“Clinical evaluation and patient experience of a stationary intra-oral tomosynthesis (s-IOT) unit using a carbon nanotube x-ray source array”

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1. SIGNIFICANCE

1.1. Improving caries detection is a high oral health priority

Caries is the world's most common dental disease. The WHO estimates that 60-90% of school children and nearly all adults have dental caries at some point in time(1). If carious lesions are detected early enough, i.e. before cavitation, they can be arrested and remineralized by non-surgical means. When left undetected, they could evolve into more serious and destructive conditions that may require expensive restorations, endodontic treatment, and, in some cases extractions. Despite advances made in dental imaging including digital detection and computed tomography (CT), *the diagnostic accuracy for caries has not seen significant improvement in many years and remains low*.

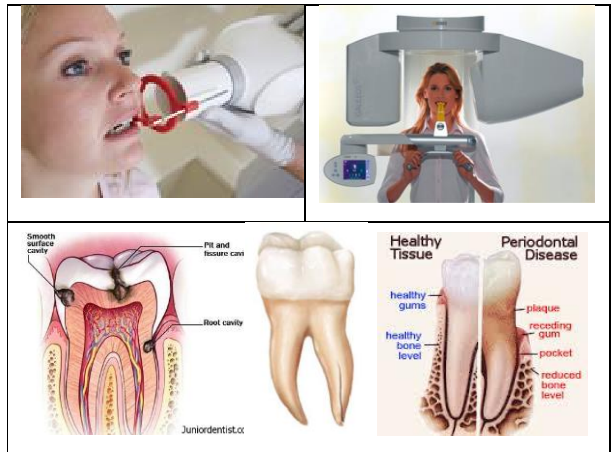
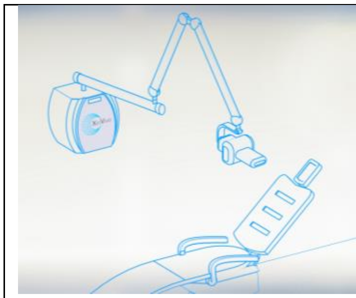


Figure 1: 1st row: 2D intraoral x-ray (left) and dental CBCT (right). 2nd row: schematics of caries, vertical root fracture and periodontal bone loss, which are difficult to detect with the current technologies.

The sensitivity of 2D intraoral radiography, the current gold standard for caries diagnosis, ranges from 30% to 70% for different types of caries, due to the fundamental limitation of structure superimposition (2, 3). Cone-beam CT (CBCT) requires as much as 100X the radiation, but does NOT improve caries detection due to its inferior resolution and imaging artifacts compared with intraoral imaging (4-8). The diagnostic accuracy for some other common dental conditions such as root fractures, and periodontal bone loss (**Figure 1**) have also remained low (9, 10). There is a clear *clinical and market need for better diagnostic technologies.*

1.2. We have invented a new technology with significantly increased sensitivity

Our invention, *stationary intraoral tomosynthesis (s-IOT*), overcomes the limitations of the current dental imaging technologies for diagnosis of dentoalveolar diseases(11, 12). It provides depth information and removes structural overlaps that obscure anatomical details in 2D imaging. It offers better in-plane resolution, less imaging artifact, and faster image acquisition at lower dose and cost comparing to CBCT (Figure **2**). Our preliminary results have shown that s-IOT provides significantly *increased detection sensitivity*, more accurate assessment of lesion depth and improved interpretation ease across a wide variety of clinical settings compared to the current dental imaging technologies.



Key features:

- Significantly higher sensitivity than 2D x-ray and CT
- Low dose (same as 2D intraoral)
- Low cost compared to CT
- Short image time (1 s)
- Seamless integration with current data management system
- Perform all tasks of current 2D intraoral

Figure 2: An illustration of the s-IOT device and its key advantages comparing to 2D intraoral and CBCT.

The clinical applications of s-IOT are not limited to caries detection, but include secondary caries detection, root fracture detection, alveolar bone assessment, root anatomy and periapical assessment, 3D assessment of dental developmental anomalies, and preliminary implant site assessment. Early disease detection and treatment will promote the oral health of patients worldwide.

1.3. Pathway for clinical translation and commercialization

The dental community has received the s-IOT technology enthusiastically. *Over 80% of the 250 NC dentists surveyed expressed interests in purchasing this device* at our estimated price range. The research won an award from the dental association, and was recently featured in "*Dentistry Today*" and on the WRAL Evening News (http://wral.com/14923174).

Steps toward translation and commercialization: (1) The feasibility study was performed with funding from a recently completed NIH SBIR grant; (2) Two patent applications were filed by UNC and licensed by Xintek; (3) Xintek formed a new subsidiary XinVivo to commercialize the technology; (4) Seed equity investment has been secured to construct the first clinical prototype; and (5) Potential partnerships with market leaders (Carestream Dental and Planmeca) are under discussion.

