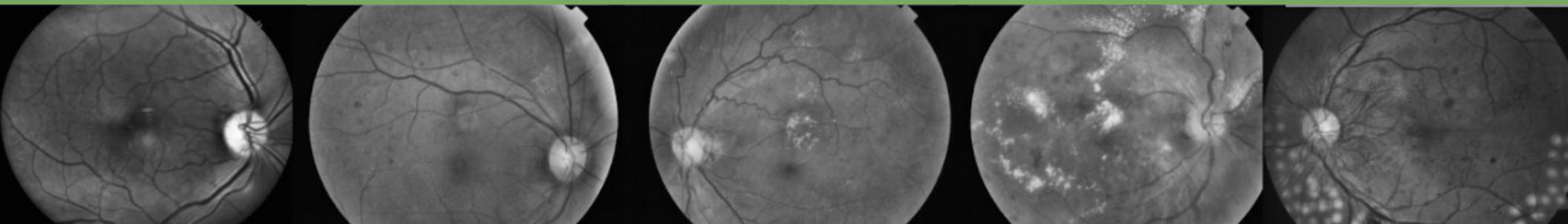


Novel Stage Optimized Image Processing to Improve Deep Learning Driven Diagnosis of Diabetic Retinopathy

Ella Yee | BMED055 | Harker Upper School
San Jose, California | USA



Research Background and Objectives

Problem Statement

- Diabetic retinopathy (DR) is an eye condition caused by diabetes and is a leading cause for **blindness**.¹ 50% of patients are diagnosed too late to prevent vision impairment.²
- Patients can develop diabetic retinopathy **up to 10 years** after the onset of diabetes.²
- They are usually asymptomatic until later stages where risks for permanent vision loss accelerate and significantly increase.
- Yet, early diagnosis and treatment **decrease the risks of vision impairment by 95%**.³
- Current research shows that deep learning models can be effective at diagnosing DR through fundus images⁴⁻¹⁵, yet no research so far has integrated deep learning research with stage by stage DR prognosis, including specific focus on the earliest and most critical stage (stage 1).

