Linear and Deformable Image Registration with 3D Convolutional Neural Networks

Stergios C. et al.

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BITS Pilani

Outline

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where	C	cost function
	I_T	target image
	I_S	source image
	θ	transformation parameters
	T_θ	transformation function

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- The task is to optimize a cost function over two images by tuning the parameters of a transformation function which tries to warp the source image to target image.

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  - Allows a non-uniform mapping between images.
  - Measure and/or correct small, varying discrepancies by deforming one image to match the other.
  - Vector field/deformation field T_θ is computed from I_T to I_S.
  - Inverse warp transform I_S into I_T's coordinate system.

Deformable Registration: Clinical Relevance

- internal organs are non-rigid
- physical brain deformations during neurosurgery
- normal squishing, shifting and emptying of abdominal/pelvic organs and soft tissues
- Patient motion during image scanning
- **Lung motion during respiration**

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- Ambiguity between homogeneous regions. Multiple solutions possible.(not Unique)
- Solution search space is often ∞-dimensional.

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- $\mathcal{R}$ aims to favor specific properties desired in the solution.
- Helps tackle the ill-posedness of registration problem.
- Adding a regularization term can provide **provable uniqueness** and a **computable subspace**.

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- Modeling Complex Equations?
- **Neural Networks!**

Existing Methods

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  - Sensitive to application setting
  - involve multiple hyper-parameters
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  - Sensitive to application setting
  - involve multiple hyper-parameters
  - computationally expensive
- Limitations of Deep learning based methods:
  - dependency on linear component of the transformation
  - **dependency on ground truth displacement (supervised learning)**

Contributions of Stergios C. et al.

- coupling linear and deformable registration within a single architecture.
- independent of different similarity metrics
- reduced computational time
- associating with clinical data to classify patients with interstitial lung disease (ILD).

Outline

Dataset

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- Lung fields were annotated for 82 images and were labeled as healthy/not healthy.
- Pre-processing:
  - image intensity values clipped between the range [0,1300] and normalized to [0,1].
  - images were scaled down by a factor of 2/3 using cubic interpolation to a final size of 64x192x192.
  - 28 patients data were selected for training using random sampling and remaining 13 were used for validation.

