# Villous Structural Study Based on Multilevel Registration**

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## Goal

*In this study we analyze various characteristics of a placental tissue using a sequence of digitized hematoxylin and eosin (H&E) stained histology slides. In particular, we study variation in tissue and blood density along a sequence of placental slices. We also extract a villous tree structure from this image sequence.*

## Summary of Methods

To achieve this, registration of these images is a crucial step. This is a large-scale problem, as the size of 'each' histology slide could be as large as 500MB. We proceed with the registration sequentially i.e. we register the $(n+1)^{st}$ slide to the $n^{th}$ slide. To this end, we use 'multilevel rigid registration'. In this approach, we scale down the images dyadically and then input the rigid-transformation parameters, i.e. translation vector, angle of rotation and scale, to the next level of registration. This significantly reduces computing time (The result of the entire sequential registration can be downloaded from the following URL: http://tinyurl.com/3xxfoas.) After registration, we use a novel image analytic algorithm to segment tissue and blood. This technique consists in identifying the tissue and blood based on color segmentation.

## Registration

In studying the hematoxylin and eosin (H&E) stained images we need to study a sequence of images rather than one image. These images may not have the same orientation, scale, or alignment. This problem occurs in many image processing applications while dealing with multiple images of same/similar objects. This makes *image registration* one of the fundamental tasks in image processing. The task of *image registration* is to find an optimal geometric transformation between images [2].

## Rigid Registration

In case of the H&E images we performed experiments on the set of 120 consecutive images. Due to the large size of these images, for computational purposes the images were down-sampled and only the green channel was used in the computations. We first performed rigid registration, with the assumption that the consecutive images need to be corrected for translation, rotation, and scaling. To this end, we solve the following minimization problem

$$\inf_R E = \int |T(x,y) - S(R(x,y))|^2 \, dxdy.$$

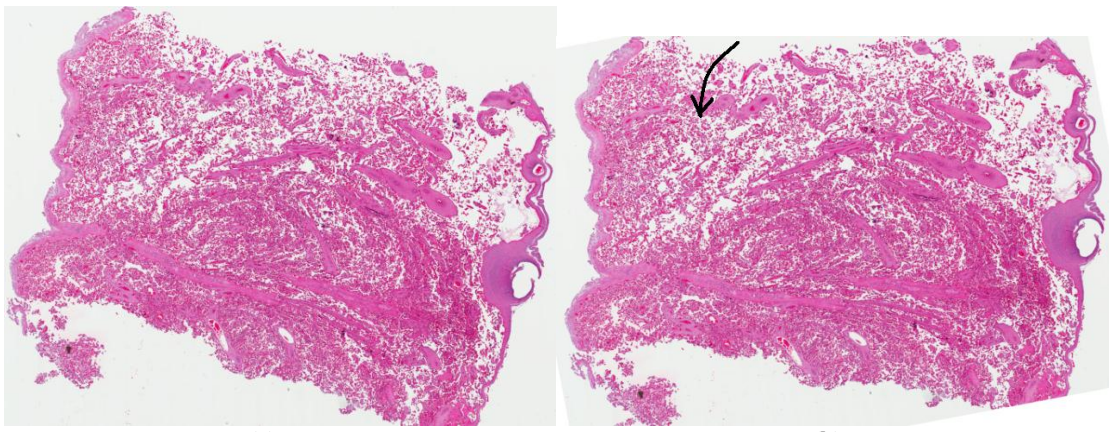
Here $T$ is the target image, $S$ is the source image which needs to be rigidly transformed to the target image, through a rigid transformation, $R$. The rigid transformation $R$ is of the form,

$$R(x,y) = \alpha \begin{pmatrix} \cos\theta & \sin\theta \\ -\sin\theta & \cos\theta \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix} + \begin{pmatrix} t_x \\ t_y \end{pmatrix}$$

where $(t_x, t_y)$ is the translation vector, $\theta$ is the angle of rotation, $\alpha$ is the scaling factor,. Thus, we need to find the vector $z = (t_x, t_y, \theta, \alpha)$ that minimizes the energy $E$. This can be done with the Newton's method [3], which takes form of the following iteration

$$z_{k+1} = z_k - \nabla^2 E_k^{-1} \nabla E_k.$$

The iterations are initialized with the zero vector $z_0 = (0, 0, 0, 1)$.



(a) (b)

Figure 1: In (a) we see an image that was rigidly registered to a previous image in the original dataset. The transformed image is depicted in (b).