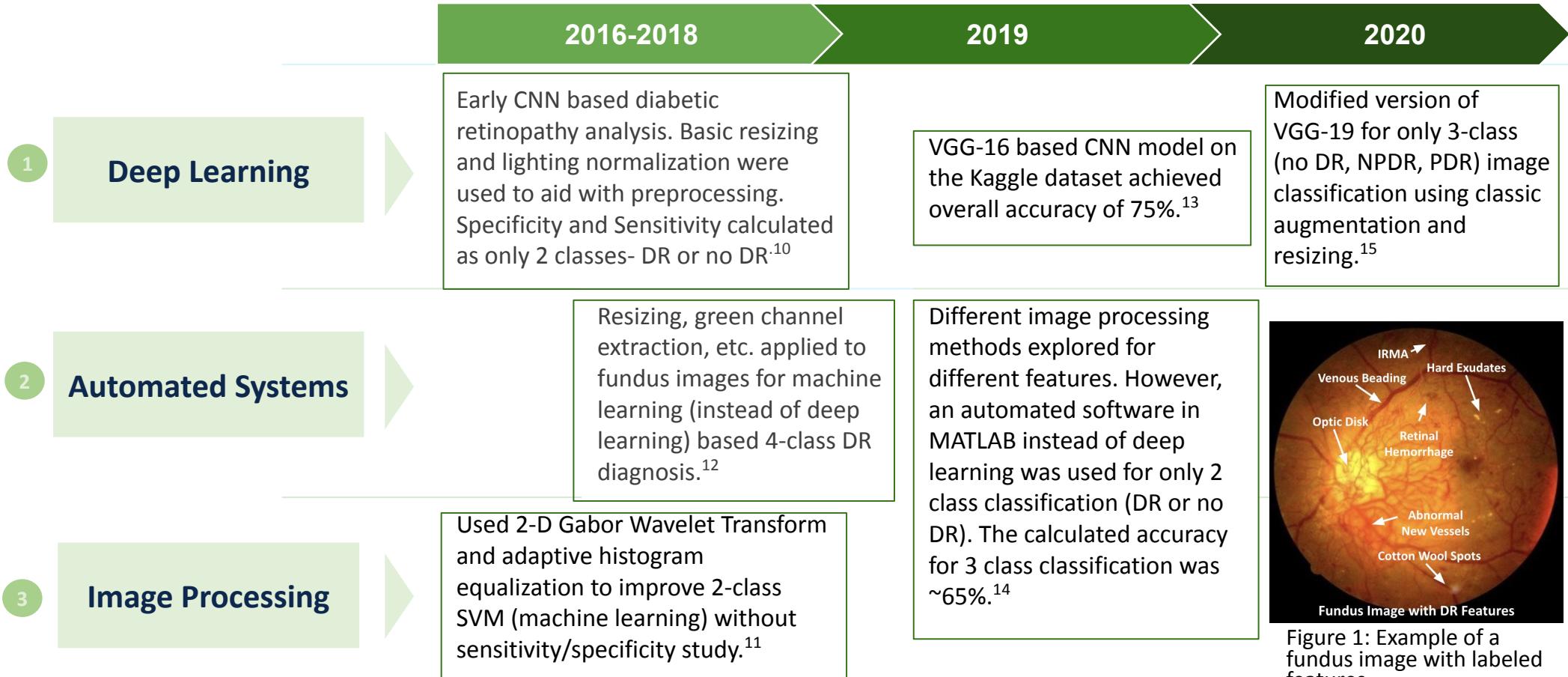
Objectives

- Systematically evaluate four image classification deep learning models for best baseline performance in 5-class diabetic retinopathy diagnosis as a foundation for optimizations.
- In addition to augmentation and resizing optimizations, develop **stage optimized image processing methods for the first time** to improve the accuracy, specificity, and sensitivity of deep learning driven diagnosis of diabetic retinopathy.
- Identify image processing methods that can **minimize the missed diagnosis rate of early stage** mild nonproliferative diabetic retinopathy.

Significance of This Research

- Current research is focused on improving overall accuracy, sensitivity, and specificity for Convolutional Neural Network (CNN) models used for DR diagnosis.
- Detection in the early stages of DR is most challenging, due to the lack of symptoms present, yet it is also the most important to prevent vision impairment
- Because the stage is medically critical and differentiated in the treatment, this project addresses the research gap by taking a new approach focusing on **deep learning driven diagnosis metrics stage by stage** for all 5 stages with a specific focus on **decreasing missed diagnosis of early stage DR**.

Summary of Previous Research on AI Based DR Diagnosis



Abbreviations: DR is diabetic retinopathy, NPDR is non-proliferative diabetic retinopathy, and PDR is proliferative DR.

Research Question + Hypothesis

Do different image processing algorithms optimize metrics for each stage of DR?
My hypothesis is using stage optimized image processing methods can improve accuracy, sensitivity, and specificity of deep learning driven diabetic retinopathy diagnosis for each stage.

My Research Approach and Focus

- 1) Develop **new deep learning models** which are able to calculate and analyze metrics for each stage of DR in addition to overall analysis
- 2) In depth analysis of various **image processing techniques** to study the **stage specific effects** (**This is the first systematic study**)
- 3) Focus on optimizing techniques for minimizing **missed diagnosis of stage 1 DR**, the most devastating misdiagnosis

