Map3D: Registration Based Multi-Object Tracking on 3D Serial Whole Slide Images

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Abstract—There has been a long pursuit for precise and reproducible glomerular quantification on renal pathology to leverage both research and practice. When digitizing the biopsy tissue samples using whole slide imaging (WSI), a set of serial sections from the same tissue can be acquired as a stack of images, similar to frames in a video. In radiology, the stack of images (e.g., computed tomography) is naturally used to provide 3D context for organs, tissues, and tumors. In pathology, it is appealing to do a similar 3D assessment for glomeruli using a stack of serial WSI sections. However, the 3D identification and association of large-scale glomeruli on renal pathology is challenging due to large tissue deformation, missing tissues, and artifacts from WSI. Therefore, existing 3D quantitative assessments of glomeruli are still largely operated by manual or semi-automated methods, leading to labor costs, low-throughput processing, and inter-observer variability. In this paper, we propose a novel Multi-Object Association for Pathology in 3D (Map3D) method for automatically identifying and associating large-scale cross-sections of 3D objects from routine serial sectioning and WSI. The innovations of the Map3D method are three-fold: (1) the large-scale glomerular association is principled from a new multi-object tracking (MOT) perspective; (2) the quality-aware whole series registration is proposed to not only provide affinity estimation but also offer automatic kidney-wise quality assurance (QA) for registration; (3) a dual-path association method is proposed to tackle the large deformation, missing tissues, and artifacts during tracking. To the best of our knowledge, the Map3D method is the first approach that enables automatic and large-scale glomerular association across 3D serial sectioning using WSI.

Index Terms—pathology, renal pathology, MOT, registration, tracking

I. INTRODUCTION

O

VER the past decade, rapid advances in whole slide imaging (WSI) and image processing has let to a paradigm shift in analyzing large-scale high-resolution renal pathology images [1]. These advances are largely attributed to the progress in deep learning techniques, which have enabled high throughput object quantification for clinical research and practice. However, current quantitative assessments of glomeruli are still primarily performed on a single two-dimensional (2D) section, which is error-prone due to the heterogeneity of glomeruli across serial sections. For example, [2] elucidated that the 2D phenotyping on a percentage of glomerulosclerosis could be misleading compared with 3D phenotyping. Moreover, several important glomerular phenotypes are ideally gained in 3D, such as glomerular volume and atubular glomeruli. Atubular glomeruli are glomeruli that have lost connection with the proximal tubule, which can only be confirmed when all WSI sections are visually examined from a 3D nephron [3].

Even the 3D assessments are more precise and reproducible, it is technically challenging to perform scalable 3D glomerular quantification on kidney WSI, since thousands of 2D glomerular cross-sections (image patches) need to be associated from serial sectioning, along with large tissue deformation, tissue loss, and artifacts from tissue sectioning and imaging (Fig. 1). As a result, current 3D glomerular studies are still heavily relying on manual or semi-automated approaches, leading to increased labor costs, low-throughput image analysis and potential inter-observer variability.

To progress our goal of large-scale glomerular identification and association in 3D, we principle this problem from a new multiple object tracking (MOT) perspective, splitting the challenging task to consequential steps (object detection, affinity estimation, and 3D association). However, there are still unique challenges for developing MOT on renal pathology as opposed to the canonical MOT tasks in computer vision. For example, the resolution of a pathology image is in orders of magnitude higher than typical natural images, bringing challenges in detection and association. Large deformation, missing tissues, and artifacts are typically inevitable during section preparation and imaging. Moreover, no large-scale annotated training data are publicly available, impeding the utilization of deep learning based MOT algorithms. To address these challenges, the deep learning based object detection and registration based association are aggregated to offer high throughput object detection and annotation free association. The proposed method is enabled by taking the advantages from both computer vision and medical image processing.

