Mayo Clinic & UWL Collaborative Seed Grant Program

Proposal Title	*Computer-aided Diagnosis with Breast Ultrasound*
Co-Leader(s) and Primary Appointment(s)	*Mayo: Rich Ellis, Department of Radiology/Breast Imaging Section* *UWL: Jeff Baggett, Professor of Mathematics, Song Chen, Associate professor of Mathematics*
Collaborators	*Mayo:* *UWL: graduate and undergraduate students*
Project Timeframe	*March – December 2021*
Primary Institution (Site of Research)	*Mayo Clinic Health System – Southwest Wisconsin (La Crosse)*
Project Goals	*Develop an AI-based computer diagnosis system for Breast Ultrasound Lesion Assessment*
Date Project to be Initiated	*March 15, 2021*

Abstract (500 words)

A feasibility study is proposed to develop state-of-the-art breast ultrasound lesion interpretation support software for radiologists using large case studies from Mayo Clinic Enterprise and advanced AI technology supported by UWL Mathematicians and Data Scientists and graduate students. The AI technology will combine deep learning models based on convolutional neural networks, machine learning models, and automated human rule-based models used by expert radiologists.

An anticipated outcome is demonstrable improvement and accuracy in radiologist intra- and inter-observer breast ultrasound lesion interpretation and BI-RADS® Assessment Category, especially for indeterminate lesions. This improvement and accuracy in radiologist interpretation will have a direct impact on patient medical care and the cost of medical care.

There are three main objectives:

1. Build and train various neural network deep learning/machine models for classifying breast ultrasound lesions into the correct BI-RADS® assessment category. Even though similar models have been developed, the models will have to be rebuilt and calibrated for the high-quality Mayo Clinic data.
2. Build a second algorithm that mimics systems used by experts to determine a BI-RADS® classification of a lesion. This system relies on characteristics of the lesion, such as lesion shape, orientation, margins, internal and external lesion characteristics, along with lesion elasticity and vascularity, which are normally determined by the radiologist. Machine learning algorithms and/or rule-based (based on rules proposed by experts) algorithms will be used to estimate the characteristics from the image with optional user input.
3. Combine the models developed in the first two objectives into a single system that out-performs each of the previous models.

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Lay Abstract, for Community Press (150 words)

Mayo Clinic - La Crosse radiologist, Dr. Rich Ellis, is collaborating with data scientists Dr. Jeff Baggett and Dr. Song Chen from UW-La Crosse to develop state-of-the-art software for the detection of malignant tumors in breast ultrasound images. The software will use both recent advances in deep learning technology and radiology expert informed decision rules to achieve better accuracy than previously possible.

1. Project Objectives / Aims (one page)

Two PIs from UW-La Crosse, Song Chen, and Jeff Baggett, along with students, will collaborate with Dr. Rich Ellis from Mayo Clinic to develop computer-aided diagnosis (CAD) software for producing breast cancer diagnoses from raw breast ultrasound images. The ultimate goal is to produce software that performs at least as well as human experts in the accurate interpretation and clinical assessment of breast lesions detected via ultrasound.

Phase 1 of this project is a feasibility study to determine if we can synthesize the diagnosis of one or more machine and/or deep learning models with an automated human, rule-based system to achieve better than ever CAD assessments. Here are the objectives:

- **Objective 1 - Automated CAD using AI:** Use machine learning and deep learning algorithms to determine regions of interest and classify potential lesions in the correct American College of Radiology/Breast Imaging Reporting and Data System (BI-RADS®) Assessment Category (*ACR BI-RADS atlas: breast imaging reporting and data system*). This approach is completely automated and functions as a black box in which an image or images are fed to the model which produces a classification and location of a lesion. This model can also show regions in the image of the lesion that are significantly related to the predicted classification, but they may not be recognizable by a human expert as characteristics of the lesion.
- **Objective 2 - Automated CAD by mimicking human experts:** Build a second algorithm that mimics systems used by experts to determine a BI-RADS® classification of a lesion. This system relies on characteristics of the lesion, such as lesion shape, orientation, margins, internal and external lesion characteristics, along with lesion elasticity and vascularity, which are normally determined by the radiologist. Machine learning algorithms and/or rule-based (based on rules proposed by experts) algorithms will be used to estimate the characteristics from the image with optional user input. The characteristics will then be converted to a BI-RADS® classification by an expert determined rubric and/or an AI. This approach can be fully automated if machine learning or rule-based algorithms are used to extract the expert-identified characteristics from the ultrasound image(s).
- **Objective 3 - Synthesis of the two systems:** Synthesize the two lesion assessment systems to produce an improved estimate of the BI-RADS® Assessment Category.