Network Architecture

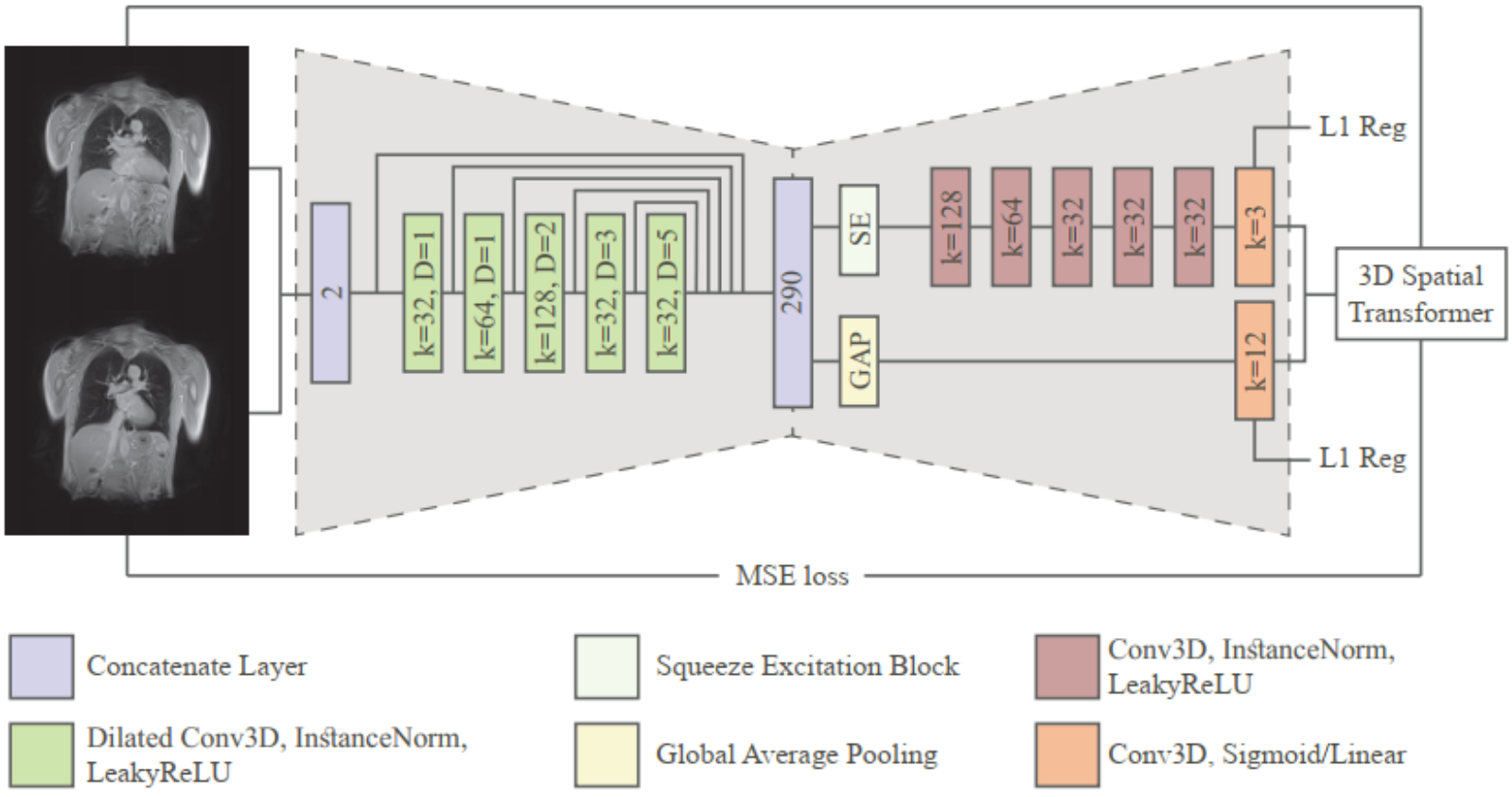

Figure 1: Overview of Network Architecture

Network Architecture: PyTorch

```
class Register3d(nn.Module):
    def __init__(self):
        super(Register3d,self).__init__()
        self.encoder = Encoder()
        self.d_decoder = DRB()
        self.a_decoder = LRB()
        self.transformer = Transformer3d()

    def forward(self,source,target,linear = False):
        x = self.encoder(source,target)
        d1 = self.d_decoder(x)
        if not linear:
            t = self.transformer(d1)
        else:
            d2 = self.a_decoder(x)
            t = self.transformer(d1,d2)
        return (t,d1,d2)
```

Network Architecture: Encoder

- takes as input the source and target image concatenated along channels axis.
- Consists of 5 layers of 3x3x3 dilated convolutions each followed by instance normalization and LeakyReLU.
- the outputs of each layer are finally concatenated to provide multi-resolution feature merging which is then fed into the 2 branches of the decoder.

Encoder: Insights

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- gridding problem: as zeros are padded between two pixels in a convolutional kernel, the receptive field of this kernel only covers an area with checkerboard patterns - only locations with non-zero values are sampled, losing some neighboring information.
- dilation rate increases as Fibonacci sequence (1,1,2,3,5) as opposed to exponentially. This mitigates the gridding problem by providing a less steep dilation rate increase and thus denser sampling.

Encoder: Insights (Contd.)

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- Instance normalization
  - provides invariance to intensity and contrast shift
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  - could mitigate problems caused by difference in imaging devices.
- multi-resolution feature merging
  - permits the aggregation of features from all different scales and levels of abstraction
  - facilitates the flow of gradients through the network and therefore allows faster training.