Proposed Deep Learning Model and Stage Customized Image Processing Algorithms

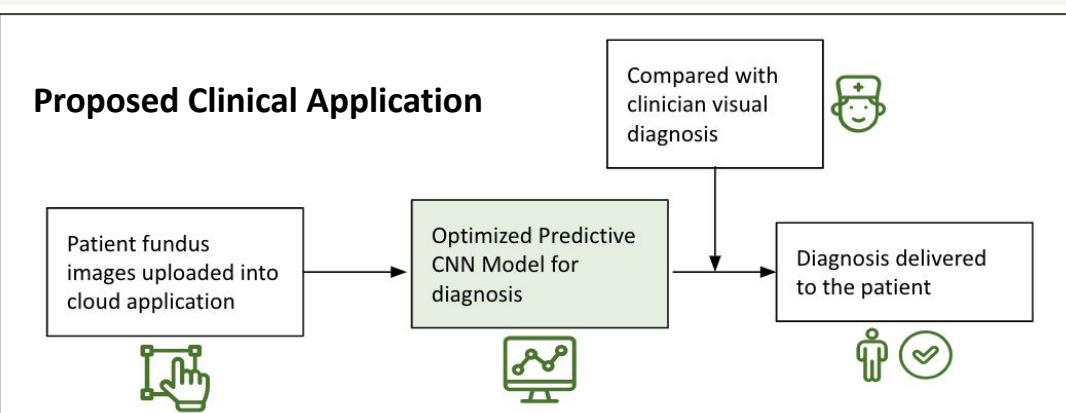
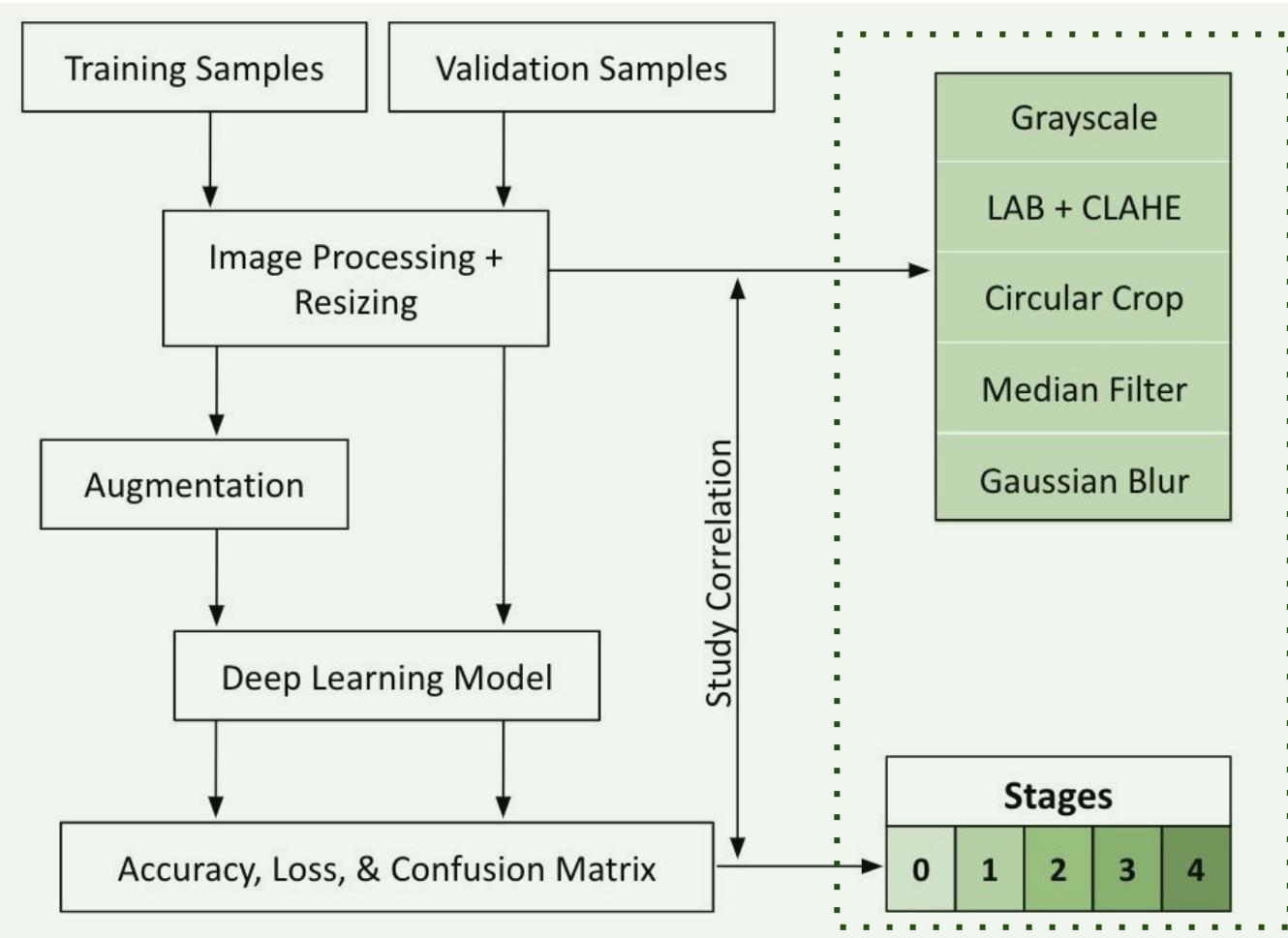
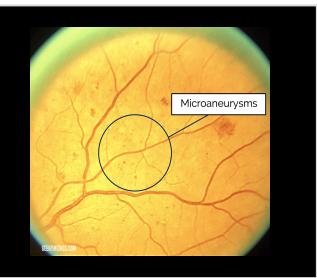
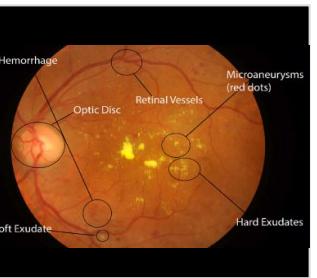
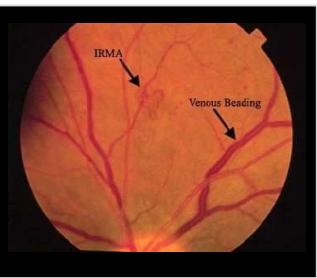
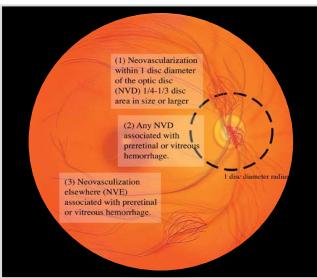