If the final algorithm achieves satisfactory performance, then future efforts will be as follows:

- **Phase 2**: Improve the model and make it scalable so that it can be trained on very large datasets. Incorporate additional information into the model like patients' age, pre-test probability of breast cancer, etc.
- **Phase 3**: Build a practical application that can be accessed from ultrasound unit and radiologist clinical workstations to produce automated assessments in real or near-real-time.

  We plan to perform beta testing at the Mayo Clinic Health System-Southwest Wisconsin (La Crosse) to demonstrate feasibility. With anticipated successful beta testing and demonstrated feasibility, we plan to offer the software for continued testing and more robust machine learning and deep learning from other Mayo Clinic Enterprise sites. Once the software system is validated to perform at the desired level to successfully aid radiologists in breast ultrasound imaging interpretation, we anticipate its universal use across the Mayo Clinic Enterprise. This product provided it obtains FDA clearance, could also become a commercial product for Mayo Clinic and UW-L.

2. Background/Significance (1-2 pages)

Significance:

A. **Clinical need:** Ultrasound is the most user-dependent clinical imaging modality with the largest range of radiologist lesion interpretation and positive biopsy rate (both inter-radiologist and intra-radiologists). The positive biopsy rate across the Mayo Clinic Enterprise for breast ultrasound lesions ranges between 31-51% *(Radiology DataMart Dashboard, January 1, 2019, to November 1, 2020)*. This results in non-uniform patient management. An accurate, automated system is especially needed for indeterminate lesions that are not easily recognized as benign or malignant. Such a system could both improve patient care and reduce medical costs.
B. **Important Collaborative Project:** For an AI-based system such as the one we propose to be successful, it will require excellent physician support as well as the support of AI and Data Science experts. It also requires a large volume of image data that has been classified by experts to be used for initial training and testing as well as for ongoing improvements. All of these elements can be provided by the proposed collaboration between UWL and Mayo Clinic.
C. **Commercial Potential and Medical Impact:** This type of supportive imaging software will have wide appeal and the software could eventually be integrated into advanced breast ultrasound units and radiologist computer workstations. The result would be improved patient medical care, reduced cost, and better patient outcomes.

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Background: Here is some background information for each of three objectives:

- **Objective 1 - Automated CAD using AI:** Recent advances in AI/machine learning research, particularly convolutional neural networks (CNN) and related techniques, have boosted performance in image classification and object detection tasks to be comparable to and even better than those of humans. Meanwhile, improvements in computing have greatly reduced the resources and time needed to process large amounts of data. These advances enable promising new approaches to build CAD systems.

  The real-world application of AI approaches to CAD remains difficult. First, it is difficult to obtain the large amount of clinical data needed for the training of the neural network due to ownership and privacy (HIPAA) issues. Second, the performance of the algorithm largely depends on the quality of the data, where human expertise is needed to label a large set of images with high accuracy. Meanwhile, the structure of the neural network, the algorithm hyperparameters, etc. vary considerably for different organs, imaging modalities, and data sets so that there is no one-size-fits-all deep learning algorithm for CAD.

  State-of-the-art CAD algorithms using deep learning for binary classification (benign or malignant) of ultrasound breast lesions have been able to achieve as high as 87% accuracy *(Cao, et. al.)*.
- **Objective 2 - Automated CAD by mimicking human experts:** This approach attempts to achieve accurate classification using characteristics of the ultrasound breast lesions that have been determined to be important by human experts. These characteristics can be determined by three approaches or combinations thereof:
  - An expert radiologist can input characteristics of a lesion that has been detected by the AI in Objective 1. For example, the radiologist might determine that the margin of the lesion is not circumscribed and has an angular shape.
  - A rule-based system may be implemented as a computer algorithm for determining some of the characteristics. For example, the margin of the lesion might be automatically extracted by an image processing algorithm, and an expert determined rule is used to determine that the shape is angular.
  - If enough data is available machine learning algorithms can be trained to predict the characteristics of each lesion. For example, the image(s) are input to an algorithm that categorizes the shape of the margin of the lesion.