Encoder: PyTorch

```
class Encoder(nn.Module):
    def __init__(self):
        super(Encoder,self).__init__()
        self.conv1 = nn.Conv3d(6,32,3, padding = 1)
        self.conv2 = nn.Conv3d(32,64,3,padding = 1)
        self.conv3 = nn.Conv3d(64,128,3,padding = 2,dilation = 2)
        self.conv4 = nn.Conv3d(128,32,3,padding = 3,dilation = 3)
        self.conv5 = nn.Conv3d(128,32,3,padding = 5,dilation = 5)
    def forward(self,source,target):
        x0 = torch.cat(source,target,dim=1)
        x1 = F.leaky_relu(F.instance_norm(self.conv1(x0)))
        x2 = F.leaky_relu(F.instance_norm(self.conv1(x1)))
        x3 = F.leaky_relu(F.instance_norm(self.conv1(x2)))
        x4 = F.leaky_relu(F.instance_norm(self.conv1(x3)))
        x5 = F.leaky_relu(F.instance_norm(self.conv1(x4)))
        return torch.cat((x0,x1,x2,x3,x4,x5),dim=1)
```

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- **Deformable Registration Branch (DRB)** comprises of a squeeze and excitation block followed by multiple 3x3x3 convolutions each followed by instance norm and LeakyReLU. The final layer has sigmoid activation and its activations are multiplied by 2 to get a spatial gradient sampling grid.

Decoder: PyTorch

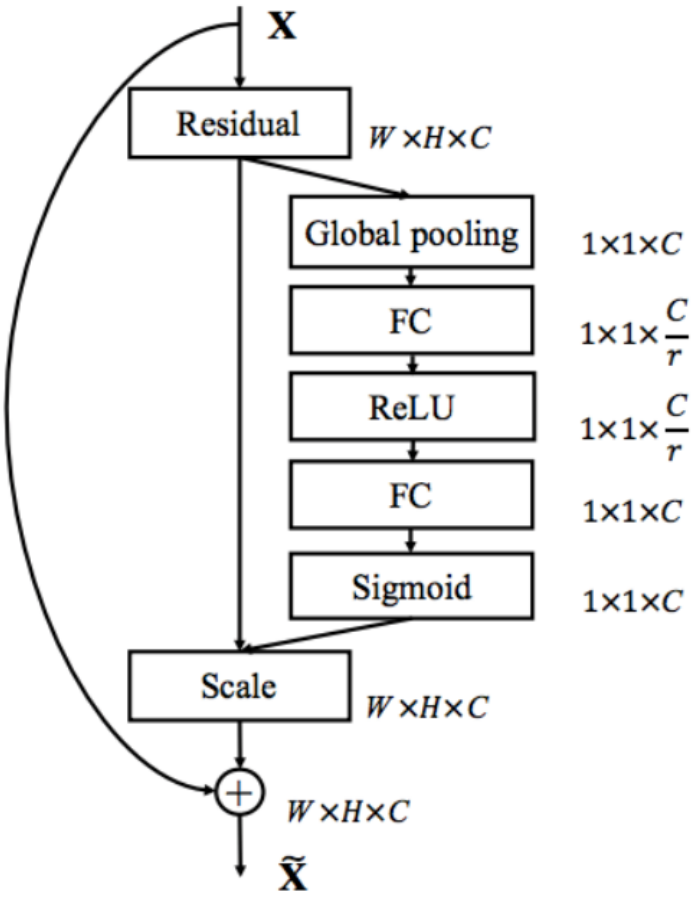
```
class LRB(nn.Module):
    def __init__(self):
        super(LRB,self).__init__()
        self.conv1 = nn.Conv3d(290,12,1)
    def forward(self,inputs):
        x = self.conv1(F.adaptive_avg_pool3d(inputs,(None,None,None,1,1))).view(-1,3,4)
        return x
```

```
class SqueezeExcitation(nn.Module):
    def __init__(self,channel,reduction=16):
        super(SqueezeExcitation,self).__init__()
        self.conv1 = nn.Conv3d(channel,channel//reduction,1)
        self.conv2 = nn.Conv3d(channel//reduction,channel,1)
    def forward(self,x):
        return x*F.sigmoid(self.conv2(F.relu(self.conv1(F.adaptive_avg_pool3d(x,(None,None,1,1))))))
```