Figure 2: Diagram of Proposed Newly Developed Deep Learning Model and Stage Customized Image Processing Algorithms

- (1) **Platform Selection**
 - (a) Python Keras / TensorFlow/ CV-2 image processing
- (2) **Datasets:** 2019 APTOS DR (3662 images), EYEPACS (35126 images)
- (3) **Datasets Generation**
 - (a) Review dataset distribution and visualize dataset
 - (b) Split between training (80%) and validation (20%) data
- (4) **Evaluate four CNN deep learning models:** ResNet50, VGG16, InceptionV3, EfficientNetB7
- (5) **Evaluate different optimization methods iteratively by DR stage:** model selection, augmentation, resolution/sizing, image processing method, and iterative categorization. Evaluate confusion matrix.
- (6) **Optimize metrics:** accuracy, specificity, and sensitivity and with a specific focus to minimize misdiagnosis rate of Mild NPR as Normal.

Symptom Analysis and Feature Extraction in Fundus Images by Stage

	0- Normal	1- Mild NPDR	2- Moderate NPDR	3- Severe NPDR	4- PDR
APTOPS (primary) 3662 images	1805	370	999	193	295
EYEPACS₁₆ images	25810	2443	5292	873	708
¹⁷ Features	No NPDR and PDR features	Microaneurysms (MA) only.	MA, hemorrhage and one of the following: Retinal hemorrhage, hard exudates, cotton wool spots, and venous beading	Any of the following but no PDR features: > 20 hemorrhages in each quadrant, venous beading in 2+ quadrants, prominent	Neovascularization, vitreous /preretinal hemorrhages
Symptoms	None	MA is asymptomatic. Does not affect vision.	Usually will not affect vision unless near fovea	Larger affected areas can create vision distortion or blurring	Light hemorrhage can create floaters or blurring. Heavy bleeding will block vision. Scar tissues can detach retina.
Prognosis	Regular check ups.	Follow up in 6-12 months. Active management can slow progression and decrease risks for vision loss by 95%.	Follow up in < 6 month. Up to 26% become PDR within a year.	Follow up in <4 months. Up to 50% become PDR within a year and at high risk for vision loss.	Follow up in <2-3 months. Up 45% become high risk PDR within a year. High risk for permanent vision loss.
Images of Different Stages of DR Taken by Fundus Cameras					

