

# Quantitative Ultrasound for Periodontal Soft Tissue Characterization

Sedigheh Poul<sup>a,\*</sup>, Ankita Samal<sup>a</sup>, Amanda Rodriguez Betancourt<sup>b</sup>, Carole Quesada<sup>a</sup>, Hsun-Liang Chan<sup>b</sup>, Oliver D. Kripfgans<sup>a,c,\*\*</sup>

<sup>a</sup>*Department of Radiology, University of Michigan School of Medicine, Ann Arbor, Michigan, United States*

<sup>b</sup>*Department of Periodontics and Oral Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan, United States*

<sup>c</sup>*Department of Biomedical Engineering, University of Michigan, Ann Arbor, Michigan, United States*

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## Abstract

Periodontal (gum) diseases reportedly affect 45.9% of adults 30 years of age or older in the United States. Current diagnostic methods for clinical assessment of periodontal soft tissues are visual examination, palpation which are subjective and qualitative, and bleeding on probing (invasive) which is the late indicator of tissue destruction. Therefore, there is a critical need for research on noninvasive modalities for clinical assessments of periodontal tissues. Quantitative Ultrasound (QUS) analysis has shown promising results in noninvasive characterization of various soft tissues; however, it has not been used in periodontics. This study is among initial investigations into the application of QUS for periodontal tissue characterization in the literature. Here, QUS analysis of oral soft tissues (alveolar mucosa and gingiva) is performed in an *in vivo* animal study including 10 swine (6 females and 4

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\*Corresponding Author 1: ssheykho@umich.edu

\*\*Corresponding Author 2: greentom@umich.edu

males) in which ultrasonic scanning was performed at the first molar of all four oral quadrants, resulting in a total of 40 scans. We investigated first order ultrasonic speckle statistics of oral tissues by using the two-parameter Burr model (power-law  $b$  and scale factor  $l$ ) and the two-parameter Nakagami model (shape factor  $m$  and scale factor  $\alpha$ ; where  $\alpha$  represents the echo intensity). Parametric imaging of these parameters was created using a sliding kernel method sweeping regions of interest with a kernel size of 10 wavelengths chosen from a separate phantom study. Parametric images were superimposed onto the B-mode image to incorporate additional information to its anatomic references and grayscale echogenicity as well as facilitating visual comparisons of the two oral tissue types. Results show that the gingiva and alveolar mucosa are distinct from average Burr and Nakagami parameters. The difference between the two tissue types using model parameters are statistically significant ( $p - value < 0.0001$ ). Comparing average parameters in swine population, the Burr power-law parameter and Nakagami shape factor are both higher in gingiva than alveolar mucosa while the Burr and Nakagami scale factors are both lower in gingiva. Findings from QUS analyses are in agreement with observation in histology images from the Masson's Trichrome and hematoxylin-eosin (H&E) staining methods. Both stains show different underlying structure in the two tissue types with gingiva demonstrating denser underlying structure. Linear classifications of these two tissue types using two-dimensional parameter spaces of the Burr and Nakagami models result in a segmentation accuracy of 93.51% and 90.91%, respectively. We propose that QUS holds promising potentials to be employed for the assessment of periodontal soft tissues with the aim of

improving diagnostic sciences of periodontology and implant dentistry. QUS could become an objective and quantitative diagnostic tool for the quantification of periodontal soft tissue pathologies and thus, improving dental healthcare.

*Keywords:* Quantitative ultrasound, periodontal tissues, speckle statistics, Burr model, Nakagami model, alveolar mucosa, gingiva, parametric imaging, histology.

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## 1. Introduction

Periodontal (gum) diseases are reported to affect nearly half (45.9%) of the adult populations aged  $\geq 30$  years in the United States [1]. These diseases concern various oral soft tissues that support and surround teeth such as marginal (free) gingiva, attached gingiva and, alveolar mucosa, which are illustrated in **Figure 1** for a swine model. The most prevalent periodontal diseases affecting these tissues are periodontitis and gingivitis which are a continuum of inflammatory diseases. Periodontitis is initiated by bacteria infection, potentiated by inflammation, resulting in periodontal attachment loss of soft tissues from bone as well as causing actual bone loss. As periodontitis progresses, it could cause tooth loss. It is also related to systemic diseases, such as cardiovascular diseases and diabetes. On the other hand, gingivitis is considered reversible, involving gingival inflammation without clinical signs of bone loss [2]. If oral diseases, affecting both soft and hard tissues, are not addressed at early stages, those could impose immense pain as well as excessive economic burdens on the population, (it is reported to have caused direct and indirect burdens of as high as \$154.06B in the United States in 2018 [3]).

Among diagnostic modalities in dentistry for clinical assessments of soft tissue is bleeding on probing (BOP). BOP is an invasive method in which a probe with ruler markings of 1 mm increments is inserted and gently pushed into the pocket/sulcus between the crown and the marginal (free) gingiva (see **Figure 1**). Probing depth as well as potential bleeding are frequently recorded at office visits as a surrogate for gingival inflammation and are a part of standard of care as BOP is a sign of periodontal inflammation.

Normal probing depth is equal or less than 3 mm, beyond which attachment/bone loss around a tooth is suspected. Apparently, BOP has several limitations: it is invasive, often time exerting unpleasant experiences on patients. Also, BOP is subjective, as penetration force/insertion angle of the probe and tissue texture can vary the readings significantly. Also, probing depth is insensitive in the sense that it is only able to differentiate increments of 1 mm and small-scale penetration depths bare reading errors. Additionally, common variations in gingival thickness induced by different biotypes in different patients could increase the complexity of obtaining an objective assessment of inflammation by BOP [4]. This method is qualitative as it describes either no, slight, or profuse/spontaneous bleeding. BOP is a measure of tissue destruction at a late and already irreversible stage [5]. It is noteworthy that although lack of BOP observation is a strong indication of negative inflammation, BOP observations do not necessarily indicate the existence of an underlying inflammation [6]. Another traditional diagnostic method in dentistry is the visual observation which suffers from some of limitations as those listed for BOP. For example, swollen and erythematous tissue is indicative of periodontal inflammation. However, pigmented and thick tissue can mask these cardinal signs. Therefore, it is crucial to investigate non-invasive diagnostic modalities for objective and quantitative characterization of oral soft tissues from clinical workflow aspects as well as for improving public health and alleviating the associated financial burden.

Towards this clinical goal, an imaging modality with promising potentials for oral soft tissue characterization is ultrasound (US) imaging. As a non-invasive, non-ionizing, real-time, inexpensive, and well-established modality,

US has been employed for imaging and characterization of various biological soft tissues such as liver, thyroid, muscle, etc. at differing depths and image resolutions [7, 8, 9]. In dentistry, US B-mode (brightness-mode) imaging has been employed for lesion detection, measuring gingiva thickness and to delineate the surface of hard tissues (bone/crown) [10, 11, 12, 13]. Moreover, ultrasound-based elasticity estimations of oral soft tissues have been investigated in different studies [14, 15]. Ultrasound imaging offers information beyond B-mode imaging. One important aspect to employ ultrasound imaging is quantitative ultrasound (QUS). In QUS analysis of tissues, the goal is to find quantitative parameters from uncompressed raw ultrasound scan data that can be linked to some measure of underlying structure of tissues, which could offer clinical potentials for tissue characterization [8, 16, 17]. While B-mode images provide information about landmark anatomical structures of tissues, it fails to provide information and contrast of the underlying soft tissue structure. QUS parameters could add more information to B-mode images, represented as a parametric image overlay. Although QUS analysis has been extensively applied to characterize various biological tissues [18, 19, 20, 21, 22], it has never been applied in clinical periodontics for soft tissue characterization and there are only few studies with limited analysis involving QUS for periodontal soft tissues. For example, in the study reported in [23], US B-scan echogenicity in layers of oral soft tissues were compared using a measure of echo levels. Nevertheless, the employed method deviates from standard techniques of analyzing US image echogenicity parameters quantitatively.

One class of QUS analysis in medical imaging of tissues is focused on mod-

eling first order statistics of ultrasound speckle. Speckles are granular (grey) textures observed in B-mode tissue images. Speckles result from the interference of backscattered waves echoed back from various tissue scatterers close to each other during ultrasound pulse-echo imaging. Although speckles have a negative impact on B-mode image quality and are filtered out for US image representation, speckle patterns could incorporate information about underlying tissue structure and thus, could have clinical significance. Modeling ultrasound speckle statistics may result in deriving quantitative parameters that can be correlated to tissue pathology not visible on B-mode images. A number of well-established distributions for speckle modeling in QUS include Rayleigh [24, 25], Homodyned-K [26, 27, 28], Nakagami [29, 30, 31], and more recently the Burr model [32, 33, 34]. All these distributions have been widely used for QUS-based tissue characterization. However, to the best of our knowledge, characterization of periodontal soft tissues using speckle modeling and these well-established distributions have not been reported in the literature. Here, we aim at characterizing periodontal soft tissue by investigating US speckle statistics using the Burr and Nakagami models in an *in vivo* animal study on swine oral tissues. Moreover, we present parametric imaging of these QUS parameters as an additional information to that of B-mode images. Additionally, histology images of swine oral tissues were acquired using Masson's Trichrome and hematoxylin-eosin (H&E) stains with a 20x magnification microscopy imaging to compare tissue structures with QUS analysis. Gingival and alveolar mucosal tissues were compared. QUS-based parametric imaging may have potential to be used as an augmented tool to current imaging modalities in dentistry such as cone beam computed

tomography (CBCT) to further aid oral surgeons and to provide diagnostic value to clinical assessment in oral examinations.

Before we delve into the QUS analysis, we will first present a concise overview of oral soft tissue anatomy to introduce necessary information and terms used within the rest of the paper.

