(y(x)) = 0 \text{ for } x \in \Sigma_R^{Vessel}.$$
(2)

In the registration problem (2) the requirement that vessels of the reference and vessels of the template may not overlap are directly modeled as hard constraints C(y) = 0 on  $\Sigma_R^{\text{Vessel}}$ . Although this is the problem we are interested in, computing a solution of the constrained optimization problem is quite involved. To this end and for practical purpose, we relax the hard constraints by introducing a quadratic penalty term

$$P(y) := \frac{1}{2} \|C(y)\|_{L^2(\Sigma_R^{\text{Vessel}})}^2 = \frac{1}{2} \int_{\Sigma_R^{\text{Vessel}}} C(y(x))^2 \, dx.$$

Then, our strategy is to compute an approximate solution to the constrained approach (2) by solving the unconstrained penalty problem to find a deformation y such that

$$D(y) + \alpha S(y) + \beta P(y) = \min$$
(3)

where  $\beta > 0$  is parameter that weights the influence of the constraints and needs to be chosen large. Note that due to the properties of the norm we have

$$P(y) = 0 \quad \Leftrightarrow \quad C(y) = 0 \text{ on } \Sigma_R^{\text{Vessel}}$$

$$\partial_{1}^{h}R_{i-\frac{1}{2},j} = \frac{R_{i,j} - R_{i-1,j}}{h_{1}}$$

$$\partial_{2}^{h}R_{i,j-\frac{1}{2}} = \frac{R_{i,j} - R_{i,j-1}}{h_{2}} \qquad \bullet \qquad R_{i,j}$$

$$\partial_{2}^{h}R_{i,j+\frac{1}{2}} = \frac{R_{i,j+1} - R_{i,j}}{h_{2}}$$

$$\partial_{1}^{h}R_{i+\frac{1}{2},j} = \frac{R_{i+1,j} - R_{i,j}}{h_{1}}$$

Figure 1. Discretization of derivatives for the NGF distance measure

such that a solution y with P(y) = 0 also satisfies the constraints  $y(\Sigma_R^{\text{Vessels}}) \cap \Sigma_T^{\text{Vessels}} = \emptyset$  exactly. In practice we cannot expect this will happen and P will take small values greater than zero that correspond to the case of small overlaps at vessel boundaries.

In general, we could solve a sequence of sub-problems for increasing values of  $\beta$  such that in the limit we converge to the solution of the constrained approach (2). However, it is well-known that this strategy is numerically unstable for very large values of  $\beta$  such that  $\beta$  needs to be chosen moderate.<sup>7</sup> To compute a solution of the constrained approach we can use more sophisticated methods, e.g., quadratic programming or the augmented Lagrangian approach.<sup>7</sup> However, from a practical point of view tiny overlaps are tolerable such that for practical purpose the penalty approach seems reasonable. Furthermore, we can also improve the situation by choosing the segmentations bit larger than necessary and extend them by adding small margins.

Next we describe our numerical implementation. We start with the discretization of the unconstrained penalty approach (3).

#### **3. DISCRETIZATION**

For the registration we discretize (3) using finite differences for derivatives and common mid-point rule for the discretization of integrals. For ease of presentation we restrict ourselves to the two-dimensional case. The discretization for higher dimension is analogues. Furthermore, we assume for simplicity, the rectangular domain  $\Omega$  is the unit square  $\Omega = (0, 1) \times (0, 1)$ . We start by discretizing  $\Omega$  with a uniform grid composed of  $m_1 \times m_2$  cells with mesh-size  $h_1 = 1/m_1$  and  $h_2 = 1/m_2$ . Furthermore, let

$$x_{ij}^h := \left(h_1\left(i + \frac{1}{2}\right), \ h_2\left(j + \frac{1}{2}\right)\right)^{\top}$$

and

$$\Omega^h := \{x_{ij}^h : i = 1, 2, \dots, m_1 \text{ and } j = 1, 2, \dots, m_2\}$$

be the set of all cell-centers.