Abbreviations: NPDR is non-proliferative diabetic retinopathy, and PDR is proliferative DR.

Source: Images sourced from APTOS 2019¹⁶, geekmedic.com, sciencedirect.com, researchgate.com and MDatL.com

CNN Model Benchmarks for Diagnosis of Diabetic Retinopathy

CNN Model	Image Classification Accuracy ⁹ for General Image Databases		Diabetic Retinopathy Fundus Image Classification Metrics for APTOs Dataset			Model Benchmarking
	ImageNet Top-1 Database	ImageNet Top-5 Database	Accuracy	Sensitivity	Specificity	
ResNet50	75%	92%	83.38%	71.25%	97.61%	
VGG-16	71%	90%	84.20%	84.20%	94.84%	
InceptionV3	78%	94%	82.01%	82.01%	92.55%	
EfficientNetB7	84%	97%	80.63%	80.63%	93.93%	

Image Augmentation

- Augmentation methods used include random rotations up to 360°, random brightness in range [0.5, 1.5], zooming in range [1, 1.2], random zca_whitening, & random vertical axis reflections
- Image Augmentation reduced gap between training and validation accuracy (overfitting)

Image Resizing

- Images were normalized and resized to 512x512, 320x320 (baseline), and 224x224 pixels.
- Larger image size led to better overall performance as expected because the larger image size includes more details relevant to DR in the images. However, larger image size requires more compute resource and time.

Model	Before Augmentation			VGG16			Resnet50			
	Accuracy	Sensitivity	Specificity	Size (px by)	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity
ResNet50	83.6%	83.4%	95.7%	512x512	84.4%	84.3%	95.0%	85.4%	85.4%	96.1%
VGG16	82.3%	82.2%	93.5%	320x320	84.2%	84.2%	94.8%	83.4%	83.4%	95.7%
Model	After Augmentation			224x224	80.5%	80.5%	92.8%	80.8%	80.8%	90.8%
	Accuracy	Sensitivity	Specificity							
ResNet50	83.8%	83.8%	95.9%							
VGG16	83.6%	83.2%	94.5%							

Findings from Model Augmentation & Image Resizing

- Image augmentation reduced overfitting without significantly impacting metrics and will be used in all future models.
- 512x512 pixels boosted the results for both VGG16 & ResNet50 and will be used in all future models.

Study of Image Processing Algorithms for Stage Specific Optimization

Image Processing Algorithms for DR Features

Method		Description	Purpose	Related Features/Stage
Split into components of color models + increase contrast while limiting noise	Grayscale	Convert from RGB to grayscale.	Distinguish features from background. Remove color as a distraction.	Most white/gray features: cotton wool spots, exudates, etc. in stages 2-4.
	LAB + CLAHE	Transform from RGB to LAB (L for lightness and A and B for the color components green-red and blue-yellow). Apply CLAHE to L.	Apply CLAHE to L to limit the contrast amplification and noise amplification.	Features with red and yellow components (e.g. hemorrhages, exudates). Contrast can apply to all stages.
	HSV + CLAHE	Transform from RGB to HSV (Hue, Saturation, Value). Apply CLAHE to limit noise amplification.	Color can be detected with reduced the influence of light intensity from the outside.	Stages with more color variations, e.g. 3-4. Contrast can apply to all stages.
Noise reduction and removal	2D Median Filter	Perform median filtering across 5x5 pixel blocks	Non-linear filtering preserves fine features in an image while filtering noise. Reduce random variations.	Effective for fine features like microaneurysm in stage 1.
	Circular Crop + Gaussian Blur	Extracts largest circular region possible from image of eye. Convolves the image with a Gaussian function for noise reduction.	Removes effects of truncated images of and black space outside of eye. Reduces noise and makes edge detection easier.	Features with clearer edges, e.g. venous beading and neovascularization in stage 4.

