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Unsupervised Deep Learning based Longitudinal Follicular Growth Tracking during IVF Cycle using 3D Transvaginal Ultrasound in Assisted Reproduction

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***Abstract*— Longitudinal follicle tracking is needed in clinical practice for diagnosis and management in assisted reproduction. Follicles are tracked over the in-vitro fertilization (IVF) cycle, and this analysis is usually performed manually by a medical practitioner. It is a challenging manual analysis and is prone to error as it is largely operator dependent. In this paper we propose a two-stage framework to address the clinical need for follicular growth tracking. The first stage comprises of an unsupervised deep learning network SFR-Net to automate registration of each and every follicle across the IVF cycle. SFR-Net is composed of the standard 3DUNet [1] and Multi-Scale Residual Blocks (MSRB) [2] in order to register follicles of varying sizes. In the second stage we use the registration result to track individual follicles across the IVF cycle. The 3D Transvaginal Ultrasound (3D TVUS) volumes were acquired from 26 subjects every 2-3 days, resulting in a total of 96 volume pairs for the registration and tracking task. On the test dataset we have achieved an average *DICE* score of 85.84% for the follicle registration task, and we are successfully able to track follicles above 4 mm. Ours is the novel attempt towards automated tracking of follicular growth [3].**

***Clinical Relevance*— Accurate tracking of follicle count and growth is of paramount importance to increase the effectiveness of IVF procedure. Correct predictions can help doctors provide better counselling to the patients and individualize treatment for ovarian stimulation. Favorable outcome of this assisted reproductive technique depends on the estimates of the quality and quantity of the follicular pool. Therefore, automated longitudinal tracking of follicular growth is highly demanded in Assisted Reproduction clinical practice. [4]**

I. Introduction

Longitudinal tracking of follicular growth is a vital component of in-vitro fertilization (IVF) assessment and timing [5]. It essentially employs a technique for assessing ovarian follicles at regular intervals and documenting their pathway to ovulation. Detecting and tracking follicles in the longitudinal scan is important to monitor their growth, as determining the dosage of hormone for stimulating the ovary depends on the rate of growth of each follicle [3]. Longitudinal tracking of follicular growth also assists in identifying those subjects who do not respond to the initial dose of hormone and may be considered for subsequent increased doses [6].

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3D Transvaginal Ultrasound (3D TVUS) is the preferred mode of tracking follicles. Ultrasound monitoring may begin on day 3 of the IVF cycle to assess a baseline size as well as to exclude any cysts that remain from previous hyper-stimulation or otherwise, and is then monitored every alternate day till day 14. Fig. 1 shows the manual longitudinal tracking of follicular growth to determine hormonal doses for ovarian stimulation in one IVF cycle.

Longitudinal tracking of follicular growth involves segmenting follicles for every longitudinal scan and then registering the segmentations to track the growth of each individual follicle. However, follicle segmentation and longitudinal tracking is a challenging task due to the following reasons – i) certain follicles suddenly disappear or regress in size, ii) blurring of follicular boundary, iii) follicular movement inside the ovary, and iv) irregular follicular growth i.e. close to the end of the IVF cycle there is a rapid growth of follicles and a follicle which was dominant on say, day 3 of the cycle, may not be dominant at the end of the cycle.

Due to the above mentioned reasons, longitudinal tracking of follicular growth is an extremely difficult and time-consuming task even for expert medical practitioners. We propose a two-stage framework involving an unsupervised deep learning registration model and a tracking algorithm to realize this outcome. Our work on longitudinal tracking of follicular growth is in addition to our lab's continuous research output in quantification applications [3,4,6-9] and clinical research papers [10,11] in the Assisted Reproduction domain.

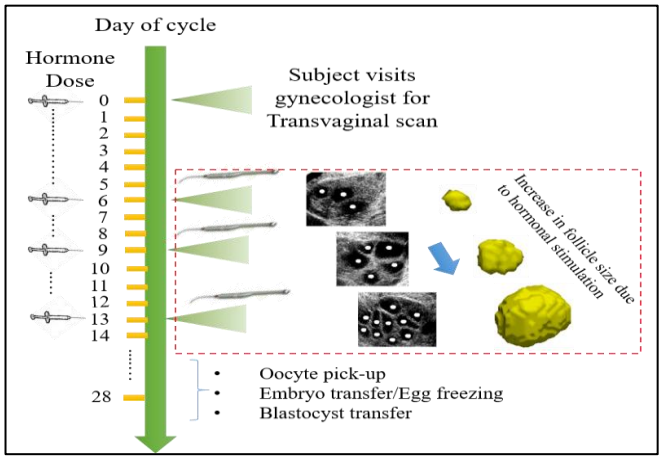

Figure 1: Representation of an IVF cycle. 3D TVUS volumes are acquired starting from day 0 till day 14. Hormonal doses are determined depending on the follicular growth.