  Once the characteristics are determined they can be fed to either an expert-designed rubric or to a trained machine learning model for BI-RADS® classification of the lesion. An algorithm that relied on a manually drawn margin of each lesion to determine morphological characteristics was able to achieve

98% accuracy for binary classification of lesions on the training data, but it is unknown how this approach might fare on test data *(Daoud, et. al.)*.

- **Objective 3 - Synthesis of the two systems:** There are many approaches to combining the output of multiple predictive models. We plan to explore several of these approaches:
  - Ensemble Learning Methods: These methods use multiple learning algorithms to achieve better predictions. After completing objectives 1 and 2, we will have multiple BI-RADS® classifiers available and will explore a variety of different ensemble methods for combining the classifiers.
  - Combining features from previous models: In Objective 1 the AI will identify parts of the image in the ROI that are significantly related to the classification of the lesion. These features of each image along with the morphological features identified in Objective 2 will be used to train another predictive model.

  The performance of these multiple approaches will be compared and the best model selected for our prototype CAD software.

3. Innovation (half page)

There are existing studies that use CNN and related deep learning approaches for breast ultrasound CAD (see Cao, et al. and references therein). There have also been semi-automated approaches to using human rule-based systems (see Daoud, et al. and references therein.) However, to the best of our knowledge, this is the first attempt to fully automate a human rule-based system and synthesize it with a deep learning approach to achieve a high-accuracy CAD system for identifying and interpreting ultrasound detected breast lesions.

We have a strong chance of being able to make significant progress on an improved CAD system for several reasons:

- Mayo Clinic can provide, from across its enterprise, more high-quality data - labeled breast ultrasound images - than has been available to other researchers. This is critical to the successful development, testing, and continual updates of AI systems.
- The Mayo Clinic PI is a subspeciality-trained clinical breast radiologist, with over 25 years of experience. In addition, a former National Institutes of Health/Howard Hughes Research Scholar and graduate student in molecular biology at the University of Illinois, Champaign-Urbana.
- The UWL PIs have a strong background in image processing, object recognition and optimization all of which are critical in the development of an AI-based CAD system.
- UWL also has a reservoir of undergraduate and graduate students who would like to obtain real-world experience in deep learning and software development. Students in both the Masters of Science in Data Science and Masters of Science in Software Engineering could be involved.

4. Qualification of Investigators and Collaboration/Team Building Potential (half page)

Mayo: Rich Ellis is a current Mayo Clinic Enterprise Breast Imaging Subject Matter Expert while serving as site PI for Density MATTERS research trial and STRIVE research trial. Basic science research experience includes as a graduate student at the University of Illinois-Champaign/Urbana and National Institutes of Health/Howard Hughes Research Scholar. He is subspecialty-trained in breast imaging, with over 25-years of clinic practice as a dedicated clinical breast radiologist.

UWL: Jeff Baggett has a background in optimization which is the basis of machine learning and deep learning algorithms. He has worked in image segmentation and published multiple articles and technical reports related to optimization. His Ph.D. in scientific computing was earned at Cornell and augmented by postdoctoral research at Stanford University. He is also the academic director of the Master of Science in Data Science program at UWL.

UWL: Song Chen graduated from Auburn University with a Ph.D. in applied math while specializing in scientific computing and numerical methods. He conducts research in data science and has done several commercial projects on CADx, such as the tongue image diagnosis for diabetes and pneumonia detection via lung medical images. He has also published multiple articles in machine learning and led various master/undergraduate research projects on image processing.

5. Methods (2 pages): Below are the methods for the three main steps in this project:

Step 1 - Acquiring and Pre-Processing the Images:

Mayo Clinic will provide raw breast ultrasound images that have been labeled to include characteristics of the lesion describing the periphery, margin, and internal regions using standardized lesion nomenclature provided by the American College of Radiology BI-RADS® Atlas. Mayo Clinic will also supply the biopsy results and the Radiologist's BI-RADS® Assessment Category. This is all of the data that will be used to build our predictive models.

Given that there is no alteration to patient care or imaging parameters for the study, we will seek an IRB waiver for patient consent. All patient information will be de-identified, as no identified patient information is necessary for this study once the ultrasound image, corresponding radiology report, and corresponding pathology reports are linked. This study will use Mayo Clinic's secured cloud-based data repository for access to the de-identified imaging and report information.

After UWL obtains the images various image processing techniques such as cropping, filtering, enhancement, noise reduction, etc. will be applied to the raw images at this stage. The aim is to standardize the inputs before being fed to the neural network models in order to improve the predicting accuracy (*Gonzalez and Woods*).