### ***1.1. Oral soft tissues: anatomy***

Oral soft tissues are comprised of different components, such as gingiva, alveolar mucosa, buccal mucosa, and epithelium, each with different physiological properties suitable for a particular function during the mastication (chewing) process. The gingiva (G) and alveolar mucosa (M) are located closely in the proximity of teeth (crowns); however, the two types of tissues are distinct and have different ultrastructure. They are considered two important components of oral soft tissues that have drawn significant clinical studies due to the frequent occurrence of dental issues associated with qualitative and/or quantitative changes in gingiva and alveolar mucosa tissues [35]. These tissues along with other structures of hard and soft tissues are illustrated in **Figure 1** in a swine model.

#### *Gingiva*

Gingiva is a dense fibrous connective tissue having load-bearing intracellular layers and its primary role is to protect the root and alveolar bone from deformation and degradation. Connective tissues within the gingiva are mostly comprised of collagen fibers organized in different patterns: (i) thick collagen fibers arranged densely, and (ii) short and thin collagen fibers arranged sparsely along with fine-sized network (reticular) structures of fibers

as well as some diffuse collagen fiber patterns [36]. Gingiva comprises various fiber arrangements as also illustrated in **Figure 1**, which includes: alveolingival fibers (originating from bone to epithelium), dentogingival fibers (stretched from tooth root to gingival region), circumferential fibers (encompassing the tooth), and dentoperiosteal fibers (from the tooth root to the bone). In terms of vasculature, gingiva has dense capillary vessels ( $\geq 15 \mu\text{m}$  in diameter) that are mostly perpendicular to the gingival surface and lack connective vessels, with sparse large vessels at higher depth [37]. The gingiva consists of two main parts: the free gingiva, which wraps around the tooth and is free (not attached) from one side and, the attached gingiva which is attached to the free gingiva from one side and is firmly connected to the alveolar bone on the other side. Among periodontal soft tissues, the gingiva has relatively higher exposure to the external mechanical forces (cyclic and non-cyclic) applied from mastication compared to other oral soft tissues and thus, has a stiffer nature [38]. The gingiva is covered by an additional highly keratinized layer called epithelium (E) that forms a biological seal around the gingiva, lowering penetration of some substances into the oral soft tissues beneath it [39, 38].

#### *Alveolar Mucosa*

Alveolar mucosa is a membrane that lines the bone. Unlike gingiva, alveolar mucosa is less exposed to abrasive forces and is mainly non-keratinized. It has a higher level of elastic fibers which makes the alveolar mucosa more elastic compared to the gingiva whereas the gingiva contains higher collagen fiber levels cross-linked and possesses some resistance to tensile loads. These elastic fibers tend to make alveolar mucosa return to the resting state when

being extended. Moreover, it is distinguished by a higher blood vessel supply, ranging from capillaries to larger ones and appears pinkish compared to the gingiva's brighter white-pink color [40]. The interstitial fluid within the vasculature provides cushioning when tissue is under large masticatory loads.

## 2. Theory

In QUS, the first order speckle statistics is the probability distribution of the envelope of ultrasound echo amplitudes. Modeling speckle statistics could provide information about scatterer structure within tissues. This section provides the theoretical background for modeling first order ultrasound speckle statistics and also QUS parametric imaging using Burr and Nakagami models.

### 2.1. *The Burr model for speckle statistics modeling*

Recently, a new framework has been proposed to model the first order statistics of ultrasound echo amplitude from tissue backscattering which is based on a key assumption that scatterers within tissues are multi-scale fractal and their number density follows a power-law distributions with the characteristic size of scatterers ( $b$  as the key power-law parameter related to scatterers' density). The mathematics under this framework resulted in the Burr distributions for describing the first order statistics of ultrasound echo amplitude, which was the first application of the Burr model within the area of medical imaging [32, 33, 34]. The Burr distribution was first derived in the 1940s without any implications to the field of ultrasound medical imaging [41]. This framework was initially employed to describe ultrasound speckle statistics from *in vivo* livers in normal and abnormal conditions [42, 22] as

well as for describing the speckle statistics from a set of simulated scattering structures in the form of cylindrical and spherical scatterers in which number densities of multi-scale scatterers followed a power-law distribution with radii [34, 43, 44]. The results from these studies showed that the Burr distribution successfully and efficiently described US speckle statistics. Later, the Burr distribution was employed in optical coherence tomography (OCT) scans and it was reported that the Burr distribution shows promising results in modeling speckle statistics in OCT scans [45, 46]. Under this framework, the histogram of backscattered echo amplitudes ( $A$ ) can be modeled as a probability density function (PDF), denoted as  $P(A)$  in equation 1 with two underlying parameters: the key power-law parameter  $b$  and a scale factor  $l$ , as following:

$$P(A) = \frac{2A(b-1)}{l^2[(\frac{A}{l})^2 + 1]^b} \quad (1)$$

The two parameters of  $b$  and  $l$  have shown potential in characterizing changes in scattering structures of soft tissues such as normal and fibrotic livers [42, 22]. To estimate the Burr parameters from the tissue backscatter within a selected region of interest (ROI), we can fit the echo envelope PDF of the speckle data to equation 1 and derive the underlying parameters. Also, the Burr parameters can be estimated locally from the local statistics of speckle data using a sliding window approach where the ROI is swept by a small kernel and a local estimation map of the Burr parameters is calculated. To do so, we could utilize some relationships between one or multiple statistical moments of the echo amplitude and the Burr parameters to find a system of two equations with two unknown parameters [47]. One statistic to employ is the first moment of the echo amplitude, i.e. mean: denoted as  $E[A]$  and

reported in equation 2 . The right hand side of this equation is a function of both  $b$  and  $l$ . Other statistics could be the ratio of the square of the first moment of the echo amplitude,  $(E[A])^2$ , to the first moment of the echo intensity,  $E[A^2]$ , as shown in equation 3. The right side of this equation only depends on  $b$ . Using these two equations, one can obtain local estimations of the Burr parameters.

$$E[A] = \frac{(b-1)l\sqrt{\pi}\Gamma(b-\frac{3}{2})}{2\Gamma(b)} \quad (2)$$

$$\frac{(E[A])^2}{E[A^2]} = \frac{(b-2)\pi(\Gamma(b-\frac{3}{2}))^2}{4(\Gamma(b-1))^2} \quad (3)$$

## 2.2. Nakagami Distribution

The probability distribution of the echo amplitude envelope from the two-parameter Nakagami distribution is modeled according to equation 4 where  $m$  is the Nakagami shape parameter and  $\alpha$  is the Nakagami scale factor. These two parameters are estimated statistically from equation 5 and equation 6. It is noted that the Nakagami  $m$  parameter determines the form of the speckle statistics PDF: if  $m < 1$ , it is pre-Rayleigh and a heavy-tailed distribution, if  $m = 1$ , it corresponds to Rayleigh behavior and for  $m > 1$ , it demonstrates a post-Rayleigh distribution [31]. The Nakagami scale factor  $\alpha$  represents the total intensity of the backscattered echo within the region under analysis

$$f(r) = \frac{2m^m r^{2m-1}}{\Gamma(m)\alpha^m} e^{-\frac{m}{\alpha}r^2} U(r) \quad (4)$$

$$m = \frac{(E[A^2])^2}{E[A^2 - E[A^2]]^2} \quad (5)$$

$$\alpha = E[A^2] \quad (6)$$

In these equations,  $f(r)$  is the Nakagami density function and  $U(r)$  is the unit step function.

### 3. Materials and Methods

#### *3.1. Study design for intraoral US imaging of periodontal soft tissues*

For the QUS investigations of periodontal soft tissues *in vivo*, there are some challenges associated with intraoral US imaging itself which require an intricate study design and customized scanning setup to tackle them [48]. Two most important ones are dealing with the intraoral scanning of inherently small-sized periodontal soft tissues and also the mixed presence of hard and soft tissues. In addition, in intraoral scanning, the buccal (cheek) region imposes a less accommodating condition to foreign objects such as an ultrasound transducer. This limits the capability of freely placing and maneuvering the transducer when scanning the tissue. To address these challenges, we benefited from using a, recently introduced, tooth brush-sized high-frequency US transducer [49]. Its physical design and ability to provide high-resolution images was made for the purpose of intraoral imaging [48] through a collaboration of clinicians and scientists (co-authors H-L.C. and O.D.K) at the University of Michigan (Ann Arbor, MI) and the Mindray Innovation Center (Mindray Inc., San Jose, CA). This US transducer is shown in **Figure 2 (a)** and **(b)**, with its in situ placement in **Figure 2 (c)**. In order to acquire high-quality gingival and mucosal scans, a standoff gel pad was placed onto the aperture surface to shift the tissues of interest to the focal region of the transducer, as shown in **Figure 2 (d)**. Having in mind the anatomical structure of oral tissues shown in **Figure 2 (e)**, a sample of US scan of periodontal soft tissues in a swine model is presented in **Figure 2 (f)**. Regions of the gingiva, mucosa, epithelium, muscle as well as crown and bone are annotated

to help distinguish regions of interest for QUS analysis. It is noted that in the B-scan presented in **(f)**, the transducer is located on the right edge of the image. The B-scan sample shows that the epithelium appears as a hyper-echoic (bright) region, indicating a higher US backscatter intensity from this region. This higher scattering phenomenon may result from contributions of dense keratinized tissue (higher impedance). Also, the normal orientation of the stratified epithelium layer with respect to the transmitted pulse from the US probe may produce the strongest reflection compared to other angles.