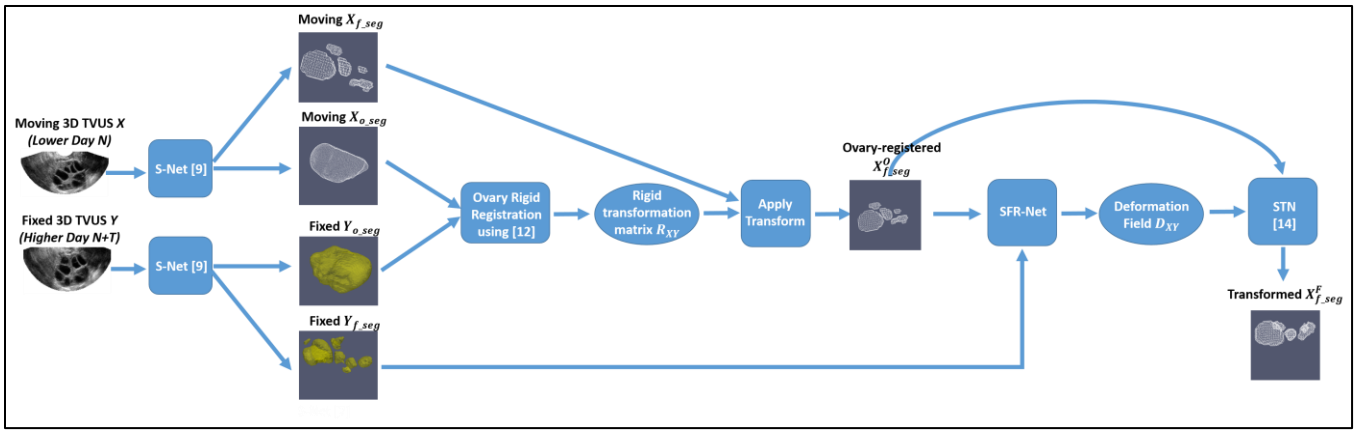

Figure 2: Overview of follicle registration framework. Registration is performed on two 3D TVUS volumes X and Y obtained from the same subject with a gap of T days, where $T < 4$.

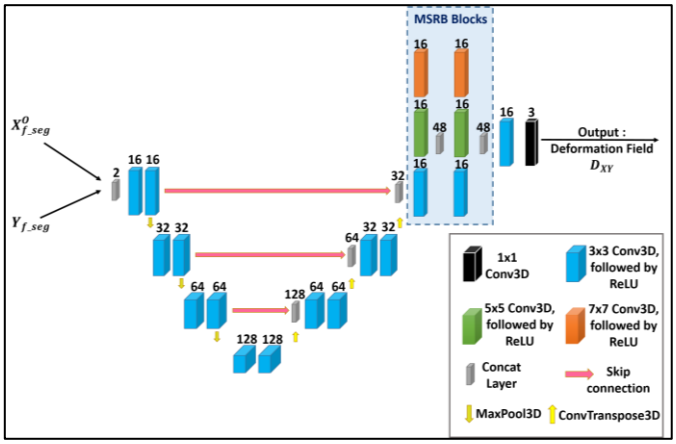

Figure 3: SFR-Net architecture; The number on top of each layer denotes the number of channels outputted by that layer. $X^O_{f\_seg}$ and Y_{f_seg} retain the same meaning as shown in Fig. 2 and described in the Methodology section.

II. METHODOLOGY

In this section, we present the registration framework to estimate the deformation field (D_{XY}) for registration of moving 3D TVUS volume X with fixed 3D TVUS volume Y, followed by the tracking algorithm to track follicles throughout the IVF cycle.