This NC TraCS grant is critical to fund the first patient evaluation at the UNC Oral and Maxillofacial Radiology Clinic, and to further advance the technology.

2. INNOVATION

2.1. s-IOT enabled by the CNT x-ray source array technology

Digital tomosynthesis uses a series of limited-angle projection images to produce a 3D representation of the object (13). A variation of this technique called Tuned Aperture CT(14) (TACT) was shown to improve the diagnostic accuracy for a number of tasks compared to 2D intraoral x-ray in bench-top phantom studies (14, 15). The technology however was not feasible for patient imaging. It took ~30 minutes for a scan (vs. ~ 1 s for a 2D x-ray) and required high operator skills for positioning, because the x-ray tube needed to be precisely moved and positioned at different locations to acquire the multiple projection images. The image reconstruction time was also very long due to inefficient algorithm.

The working mechanism of s-IOT is illustrated in **Figure 3**: (1) A carbon nanotube (CNT) x-ray array technology invented by our team at UNC(16-18) is utilized to *generate a scanning x-ray from different directions without any mechanical motion; (2)* A high-frame-rate digital intraoral sensor captures the projection images in synchronization with the x-ray exposure; (3)

An optical pattern recognition method developed in our lab is used to determine the imaging geometry; and (4) A high-speed iterative reconstruction algorithm written by us (19) processes the projection images to generate tomosynthesis image slices in real-time. *In s-IOT, a complete 3D scan takes less than 1 second; the total imaging dose used is the same as a single 2D intraoral radiograph*. The 3D tomosynthesis slices are reconstructed and displayed layer by layer in the depth direction to "virtually dissect" the object.

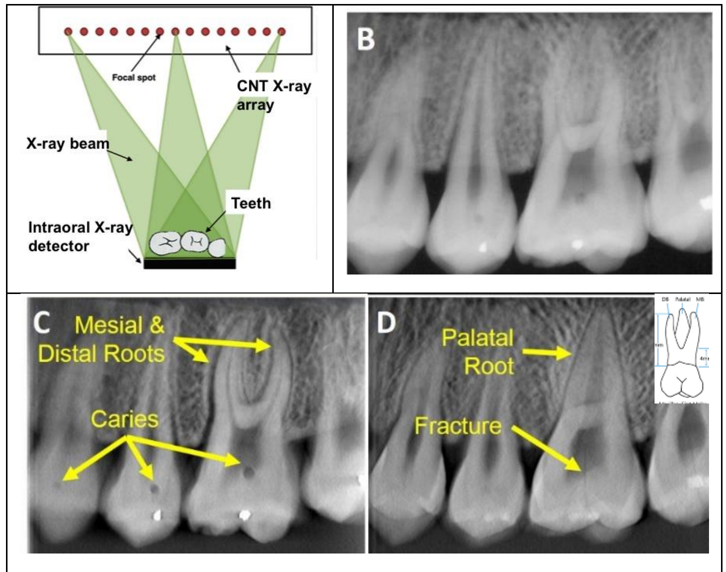


Figure 3: (A) conceptual illustration of s-IOT. (B) x-ray image of a phantom using clinical 2D intraoral x-ray. Reconstructed s-IOT image slices of the same phantom, at two different depths, showing: 1) mesial and distal buccal roots (C) and the palatal (D), 2) all 3 simulated caries, and 3) fracture (D). In contrast, 2D x-ray (B) did not resolve the root structure, missed one caries, and missed the fracture(12).

2.2. **Preliminary results: s-IOT outperforms current dental imaging modalities.**

A bench-top s-IOT device was constructed and used for evaluation and system optimization. The performance was compared with clinical 2D intraoral x-ray by imaging phantoms (20) and extracted human teeth. **Figure 3** shows examples of phantom images where: (1) ***carious*** *lesions are missed or barely discernable on the 2D image (B), but are clearly visible in the tomosynthesis reconstruction slices* (C,D); (2) s-IOT clearly resolved the front and back **roots** of the upper molar teeth (C, D) that was overlapped in the 2D image (B); and (3) s-IOT identified **root fractures** (D) that was missing in 2D (B).

A reader study was performed with eight experienced UNC dental radiologists reviewing the images of the extracted human teeth taken from s-IOT and 2D intraoral. Micro-CT images served as the ground truth. The results showed that the average sensitivity of s-IOT increased by 36% compared to that of 2D intraoral, *the largest reported increase by any modality in modern dental imaging*, without compromising specificity or *increasing the imaging dose*.