In this paper, we propose the Multi-Object Association for Pathology in 3D (Map3D) method, for the scalable and automatic glomerular association on 3D renal pathology. Briefly, our previously proposed CircleNet method [4], is adapted from a human kidney to the mouse kidney for large-scale glomerular detection. Then, a registration based affinity estimation method, called quality-aware whole series (QaWS) registration, is developed to not only estimate the pixel-wise affinity across the different sections, but also offer the automatic quality assurance (QA) for the entire stack of images. The automatic QA is important when deploying the Map3D on large-scale dataset. Last, the dual-path association (DPA) algorithm is introduced to associate all detected glomerular cross-
sections in a 3D context, addressing the continues tracking for missing tissues and artifacts. Serial whole kidney sections from 20 mice are used to train and validate the performance of the proposed method. These experiments show that Map3D is a promising step towards the ultimate goal of reducing labor costs involved in densely annotating and associating all glomeruli from serial sections in one kidney from a manual (30 laboring hours per kidney) to a fully automatic manner.

To summarize, the innovations of the Map3D method are in three-fold: (1) a novel holistic MOT framework is proposed to address the challenging 3D glomerular identification and association on high-resolution images with large deformation; (2) the QaWS registration is proposed to not only provide affinity estimation but also offer automatic kidney-wise quality assurance (QA) for registration; (3) a Dual-path 3D association method DPA is presented to tackle the missing tissues and artifacts during serial sectioning of WSI. To the best of our knowledge, the Map3D method is the first method that works toward automatic and large-scale glomerular identification and 3D associations across routine serial sectioning WSI.

II. RELATED WORKS

A. Multi-object Tracking

MOT has been an essential research area in computer vision for decades. Its primary aim is to track multiple objects from a video. Recent advances in deep learning have changed the paradigm of MOT from a model-based policy to data-driven approaches [5]. The current focus has been centered on a “tracking-by-detection” principle. The MOT algorithms can be roughly classified into two families.

The first family treats MOT as an online estimation study since the real-time performance is required in many computer vision tasks, such as self-driving, video surveillance, and cell phone applications. In such scenarios, the tracking status of the current frame is determined by previous observations utilizing the current time point as an online learning procedure [6], [7], [8]. Yan et al. [6] capture target candidates from both detector and independent single object trackers, by integrating the messages to determine optimal tracking. Xiang et al. [7] deploy the MOT as a Markov decision process using annotated training data.

The second family tackles MOT as a global optimization problem using offline optimization by utilizing both previous and future slides to determine the current status of tracking. The most commonly used global data association algorithms are the Hungarian algorithm [9], [10], multiple hypotheses tracking [11], and network flow [12], [13]. The quality of the tracking is largely relied on the accuracy of detected objects from the external detector.

Recently, deep learning has been widely used in MOT due to high accuracy and computational efficiency. Most recent solutions rely on a powerful discriminant technique [14], [15] for robust affinity estimation. Tang et al. [16] propose a deep learning based affinity estimation method. Sadeghian et al. [8] employ a convolutional neural network (CNN) and a long short-term memory (LSTM) to model long-term temporal dependencies by aggregating clues from interaction, motion, and a person re-identification model using a dynamic CNN-based framework. Recently, end-to-end deep learning solutions have been developed [17], [18] to further leverage tracking...
Fig. 2. The overview as well as each step are presented in this figure. The overview panel shows the three major steps in our MOT framework: (1) object detection, (2) affinity estimation, and (3) multi-object association. In step 1 object detection, deep learning based high-throughput detection method is used to detect all glomeruli. In step 2 affinity estimation, both affine and non-rigid registration are used to achieve pixel-wise correspondence between sections. In step 3 multi-object association, the dual-path association (DPA) is used to perform object tracking with missing tissues.

In this paper, we define object association on 3D renal pathology as a MOT task. Different from recent MOT studies, no large-scale training data are available to train a deep learning based solution. Moreover, the sense in the pathology “video” (serial sections) have global rotation, deformation, and artifacts. Therefore, we propose the registration based MOT method, inspired by the recent innovations in 3D registration and reconstruction on pathological images [19], [20], [21]. Unlike these studies, which achieve the “perfect” 3D reconstruction of the entire WSI stack, we employ the registration as an intermediate step to estimate the affinity between glomerular detection results. Therefore, we only emphasize the registration across neighboring sections (frames) in a MOT context.