## 3.1 Discretization of the Distance Measure

Recall, the NGF distance of two images is given by

$$D(R,T) = \frac{1}{2} \int_{\Sigma_R^{\text{Liver}}} 1 - \left( \frac{\nabla R(x)^\top \nabla T(x)}{\|\nabla R(x)\| \|\nabla T(x)\|} \right)^2 dx$$

For the discretization of the integral we use the mid-point rule and we approximate derivatives of the integrand by a second-order finite difference scheme. To this end consider a single cell with cell-center  $x_{ij}^h$  and we want compute an approximation to

$$1 - \left(\frac{\nabla R_{ij}^{\top} \nabla T_{ij}}{\|\nabla R_{ij}\| \|\nabla T_{ij}\|}\right)^2 = 1 - \frac{(\partial_1 R_{ij} \partial_1 T_{ij} + \partial_2 R_{ij} \partial_2 T_{ij})^2}{(\partial_1 R_{ij}^2 + \partial_2 R_{ij}^2) (\partial_1 T_{ij}^2 + \partial_2 T_{ij}^2)}$$

where  $R_{ij}$  and  $T_{ij}$  are short-hand notations for the values at grid point  $x_{ij}^h$ . First we compute second order approximations to the partial derivatives located on the edges of the cell by short differences to its neighbors, see Figure 1. Next, we multiply and square, respectively, these differences resulting second order approximations to  $\partial_{\ell}R \partial_{\ell}T$ ,  $(\partial_{\ell}R)^2$ , and  $(\partial_{\ell}T)^2$ ,  $\ell = 1, 2$ . Finally, we average all values to the cell-center and sum them up. Since averaging is independent from the mesh size and also second order accurate, we finally obtain second order approximations at the cell-center. Summarizing, we have the following approximations

$$\nabla R_{ij}^{\top} \nabla T_{ij} \approx \frac{1}{2} \Big( \partial_1^h R_{i-\frac{1}{2},j} \, \partial_1^h T_{i-\frac{1}{2},j} + \partial_1^h R_{i+\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} \Big) + \frac{1}{2} \Big( \partial_2^h R_{i,j-\frac{1}{2}} \, \partial_2^h T_{i,j-\frac{1}{2}} + \partial_2^h R_{i,j+\frac{1}{2}} \, \partial_2^h T_{i,j+\frac{1}{2}} \Big) \Big) \Big( \partial_1^h R_{i-\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} + \partial_1^h R_{i+\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} \Big) + \frac{1}{2} \Big( \partial_1^h R_{i,j-\frac{1}{2}} \, \partial_2^h T_{i,j-\frac{1}{2}} + \partial_2^h R_{i,j+\frac{1}{2}} \, \partial_2^h T_{i,j+\frac{1}{2}} \Big) \Big) \Big) \Big( \partial_1^h R_{i-\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} + \partial_1^h R_{i+\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} \Big) \Big) \Big) \Big) \Big( \partial_1^h R_{i-\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} + \partial_1^h R_{i+\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} \Big) \Big) \Big) \Big) \Big) \Big) \Big( \partial_1^h R_{i+\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} + \partial_1^h R_{i+\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} \Big) \Big) \Big) \Big) \Big) \Big) \Big( \partial_1^h R_{i+\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} \Big) \Big) \Big) \Big) \Big) \Big( \partial_1^h R_{i+\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} \Big) \Big) \Big) \Big) \Big) \Big) \Big) \Big) \Big( \partial_1^h R_{i+\frac{1}{2},j} \, \partial_1^h T_{i+\frac{1}{2},j} \,$$

and

$$\begin{aligned} \|\nabla R_{ij}\|^2 &\approx \frac{1}{2} \left( \partial_1^h R_{i-\frac{1}{2},j}^2 + \partial_1^h R_{i+\frac{1}{2},j}^2 \right) + \frac{1}{2} \left( \partial_2^h R_{i,j-\frac{1}{2}}^2 + \partial_2^h R_{i,j+\frac{1}{2}}^2 \right), \\ \|\nabla T_{ij}\|^2 &\approx \frac{1}{2} \left( \partial_1^h T_{i-\frac{1}{2},j}^2 + \partial_1^h T_{i+\frac{1}{2},j}^2 \right) + \frac{1}{2} \left( \partial_2^h T_{i,j-\frac{1}{2}}^2 + \partial_2^h T_{i,j+\frac{1}{2}}^2 \right). \end{aligned}$$

Alternatively, we could have used long differences to compute derivatives at the cell-centers directly or we could first average the short differences on the edges to cell-centers and then squaring and multiplying them. On first sight this seems easier to do and also results a second order discretization. The drawback is that this procedure introduces an artificial null-space. That is, such approximation takes zero values even if neighbored grid points have different gray-values and therefore derivatives are non-zero.