Findings from Study of Image Processing Methods

- I studied combinations of noise reduction, contrast, different color representation models and matched them with stage specific features.
- From my study of image processing techniques, I drew the conclusion that a balance has to be achieved between:
 - Increasing contrast for feature identification
 - Removing noise
 - Preserving relevant information/avoiding distortions of the identification features.

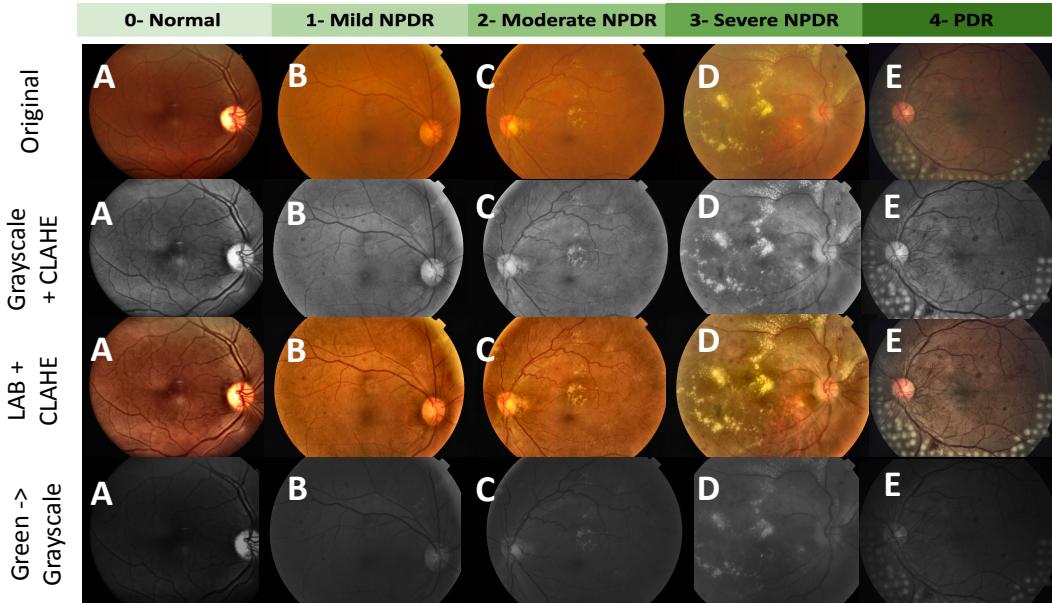


Figure 3: The effects of 3 image processing methods on images for each stage of DR

	Proposed Image Processing	Proposed Image Processing	Pratt et al. ¹⁰	Dekhil et al. ¹³
Number of classes	3 classes	5 classes	5 classes	5 classes
Accuracy	90.2%	83.5%	75%	75%
Sensitivity	81.7%	83.7%	30%	N/A
Specificity	94.9%	97.9%	95%	N/A
Misdiagnosis of Mild NPDR (1) as Normal(0)	1.01%	1.32%	Not studied	Not studied
By DR stage with stage optimized image processing	Accuracy = 89% Sensitivity = 84.4% to 97.6% Specificity = 91.2% to 98.2%	Accuracy = 88.9% to 98.8% Sensitivity = 60.5% to 98.8% Specificity = 90.1 to 98.8%	Not studied	Not studied

3 classes only: Normal, NPDR (Stages 1 & 2), PDR(Stages 3 & 4)

