同行专家业内评价意见书编号：20240854242

附件1

浙江工程师学院（浙江大学工程师学院）
同行专家业内评价意见书

姓名： 黄杰

学号： 22160235

申报工程师职称专业类别（领域）： 电子信息

浙江工程师学院（浙江大学工程师学院）制

2024年03月28日

一、个人申报

（一）基本情况【围绕《浙江工程师学院（浙江大学工程师学院）工程类专业学位研究生工程师职称评审参考指标》，结合该专业类别(领域)工程师职称评审相关标准，举例说明】

1.对本专业基础理论知识和专业技术知识掌握情况：
在理论知识方面掌握了基于受激拉曼散射的分子光谱显微成像的原理，这项技术在科学研究和医学领域中具有重要意义。此外，对生殖健康领域的知识也进行了广泛了解，包括体外受精、显微取精手术等。在实践中，积极参与了病理组织冰冻切片、HE染色等操作的学习和实践。而对于深度学习技术，我也进行了深入研究和实践，这一前沿技术在图像处理和分析中具有重要作用，将其成功应用于分子光谱显微成像数据的处理和分析中。这些经验不仅增强了我的实践能力，也为我在相关领域的研究和工作提供了坚实的基础。

2.工程实践的经历：
基于分子光谱显微成像与深度学习实现无精子症快速诊断。
承担了分子光谱显微成像的任务，并且负责了数据的采集、处理，以及深度学习模型的训练工作。在分子光谱显微成像方面，运用先进的成像技术，如受激拉曼散射和二次谐波显微成像相结合，对样本进行高分辨率的成像。这项工作涉及了光学成像系统的调试、数据采集和图像处理等方面的工作。
同时，负责处理采集到的大量数据，进行预处理、特征提取等操作，以便后续的分析和建模。在深度学习模型的训练方面，运用了弱监督的MIL-CNN（多示例学习 -
卷积神经网络）模型框架，对采集到的数据进行训练和优化，以实现对样本的分类任务。这一过程涉及了数据的标注、模型的选择和调优、训练过程的监控和调整等多个环节。

3.在实际工作中综合运用所学知识解决复杂工程问题的案例（不少于1000字）：
全世界有大量育龄期夫妇受到不孕不育疾病的影响，其中约有40%的不孕不育夫妻是由于男性因素引起的。针对男性生育障碍，显微取精手术是主要的治疗方法。这种手术通过在睾丸组织中寻找粗大饱满、混浊的生精小管来获取精子，因为这样的小管内存在精子的可能性最大。然而，目前的选择方式仅仅依赖于对生精小管外表面颜色和体积的主观判断，无法准确评估管腔内是否存在精子。虽然睾丸病理活检能够准确判断生精小管内部的精子情况，但传统的病理检测方法操作繁琐，耗时较长，无法在手术中进行评估，且染色后的组织无法用于精子提取。因此，迫切需要一种新的方法来实现术中实时评估精子发生，并提高显微取精结合体外受精的成功率。本项目多模态的受激拉曼散射成像结合深度学习技术实现快速准确判断生精小管有无精子。
睾丸组织生精小管中存在一系列的生精细胞和支持细胞，且不是均匀地分布，这极大地提高诊断是否存在精子的难度。由于组织样本具有较高的异质性，采用有监督的训练方法对每一个小块打上相同的标记会引入错误标记，同时最终的预测结果会受到小块类别所占的百分比阈值选择的影响。在真实诊断过程中，病理学家通常能够仅根据一个小范围区域存在精子来判定整个生精小管正常。按照类似的原则，弱监督学习算法可能更适合本节的分类任务。其中一种算法是多示例学习，与将每个小块视为独立标签的监督学习方案不同，这种方法将每个完整的生精小管图像打上标签，而图像切割得到的小块未被标记。多示例学习通常用于解决具有模糊标签或部分标签的问题。
本次任务采用多示例学习框架完成基于弱监督分类的卷积神经网络模型训练。整个流程首先通过多模态的受激拉曼散射平台成像人体生精小管脂质、蛋白质和胶原纤维三通道的图像，并融合为RGB
图像。采用了扇形切割方法对图像进行切割操作，并输入多示例学习框架进行模型训练。ResNeXt50

（32X4d）是一种基于ResNet的深度神经网络，通过引入分组卷积提高模型的表示能力和多样性，在图像分类等任务中表现出色。因此，本次分类任务基于此模型完成训练。在初始化模型时，加载预训练权重参数作为模型的初始化参数。最终训练出来的模型达到96%的分类准确率，并且各项性能高于有监督的卷积神经网络模型。