For an accurate QUS analysis of periodontal soft tissues, two experimental studies were designed here: the first experiment focused on scanning and analyzing homogeneous custom-designed phantoms without any macro inclusions (CIRC Inc., Virginia, USA), and the second part focused on investigating *in vivo* periodontal soft tissues of swine. The phantom study aimed at finding the optimal window (kernel) size for accurate and robust local QUS parameter estimations. Specifically, it was meant to minimize variability caused by an overly small kernel size and concurrently, to avoid excessively large kernel sizes that result in loss of spatial resolution in QUS parameter estimations.

Swine models were selected for this study due to the resemblance of human and swine oral soft tissues from histology and morphology aspects [50]. Animals (N=10) were obtained from Sinclair Bio Resources (Auxvasse, MO, USA) under a study protocol approved by the Institutional Animal Care and Use Committee (PRO00010333). Four males and six females were investigated. Intraoral US scanning was performed at the mid-facial location of all four first molars (M1), which we refer to by combinations of L (left) /

R (right) and mandible (MAND) / maxilla (MAX). It is noted that a small notch was manually created on all teeth as a landmark visible on ultrasound images.

### *3.2. US data acquisition and parametric imaging*

Ultrasound imaging data for both phantom and swine studies were acquired by employing a clinical Mindray ultrasound imaging system (ZS3, Mindray Innovation Center, San Jose, CA, USA) equipped with a high-frequency linear array transducer, now commercially available (L30-8, ZS3, Mindray Inc., San Jose, CA) introduced earlier in **Figure 2 (a)** and **(b)**. The center frequency of the transducer is 18 MHz, the imaging depth and the lateral field of view commonly used are approximately 15 mm and 13 mm, respectively and the transducer elevational focus is at the depth of 8 mm. The raw RF-data were demodulated, and the envelope detected using a Hilbert transform. B-mode images were reconstructed using the logarithmically compressed envelope data within a dynamic range of 70 dB. The Burr model parameters ( $b$  and  $l$ ), and the Nakagami model parameters ( $m$  and  $\alpha$ ) were locally estimated in user-defined ROIs within the gingiva and the mucosa for each swine to provide additional information about tissue structure using an estimation kernel approach. The sliding kernel moved across ROIs (along horizontal and vertical directions) with an overlap ratio of 70%. Parameter estimations derived from the kernel at each location within the ROI was assigned to the center of the kernel. Linear interpolations were performed between estimations for adjacent centers to obtain a smoother parametric image. Model parameter estimations were mapped as colored parametric images overlaid on the B-mode images. The optimal

kernel (window) size for tissue parametric imaging was obtained from the phantom study.

### *3.2.1. Optimal window size*

In statistical estimations of the Burr and Nakagami parameters for parametric images, there is a trade-off between the spatial resolution of local parameter estimation and statistical variability in estimated parameters. If the window size (WS) is too small, the speckle within the kernel provides unrobust estimations, i.e., the parameters don't converge. On the other hand, the size of respective tissues under study imposes limitations on the size of the associated ROI and consequently, how large the window can be. The gingival and alveolar mucosal tissues are inherently small, often about 2 mm thick, which limits the ROI size for the QUS analysis. This trade-off was investigated by evaluating model parameters as a function of WS. Phantom scan envelope data were used to create parametric images of rectangular ROIs (5 mm by 2.5 mm) located in the center of the field of view. WS ranged from 2 to 18 wavelengths with an interval of 2 wavelengths. All data processing in this study was performed using MATLAB (R2023a, MathWorks Inc., Natick MA, USA).

### *3.2.2. ROI selection criteria for outlining gingival and mucosal tissues*

For ROI selection, the largest possible ROIs were selected for each tissue, excluding regions of hard tissues such as bone, crown as well as the epithelial layer and rete pegs, as those will affect the QUS parameter estimations representing gingiva and mucosa characteristics.

### 3.3. *Histology images*

After acquiring *in vivo* intraoral US scan data, animals were euthanized and tissue block samples were collected from US scanning sites. Samples incorporated oral soft and hard tissues such as alveolar mucosa, gingiva, bone and crown, allowing for transverse cross-sectional cuts of oral sites to be a part of histology images as also observed via US imaging. Tissue samples were collected and immersed in 10% formalin to be preserved from decay and maintain tissue structure for further tissue staining and processing. Tissue blocks were placed in 10% EDTA (Ethylenediaminetetraacetic acid) for demineralization for 3 to 6 months and then embedded within paraffin wax to maintain its shape as well as to create a support frame and facilitate tissue slicing (5 micron-thickness). Slices were stained using two separate methods: Masson's Trichrom and H&E techniques.

The Masson's Trichrome stain is a three-color staining method employed to reveal collagen structures of hard and soft tissues with its signature blue color for collagen. In this stain, red represents cytoplasm/red blood cell and dark purple/black shows nuclei. For example, dentine with its dominant collagen matrix is stained blue and keratin is stained as red. On the other hand, H&E as the most common staining method, is a two-color stain method that displays the underlying tissue morphology with a purplish color for nuclei and varying shades of pink color for cytoplasm, extracellular matrix and other structures. Stained tissue slices were imaged using an optical microscope (E800, Nikon Instruments Inc., Melville, NY) with 4x and 20x magnifications for overall and local imaging of slices, respectively.

#### 4. Results

**Figure 3** shows nine pairs of parametric images for the Burr two parameters superimposed onto the same B-scan image for nine WSs. In each pair of parametric images, the left-side image represents the Burr power-law parameter  $b$  and the right-side one shows the Burr scale factor  $l$ . Burr parameters were estimated within a rectangular (5 mm by 2.5 mm) ROI shown as white solid box. The dynamic range of all colorbars were set equal to provide for an absolute comparison of results across all WSs.

It is observed that the sliding WS of 2 produces parametric images with highly fluctuating statistical estimations, showcasing that local estimations may vary widely over a large dynamic range (color saturations beyond the colorbar range are observed). This is consistent with the expectation that speckle data from small kernels highly fluctuates, i.e., statistical estimations from excessively small kernels are not robust. By increasing WS from 2 to 10 wavelengths, we observe an improvement in homogeneity of both Burr parameters,  $b$  and  $l$ . Comparing parametric images produced from WS of 10 to 16 show the presence of a small non-homogeneous region (visible as a yellow patch) where local Burr  $b$  and  $l$  are persistently higher. Therefore, these local estimations are independent of the size of sliding kernel and are associated with local variations in underlying phantom structures from the Burr model standpoint. It is noted that for the sliding kernel size of 16 and 18, it transitions from a local parameter estimator to a global estimator over the whole ROI. This global estimation manifests itself as a parametric image being too uniform in which information on local variations are lost (averaged out).

**Figure 4** shows parametric images for the Nakagami shape parameter  $m$  and scale factor  $\alpha$  for different WSs, similar to what was done with the Burr model in **Figure 3**. For the Nakagami model, parametric images show that at a WS of 10 wavelengths and more, variations in local parameter estimations are not as intense as for smaller kernel sizes. Similar to the Burr model, there exists a small non-uniformity (shown as color saturation beyond the colorbar range) in parametric images, independent of the WS. A more detailed investigation into the effect of WS on the Burr and Nakagami parameter estimation is presented in **Figure 5** as errorbar plots using estimations in **Figure 3** and **Figure 4**, respectively. In this figure, black diamonds represent means and errorbar lengths represent single standard deviations. The case of the smallest WS (2 wavelengths) was excluded from **Figure 5** as it showed an unreasonably large standard deviation exceeding the normal range of y-axis. This figure shows that standard deviations for the Burr parameters are decreasing significantly and monotonically when transitioning from smaller to larger kernel sizes, with the estimation average becoming stable at WS of 10 wavelengths (approximately 0.64 mm at 24 MHz) and more. This WS provides sufficient speckle data for a reasonable and robust statistical estimation of parameters where the average model parameters converges and becomes stable with further increase in WS, varying within a small range less than 5% for the two scale factors and less than 10% for the power-law and shape parameters. This confirms the earlier finding from visual assessments of the WS effect on the Burr parametric images above. For the standard deviation, it decreases significantly at first for the Nakagami parameter, but its change becomes less significant at a WS of 10 wavelengths and higher.

This consistently higher standard deviation even at the largest WS may be related to the underlying structure of the phantom and might not represent a WS dependence *per se*. As a note on the optimal WS selection from a practical standpoint of obtaining parametric image for relatively small-sized periodontal soft tissues, the WS of 10 wavelengths reasonably meets criteria of accuracy and tissue size limitation. Therefore, it is suggested as the optimal kernel size for the Burr and Nakagami parametric imaging of swine tissues.

#### *4.1. Parametric imaging for in vivo swine scans*

The parametric images of the Burr and Nakagami parameters of periodontal soft tissues were obtained in ultrasound scans of 10 swine at the baseline condition (no inflammation) using the optimal sliding WS of 10 wavelengths. The results were statistically compared in gingiva versus alveolar mucosa within reasonable ROIs selected for each scan. An example of parametric image of the Burr  $b$ , Burr  $l$ , Nakagami  $m$  and Nakagami  $\alpha$  overlaid on corresponding B-scans are shown in **Figure 6** with the reference B-scan. The ROIs selected for these parametric images include the marginal and attached gingiva, alveolar mucosa, epithelium as well as muscle tissues and is meant to show the variations of estimated parameters over the whole scanned region. However, for the quantitative characterization of gingiva and alveolar mucosa, individual ROIs are selected for each tissue excluding any bone, epithelium layers or other regions not associated with these tissues. An example of the ROI selection from these two tissue types is shown in **Figure 7** and **Figure 8** for the Burr and Nakagami parametric imaging. In these

two figures, top rows represent ROI for the gingiva and bottom rows show alveolar mucosal ROI, with the reference B-scan is presented in **(e)**. It is observed that for the gingival tissue, the estimated Burr power-law parameter  $b$  and the Nakagami shape parameter  $m$  map to a brighter (yellow) colormap, corresponding to higher estimated values compared to mucosal tissues. On the other hand, the Burr scale factor  $l$  and the Nakagami scale factor  $\alpha$  for gingival tissues are lower than mucosal tissues based on the colormap comparison.