B. Deep Learning Based Glomerular Quantification

WSI represents a paradigm shift, enabling clinicians to diagnose patients and guide therapeutic planning by navigating a virtual slide. Imaging advances have driven increasing demands in high throughput image quantification for clinical decision support. Excitingly, the explosive growth in deep learning technologies has been adapted to the field of renal pathology to match such needs [22]. Many deep learning studies have been focused on glomerular quantification since its role is essential in Nephrology. The current glomerular quantification methods are mostly 2D based quantification, whose tasks can be categorized as classification [23], [24], detection [25], [26], [27], [28], and segmentation [29], [30], [31], [32], [23], [23]. Beyond basic quantification, many recent works have performed further diagnosis upon the such a preliminary quantification [34], [35]. A recent study even provided the dense estimation of a renal pathology image with comprehensive ten tissue classes [36]. Current quantitative assessment of glomeruli is still mainly performed on a single 2D section. Distinct from previous glomerular quantification methods, we propose a 3D quantification framework, by principle the problem from a MOT perspective.

III. METHODS

The entire framework of the proposed Map3D is presented in Fig. 2. The Map3D pipeline consists of three sections: (1) glomerular detection, (2) QaWS registration based affinity estimation, and (3) DPA based 3D association.

A. Object Detection

The glomerular detection was implemented by our previously proposed CircleNet method [4], which has the aim to develop an optimized bounding circle representations for glomerular detection. As the CircleNet achieved superior
performance for glomerular detection compared with current benchmarks, we directly applied CircleNet as the detection method in this study. To adapt the detection method to mouse kidneys, we fine-tuned the CircleNet using image patches from 927 and 125 glomeruli as training and validation data, since the original CircleNet approach was trained by human glomeruli [4]. To be compatible with the prevalent MOT workflow, all the detection results are saved as bounding boxes with their corner coordinates. The similarities between different bounding boxes are measured by Intersection Over Union (IOU).

B. Quality-aware Whole Series Registration

After achieving the bounding boxes from detection, the standard operation in MOT is to calculate affinity measurements across detected objects. In the pathological WSI image, if the 3D serial sectioned images are regarded as a video, the unique challenge is the high resolution of each video “frame” (i.e., one section). However, there are also unique benefits for tracking objects across sections in WSI. For example, the relative locations of different tissues are more stable than computer vision. Inspired by these facts, we decided to use image registration as the affinity estimation method, inspired by [19].

Different from [19], which had the purpose to achieve “perfect 3D reconstruction of the entire WSI stack, we consider the registration as an intermediate tool to estimate the affinity between glomerular detection results. Therefore, we are not aiming to align all sections into a single space, but only emphasize about the registration across neighboring sections (frames) as a canonical MOT setting.

An important limitation of registration based tracking is the registration failure, Which might break all tracking numbers. When deploying the Map3D on the larger cohort, it is appealing that the algorithm itself could be able to feedback the quality of registration across the series. Therefore, we propose the QaWS registration method, to perform self-QA to classify the quality of the registration on the entire series as "good", "acceptable", and "unknown". In this section, we focus on introducing the pair-wise registration in QaWS registration, while the details of self-QA method with cycle-consistent registration failure detection, is introduced in the next section.

The pair-wise registration are employed to find the pixel-to-pixel correspondence between different pathological images. The correspondence is used to calculate the affinity score between detected objects using IOU. Our registration consists of scale-invariant feature transform (SIFT) [27] affine registration and advanced normalization tools (ANTS) [38] non-rigid registration. We define $i$ is the $t$th section (frame) in the entire series with length $T$, while $i$ is the index of pixel $x_i$ in the image $I$, with $N$ pixels.

\[
M_{f_1} = \arg \min_{M} \sum_{i=1}^{N} ||A(x_{i}^{t+1}, M) - x_{i}^{t+1}||
\]

\[
\phi_{f_1} = \arg \min_{\phi} \sum_{i=1}^{N} ||D[\phi_{A}(x_{i}^{t+1}, M_{f_1}), \phi] - x_{i}^{t+1}||
\]

In Eq. (1), $A$ indicates the affine registration with matrix $M$, while $D$ represents the non-rigid ANTs registration with deformation filed $\phi$. $f_1$ indicate the 1st forward registration in the cycle-consistent registration failure detection (Fig. 3). C. Cycle-consistent Registration Failure Identification

To enable the quality-awareness for the entire series, we employ the additional registration pair between section $t + 2$ and $t + 1$ (Fig. 3).