Accuracy = % correctly diagnosed patients

Sensitivity = average sensitivity of 3 classes

Specificity = average specificity of 3 classes

Pratt et al. Dekhil et al. definitions

Accuracy = percent of correctly diagnosed patients

Specificity = patients identified as not having DR/true number of

Sensitivity = patients identified as having DR/true number patients with DR

Metrics calculated using same definitions as respective related work

Proposed Image Processing used for comparison is Grayscale->CLAHE2 along with augmentation and 512 x 512 resolution

Results from Comparison to Previous Work

- With optimized image processing techniques, my proposed model offered higher metrics than previous work in the categories of accuracy, sensitivity, and specificity.
- Misdiagnosis of Mild NPDR (Stage 1) as Normal (Stage 0) can be reduced to 1.01-1.32%. This area was not previously addressed by related work.

Stage by Stage Image Processing Design and Results

	Misdiagnosis of Mild NPDR (1) as Normal(0)	Overall/System	By Class/DR Stage Metrics														
			0 - Normal			1 - Mild NPDR			2- Moderate NPDR			3- Severe NPDR			4- PDR		
			Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity
Baseline	6.58%	83.4% 71.2% 97.6%	97.9% 97.6% 98.2%	93.0% 63.2% 96.5%	87.8% 80.5% 90.9%	93.7% 57.9% 95.7%	94.4% 55.9% 97.8%										
Green > Grayscale	6.58%	81.6% 67.9% 97.6%	97.8% 97.6% 98.0%	91.9% 60.5% 95.6%	86.8% 82.3% 88.8%	93.1% 60.5% 94.9%	93.5% 28.8% 99.3%										
HSV->CLAHE	6.58%	85.3% 74.0% 98.5%	98.5% 98.5% 98.5%	93.7% 61.8% 97.4%	88.5% 89.1% 88.2%	94.9% 34.2% 98.3%	95.1% 59.3% 98.2%										
Median filtering	5.26%	84.3% 72.3% 98.5%	98.5% 98.5% 98.5%	93.8% 65.8% 97.1%	87.2% 90.5% 85.8%	94.6% 7.9% 99.4%	94.5% 54.2% 98.1%										
LAB->CLAHE	3.95%	85.7% 74.6% 98.8%	98.8% 98.8% 98.7%	93.3% 61.8% 96.9%	88.9% 87.7% 89.4%	94.9% 42.1% 97.8%	95.6% 62.7% 98.5%										
Grayscale	3.95%	82.6% 69.5% 97.9%	98.5% 98.2% 98.7%	92.2% 65.8% 95.2%	86.7% 86.4% 86.8%	94.1% 31.6% 97.5%	93.7% 35.6% 98.8%										
Circular crop+Gaussian Blur	2.63%	78.7% 62.1% 98.2%	98.2% 98.2% 98.2%	90.9% 50.0% 95.7%	83.2% 84.1% 82.9%	92.7% 21.1% 96.7%	92.3% 22.0% 98.5%										
Grayscale->CLAHE	1.32%	83.5% 71.2% 97.9%	98.2% 97.3% 99.0%	91.5% 64.5% 94.6%	85.6% 81.8% 87.2%	95.7% 36.8% 99.0%	95.3% 59.3% 98.5%										

By stage definitions

Accuracy = $TN + TP / (TN + TP + FN + FP)$

Specificity = $TN / (TN + FP)$

Sensitivity = $TP / (TP + FN)$

Overall/System definition

Accuracy = percent of correctly diagnosed patients

Specificity = number of patients correctly identified as not having DR/ number of total true number of patients without DR

Sensitivity = number of patients correctly identified as having DR/number of total true number patients with DR