A. Registration Framework

An overview of our approach for the registration framework is shown in Fig. 2. X and Y are 3D TVUS volumes of the same subject with a gap of T days, where $T < 4$. We propose a two-step process to register the 3D follicle segmentations obtained from the longitudinal data. The 3D follicle segmentation maps X_{f_seg} and Y_{f_seg}, and 3D ovary segmentation maps X_{o_seg} and Y_{o_seg}, are obtained by feeding X and Y respectively to an in-house ovary and follicle segmentation network S-Net [9]. Using the 3D ovary segmentation maps X_{o_seg} and Y_{o_seg}, we first register the ovary in them and obtain the rigid transformation matrix R_{XY}. We apply R_{XY} on X_{f_seg} to obtain 3D ovary-registered follicle segmentation map $X^O_{f\_seg}$ so that $X^O_{f\_seg}$ and Y_{f_seg} are properly aligned. Since the 3D TVUS volumes X and Y are of the same subject with a gap of less than 4 days, there is minimal change in the ovarian volume and we consequently perform rigid registration to align them [4]. This is done by computing the distance maps for the ovary segmentations, which are then aligned using the *BRAINSFit* module [12]. For performing follicle registration on ovary-registered volumes, we propose a novel unsupervised deep learning based deformable registration model SFR-Net inspired from Balakrishnan et al. [13]. SFR-Net takes $X^O_{f\_seg}$ and Y_{f_seg} as input and produces the deformation field D_{XY} as output.

The architecture of SFR-Net is shown in Fig. 3. SFR-Net comprises of the standard 3DUNet with Multi-Scale Residual Blocks (MSRB) at the top-most level of the 3DUNet. To cater to the variation of follicle size from 2 mm to 30 mm, we use differing kernel sizes 3, 5, and 7, for our MSRB blocks. These blocks detect image features at multiple scales so as to fully exploit the potential features of the image. Thus the different filter size allows to effectively register follicles of varying sizes across the IVF cycle – smaller follicles of size 2-10 mm in early days of the cycle and larger follicles of size 17-30 mm at the end of the cycle. The SFR-Net outputs the deformation field D_{XY} which is applied to $X^O_{f\_seg}$ using a pre-defined Spatial Transformation Network (STN) [14]. This results in the final follicle-registered 3D follicle segmentation $X^F_{f\_seg}$, which is used in longitudinal tracking of follicular growth.

FOLLICLE TRACKING ALGORITHM

for N **in** *range of IVF cycle* **do**
  F^N ← follicles at day N
  F^{N+T} ← follicles at day $N+T$
  $Freg^N$ ← follicles at day N registered to day $N+T$

  Sort $Freg^N$ **in descending order based on size of follicles**
  Sort F^{N+T} **in descending order based on size of follicles**

  for $j = 0$ **to** len(F^{N+T}) **do**
    if len($Freg^N$) **is ZERO then**
      exit
    else
      ans ← F_i^N where **MAX** { **DICE** (F_j^{N+T}, $Freg_i^N$) } and $i = 0$ to len($Freg^N$)
      remove ans **from** $Freg^N$
    end if
  end for
end for

Figure 4: Pseudocode to track individual follicles between two 3D follicle segmentation maps differing by T days where $T < 4$.

B. Tracking Algorithm

Our tracking algorithm tracks individual follicles in two follicle-registered volumes having a gap of T days in the IVF cycle, where $T < 4$. The pseudocode for the tracking algorithm is shown in Fig. 4. F^N and F^{N+T} are the 3D follicle segmentation maps of 3D TVUS volumes on day N and day $N+T$ respectively. $Freg^N$ is the 3D follicle segmentation map obtained after registering F^N to F^{N+T} using the registration framework described above. F_j^{N+T} (the j^{th} follicle in F^{N+T}) is identified as F_i^N (the i^{th} follicle in F^N) if the value of *DICE* (F_j^{N+T}, $Freg_i^N$) is maximum across all follicles in F^N.

III. Experimental Setup

A. Dataset

We have obtained 3D TVUS volumes for 26 subjects from *Krishna IVF Clinic (KIVF)* [15]. The volumes have been acquired by a trained sonographer using Samsung Medison WS80A Ultrasound equipment, with an endovaginal probe V5-9 [16]. All the datasets have been captured from subjects who were undergoing Assisted Reproduction treatment. The datasets are of resolution 100×100×100. For each subject, 3D TVUS volumes have been acquired every 2 or 3 days during the IVF cycle resulting in 96 data pairs.