The sample of processed images will be divided into the training set (85% of the total sample size) for model construction, and the test set (15% of the total sample size) for model evaluation. The same split data will be used to construct and evaluate all of the models discussed below.

Step 2 - Work on Objectives 1 and 2 in parallel

Each of the two objectives below will be worked on by one or more UWL students in collaboration with the PIs.

Step 2a: For **Objective 1 - Automated CAD using AI,** we turn to convolutional neural networks (CNN) based deep learning algorithms.

a. There are two state-of-art algorithms for object detection and classification. Region-based CNN (RCNN) proposes regions of interest before predicting the probability of each possible classification and one-shot object detection (OSOD) combines the two tasks, that is, it predicts the location and probability simultaneously. RCNN-based methods tend to be the most accurate while one-shot detection methods are more efficient and simpler to implement. We will test variations of each algorithm, including masked-RCNN, fast-RCNN, YOLOv4, SSD, etc. to achieve a balance of accuracy and speed. This approach has been shown to work well *(Cao, et. al.)*, but we must repeat the work to calibrate the models for our data.
b. Once we have identified the best approach we will apply the model to all of the images to extract features in each image that are significantly related to the classification of the lesion. These features will be saved to be used in Step 3.

Step 2b: For **Objective 2 - Automated CAD by mimicking human experts,** we will likely need a combination of methods to achieve satisfactory results. In this objective, we want to automatically extract characteristics of the lesion describing the periphery, margin, and internal regions. Once all of the images have been processed to obtain the characteristics, the characteristics will be used to train a machine learning model to predict the classification of each lesion. The same characteristics will also be used to predict lesion classifications from a human-designed rule-based algorithm. (*ACR BI-RADS atlas: breast imaging reporting and data system*, *Stavros et. al., Stavros*).

To extract the characteristics from each image we will explore three different approaches:

a. We will train separate machine learning models to predict each characteristic from the image of the lesion. This approach typically requires a large number of training images.
b. We will build a rule-based system that will use techniques from image processing and human-designed rules to extract the desired characteristics of the lesion.
c. It's likely that we'll have to use a combination of the two approaches just described to attain the most accurate AI algorithms. The user will also be able to input all of the characteristics or choose to override some of the automatically generated characteristics.

Once results from each of Objectives 1 and 2 are obtained we will turn to the last step.

Step 3 - Complete Objective 3 - Synthesis of the two systems

For this objective, we will be combining one or more models constructed in each of the previous objectives to attempt to achieve better predictions. There are numerous ways to do this, but we'll start with two:

a. We will explore several well-known ensemble methods that run multiple models and use various mechanisms to combine the predictions of all of the models to achieve a better prediction.
b. We will also investigate another approach that will take the computer-generated image features found by the models in Objective 1 and combine them with the lesion characteristics determined by the models in Objective 2 into a new data set that will be used to train new machine learning models to predict breast lesion classifications.

6. Expected Results/Outcomes/Deliverables (1 page)

We expect we will achieve one of the best breast ultrasound lesion interpretation support aids for radiologists using large case studies from Mayo Clinic Enterprise and advanced AI technology supported by UW-L Mathematicians and Data Scientists and graduate students. An anticipated outcome is demonstrable improvement and accuracy in radiologist intra- and inter-observer breast ultrasound lesion interpretation and BI-RADS Assessment Category, especially for indeterminate lesions. This improvement and accuracy in radiologist interpretation will have a direct impact on patient medical care and the cost of medical care. Once our objectives are achieved within Mayo Clinic Enterprise, we hope to work in collaboration with Mayo Clinic Venture and WiSys Technology Foundation for FDA clearance as a commercial software product. A portion of the commercial software proceeds can help support ongoing and future UW-L and Mayo Clinic Collaborative research initiatives.

In addition to the feasibility study mentioned just above we anticipate publications in practice-oriented journals such as the American Journal of Radiology, the American Roentgen Ray Journal, and the Journal of the Society of Breast Imaging.

Finally, we anticipate that up to four graduate students in the Masters of Science in Data Science program at UWL will fulfill the requirements for their capstone projects by contributing to this effort.

7. Timeline/Milestones (half page): All dates are in 2021:

We plan to have two pairs of students working on this project. The first pair will be working through August when they will submit complete capstone projects for their Master of Science in Data Science requirements. The second pair will work through December to complete their capstone projects.