Decoder: PyTorch

```
class DRB(nn.Module):
    def __init__(self):
        super(DRB,self).__init__()
        self.se = SqueezeExcitation(290)
        self.conv1 = nn.Conv3d(290,128,3,padding = 1)
        self.conv2 = nn.Conv3d(128,64,3,padding = 1)
        self.conv3 = nn.Conv3d(64,32,3,padding = 1)
        self.conv4 = nn.Conv3d(32,32,3,padding = 1)
        self.conv5 = nn.Conv3d(32,32,3,padding = 1)
        self.conv6 = nn.Conv3d(32,3,3,padding = 1)
    def forward(self,inputs):
        x = self.se(inputs)
        x = F.leaky_relu(F.instance_norm(self.conv1(x)))
        x = F.leaky_relu(F.instance_norm(self.conv2(x)))
        x = F.leaky_relu(F.instance_norm(self.conv3(x)))
        x = F.leaky_relu(F.instance_norm(self.conv4(x)))
        x = F.leaky_relu(F.instance_norm(self.conv5(x)))
        x = 2*F.sigmoid(self.conv6(x))
        return x
```

Deformable Registration Branch (DRB) : Insights



- Squeeze and Excitation Block:
  - in a normal convolution operation all channels contribute equally to the output feature map.
  - SE-block allows to add an adaptive scale to control the contribution of each input channel to the output feature map.

Deformable Registration Branch (DRB) : Insights

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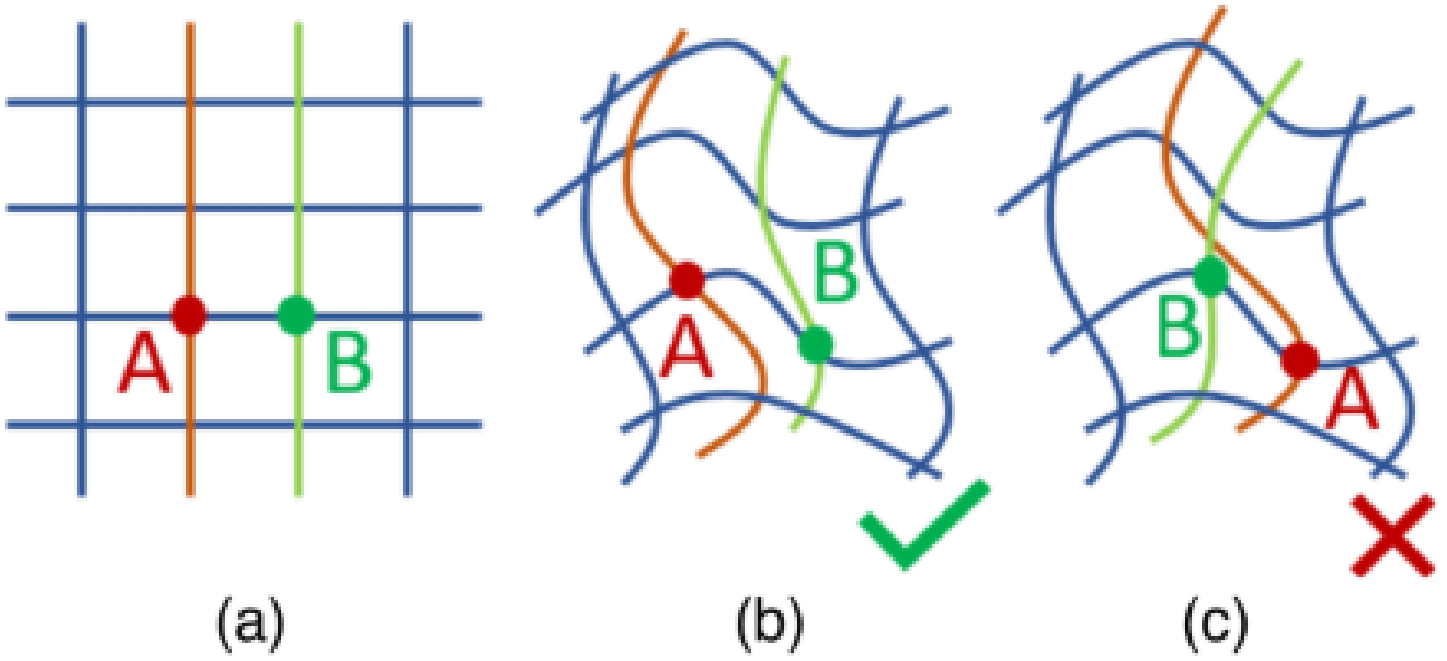
- Thus, for each voxel we have 3 values between [0,2] representing the spatial gradient along each of the three axes (x,y,z).
- The spatial gradient gives a measure of displacement of consecutive pixels.
- limiting the maximum value of gradients to two allows for control of maximum displacements among consecutive pixels.
- such an approach ensures generation of smooth deformations that avoid self-crossing.