进一步采用了梯度加权类激活热图方法分析模型结果的可解释性，探究该方法是否能够有效地识别生精小管的重要特征并进行定位。基于梯度加权类激活热图计算网络的最后卷积层的变化率，该卷积层捕捉图像的最复杂和最高级的特征，与预测的类别分数相关，能够显示模型分类过程中重点关注的区域。在热图中，模型预测每个生精小管存在精子概率高的区域显示为红色，而概率较低的区域显示为蓝色。通过对正常与不正常生精小管热图可视化发现，对于正常生精小管，模型预测含有精子的高响应区域集中在生精小管中心位置；而对于不正常类型的生精小管，模型预测含有精子的高响应区域往往无法定位到生精小管内部结构相关区域，其响应区域表现为不规则且存在对图片背景高响应的情况。事实上，生精小管由支持细胞和生精细胞组成，其中的生精细胞自生精小管基底部至腔面（管腔中心），依次有精原细胞、初级精母细胞、次级精母细胞、精子细胞和精子。最终发现：模型对于含有精子的生精小管的关注区域在其中心位置，对不含精子的生精小管则关注在非中心位置甚至非组织结构区域，这一结果符合精子在生精小管管腔中心位置的实际情况。说明模型有效的识别了生精小管中存在精子的区域，对于有无精子进行了较为准确的判断。

基于多模态受激拉曼散射成像平台，采集多通道的具有诊断信息的图像，并且结合深度学习实现了具有较高准确率的生精小管分类。整个流程不需要繁琐的组织准备与处理，并且能够在较短的时间内完成，未来可能应用于无精子症的术中病理诊断。通过直观的热力图可视化可以帮助病理学家更好地了解模型学习的表征信息，进而确定模型辅助分类结果的合理性，更加客观地判断生精小管是否存在精子。总之，通过多模态受激拉曼成像和深度学习技术可以帮助医生更快速、准确地识别和分类正常生精与不正常生精的生精小管，从而提高病理诊断的效率和准确性；同时，通过可视化手段了解模型学习的特征信息，这有助于提高临床病理诊断的可解释性和可信度。

（二）取得的业绩（代表作）【限填3项，须提交证明原件（包括发表的论文、出版的著作、专利证书、获奖证书、科技项目立项文件或合同、企业证明等）供核实，并提供复印件一份】					
1. 公开成果代表作【论文发表、专利成果、软件著作权、标准规范与行业工法制定、著作编写、科技成果获奖、学位论文等】					
成果名称	成果类别 [含论文、授权专利（含发明专利申请）、软件著作权、标准、工法、著作、获奖、学位论文等]	发表时间/授权或申请时间等	刊物名称/专利授权或申请号等	本人排名/总人数	备注
Rapid azoospermia classification by stimulated Raman scattering and second harmonic generation microscopy	国际期刊	2023年10月05日	Biomedical Optics Express	1/9	
In situ molecular mapping of human testicular tissues by mid-infrared photothermal imaging	会议论文	2023年11月27日	conference-proceedings-of-spie	1/6	
Unveiling molecular signatures for disease classification by spectroscopic imaging	会议论文	2024年03月12日	conference-proceedings-of-spie	1/5	

2.其他代表作【主持或参与的课题研究项目、科技成果应用转化推广、企业技术难题解决方案、自主研发设计的产品或样机、技术报告、设计图纸、软课题研究报告、可行性研究报告、规划设计方案、施工或调试报告、工程实验、技术培训教材、推动行业发展中发挥的作用及取得的经济社会效益等】

（三）在校期间课程、专业实践训练及学位论文相关情况	
课程成绩情况	按课程学分核算的平均成绩： 83 分
专业实践训练时间及考核情况(具有三年及以上工作经历的不作要求)	累计时间： 1.1 年（要求1年及以上） 考核成绩： 80 分（要求80分及以上）
本人承诺	
个人声明：本人上述所填资料均为真实有效，如有虚假，愿承担一切责任，特此声明！ **申报人签名：**	

二、日常表现考核评价及申报材料审核公示结果

日常表现考核评价	非定向生由德育导师考核评价、定向生由所在工作单位考核评价： ☑优秀 ☐良好 ☐合格 ☐不合格 德育导师/定向生所在工作单位分管领导签字（公章）：2024年3月29日
申报材料审核公示	根据评审条件，工程师学院已对申报人员进行材料审核（学位课程成绩、专业实践训练时间及考核、学位论文、代表作等情况），并将符合要求的申报材料在学院网站公示不少于5个工作日，具体公示结果如下： ☐通过 ☐不通过（具体原因：　　） 工程师学院教学管理办**公室**审核签字（公章）：　　年　月　日

浙 江 大 学 研 究 生 院

攻读硕士学位研究生成绩表

学号：22160235	姓名：黄杰	性别：男	学院：工程师学院	专业：电子信息	学制：2.5年
毕业时最低应获：26.0学分	已获得：26.0学分			入学年月：2021-09	毕业年月：2024-03
学位证书号：1033532024602209		毕业证书号：103351202402600435			授予学位：电子信息硕士