2.3. We have an experienced interdisciplinary team

Our team of physicists (**Zhou, Lu**) and maxillofacial radiologists (**Platin, Mol**) are the inventors of the s-IOT technology, with extensive experience in developing and translating medical devices (21-23), clinical dental imaging, and commercialization. NC TraCS statistician (**Zeng**) will help perform the statistical data analysis. Zhou and Lu invented the CNT x-ray source array, the key enabling technology. We developed a novel micro-CT scanner, installed at UNC and Iowa for biomedical research; a 3D mammography system and a 3D lung imaging device, currently under clinical evaluation. Zhou and Lu have equity stakes in Xintek, the UNC spin-off.

A conflict of interest committee has been established at UNC to oversee potential COI issues.

3. APPROACH

3.1. SPECIFIC AIM 1: Characterization and Certification of Prototype Device

System characterization: The s-IOT prototype system will be characterized using phantoms following our previously established procedure (20). X-ray collimation, which is essential for safety and reducing the imaging dose, will be evaluated. The dose at the patient position will be measured using a calibrated solid-state dosimeter to insure FDA compliance. The geometry calibration procedure will be evaluated against an established method(24). Quantitative image quality evaluation will be performed. Key system performance parameters including the system modulation transfer function (MTF), artifacts spread function (ASF), contrast to noise ratio (CNR) and signal differential to noise ratio (SdNR) will be measured (25, 26). Imaging time and consistency will be evaluated. The custom-made iterative reconstruction software will be evaluated against commercial reconstruction software. All the facilities needed for this study are available in the PI's lab.

Certification: The system will be installed in the UNC-School of Dentistry (SOD) Radiology Clinic. Product safety testing and certification will be performed by MET Laboratories (www.metlabs.com), which we have previously engaged for two other x-ray imaging systems (27). We will work with the UNC EHS to ensure the system satisfies radiation safety requirement. SOD has committed the space for this study.

3.2. SPECIFIC AIM 2: Clinical Evaluation and Patient Experience

Patient selection and image acquisition: Fifty patients referred to the UNC Section of Oral and Maxillofacial Radiology for bitewing or full-mouth series exams will be recruited following completion of their ordered radiographic exams. Patients with moderate caries will be approached about participation in the study. Consenting patients will then receive a 4-bitewing exam using the s-IOT system. We will acquire both the ordered conventional radiographic exam and the s-IOT exam. The same group of patients will be tested for both caries detection evaluation and patient care experience.

Caries detection: Three UNC SOD dentists will be recruited to independently review each radiographic exam to diagnose caries presence/absence. Discrepancies between reviewers will be reconciled by consensus.

Verification: In vivo assessment of the true state of a proximal tooth surface is challenging. For the purpose of this study, cases where a proximal tooth surface received a caries diagnosis on the s-IOT images and not on the conventional images, or vice versa, are of particular interest. For these cases, the patient's clinician will be contacted to perform reversible mild clinical tooth separation to allow visual assessment of caries status.

Data analysis: The goal of the data analysis is to test (1) whether differences in the caries detection rate between s-IOT and conventional radiographs are present and (2), if so, whether these differences result from s-IOT being more sensitive. With 50 patients x 4 images/patient x ~4 teeth/image x 2 surfaces/tooth = 1600 surfaces, we expect sufficient statistical power to detect diagnostic differences.

A statistical test for paired nominal data, such as the McNemar's test, would be used to test the first hypothesis while accounting for within-patient and within-tooth/image correlations. Sensitivity, specificity and diagnostic accuracy are calculated from the clinically verified cases to characterize and quantify the modalities and will be compared regarding the second component of the hypothesis. To obtain proper inference to account for complex correlations within the same patient, or the same tooth, or the same image, resampling approach based on bootstrapping over 50 patients will be used to obtain correct variances for all statistics. <u>NC TraCS statistician (Zeng) will help perform the above data analysis</u>.

Patient experience: Each subject will be given a brief survey regarding the overall comfort, time, and experience differences between the two imaging systems. The investigators will also complete a similar brief survey regarding the overall confidence in diagnosis, time, and the number of required radiographic re-takes. The statistical different between two images systems will be analyzed.

4. RISK AND REMEDY

Our team has considerable experience in characterizing, and certifying medical devices. We do not anticipate any risk in this aspect of the project. Prior to implementation, the Radiation Safety Committee and IRB will assess this study. There is minimal risk to participants, investigators, and study personnel. The radiation dose from the s-IOT exam is comparable to the dose from the conventional 2D bitewing exam, dictating that the additional radiation burden to the patient represents no greater than minimal risk and technically does not require review and approval by the RSC (5 or fewer dental x-rays). Given the high patient volume at the UNC SOD, we do not anticipate problems with patient availability and recruitment. The sampling, 1600 distinct teeth surfaces, is substantially larger than what we have previously used for similar studies, and should provide sufficient statistical power to detect the diagnostic differences.

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