Deformable Registration Branch (DRB) : Insights



Non-negative values for spatial gradients ensure no **self-crossing**.

Deformable Registration Branch (DRB) : Insights

- A spatial gradient value of 1 indicates there is no change in the distance between the consecutive pixels along the given axis.
- A value less than 1 indicate the distance between the pixels will decrease along the given axis.
- A value greater than 1 indicate the distance between the pixels will increase along the given axis.

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Generating sampling grid from spatial gradients

$$[G(p)]_d = \sum_{i=0}^{p} \phi_{id}$$

with $[G(p)]_d$ d-component of sampling grid G at voxel p

ϕ_{id} d-component of spatial gradient ϕ at voxel i

Linear Registration Branch (LRB)

- once the affine transformation matrix is calculated using the above procedure we can generate the sampling grid for each voxel in the deformed image using the following formula:

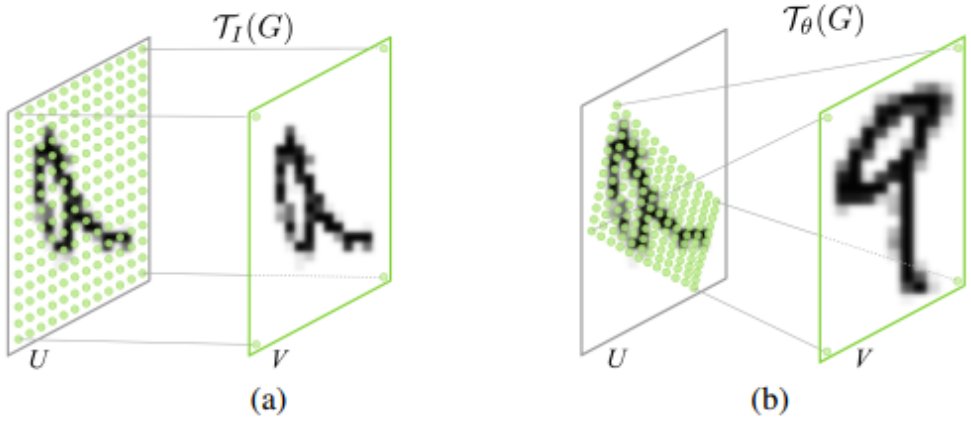
Generating sampling grid from affine matrix

$$\begin{pmatrix} x_i^s \\ y_i^s \\ z_i^s \end{pmatrix} = \begin{bmatrix} \theta_{11} & \theta_{12} & \theta_{13} & \theta_{14} \\ \theta_{21} & \theta_{22} & \theta_{23} & \theta_{24} \\ \theta_{31} & \theta_{32} & \theta_{33} & \theta_{34} \end{bmatrix} \begin{pmatrix} x_i^t \\ y_i^t \\ z_i^t \\ 1 \end{pmatrix}$$

3D Spatial Transformer

- the 3D transformer layer takes as input the source(moving) image (S), the linear(G_A) and deformable (G_N) sampling grids and performs the sampling operation $\mathcal{W}$ to produce the deformed image D.
- first the deformable grid is applied and to its output the linear sampling grid is applied:

$$\mathcal{W}(S, G) = \mathcal{W}(\mathcal{W}(S, G_N), G_A)$$



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- The warping function is thus defined as a trilinear interpolation sampling as follows:

$$\mathcal{W}(S, G)(\mathbf{p}) = \sum_{\mathbf{q}} S(\mathbf{q}) \prod_{d} max(0, 1 - |[G(\mathbf{p})]_d - \mathbf{q}_d|)$$

Training

Loss Function

$$Loss = ||R - \mathcal{W}(S, G)||^2 + \alpha||A - A_I||_1 + \beta||\Phi - \Phi_I||_1$$

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- Why regularization?
  - Without L1 regularization on A high reconstruction error may occur as the network might get stuck in a local minimum where it aligns only high level features.