## 5. Discussion

### 5.1. Statistical analysis of swine populations

To characterize these two types of periodontal soft tissues adjacent to each other at the baseline condition (no inflammation) for all swine populations, the summary of QUS analyses are presented as boxplots for the Burr and Nakagami models in **Figure 9** and **Figure 10**, respectively. In these figures,  $p$  - values are reported to compare statistical significance between the two tissue types. In each boxplot, the blue line shows statistical median for the population and the pentagon symbols represents the statistical mean of the estimations.

In **Figure 9**, **(a)** and **(b)** shows the Burr  $b$  and Burr  $l$  results. For the Burr parameters,  $p$  - values  $< 0.0001$ , indicating that  $b$  and  $l$  could show statistically significant populations when comparing gingival tissues with alveolar mucosa. The Burr  $b$  for gingiva is reported to be higher than mucosa ( $b_{Gingiva} = 6.6 (4.8|10.4)$ ,  $b_{Mucosa} = 3.6 (3.2|4.7)$ ), while the Burr  $l$  is lower in gingival tissues ( $l_{Gingiva} = 254.0(177.1|362.7)$ ,  $l_{Mucosa} = 851.8(571.6|1174.3)$ ).

It is noted that the median (and almost the mean) of the Burr power-law parameter  $b$  for the alveolar mucosa tends to be close to the range for normal soft tissues such as liver reported in the literature [22, 33] while this is elevated for gingival tissues.

In **Figure 10** for the Nakagami model, **(a)** shows that Nakagami  $m$  is statistically higher for gingiva population in comparison to the alveolar mucosa ( $m_{Gingiva} = 1.29 (1.10|1.52)$ ,  $m_{Mucosa} = 0.83 (0.50|1.04)$ ) and, **(b)** represents a statistically elevated Nakagami  $\alpha$  in alveolar mucosa compared to the gingiva ( $\alpha_{Gingiva} = 1.82 \times 10^4 (0.81 \times 10^4|3.57 \times 10^4)$ ,  $\alpha_{Mucosa} = 4.39 \times 10^5 (2.29 \times 10^5|8.50 \times 10^5)$ ). Nakagami  $\alpha$  clearly demonstrates that echo intensity in gingiva is significantly lower (an order of magnitude).

Therefore, these plots imply that the Burr and Nakagami parameters show sensitivities to periodontal soft tissue types of gingivae and mucosa and hold potentials to characterize them.

## 5.2. *Histology insight*

To cast some insight into a possible explanation for statistically distinct QUS parameters for alveolar mucosa and gingiva, we consulted their histology images. The results for Masson’s Trichrome and H&E stains are shown in **Figure 11** and **Figure 12**, respectively. In these figures, **(a)** represents histology insights (4x magnification) of the stained tissue slice incorporating both soft and hard tissues. **(b)** and **(c)** show a 20x magnified image of gingival and alveolar mucosal tissues, respectively, marked with red dashed box in **(a)**. Scale bars are also to all images for references.

Looking at histology images from both staining techniques, we notice a denser stain in gingival regions compared to alveolar mucosa, which could

suggest denser scattering sites in gingiva. This observation from histology images might align with statistical findings from our QUS analyses in two aspects, as outlined below.

- First, lower B-scan echo intensity in gingiva compared to alveolar mucosa (indicated by decreased Burr and Nakagami scale factors) is hypothesized to arise from occurrence of multiple scattering between densely-packed scattering sites in gingiva. This would result in a weaker backscatter signal from this region back to the transducer. Thus, gingiva would appear less echogenic in US B-scans compared to alveolar mucosa.
- Second, the histology finding may suggest the presence of higher densities of small, densely-packed scatterers. This could explain elevated estimations of Burr power-law parameter  $b$  (associated with the number density of scatterers) obtained for the gingiva compared to the alveolar mucosa in the QUS analysis. Additionally, the QUS analysis showed a higher Nakagami shape parameter  $m$  in gingiva compared to alveolar mucosa, indicating a transition of scattering statistics to Rayleigh and post-Rayleigh regime for gingiva. The Rayleigh scattering regime is characterized by the presence of many random small scattering sites, resulting in a diffuse scattering. Thus, the elevated Nakagami shape parameter in gingiva could be associated with the denser stain observed in the gingiva on histology images, corresponding to an increase in scattering number density, (transitions into the Rayleigh and post-Rayleigh regime).

This histology findings may support our QUS results.

The PDF of the US speckle data within ROIs from alveolar mucosa and gingiva are fitted to the Rayleigh distribution in **Figure 13** as an example of PDF comparison. It is observed that speckle statistics of the gingiva fits relatively better to the Rayleigh ( $R - squared = 0.95$ ) compared the alveolar mucosa ( $R - squared = 0.82$ ). This suggests a gradual transition towards Rayleigh model for gingiva compared to alveolar mucosa. In these PDFs, the Burr model is added as a reference speckle model and it is noteworthy that it is a more accurate fit to statistics of both tissue types with its distinctive heavy-tail behavior at the higher amplitudes compared to the Rayleigh model.

### ***5.3. QUS-based classifications of alveolar mucosa and gingiva***

To further investigate the separations of alveolar mucosal and gingival tissues from the QUS standpoint, averages of the Burr and Nakagami parameters are estimated for each swine from local statistical estimations. The results are illustrated as two separate 2D scatterer plots of  $l - b$  and  $m - \alpha$  in **Figure 14 (a)** and **(b)**, respectively. In **(b)**, the Nakgami  $\alpha$  axis is represented as log-scale to compress the large dynamic ranges of this parameter in alveolar mucosa and gingiva.

In these figures, orange circles represent the estimations for alveolar mucosa and blue diamond symbols show the estimations for gingiva. In each 2D space, a linear boundary is optimized to classify the 2D parameter space by maximizing the accuracy of tissue type prediction. These lines show a clear separation of mucosal and gingival tissues in 2D space of QUS parameters estimated from the US speckle statistics. For the Burr model, the linear clas-

sification line gives an accuracy of 93.51%, a sensitivity (true positive rate) of 97.44%, and a specificity (true negative rate) of 89.47% (gingival tissue is assumed to be the positive class). For the Nakagami model, accuracy, sensitivity and specificity are 90.91%, 97.44%, and 84.21%, respectively. For both model, linear classification lines accurately classify all but one gingival case, leading to obtaining similar estimations for sensitivities, however the Burr model estimates more accurate alveolar mucosal cases, resulting in higher specificity than the Nakagami model. By comparing these statistics, the Burr model represents a relatively better separation of the two tissue types, with a slightly higher accuracy and also specificity.

Further, the classification of the two tissue types is investigated by combining the Burr and Nakagami parameters resulting in four features of  $b$ ,  $l$ ,  $m$ , and  $\alpha$ , to assess the multi-parametric classification accuracy. To represent the clustering of the two classes with four parameters in a reduced dimensionality (3D) space, the principal component analysis (PCA) is performed on the parameter (feature) space to map the original parameters into a new set of variables, a.k.a. principal components (PCs). PCs are basically directions in the feature space, composed of a linear combination of the original features, along which the data shows the most variation (higher variance). The maximum number of PCs in this case is four, however, we employ the first three PCs to visualize data in 3D. These PCs are the most significant representations of variations (dispersion) in the data. The mapped data onto the PC space along with the mapped classification boundaries are shown in **Figure 15**. The variance of data captured by the PC 1 is 55.31%, which is the direction with the highest dispersion in the data. PC 2 and PC 3 explain

25.37% and 12.38% of the variance in the data, respectively. Therefore, the first three PCs used to visualize the data in 3D PC space represent 93.06% of the variations of the data. The data are standardized before being mapped to the PC space to be scaled. Therefore, the axes range in this figure are different than the range of original parameters. The decision boundary using the four parameters gives the classification accuracy of 92.21%, which is between the two classification accuracies when applying each model separately. This accuracy is not significantly improved comparing with the 2D classifications. One potential reason behind this is the fact that multi-parametric classification is done based on maximizing the boundary margins whereas the 2D classification is performed by focusing on the accuracy itself directly. It is also noted that PCs are less interpretable representation of the data, and they mostly serve as an effective mean to represent the data in lower dimensional space while retaining most essential information from the data. For a classification with higher number of features, the PCA makes training of the classification model more effective.

## Conclusions

This study is among early investigations in the literature into applications of QUS approaches for periodontal soft tissue characterizations and serves as a crucial preliminary step with promising results towards employing QUS as an additional diagnostic tool for disease assessment in periodontics. In this study, characterization of periodontal soft tissues (alveolar mucosa and gingiva) was investigated in an *in vivo* swine model using a QUS approach based

on the Burr and Nakagami models for speckle statistics. The results showed that the Burr parameters (power-law parameter  $b$  and the scale factor  $l$ ) and also Nakagami parameters (shape parameter  $m$  and scale factor  $\alpha$ ) have potentials to distinguish clinically significant tissue types. This study demonstrated that the Burr power-law parameter and Nakagami shape parameter were significantly higher in gingiva compared to alveolar mucosa while the Burr scale factor and the Nakagami scale factor were significantly lower in gingiva. The QUS findings were hypothesized to be aligned with qualitative assessments of histology using Masson's Trichrome and H&E staining techniques. The two tissue types were classified in 2D parameter spaces using the QUS parameters from the Burr and Nakagami models which yielded a separation accuracy of 93.51% and 90.91%, respectively. The classification of the two tissue types using parameters from the two models in 4D resulted in a classification accuracy of 92.21%. Further studies should assess the effect of disease conditions such as oral soft tissue inflammation on QUS parameters. Our results indicate that QUS could potentially become an augmented tool in periodontics, as an objective, quantitative and noninvasive technique for disease diagnosis, longitudinal monitoring of healing, and feedback for indicated interventions.