\[
M_{f_2} = \arg \min_{M} \sum_{i=1}^{N} ||A(x_{i}^{t+2}, M) - x_{i}^{t+1}||
\]

\[
\phi_{f_2} = \arg \min_{\phi} \sum_{i=1}^{N} ||D[\phi_{A}(x_{i}^{t+2}, M_{f_2}), \phi] - x_{i}^{t+1}||
\]

To form a cycle loop of the registration, we also perform a interleave registration from $t + 2$ to $t$ . The $f_1$ and $f_2$ indicate the 1st and 2nd forward registration in the cycle-consistent registration failure detection, while the $b$ indicate the registration is performed for backward registration (Fig. 3).

\[
M_{b} = \arg \min_{M} \sum_{i=1}^{N} ||A(x_{i}^{t+2}, M) - x_{i}^{t+1}||
\]

\[
\phi_{b} = \arg \min_{\phi} \sum_{i=1}^{N} ||D[\phi_{A}(x_{i}^{t+2}, M_{b}), \phi] - x_{i}^{t}||
\]

With the affine registration matrix and deformation fields from the pair-wise and interleave registration. We will achieve the $I_t$ applying all affine and non-rigid deformation fields on the image $I_t$ as Eq.(7). Note that, the inverse affine and deformation fields are used in the $(M_{b}^{-1}, \phi_{b}^{-1})$ to transfer the deformed image back to original space.

\[
I_t = I_t \circ (M_{f_1}, \phi_{f_1}) \circ (M_{f_2}, \phi_{f_2}) \circ (M_{b}^{-1}, \phi_{b}^{-1})
\]

Then, the mutual information $MI$ is calculated between the $I_t$ and $I_t$. The failed cycle-consistent score $FC$ is assigned to 1 when the $MI$ is lower than the threshold $Q$, which is empirically set to 1 in this study.

\[
FC_t = \begin{cases} 
1, & MI(I_t, I_{t'}) < Q \\
0, & MI(I_t, I_{t'}) \geq Q
\end{cases}
\]

By running the cycle-consistent assessments on all three consecutive sections, the automatic quality evaluation across the entire series will be achieved. Briefly, we will calculate the total failed cycle-consistent score $FC_{total} = \sum FC_t$. The quality of the entire series is marked as "good", if $FC_{total} = 0$; "acceptable", if $0 < FC_{total} \leq 3$; "unknown" if $FC_{total} > 3$. The "good" quality indicates all cycle-consistent assessments pass the QA threshold. The "acceptable" threshold is three since a bad quality section will at most fail three cycles, which is acceptable for Map3D using the following 3D association step. If $FC_{total} > 3$, we mark the series as unknown, as more heterogeneous problems might happen for that series.
IV. EXPERIMENTAL DESIGN

A. Data

20 mouse kidneys have been digitized from our previous studies. Each mouse kidney was prepared by staining with Immunohistochemistry (IHC). Each mouse kidney is cut into 7 to 17 sections. WSI were acquired for all sections at 20x magnification (0.5 μm pixel resolution) with 8 μm sections.

B. Experimental Design

To evaluate the performance of object tracking, we manually annotate a single mouse kidney with the largest number of sections (17 sections), and placed manual bounding boxes and tracking numbers across 17 sections. The entire manual process of annotating and QA one single kidney took 30 hours of human laboring. This sample includes 297 glomeruli and 1605 2D detection results. The manual annotations are saved as sections indices, detection coordinates, and tracking numbers.

To choose the optimal hyper parameters for registration and association, we manually annotate and track another mouse kidney as the validation data. For our validation purposes, we only annotate three adjacent representative sections, with missing tissue, to save the manual effort. The validation images consist of 66 glomeruli from 172 2D detection results. This validation kidney is used to determine the optimal threshold $S$ of the IOU when associating detection results (see “Ablation Study”).

Aside from the testing and validation kidneys, we chose another 10 kidneys (8 training and 2 validation) for fine-tuning the CircleNet detection method. Since the data will only be used for detection, we only annotate one 2D whole section from each kidney. For the results, 927 and 125 glomerular detection results are manually annotated as training and validation data. As all glomeruli were annotated on the testing kidney, the testing data with 1605 glomerular detection results will be used to evaluate detection performance as well.

Last, to perform the ablation study of comparing different registration methods, we manually trace one 3D glomerulus for 12 kidneys, to form 102 adjacent pairs of sections for registration.