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- Why regularization?
  - Without L1 regularization on A high reconstruction error may occur as the network might get stuck in a local minimum where it aligns only high level features.
  - Without the smoothness regularizer on ϕ, spatial gradients decoder network can predict very non-smooth grids which makes it prone to fall in local minimum.

Training (Contd.)

hyper-parameters:

- **optimizer:** Adam
- **initial learning rate:** 10^{-3}
- **reduce LR on plateau:**
  - patience: 50 epochs
  - factor: 0.9
- **early stopping patience :** 100 epochs
- **batch size:** 2
- **regularizers:** $\alpha = \beta = 10^{-6}$

Outline

Evaluation

- Dice Coefficient Metric
  - measured on lung masks after source deformation.
- Average error over all axes of predicted locations for 11 manually annotated landmark points was also calculated.
- Compared with two different state-of-the-art methods
  - Symmetric Normalization(SyN)
  - deformable method with variety of similarity metrics (MI,NCC,DWM)

Results

- Two different types of test:
  - Inhale-Exhale (13 validation pairs)
  - All combinations (169 validation pairs)

Method	Inhale-Exhale	All Combinations	Time/subject(s)
Unregistered	75.620±10.89	57.22±12.90	-
Deformable with NCC	84.25±6.89	76.10±7.92	1(GPU)
Deformable with DWM	88.63±4.67	75.92±8.81	2(GPU)
Deformable with MI	88.86±5.13	76.33±8.74	2(GPU)
Deformable with all above	88.81±5.85	78.71±8.56	2(GPU)
SyN	83.86±6.04	-	2500(CPU)
Proposed w/o Affine	91.28±2.47	81.75±7.88	0.5(GPU)
Proposed	**91.48±2.33**	**82.34±7.68**	0.5(GPU)

Table 1: Dice Coefficient Score(%) calculated over the deformed lung masks and the ground truth

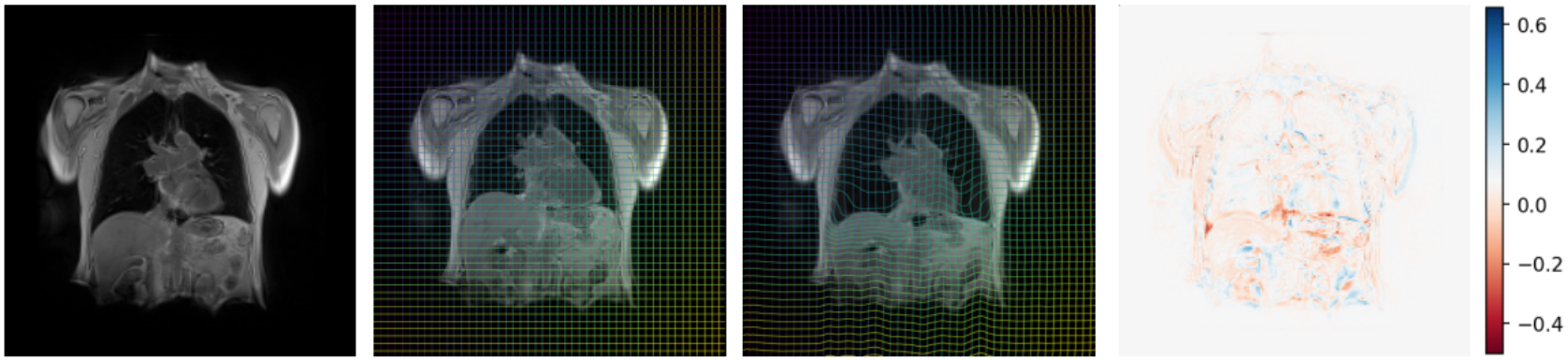
Results (Contd.)