B. Loss function and network parameters

We randomly select 80 3D TVUS volume pairs from 22 subjects for training. The SFR-Net is trained in an unsupervised manner using a combination of *DICE* loss L_{DICE} and regularization loss L_{SMOOTH}. We encourage a smooth deformation field using a *L2* regularizer on the spatial gradients of the SFR-Net output. Specifically, when $X_{f\_seg}^O$ and Y_{f_seg} are given as training input, the total loss function L is computed as follows:

$$\boldsymbol{L = L_{DICE} + \lambda * L_{SMOOTH}}$$

$$\boldsymbol{L_{DICE} = 1 - DICE(Y_{f_{seg}}, STN(X_{f\_seg}^O, D_{XY}))}$$

$$\boldsymbol{L_{SMOOTH} = FrobeniusNorm(\nabla D_{XY})}$$

where the terms used are defined as follows:

- $DICE(A, B) = \frac{2\times|A \cap B|}{|A|+|B|}$
- λ *is the regularization parameter*
- $STN(.)$ *denotes the output of STN network*
- D_{XY} *denotes the deformation field output of SFR-Net*
- $FrobeniusNorm\ (A) = \sqrt[2]{\sum_{a\epsilon A}|a|^2}$
- ∇ *is the difference between neighboring voxels in all three directions*

Details regarding hyper-parameters used are in Table I.

IV. Results

A. Datasets and Hardware Configuration

For evaluation, we used 16 3D TVUS volume pairs from 4 subjects that were not used for training. We performed evaluation using one *NVIDIA TESLA P100 (16GB) GPU*.

B. Quantitative Evaluation

For quantitative evaluation, we compute the *DICE* score which is the standard metric used for evaluating registration. Our solution has an average *DICE* score of **85.84%**.

TABLE I. TRAINING CONFIGURATION

Hyper parameters	Values
Input Size	100×100×100
Learning rate	1×10^{-4}
No. of epochs	200
Optimizer	Adam optimizer, with $\beta_1 = 0.9$, $\beta_2 = 0.999$
Batch size	12
Decay Schedule	The decay rate was 0.1 with value of decay step set to 750
Regularization parameter λ	1×10^{-3}
Deep learning library	Pytorch 1.5.1 [17]
CUDA version	10.1 [18]

C. Qualitative Evaluation

The visual evaluation of longitudinal follicle tracking on a single subject for days 3, 5, 7, 9, and 11 is shown in Fig. 5, with quantitative information reported in Table 2. This demonstration is for one representative subject, and is generalizable for other subjects as well. From Fig. 5 a) – d) we see that there is almost no alignment between X_{f_seg} and Y_{f_seg}. Ovary registration helps in better aligning the volumes as can be seen in Fig. 5 e) – h). We see in Fig. 5 i) – l) that our proposed follicle registration framework largely registers the volumes correctly. From Table 2, we see that there are more number of follicles in day 7 as compared to in day 9 because certain follicles suddenly disappear or regress in size, thus resulting in a reduced *DICE* score in Fig. 5 c) k). Faced with such challenging limitations, our proposed solution is still able to decently register given 3D follicle segmentation pairs and hence able to track the growth of follicles. In Fig. 5 m) – q) we demonstrate successful tracking of longitudinal follicular growth for four representative follicles above 4 mm labeled in colors magenta, turquoise, dark blue, and orange, across days 3, 5, 7, 9, and 11. Table 2 captures the diameter of each of these four representative follicles across the IVF cycle. The results for our follicle tracking algorithm was verified and validated by expert medical practitioners in *KIVF*. Hence we assert the viability of our proposed registration and tracking framework.

TABLE II. FOLLICLE DIAMETER OF REPRESENTATIVE FOLLICLES IN FIG. 5 FOR A SINGLE SUBJECT (IN MM)

Follicle Label	Day 3	Day 5	Day 7	Day 9	Day 11
Dark blue	10.30	13.98	15.01	17.94	20.58
Orange	8.32	10.24	11.26	14.82	18.86
Turquoise	7.68	8.36	9.84	12.04	14.72
Magenta	4.66	5.08	6.42	9.14	10.12
Follicle Count	21	19	17	13	16

V. Discussions and Conclusion

In this paper we propose a two-stage framework for longitudinal tracking of follicular growth. This framework involves an unsupervised deep learning registration model and a tracking algorithm. Ours is the novel attempt on this problem, achieving an average *DICE* score of 85.84% for follicle registration. The performance can be attributed to the use of MSRB blocks which generate features at multiple scales, and thus enable the network to register follicles of