Summarizing, we set

$$D^{h}(R,T) := \frac{h_{1}h_{2}}{2} \sum_{\substack{x_{ij}^{h} \in \Omega^{h} \cap \Sigma_{R}^{\text{Vessel}}}} 1 - \frac{[\nabla R_{ij}^{+} \nabla T_{ij}]_{h}^{2}}{[\|\nabla R_{ij}\|]_{h}^{2} [\|\nabla T_{ij}\|]_{h}^{2} + \varepsilon}$$

where  $[\nabla R_{ij}^{\top} \nabla T_{ij}]_h$ ,  $[\|\nabla R_{ij}\|]_h^2$ , and  $[\|\nabla T_{ij}\|]_h^2$  denotes the above approximations and we added a small tolerance  $\varepsilon$  to ensure differentiability in the case  $[\|\nabla R_{ij}\|]_h^2 = 0$  or  $[\|\nabla T_{ij}\|]_h^2 = 0$ .

Thus, the approximation of the distance only depends on the values of the images R and T at the  $m_1m_2$  grid points  $x_{ij}^h$  in  $\Omega^h$ . Fixing the reference image, we consider the discrete distance measure as a function in the  $m_1m_2$  gray values of T and we set

$$D^h: \mathbb{R}^{m_1m_2} \to \mathbb{R}, \quad T^h \mapsto D^h(R, T^h)$$

where the argument  $T^h$  is a  $m_1m_2$  vector that collects the gray values of T at the grid-points  $x_{ij}^h$ . Now, let  $y^h$  be a  $2m_1m_2$  vector that collects the values of the deformation y at the points  $x_{ij}^h \in \Omega^h$  and with some abuse of notation let  $T(y^h)$  be a  $m_1m_2$  vector that collects the values of the template evaluated at points  $y_{ij}^h$ . With this notation we finally have following discrete approximation to the distance measure

$$D(R, T(y)) \approx D^h(R, T(y^h)).$$

#### 3.2 Discretization of the Regularizer

Now we present the discretization of the regularizer. The elastic regularizer was defined as

$$S(y) = \frac{1}{2} \int_{\Omega} \mu \|\nabla y(x)\|^2 + (\mu + \lambda) |\nabla \cdot y(x)|^2 dx$$



Figure 2. Nodal discretization of the displacement for the regularizer

where

$$\|\nabla y(x)\|^2 = \partial_1 y^1(x)^2 + \partial_2 y^1(x)^2 + \partial_1 y^2(x)^2 + \partial_2 y^2(x)^2 \quad \text{and} \quad |\nabla \cdot y(x)|^2 = \left(\partial_1 y^1(x) + \partial_2 y^2(x)\right)^2$$

and  $y^1$  and  $y^2$  denote the first and second component of the deformation field. As above, we use the mid-point rule and a finite difference scheme to approximate derivatives but here based on a nodal discretization, i.e., we consider the deformation y at points, cf. Figure 2,

$$x_{i-\frac{1}{2},j-\frac{1}{2}}^{h} = (i h_1, j h_2)^{\top}$$
 for  $i = 0, 1, \dots, m_1$  and  $j = 0, 1, \dots, m_2$ 

We first approximate the partial derivatives on the edges and then square and average them to the cell center such that

result second order approximations to the squared norm of the gradient and divergence at the cell-center. Finally we weight these approximations with  $\mu$  and  $(\mu + \lambda)$ , respectively, and sum them up such that we obtain a quadratic second order approximation to the regularizer based on the values of the deformation field at the  $(m_1+1)(m_2+1)$  nodal grid points. For a compact notation we collect the values of the deformation at the nodes in a  $2(m_1+1)(m_2+1)$  vector  $y^h$  and the coefficients for our approximation in a matrix  $A^h$ . Thus,

$$S^h(y^h) := \frac{1}{2} {y^h}^\top A^h y^h$$

is a second order approximation to S(y).

Next we present the discretization of the penalty term.