学习时间	课程名称	备注	学分	成绩	课程性质	学习时间	课程名称	备注	学分	成绩	课程性质
2021-2022学年秋季学期	数值计算方法		2.0	85	专业选修课	2021-2022学年春季学期	“四史”专题		1.0	87	公共选修课
2021-2022学年秋季学期	生物医学信号处理技术与应用		2.0	84	专业学位课	2021-2022学年春季学期	医疗健康工程技术应用案例分析		2.0	88	专业学位课
2021-2022学年冬季学期	生物医学工程方法学		1.0	79	专业学位课	2021-2022学年春季学期	医疗健康工程技术综合实践		2.0	89	专业学位课
2021-2022学年冬季学期	医疗健康工程前沿技术		2.0	90	专业学位课	2021-2022学年夏季学期	研究生英语基础技能		1.0	免修	公共学位课
2021-2022学年冬季学期	智能化仪器软硬件系统设计与应用		2.0	86	专业学位课	2021-2022学年夏季学期	研究生英语		2.0	免修	公共学位课
2021-2022学年秋冬季学期	中国特色社会主义理论与实践研究		2.0	88	公共学位课	2021-2022学年夏季学期	工程伦理		2.0	93	公共学位课
2021-2022学年秋冬季学期	数据分析的概率统计基础		3.0	77	专业选修课	2021-2022学年夏季学期	自然辩证法概论		1.0	82	公共学位课
2021-2022学年秋冬季学期	研究生论文写作指导		1.0	80	专业学位课						

说明：1. 研究生课程按三种方法计分：百分制，两级制（通过、不通过），五级制（优、良、中、及格、不及格）。

2. 备注中“*”表示重修课程。

学院成绩校核章：

成绩校核人：张梦依

打印日期：2024-04-02

Research Article | Vol. 14, No. 11 / 1 Nov 2023 / Biomedical Optics Express 5569
Biomedical Optics EXPRESS

Rapid azoospermia classification by stimulated Raman scattering and second harmonic generation microscopy

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Abstract: Disease diagnosis and classification pose significant challenges due to the limited capabilities of traditional methods to obtain molecular information with spatial distribution. Optical imaging techniques, utilizing (auto)fluorescence and nonlinear optical signals, introduce new dimensions for biomarkers exploration that can improve diagnosis and classification. Nevertheless, these signals often cover only a limited number of species, impeding a comprehensive assessment of the tissue microenvironment, which is crucial for effective disease diagnosis and therapy. To address this challenge, we developed a multimodal platform, termed stimulated Raman scattering and second harmonic generation microscopy (SRASH), capable of simultaneously providing both chemical bonds and structural information of tissues. Applying SRASH imaging to azoospermia patient samples, we successfully identified lipids, protein, and collagen contrasts, unveiling molecular and structural signatures for non-obstructive azoospermia. This achievement is facilitated by LiteBlendNet-Dx (LBNet-Dx), our diagnostic algorithm, which achieved an outstanding 100% sample-level accuracy in classifying azoospermia, surpassing conventional imaging modalities. As a label-free technique, SRASH imaging eliminates the requirement for sample pre-treatment, demonstrating great potential for clinical translation and enabling molecular imaging-based diagnosis and therapy.

1. Introduction

Effective disease diagnosis and classification are crucial first steps toward successful treatment, representing a significant challenge in biology and medicine. Traditional medical imaging modalities, such as magnetic resonance imaging, positron emission tomography, and ultrasound imaging, often lack the necessary combination of high spatial resolution and molecular information provided by optical imaging methods. While fluorescence microscopy has been widely used, its potential is constrained by the limited number of simultaneous targets it can detect. Additionally, specific optical modalities, for example, Raman spectroscopy, second harmonic imaging, and

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In situ molecular mapping of human testicular tissues by mid-infrared photothermal imaging

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ABSTRACT

Non-obstructive azoospermia (NOA) is a severe male infertility condition characterized by impaired or absent sperm production in the testes. The primary treatment for NOA is microsurgical testicular sperm extraction (micro-TESE), which relies on accurately identifying healthy seminiferous tubules. In addressing this clinical need, we propose the utilization of mid-infrared photothermal (MIP) microscopy to identify spectroscopic signatures associated with NOA. Our preliminary results revealed that NOA tissues exhibited distinctive lipid distribution and reduced lipid peak intensity compared to tissues with normal sperm production. Leveraging principal components analysis (PCA), we successfully extracted key infrared spectroscopic features. When combined with logistic regression (LR), this approach achieved an impressive prediction accuracy of 95.0% in classifying testicular tissues. These findings highlight the potential of MIP microscopy in facilitating sperm retrieval by distinguishing seminiferous tubules based on their molecular composition.