## **Contributions**

*Sedigheh Poul*: Conceptualization, Methodology, Histology Imaging, Formal Analyses and Software, Validations and Visualization, Writing Original Draft and Revision;

*Ankita Samal, Amanda Rodriguez Betancourt, Carole Quesada*: Animal Ex-

periment, US Scan Data Acquisition, Review and Editing;

*Hsun-Liang Chan, Oliver D. Kripfgans*: Conceptualization, Methodology, Animal Experiment, US Scan Data Acquisition, Funding Acquisition, Review and Editing;

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## Figure Captions

**Figure 1:** Anatomical structure of swine periodontal tissues. Several types of fibers within the gingival tissues provide it with mechanical support during mastication (chewing).

**Figure 2:** (a) and (b) High-frequency ultrasound transducer for the intraoral scan, (c) the transducer positioning for mid-facial imaging of a molar tooth within the transverse plane in a swine, (d) zoomed-in view of the transducer with the standoff gel pad, (e) an illustration of oral soft tissues anatomy as a general reference for understanding B-scan structure in (f) for a swine case. Important anatomical structures of periodontal hard and soft tissues are annotated in both (e) and (f).

**Figure 3:** Burr parametric imaging for varying window size (WS in multiples of wavelength) superimposed on the associated B-mode phantom image. In each pair of parametric images, the left image shows Burr  $b$  and the right one shows Burr  $l$ . All axes are shown in millimeters.

**Figure 4:** Nakagami parametric imaging for varying window size (same phantom study as shown in **Figure 3**). In each pair, the left image shows Nakagami  $m$  and the right one shows Nakagami  $\alpha$  parameter local estimations. All axes are shown in millimeters.

**Figure 5:** Errorbar plots showing the effect of WS on the Burr parameters (top row), and on the Nakagami parameters (bottom row) as obtained from an ROI size of 5 mm by 2.5 mm in Figure 3 and Figure 4.

**Figure 6:** Parametric imaging of the Burr and Nakagami parameters in periodontal soft tissues in a swine scan using the WS of 10 wavelengths, for maxilla left first molar tooth. **(a)** reference B-scan, **(b)** Burr power-law parameter  $b$  and **(c)** Burr scale factor  $l$ , **(d)** Nakagami shape parameter  $m$  and **(e)** Nakagami scale factor  $\alpha$ .

**Figure 7:** Parametric imaging of the Burr parameters in the gingiva (top row) and the alveolar mucosa (bottom row) in a swine scan using the WS of 10 wavelengths. **(a)** and **(c)**: Burr  $b$ , **(b)** and **(d)**: Burr  $l$ . The reference B-scan is shown in **(e)**.

**Figure 8:** Parametric imaging of the Nakagami parameters in the gingiva (top row) and the alveolar mucosa (bottom row) in a swine scan using the WS of 10 wavelengths. **(a)** and **(c)**: Nakagami  $m$ , **(b)** and **(d)**: Nakagami  $\alpha$ . The reference B-scan is shown in **(e)**

**Figure 9:** Burr parameters for classification of gingiva vs. alveolar mucosa, with boxplots summarizing the average estimations within ROIs in swine cases. **(a)** Burr  $b$ , **(b)** Burr  $l$ .

**Figure 10:** Nakagami parameters for classification of gingiva vs. alveolar mucosa, with boxplots summarizing the average estimations within ROIs in swine cases. **(a)** Nakagami  $m$ , **(b)** Nakagami  $\alpha$

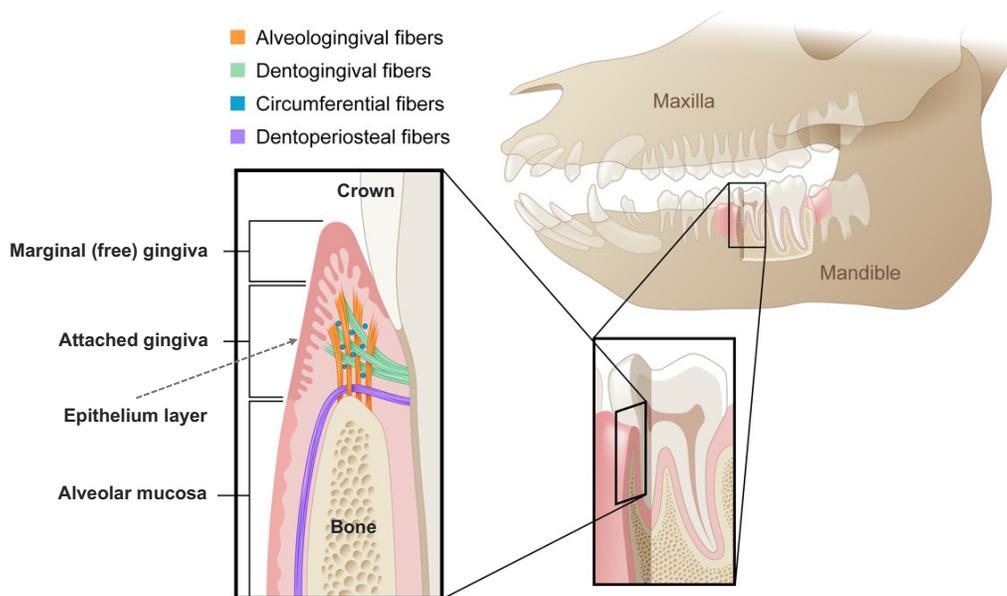
**Figure 11:** **(a)** Histology image using Masson's Trichrome stain (4x magnification). **(b)** and **(c)** are enlarged views comparing gingival and alveolar mucosal regions, respectively (20x magnification). Swine oral site: left mandibular first molar.

**Figure 12:** (a) Histology image using H&E stain (4x magnification) at the same tissue section as shown in **Figure 11**. (b) and (c) are enlarged views comparing gingival and alveolar mucosal regions, respectively (20x magnification). Swine oral site: left mandibular first molar.

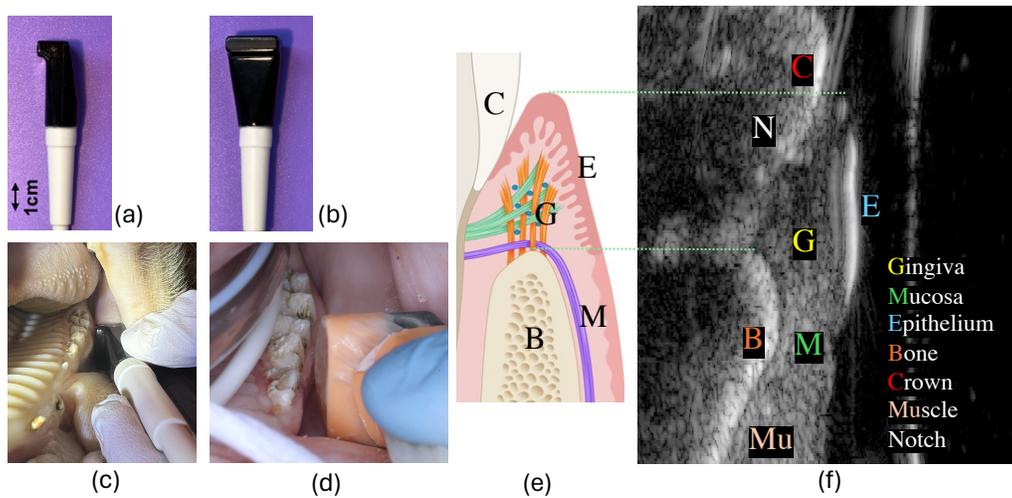
**Figure 13:** Probability distribution of US speckle data fitted to the Rayleigh (red curves) and Burr (blue curves) distributions for (a) alveolar mucosa (Rayleigh fit  $R - squared = 0.82$ ), and (b) gingiva (Rayleigh fit  $R - squared = 0.95$ ).

**Figure 14:** 2D classifications of gingiva vs. alveolar mucosa in swine cases using (a) the Burr model (Burr  $b$  vs. Burr  $l$ ), and (b) the Nakagami model (Nakagami  $m$  vs. Nakagami  $\alpha$ ). Black lines show linear boundaries between two classes of tissues. Blue diamond symbols: estimations for gingiva, orange circle symbols: estimations for mucosa.