Method	dx	dy	dz	ds
Inter-observer	1.664	2.545	1.555	3.905
Deformable with NCC,DWM and MI	1.855	3.169	2.229	4.699
Proposed w/o Affine	2.014	2.947	1.858	4.569
Proposed	1.793	2.904	1.822	4.358

Table 2: Errors measured as average euclidian distances between estimated landmark locations and ground truth marked by two medical experts.

Results: Analysis

Majority of the errors occur at boundaries, indicating that large local displacements are not captured



(a) Reference image (b) Moving image (c) Deformed image (d) Difference

Figure 2: Registration generated by the proposed architecture

Evaluation of Clinical Relevance

- a small classifier is trained for assessing clinical relevance.
- residual deformation ($G_\delta = G - G_I$) indicating voxel displacement is fed as input to a shallow neural network which classifies patients as healthy/unhealthy.
- binary crossentropy was used as loss function and initial learning rate 10^{-4}, which was halved every 50 epochs.
- 5 models were trained in parallel for 5-fold cross validation and an accuracy of 84.62 % is reported.

Evaluation of Clinical Relevance: Model

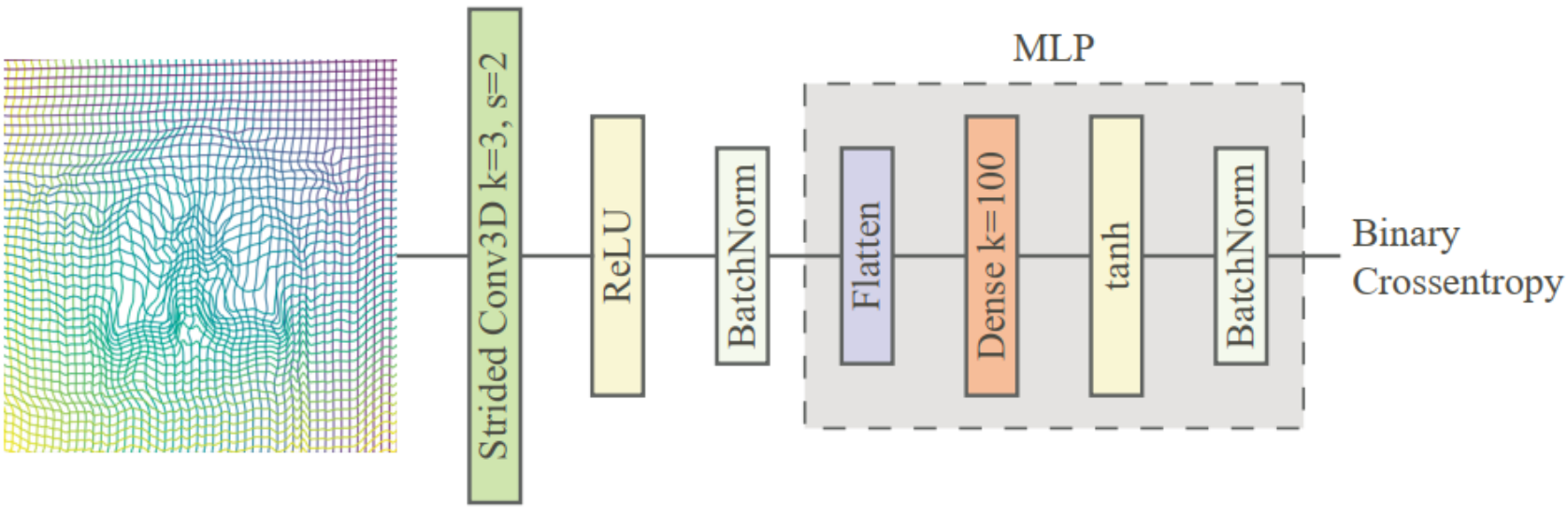


Figure 3: ILD Classifier

Outline

Conclusion

- The paper presents an unsupervised end-to-end deep learning model for image registration using an optimal transformation between pair of images.
- the model is modular with respect to similarity functions and nature of transformation
- promising results compared to other unsupervised methods
- generates deformations with no self-crossings
- computationally efficient due to GPU implementation
- **Future Scope:** Evaluation of the proposed model on registration of other modalities and other organs.