Keywords: mid-infrared photothermal, azoospermia, infrared spectra, lipid metabolism, principal components analysis, logistic regression

1. INTRODUCTION

Non-obstructive azoospermia (NOA), typically characterized by the inability of the testes to produce sperm, affects 10%-15% of all infertile men and a substantial 60% of those with azoospermia[1, 2]. For NOA patients, the detection of sperm in testicular tissue is fundamental in diagnosis and treatment. Micro-testicular sperm extraction (micro-TESE) is one of the most viable options, relying on the morphological observation (color, size) of seminiferous tubules for identifying healthy tissue for sperm identification[3, 4]. However, this method is challenged by the difficulty in distinguishing between normal and abnormal seminiferous tubules, resulting in a success rate of only 50% for NOA patients[5-7]. On the other hand, during routine testicular biopsies, hematoxylin-eosin (H&E) staining offers higher detection precision. However, the stained sperm cannot be utilized for assisted reproductive technology[8]. Consequently, there is an urgent need for a new non-invasive method capable of real-time spermatogenesis evolution and improving the success rate of micro-TESE.

In situ molecular mapping is invaluable for the clinical diagnosis and treatment of diseases. Various optical microscopic imaging techniques have been previously demonstrated, including fluorescence, Raman, and IR. Fluorescence imaging provides information on the presence and distribution of target molecules, which has found widespread application in the life sciences, such as tumor detection during surgery[9]. Vibrational spectroscopic modalities, including Raman and IR, offer label-free imaging for broad biomedical applications. Yue et al. [10] identified unexpected, aberrant cholesterol accumulation in lipid droplets of high-grade prostate cancer and metastases using Raman micro-spectrometry. Fourier transform infrared spectrometer (FTIR) spectral imaging can be utilized for characterizing and grading gliomas[11].

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 · 0277-786X · doi: 10.1117/12.2686651

Invited Paper, Best Paper Award

Unveiling Molecular Signatures for Disease Classification by Spectroscopic Imaging

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ABSTRACT

Non-obstructive azoospermia (NOA) is a severe form of male infertility characterized by impaired or absent sperm production in the testes. Microsurgical testicular sperm extraction (Micro TESE) is the primary treatment for NOA, but it faces challenges in differentiating between normal and abnormal seminiferous tubules based solely on morphology. To address this, our study employed stimulated Raman scattering (SRS) and second harmonic generation (SHG) microscopy to identify diagnostic features in human testicular tissues. Additionally, a deep learning-assisted diagnostic algorithm using multimodal imaging datasets demonstrated excellent performance in azoospermia diagnosis. Utilizing a weakly supervised Multiple Instance Learning-Convolutional Neuron Network (MIL-CNN) model framework, we achieved a 96% classification accuracy, surpassing the supervised CNN model. Gradient-weighted class activation mapping (Grad CAM) visualization confirmed the model's focus on the spermatogenic region, demonstrating the potential of SRS/SHG microscopy coupled with deep learning to accurately classify normal and abnormal spermatogenic tubules, enhancing the efficiency and accuracy of pathological diagnosis.

Keywords: stimulated Raman scattering, azoospermia, deep learning, Multiple instance learning

1. INTRODUCTION

Non-obstructive azoospermia (NOA), characterized by the inability to produce sperm, affects 10%-15% of infertile men and 60% of men with azoospermia[1, 2]. Recent advancements in reproductive medicine and assisted reproductive technology have expanded pregnancy options for couples suffering from infertility[3]. For NOA patients, detecting sperm in human testicular tissue is important for diagnosis and treatment. Microsurgical testicular sperm extraction (Micro TESE) technology is among the most commonly used methods, relying on the color and size of seminiferous tubules to locate sperm[3, 4]. However, it has some limitations due to difficulty in distinguishing between normal and abnormal seminiferous tubules, making its efficacy only about 50% in NOA patients[5].

The stimulated Raman scattering (SRS) microscope emerges as a promising technique for *in-situ* identification and characterization of biological samples[6]. Offering label-free imaging with high resolution and chemical specificity, SRS microscopy addresses the time constraints inherent in spontaneous Raman spectroscopy[7, 8], with diverse applications in biomedical research, including lipid metabolism[9-11], tumor margin detection[12, 13], and tissue imaging[14, 15]. Through selective mapping of lipid and protein distributions, SRS microscopy elucidates crucial histological characteristics pivotal for diagnosing various diseases. Furthermore, considering the association of collagen fibers with diseases [16, 17], detection of the second harmonic generation (SHG) signal becomes imperative to unveil the distribution characteristics of collagen fibers.

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