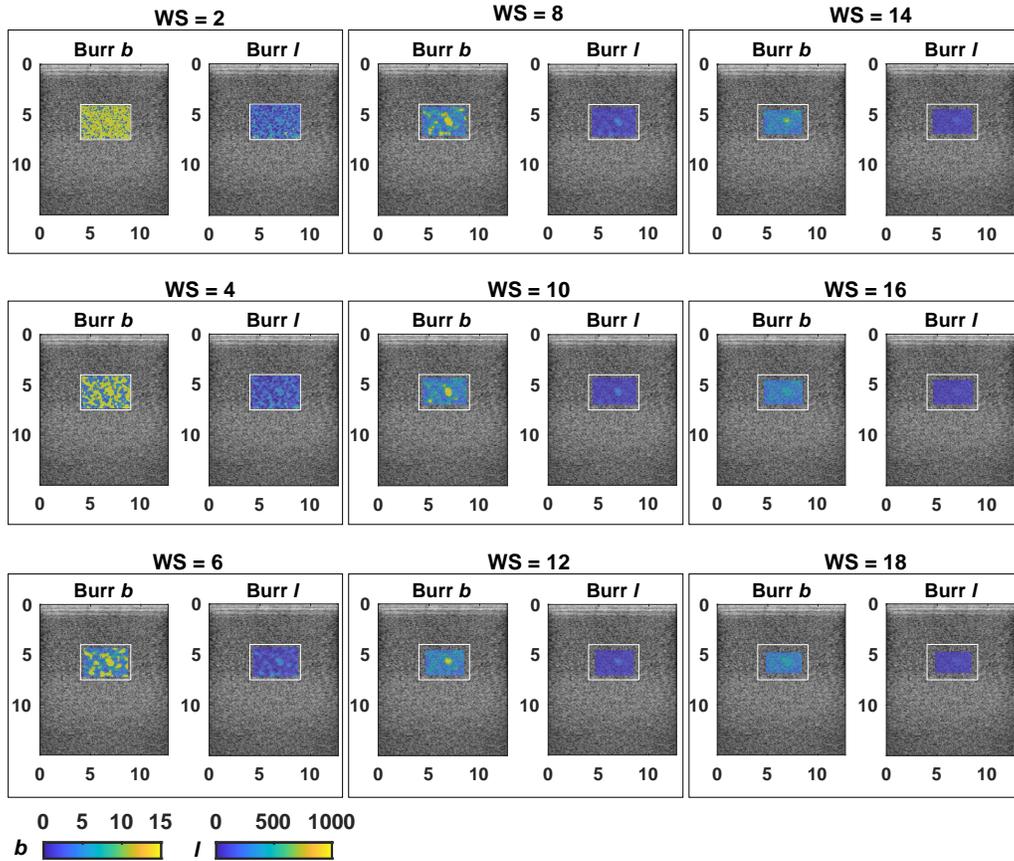
**Figure 15:** 3D Classification of gingiva vs. alveolar mucosa using combined parameters of the Burr and Nakagami models, represented in the principal component space using the first three principal components of PC 1, PC 2, and PC 3.