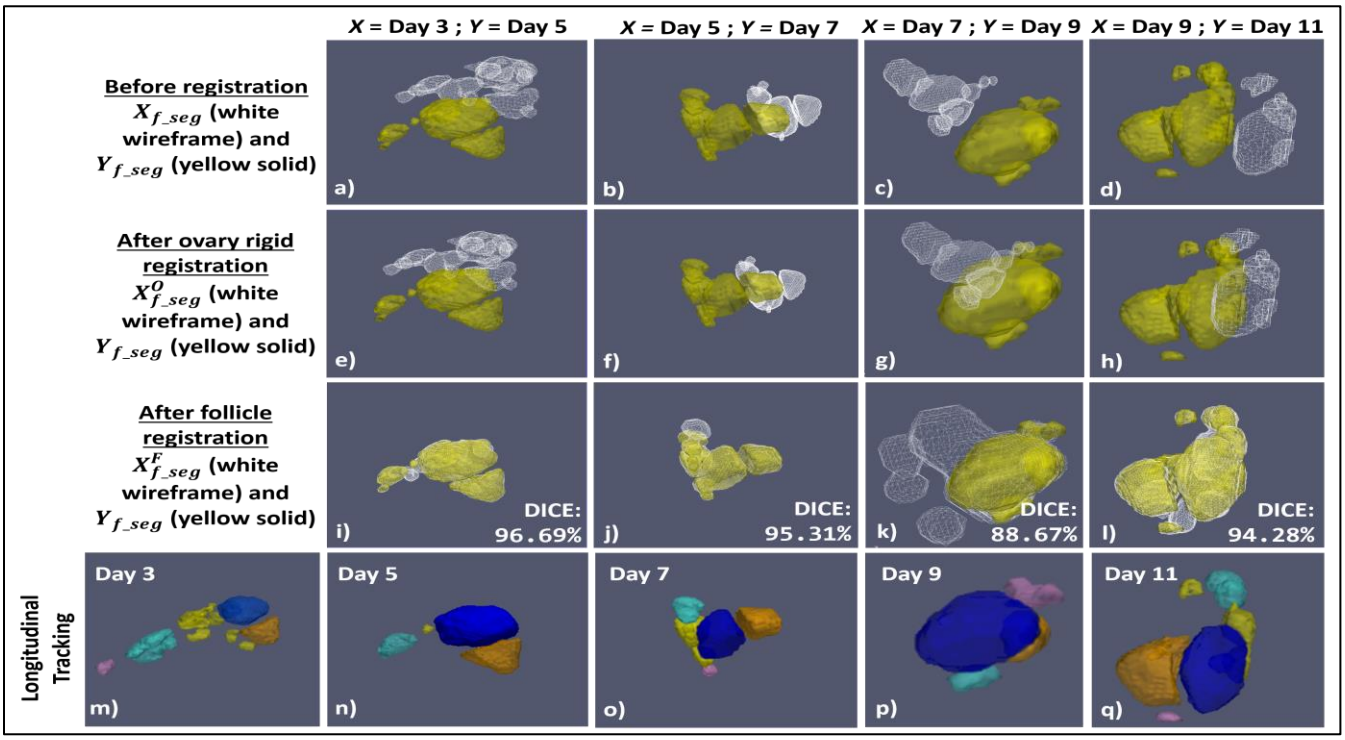

Figure 5: a) – l) Yellow solid 3D follicle rendering are of higher day fixed follicles, while white wireframe 3D follicle rendering are of lower day moving follicles; m) – q) Follicles highlighted in orange, dark blue, magenta, turquoise are representative follicles and have been tracked across days 3, 5, 7, 9, 11.

varying sizes across the IVF cycle. We are thus able to track follicles of size greater than 4 mm across the IVF cycle. Confirmation with the medical practitioners at *KIVF* gives confidence to the efficiency and viability of our proposed approach for longitudinal follicular growth tracking of follicles above 4 mm.

Our problem of longitudinal tracking of follicular growth is challenging because of the following limitations: i) certain follicles suddenly disappear or regress in size, ii) blurring of follicular boundary, iii) follicular movement inside the ovary, and, iv) irregular follicular growth. Due to this, the number of follicles in a given pair of volumes usually vary, and so the *DICE* score should not be used as the absolute metric to quantify SFR-Net. Furthermore, the performance of our framework depends on the accuracy of the segmentation masks being fed as input. The dataset size was also a limitation as we only had 80 volume pairs for training.

Our future efforts will be on acquiring more datasets for training so as to improve generalizability of the proposed framework. We will also consider the inclusion of anatomical landmark such as the ovarian artery for registration. This guiding landmark would be an effective reference to register against as its orientation is constant. Furthermore, we will provide Target Registration Error (TRE) after clinically acquiring the relevant markers to compute it.

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