## 3.3 Discretization of the Penalty

For the discretization of the penalty we first construct a smooth function C that is supported on the  $\Sigma_T^{\text{Vessel}}$ . This is done by interpolation. First we construct a binary discrete  $m_1 \times m_2$  image such that

$$C_{ij} = \begin{cases} 1 & \text{if } x_{ij}^h \in \Sigma_T^{\text{Vessel}}, \\ 0 & \text{else.} \end{cases}$$

Subsequently, we smooth the image by a convolution with a discrete Gaussian based on the one-dimensional convolution kernel [  $0.25 \ 0.5 \ 0.25$  ]. Then, for evaluating Cx) at arbitrary points x we use linear interpolation. Using the mid-point rule we have

$$P(y) \approx \frac{h_1 h_2}{2} \sum_{\substack{x_{ij}^h \in \Omega^h \cap \Sigma_R^{\text{Vessel}}}} C(y_{ij})^2.$$

Collecting the values of the deformation at grid points  $x_{ij}^h$  that lie in  $\Omega^h \cap \Sigma_R^{\text{Vessel}}$  in a  $2 \# \Omega^h \cap \Sigma_R^{\text{Vessel}}$  vector  $y^h$  and define  $C(y^h)$  as the vector that collects the  $\# \Omega^h \cap \Sigma_R^{\text{Vessel}}$  function values of C at these points we can rewrite the discrete penalty as an inner product and obtain following compact notation

$$P^{h}(y^{h}) := \frac{h_{1}h_{2}}{2} C(y^{h})^{\top} C(y^{h})$$

Now we are in place to put all three building blocks together.

#### 3.4 Discretization of the Joint Function

Above we showed how to discretize the three building blocks, distance measure, regularizer, and penalty. Therefore we used different discretization of the deformation field, i.e., a cell-centered discretization for  $D^h$ , a nodal discretization for the regularizer  $S^h$ , and a restricted cell-centered discretization for the penalty  $P^h$ . To join all of them in single function we use the nodal discretization from the regularizer and linear interpolation for values the at the cell-centers. To this end, let  $y^h$  be the vector with the values of the deformation at the nodal grid points as for the regularizer. Furthermore, we define two matrices. First, let  $Q_1$  be a matrix such  $Q_1y^h$  are the interpolated values of the deformation at the cell-centers. Accordingly, let  $Q_2$  be a matrix that interpolates  $y^h$  from the nodes to the restricted cell-centered grid  $\Omega^h \cap \Sigma_R^{\text{Vessel}}$ . Thus, we define the joint function for the registration as

$$J^{h}(y^{h}) := D^{h}(R, T(Q_{1}y^{h})) + \alpha S^{h}(y^{h} - y^{h}_{\text{ref}}) + \beta P^{h}(Q_{2}y^{h})$$
(4)

where  $y_{\text{ref}}^h$  is a vector that collect the values of  $y_{\text{ref}}$  evaluated at the nodal grid points. Note that this discretization is quite general and leaves some options due to the interpolation of the deformation field. In particular, we must not choose the same resolution for the deformation as for the images, i.e., the distance measure and the penalty. We can choose a coarse discretization for the deformation resulting less degrees of freedom yielding a small optimization problem which can significantly speedup computations.

#### 4. OPTIMIZATION

For a solution of the registration problem we compute a minimizer of the discrete joint function (4). The joint function is highly non-linear due to the distance and the penalty term such that we cannot compute a minimizer directly. To this end, we use a limited memory BFGS quasi Newton method. We do not discuss the quasi Newton method here and only summarize out a few important points. For details on limited memory BFGS see for example.<sup>7</sup>

Starting from an initial guess  $y_0^h$ , in the k-th iteration we compute a descent direction  $\delta y^h$  by

$$\delta y^h = -H_k \nabla J^h(y^h_k)$$

where  $y_k^h$  is the k-th iterate,  $\nabla J^h$  is the gradient of the objective function given by

$$\nabla J^{h}(y_{k}^{h}) = Q_{1}^{\top} \nabla T(y_{k}^{h})^{\top} \nabla D(R, T(y_{k}^{h}))^{h} + \alpha h_{1} h_{2} A^{h^{\top}}(y_{k}^{h} - y_{\text{ref}}^{h}) + \beta h_{1} h_{2} Q_{2}^{\top} \nabla C(y_{k}^{h})^{\top} C(y_{k}^{h})$$

and  $H_k$  is an approximation to the inverse of the hessian  $\nabla^2 J^h(y_k^h)$  defined by the BFGS update formula

$$H_{k+1} := \left(I - \frac{s_k g_k^{\top}}{s_k^{\top} g_k}\right) H_k \left(I - \frac{g_k s_k^{\top}}{s_k^{\top} g_k}\right) + \frac{s_k s_k^{\top}}{s_k^{\top} g_k}, \quad s_k := y_{k+1}^h - y_k^h, \quad g_k := \nabla J^h(y_{k+1}^h) - \nabla J^h(y_k^h)$$

where I denotes the identity matrix. Then we compute the next iterate by

$$y_{k+1}^h := y_k^h + \gamma \, \delta y^h$$

	With Penalty	Without Penalty
Biliary and Arterial Phase	20 Voxel	1183 Voxel
Biliary and Venous Phase	47 Voxel	1824 Voxel