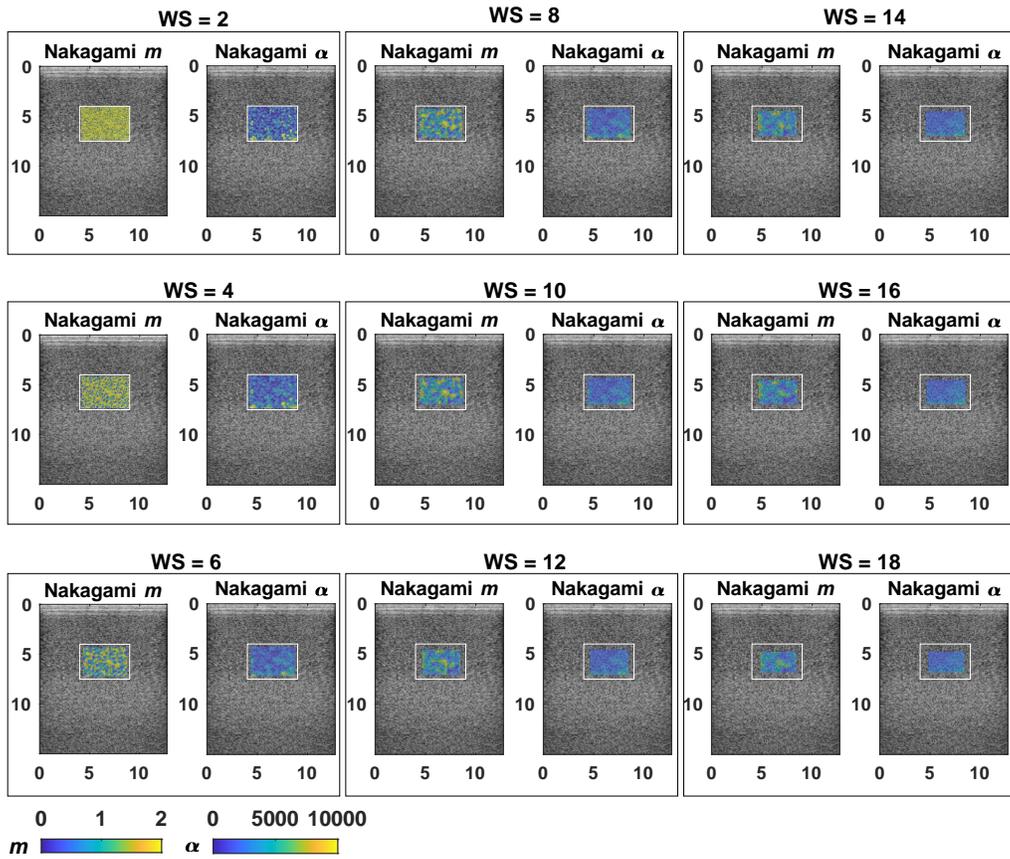
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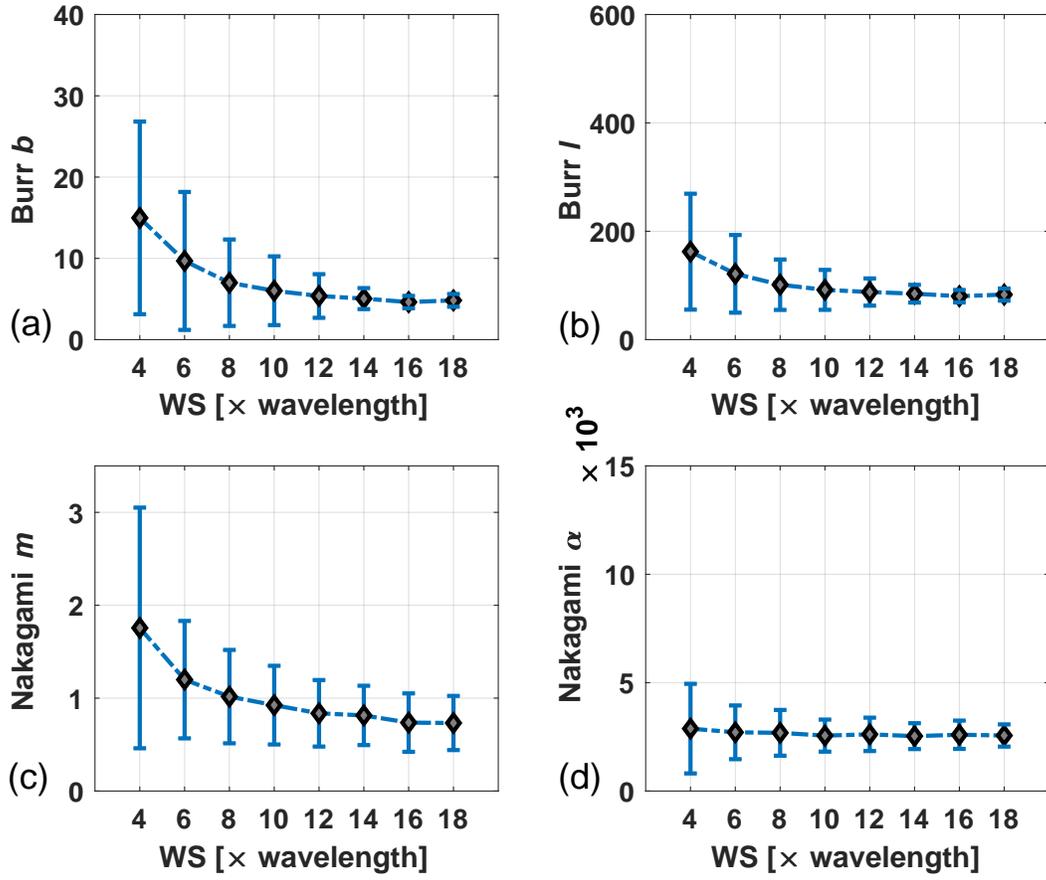
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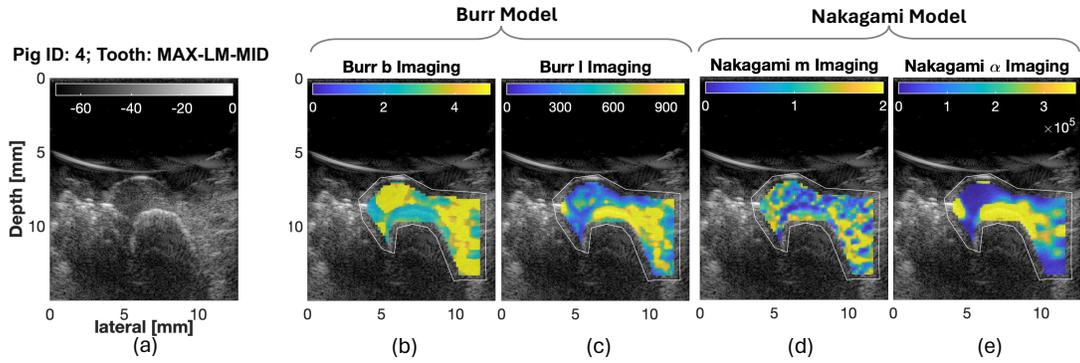
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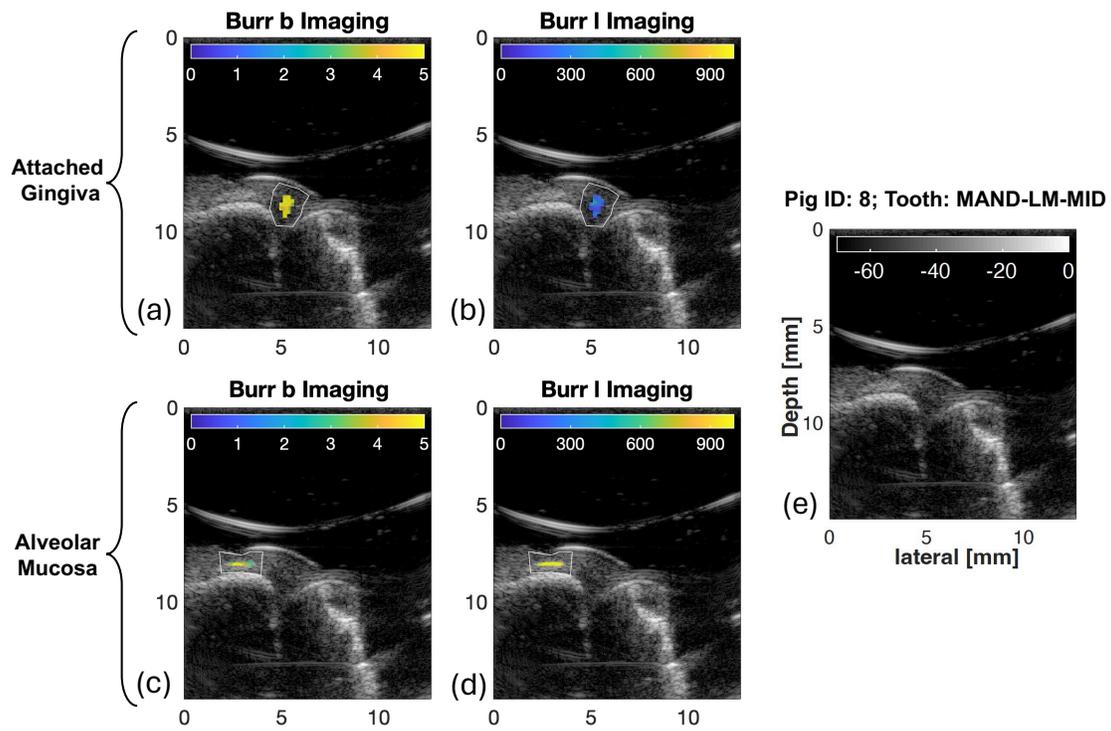
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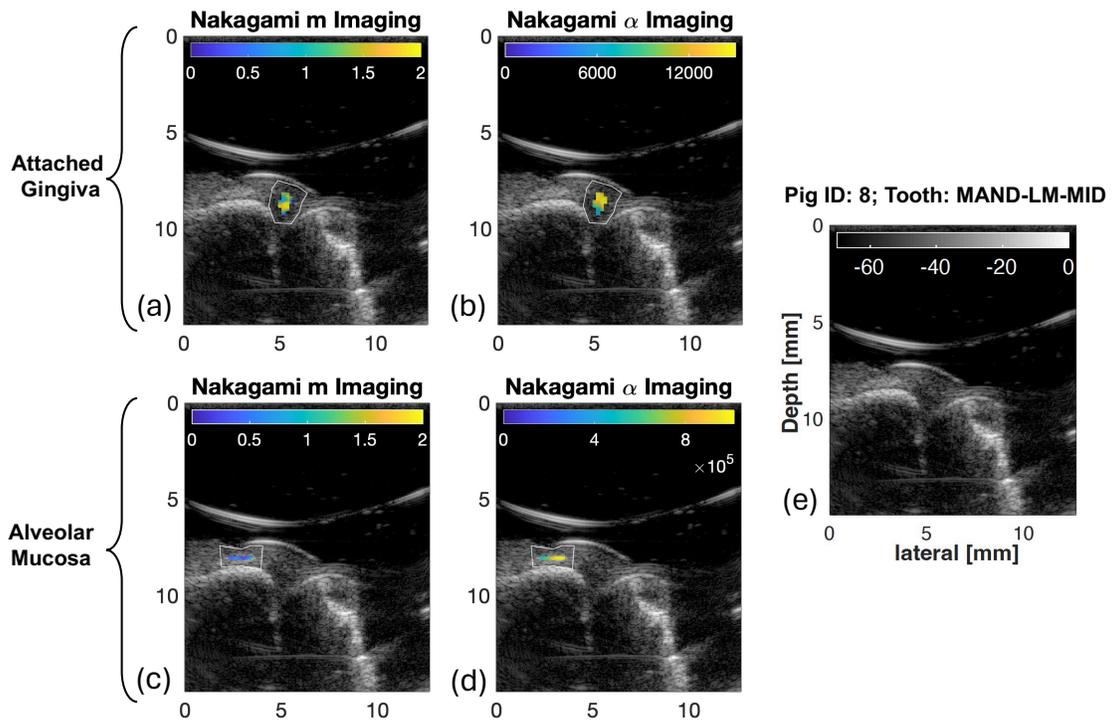
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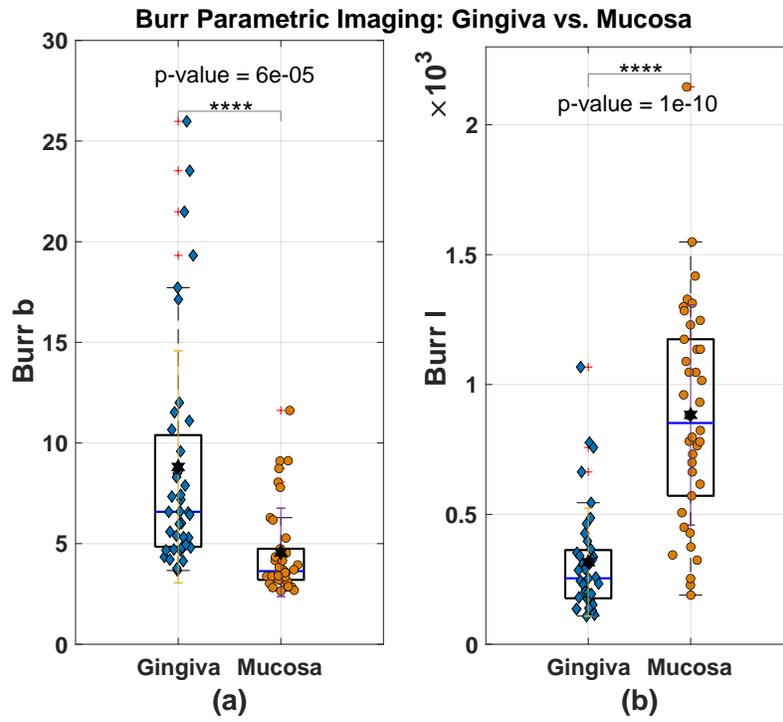
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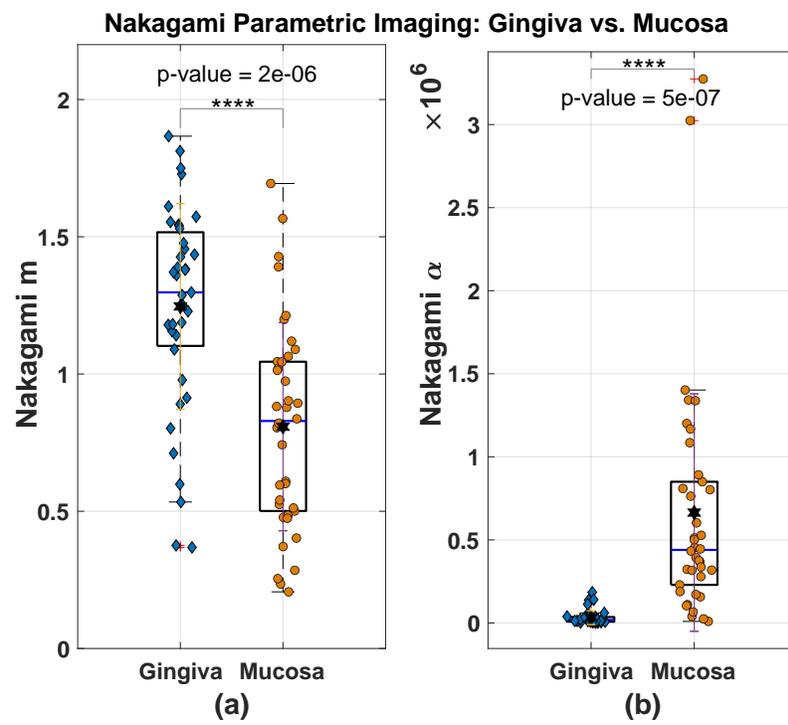
**Figure 7:** Parametric imaging of the Burr parameters in the gingiva (top row) and the alveolar mucosa (bottom row) in a swine scan using the WS of 10 wavelengths. (a) and (c): Burr  $b$ , (b) and (d): Burr  $l$ . The reference B-scan is shown in (e).