C. Evaluation Metrics

MOT. The standard MOT metrics for Multi-Target Tracking in MOT-Challenge 2015 [39] is used to verify our tracking results. All manual and automatic tracking results are saved in the MOT-Challenge 2015 format to be compatible with the official evaluation code.

Registration. In the ablation study, we also evaluate the registration performance by using the absolute distance between landmarks. The registration error is calculated between the center point of the corresponding manual glomerular detection results, using the absolute distance (in μm).

V. RESULTS

A. MOT

We performed a standard MOT evaluation on the testing data (Tab. I and II). To disentangle the effects from detection and tracking components, we evaluate the final results using (1) manual detection, and (2) automatic detection. The large-scale results are shown in Fig. 5.

MOT with Manual Detection. In this scenario, the manual detection is used as the detection results (Tab. I). These results show the MOT performance when the detection is “perfect”. The proposed Map3D with DPA achieves the best performance.
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Manual Tracking

Automatic Map3D Tracking

Fig. 4. This figure shows the tracking results on the testing images. The 17 sections are obtained from the same mouse kidney. The upper panel shows the manual tracking results, which takes 30 hours of human effort, while the lower panel shows the automatic tracking results using our proposed Map3D method with no human effort. In each panel, the first row is the WSI. The second row is the enlarged region within the red boxes in WSI, where different colors indicate different tracking numbers. The third row is all cross-sections from one tracked 3D glomerulus, where the same color is assigned with the same tracking number.

Table I

| Method       | IDF1 | IDP | IDR | Rcll | Prcn | FAR | GT | MT | PT | ML | FP | FN | IDs | FM | MOTA | MOTP | MOTAL |
|--------------|------|-----|-----|------|------|-----|----|----|----|----|----|----|-----|-----|-------|-------|--------|
| SIFT         | 85.6 | 85.6 | 85.6 | 100  | 100  | 0.00| 297| 297| 0  | 0  | 0  | 0  | 101 | 16  | 93.4  | 90.3  | 99.9   |
| ANTs         | 75.6 | 75.6 | 75.6 | 100  | 100  | 0.00| 297| 297| 0  | 0  | 0  | 0  | 177 | 16  | 88.3  | 90.3  | 99.9   |
| Map3D w/o DPA| 97.4 | 97.4 | 97.4 | 100  | 100  | 0.00| 297| 297| 0  | 0  | 0  | 0  | 7   | 16  | **99.5** | **90.3** | **99.9** |
| Map3D       | **98.9** | **98.9** | **98.9** | 100  | 100  | 0.00| 297| 297| 0  | 0  | 0  | 0  | 7   | 16  | **99.5** | **90.3** | **99.9** |

Table II

| Method       | IDF1 | IDP | IDR | Rcll | Prcn | FAR | GT | MT | PT | ML | FP | FN | IDs | FM | MOTA | MOTP | MOTAL |
|--------------|------|-----|-----|------|------|-----|----|----|----|----|----|----|-----|-----|-------|-------|--------|
| SIFT         | 48.9 | 42.5 | 57.6 | 90.1 | 66.5 | 43.1| 297| 234| 51 | 12 | 689| 150| 369 | 48  | 20.5  | 70.6  | 44.5   |
| ANTs         | 57.5 | 50  | 67.7 | 90.1 | 66.5 | 43.1| 297| 234| 51 | 12 | 689| 150| 204 | 48  | 31.3  | 70.6  | 44.6   |
| Map3D w/o DPA| 74.4 | 64.9 | 88.0 | 90.1 | 66.5 | 43.1| 297| 234| 51 | 12 | 689| 150| 6   | 48  | 44.4  | 70.6  | 44.7   |
| Map3D       | **75.3** | **65.4** | **88.6** | 90.1 | 66.5 | 43.1| 297| 234| 51 | 12 | 689| 150| 3   | 48  | **44.6** | **70.6** | **44.7** |

Detection Results. The detection results are also presented in Tab. I. The CircleNet achieved 90.1 % recall (Rcll) and 66.5 % precision (Prcn). As the detection is not the focus of this paper, the comprehensive analyses of the detection could be found in [4].