## Multilevel Rigid Registration

Due to the large size of the images, the above minimization problem can take a long time. This time also depends on the initial guess.
To tackle this problem, we used a novel multilevel rigid registration (MRR):

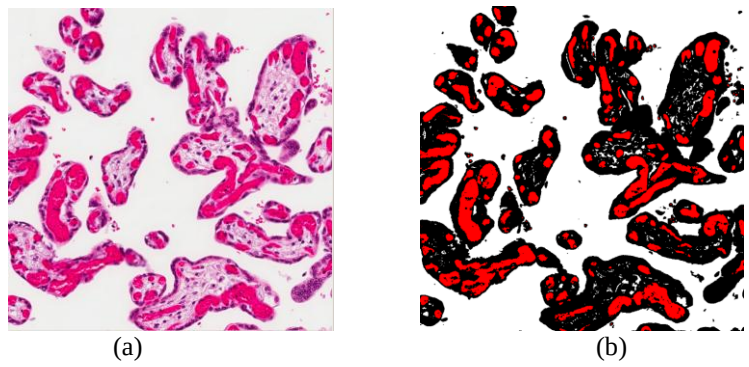
1. Resize the images $T$ and $S$ to $1/2^{N\text{ th}}$ of their sizes. Solve the above stated minimization problem to reach the solution $z^{(N)} = (t_x^{(N)}, t_y^{(N)}, \theta^{(N)}, \alpha^{(N)})$.
2. Use the initial guess $z_0^{(N-1)} = (2\,t_x^{(N)}, 2\,t_y^{(N)}, \theta^{(N)}, \alpha^{(N)})$ to solve the minimization problem with the images $T$ and $S$ resized to $1/2^{N-1\text{ th}}$ of their original sizes.
3. Repeat step 2. until we reach the original size of the images of $T$ and $S$.

We used $N=3$ in our experiments. This approach greatly reduces the computing time (*about one third*), as the initial guess is already close to the solution of the minimization problem. Figure 1 shows the result of a single registration, where the image in (a) was rigidly transformed to align with a previous image in the given dataset.

After registering the second image to the first image, this process is followed to register the third image to the second and so on… In this way, we obtain a sequence of registered images, which can be used to study various aspects of the placenta.

## Tissue Segmentation

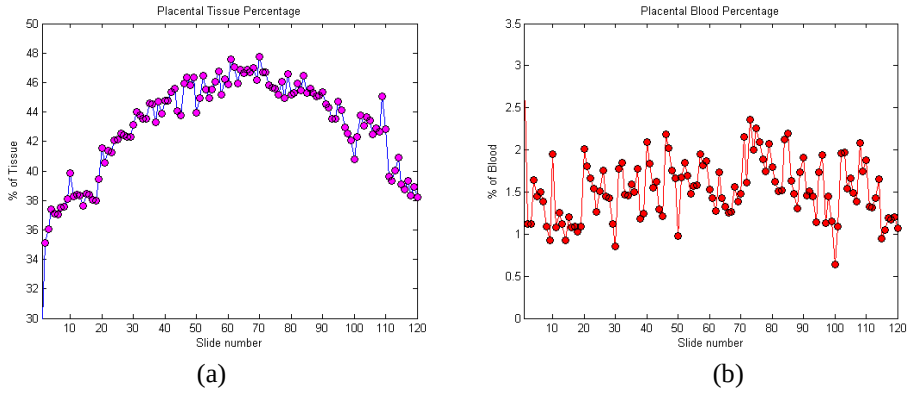
In this research we used vertical sections of a placenta, where most of the maternal fluid was drained out. Thus in the images we only had the fetal stem, capillaries, and other non-villous parts [1]. Thus we have mostly a white space where the maternal fluid should have been. This could be used to extract tissue area. To this effect we developed a Matlab program to segment out the tissue and identify the blood using color segmentation algorithms. The snapshots of the results are shown in figure 2.



(a) (b)

Figure 2: In part (a) we see part of the original H&E slide and in (b) we depict the result of the image segmentation.

Using the registered images we could extract the variation in the blood and tissue densities. The results of this study are depicted in figure 3.




(a) (b)

Figure 3: The image (a) shows variation in the tissue percentage and in (b) we see the variation of the fetal blood across the sequence of H&E slides.

## Villous Tree Extraction

The registered sequence of the H&E images could be used to track the fetal stems. In figure 4, we can see a partial depiction of the 3D villous tree.

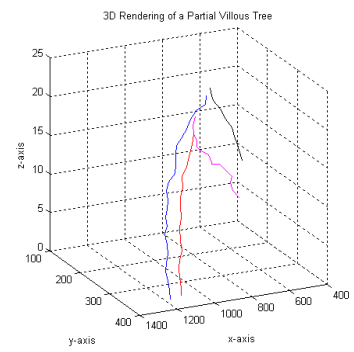



Figure 4: 3D rendering of the villous tree, extracted using the sequentially registered images.

## Conclusion

Tools developed in this research serve as an important first step in the analysis of tissue/blood distribution and villous tree extraction.

## References

[1] K. Benirschke and P. Kaufmann, *Pathology of the human placenta*, 4 ed. Springer-Verlag, 1999.
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