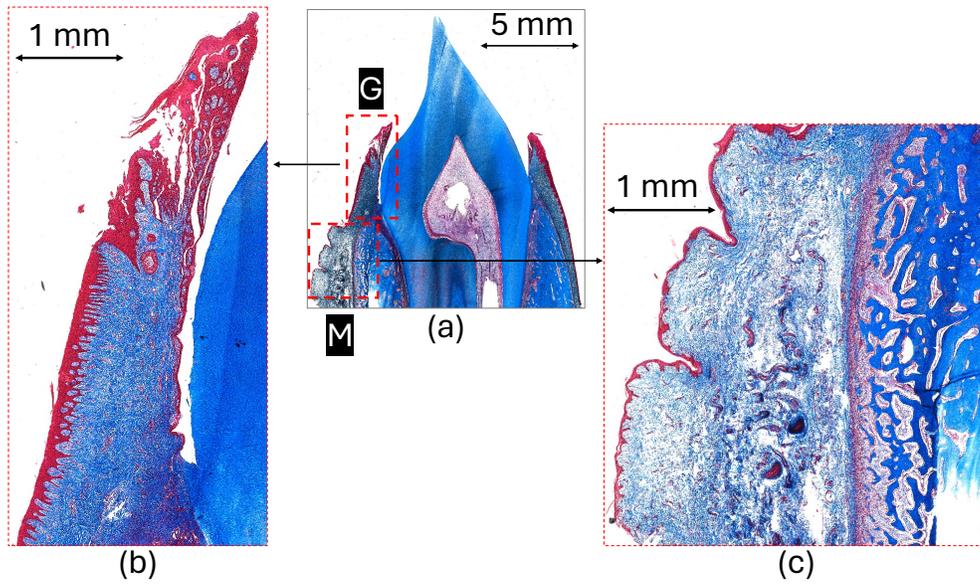
**Figure 8:** Parametric imaging of the Nakagami parameters in the gingiva (top row) and the alveolar mucosa (bottom row) in a swine scan using the WS of 10 wavelengths. (a) and (c): Nakagami  $m$ , (b) and (d): Nakagami  $\alpha$ . The reference B-scan is shown in (e).



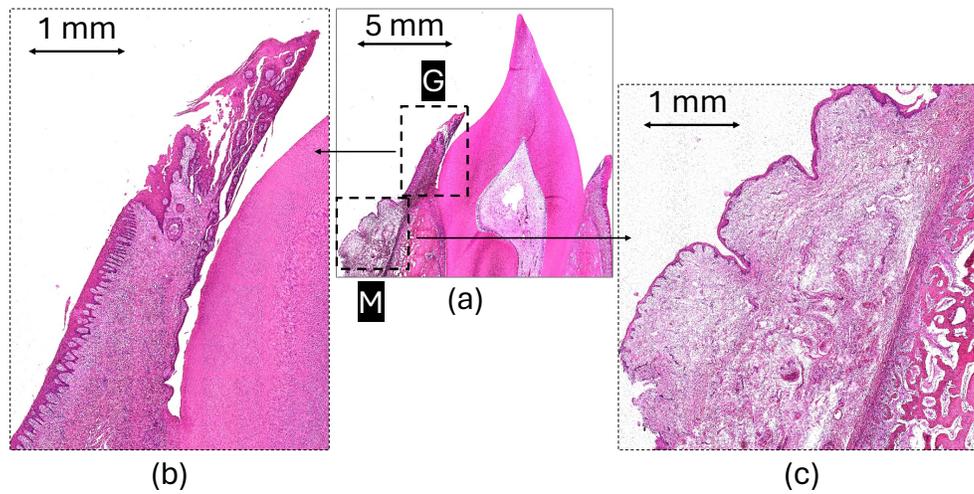
**Figure 9:** Burr parameters for classification of gingiva vs. alveolar mucosa, with boxplots summarizing the average estimations within ROIs in swine cases. **(a)** Burr  $b$ , **(b)** Burr  $l$ .



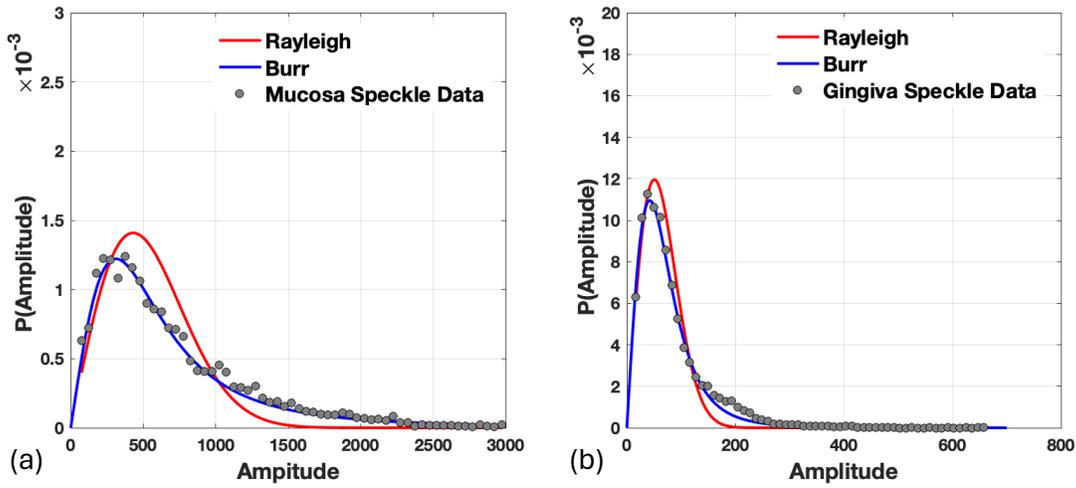
**Figure 10:** Nakagami parameters for classification of gingiva vs. alveolar mucosa, with boxplots summarizing the average estimations within ROIs in swine cases. (a) Nakagami  $m$ , (b) Nakagami  $\alpha$ .



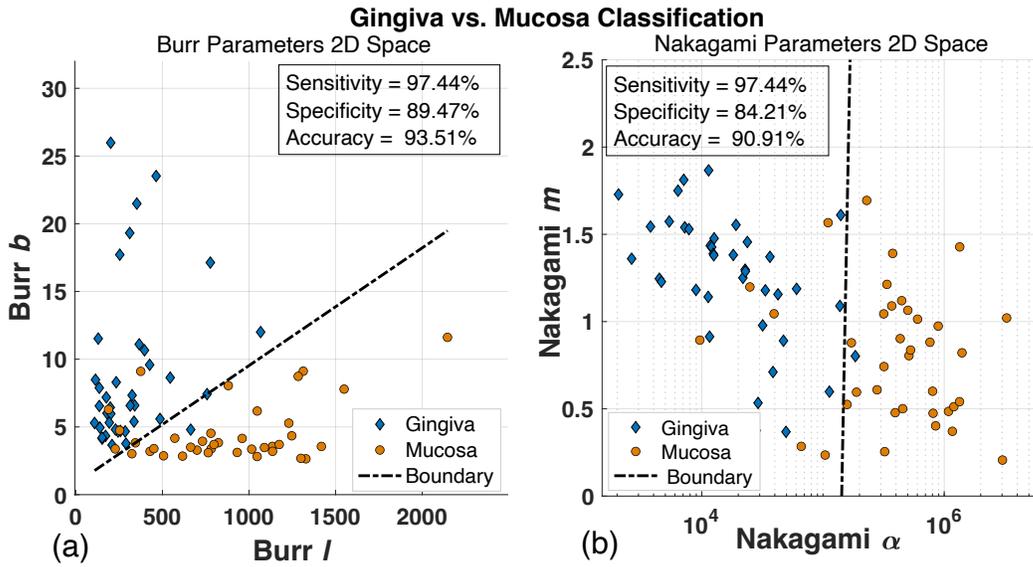
**Figure 11:** (a) Histology image using Masson's Trichrome stain (4x magnification). (b) and (c) are enlarged views comparing gingival and alveolar mucosal regions, respectively (20x magnification). Swine oral site: left mandibular first molar.



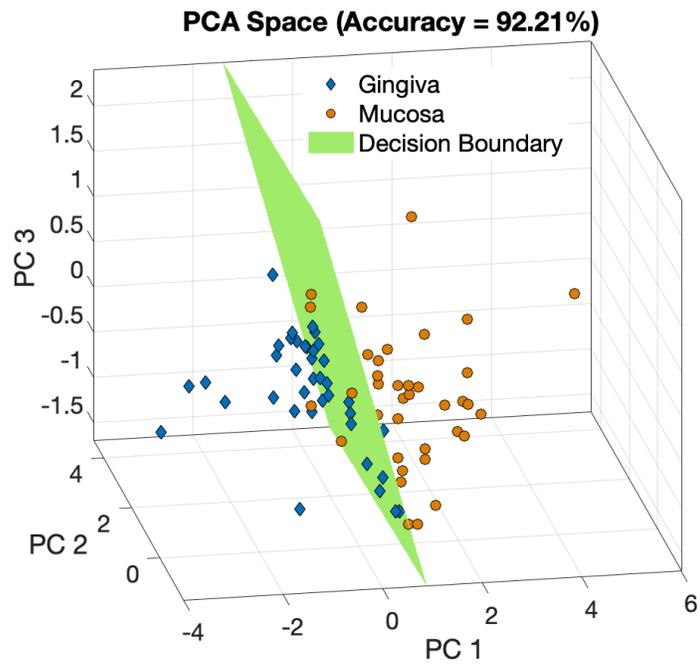
**Figure 12:** (a) Histology image using H&E stain (4x magnification) at the same tissue section as shown in **Figure 11**. (b) and (c) are enlarged views comparing gingival and alveolar mucosal regions, respectively (20x magnification). Swine oral site: left mandibular first molar.



**Figure 13:** Probability distribution of US speckle data fitted to the Rayleigh (red curves) and Burr (blue curves) distributions for (a) alveolar mucosa (Rayleigh fit  $R - squared = 0.82$ ), and (b) gingiva (Rayleigh fit  $R - squared = 0.95$ ).



**Figure 14:** 2D classifications of gingiva vs. alveolar mucosa in swine cases using (a) the Burr model (Burr  $b$  vs. Burr  $l$ ), and (b) the Nakagami model (Nakagami  $m$  vs. Nakagami  $\alpha$ ). Black lines show linear boundaries between two classes of tissues. Blue diamond symbols: estimations for gingiva, orange circle symbols: estimations for mucosa.



**Figure 15:** 3D Classification of gingiva vs. alveolar mucosa using combined parameters of the Burr and Nakagami models, represented in the principal component space using the first three principal components of PC 1, PC 2, and PC 3.