- **March:** finalize agreements and select both graduate and undergraduate students.
- **April:** Train students by reading, online coursework, and sample projects pipeline. Explore sample images. Build image data pipeline via Mayo Clinic Research Cloud which is HIPAA compliant to protect patient medical information.
- **Mid-May:** Students work on Objectives 1 and 2. The goal is to achieve prototype versions of algorithms by mid to late July.
- **August:** Start work on Objective 3. The first pair of graduate students submit final capstone project reports.
- **September-October**: Refine the models. Test variations. Select the final model, test, and evaluate.
- **November**: Finalize algorithm choice for the feasibility study at Mayo Clinic. Identify external grants.
- **December:** Submit a final report to Mayo Clinic (12/1). The second pair of graduate students submit final capstone project reports. Work on journal articles.

8. References (only key references, < 30 key citations)

ACR BI-RADS atlas: breast imaging reporting and data system. 5 ed., Reston, Virginia, American College of Radiology, 2013.

Cao, Zhantao, and et. al. “An experimental study on breast lesion detection and classification from ultrasound images using deep learning architectures.” *BMC Medical Imaging*, vol. 19, 2019, p. 51.

Daoud, Mohommad I., and et. al. “A fusion-based approach for breast ultrasound image classification using multiple-ROI texture and morphological analyses.” *Computational and Mathematical Methods in Medicine*, 2016.

Gonzalez, Rafael C., and Richard E. Woods. *Digital Image Processing*. vol. 4, Pearson, 2017.

Stavros, A. Thomas. *Breast ultrasound*. Lippincott Williams & Wilkins, 2004.

Stavros, A. Thomas, and et. al. “Stavros, A. Thomas, et al. "Solid breast nodules: use of sonography to distinguish between benign and malignant lesions.” *Radiology*, vol. 196, 1995, pp. 123-134.

9. Budget

We propose to provide four Master of Science Data Science students $2,500 competitive scholarships to work on this project, with a total budget expense of $10,000. This provides an extra incentive for students to participate in the project so that we can get our best students to participate.

We would also like to pay an undergraduate computer science student to help with writing code during Summer 2021. The cost for this would be $10 / hour x 40 hours / week x 12 weeks = $4800. Associated fringe benefits are requested at the university’s prescribed rate of 4.46% for student employees.

We have identified about 15 interested graduate students and plan to make final selections in March 2021.

There are no costs associated with supplies and external services or animals.

Personnel Costs

Person (name, if known)	Role	# hours	
Undergraduate student wages (TBD)	Assist with writing code in summer 2021	480	$4,800
Fringe benefits (4.46%)	University prescribed rate for student employees	-	$214.08
Total personnel costs			$5,014.08

Internal Services
(ex. participant payments, pharmacy dispensing costs, etc.)

Item (s)	Description	
Tuition remission	4 Master of Science Data Science Scholarships @ $2500	$10,000
Total internal services costs		$**10,000**

Total project costs: $15,014.08

10. Human Subjects/Specimens

Are human subjects involved? [X]Yes [ ]No
If yes, is there participant contact? [X]Yes [ ]No
If yes, please describe the consent approach and process: Given that there is no alteration to patient care or imaging parameters for the study, we will seek an IRB waiver for patient consent.

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Briefly describe how the study team will preserve confidentiality and assure human subject safety: Given that there is no alteration to patient care or imaging parameters for the study, we will seek an IRB waiver for patient consent. All imaging and medical reports will be de-identified in accordance with HIPAA and based in the Mayo Clinic Research Cloud.

***If yes, complete IRBE protocol and application via IRBE system following approval by the Mayo/UWL Research Coordinating Committee, or** list previously approved IRB number (if applicable): Will need review by Mayo IRB only, confirmed with Sandra Grunwald 1/26/21

11. Animal Welfare (n/a)
Are animals involved? [ ] Yes [X] No
If yes, what type of species will be requested? _______________
Where will animals be housed? _________________
List Personnel Involved: ____
If previously approved IACUC studies, list IACUC number: _____________
What institution? [ ] Mayo Clinic [ ] University of Wisconsin- La Crosse

Please send proposal by 5 PM February 1, 2021, to: MayoUWLResearch@MAYO.EDU

11. Optional Supplemental Materials
Applicants may also include NIH Biosketch or Other Support Document in addition to above.

Appended to the end of this proposal is a biosketch for Dr. Rich Ellis, and vitae for Dr. Jeff Baggett and Dr. Song Chen.