MOT with Automatic Detection. In this experiment, the automatic detection results from CircleNet are used as the detection results (Tab. I). The results exhibit that the proposed Map3D with DPA also achieved the best performance, compared with baseline methods. In Fig. 5, the propose Map3D is able to achieve more consistent tracking results by jumping over the missing tissues.

B. Ablation Studies

Using the validation set, the tracking results with different IOU thresholds $S$ are presented in Tab. III using the same Map3D tracking methods with manual detection results. The tracking results with threshold $S = 0.1$ achieves the best performance with 98.8 in IDF1, compared with ground truth.

Fig. 5. This figure demonstrates the tracking results with missing tissue and incomplete glomeruli. The proposed Map3D method with DPA is able to achieve consistent tracking results by jumping over the missing tissues.
| IOU | IDP1 | IDP | IDR | IDs | MOTA | MOTP | MOTAL |
|-----|------|-----|-----|-----|------|------|-------|
| 0.1 | 98.3 | 98.3 | 98.3 | 2   | 98.8 | 89.4 | 99.7  |
| 0.2 | 97.7 | 97.7 | 97.7 | 3   | 98.3 | 89.4 | 99.6  |
| 0.3 | 95.9 | 95.9 | 95.9 | 6   | 96.5 | 89.4 | 99.5  |
| 0.4 | 89.0 | 89.0 | 89.0 | 18  | 89.5 | 89.4 | 99.3  |
| 0.5 | 80.2 | 80.2 | 80.2 | 36  | 79.1 | 89.4 | 99.1  |

Fig. 6. The left panel shows the pair-wise registration errors (in $\mu m$) between manual landmarks across 102 pairs registration. The right panel shows the automatic whole series QA results from our QaWS registration.

tracking. Since the evaluation is performed on manual detection, the detection related metrics are not provided in Table III.

Fig. 6 shows the performance of pairwise registration and QaWS registration on 102 pairs of sections from 12 kidneys. From the left panel, the two-stage registration used in the Map3D achieves the lowest registration error. Based on our experience, the SIFT method is more sensitive to the intensities of images when finding and matching the features. The ANTs method typically failed when tackling initial deformation with large rotation. Our method takes the advantages of the two registration methods to achieve the most optimal performance.

The automatic QA from QaWS registration in presented in the right panel of Fig. 6. Among 12 kidney whole series, 8 are labeled as “good”, 2 are labeled as “acceptable”, while 2 are labeled as “unknown”. We also visually inspected the 12 whole series, where we get the consistent QA results for “good” (no global registration failure), “acceptable” (one bad quality section). For “unknown”, we found that two consecutive sections have bad imaging quality.

VI. DISCUSSION

Prior studies reveal that careful manual or semi-manual 3D quantification can provide improved quantitative performance for glomerular phenotype [2]. However, 3D automatic quantification across routine serial sectioning and WSI has not been widely enabled in renal pathology research. To this end, this project also to offer new capability of investigating the glomeruli in 3D, by deriving the 3D glomerular quantification as a MOT problem using routine serial sectioning and WSI. As a holistic solution, deep learning based detection and registration based tracking enables the previously infeasible large-scale glomerular association across 3D sections.

There are several limitations in the current version of Map3D. First, one major limitation is the computational cost for non-rigid registration. Currently, more than five minutes are required to perform a pair-wise registration, which would take hours to conduct all necessary dual-path registrations for long serial sections. The deep learning based registration methods can be introduced to the Map3D framework, which can be even further combined with detection as a holistic algorithm [40]. Secondly, the affinity estimation is performed between detected boxes and transformed boxes without modeling the local displacement. To improve the performance, the non-local patch search [41] that widely used in the Multi-atlas Segmentation (MAS) could be included to leverage the performance.

As a next step, the proposed Map3D algorithm could be used to advance the large-scale clinical research and clinical decision support. It would also enable scientific inquiry that is difficult to be answered without large-scale 3D quantification, such as investigating glomerular volume (hypertrophy) [42] in pathogenesis.

VII. CONCLUSION

In this paper, we propose the Map3D method, to principle the large-scale glomerular identification and association in 3D serial sections from a MOT perspective. The proposed Map3D consists of a glomerular detection, quality-aware QaWS registration, and a dual-path 3D association method DPA. Map3D achieves superior tracking performance compared with baseline methods in large-scale glomerular association, tackling missing tissues and artifacts.

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