Table 1. Overlap of vessels after registration with and without penalty

with  $\gamma \in (0, 1]$  determined by a line search procedure. For our implementation we use the strong Wolfe condition.<sup>7</sup>

As we can see, for each iteration we only have a matrix-vector multiplication of  $H_k$  and the gradient  $\nabla J^h$ . Therefore, we do not need not to form the matrix  $H_k$  explicitly.

We are using a limited memory version of the BFGS method. This means we only keep the L most recent BFGS-vectors, i.e.,  $s_k, s_{k-1}, \ldots, s_{k-L+1}$  and  $g_k, g_{k-1}, \ldots, g_{k-L+1}$  (provided  $k \ge L$ ). Typical values for L are L = 5 or L = 10.

For the computation of the matrix  $H_k$  we need an initial guess  $H_0$  that terminates the recursion. Thereby,  $H_0$  must be symmetric positive definite. In general  $H_0 = I$  is a valid choice but practical experience shows that this results poor convergence of the method. To this end we propose setting

$$H_0 := \alpha (\nabla^2 S^h + \epsilon I)^{-1} = \alpha (h_1 h_2 A^h + \epsilon I)^{-1}.$$

It turns out that the matrix  $A^h$  of the regularizer is symmetric positive semi definite. To ensure positive definiteness we add a small perturbation with the identity. In our experiments we used  $\epsilon = 10^{-5}$ . Furthermore, we used a conjugated gradient method (CG) with Gauss-Seidel pre-conditioning to compute a multiplication with  $\alpha(h_1h_2A^h + \epsilon I)^{-1}$ . Practical experiments also showed that performing only few CG iterations ( $\leq 50$ ) gave reasonable results.

#### 5. RESULTS

We tested our method on real data examples from multi-phase CT imaging. Therefore, we considered three data sets of the same patient each having size of 271x252x279 voxels. The first data set shows biliary vessels, the second vessels from the arterial phase, and the third one contains portal venous vessels. The goal of the experiments was to align the data from the biliary phase with the images of the arterial and venous phase, respectively. We performed two experiments where the biliary CT image served as fixed reference and the arterial and venous images were used as templates. Fig. 3 shows the data for the experiments.

In both experiments we performed rigid pre-registration and the resolution of the deformation in the nonlinear registration was fixed to  $32 \times 32 \times 32$  (cf. section 3.4). Furthermore, we chose elasticity constants  $\mu = 1$ ,  $\lambda = 0$ , the regularization parameter  $\alpha = 1$ , and for the penalty approach we set  $\beta = 10^3$ . The results with and without our new approach, i.e., minimizing (3) and (1), respectively, are presented in Fig. 4 and Fig. 5.

Due to the contrast enhancement, the CT image for the biliary vessels does hardly carry information on arterial/portal venous vessels and vice versa. Therefore, the registration is mainly driven by aligning surrounding liver tissue. In all experiments, liver contours have been aligned successfully. Using the standard approach without penalty we also aligned biliary with arterial and venous vessels. This makes sense for multi-modal registration in general but is clearly a mismatch here. In contrast, using the penalty approach, the liver contours are aligned successfully, too, but we do not have any mismatches between complementary vessels. Biliary and arterial/venous vessels do not intersect except for negligible parts of their boundaries such that after registration these vessels run in parallel and at most abut on each other as should. The resulting overlaps of vessels are summarized in Tab. 1.

## 6. CONCLUSION

We have presented a novel practical approach for elastic registration of multi-phase CT images that includes an avoidance criteria for mis-aligning complementary structures in multi-phase image registration. Our experiments show we are able to successfully register contrast enhanced CT without producing mis-matches of vessels. Furthermore, we have shown that without incorporating additional knowledge about vessels the registration by standard methods produces non-physical results. Therefore, we conclude that our new method significantly improves the results compared to related state-of-the-art approaches.





Arterial Template





Figure 3. Multi phase CT data used in the experiments



Figure 4. Registration results for biliary and arterial phase



Figure 5. Registration results for biliary and venous phase

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