NPDR is Non-proliferative Diabetic Retinopathy

PDR is Proliferative Diabetic Retinopathy

Highest value for the metric

Lowest value for the metric

Processing with best overall metrics

Stage by Stage Image Analysis Metrics

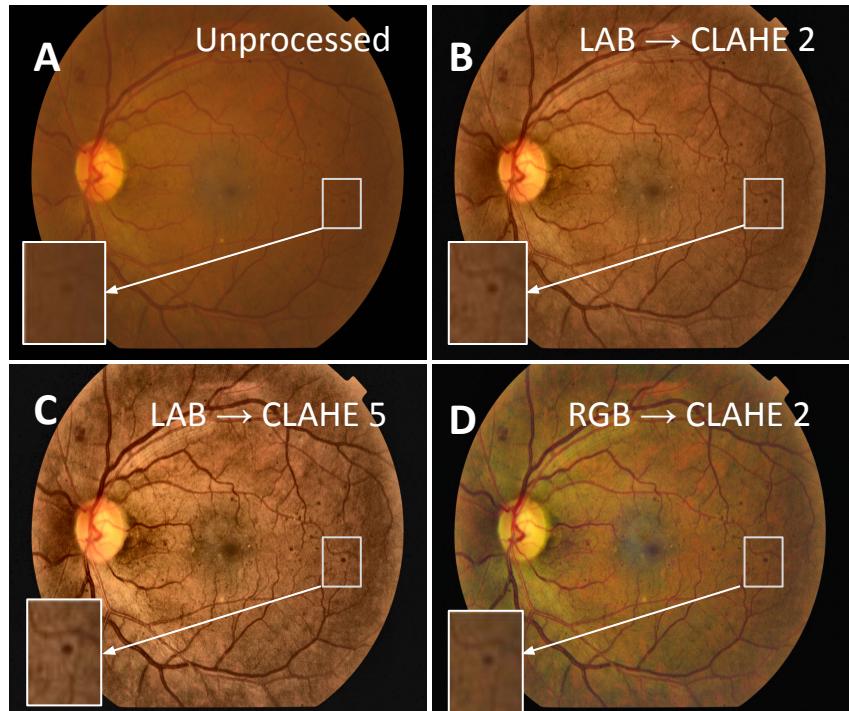
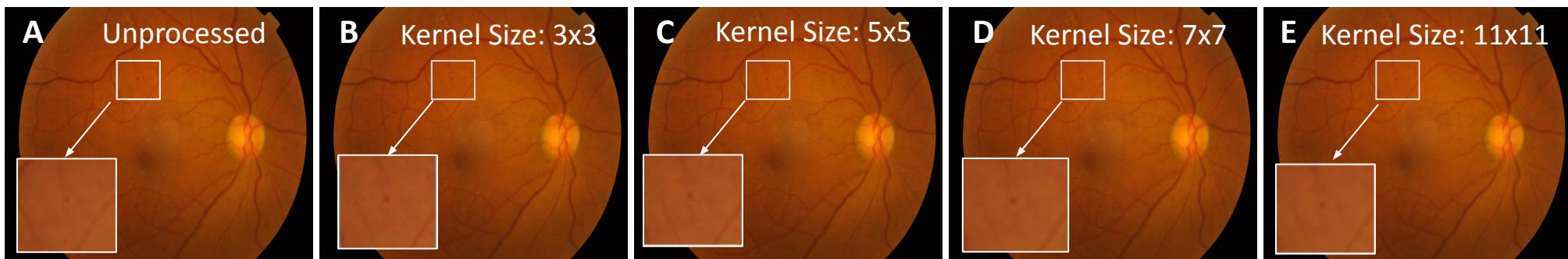
- 7 image processing algorithms were analyzed and compared to baseline results.
- I conducted stage by stage image analysis process for the first time.
- Misdiagnosis of mild NPDR (1) as normal (0) was also calculated for each algorithm.

Results, Findings, and Achievements

- Misdiagnosis of Mild NPDR (Stage 1) as Normal (Stage 0), the most devastating type of misdiagnosis, **can be dramatically reduced ~80%** from 6.58% to 1.32% with grayscale/CLAHE image processing without compromising the overall CNN system metrics.
- LAB/CLAHE** further optimizes CNN accuracy, sensitivity, and specificity for Stages 0, 2, and 4.
- Median filtering** further optimizes CNN accuracy, sensitivity, and specificity for Stage 1. **Green component/Grayscale** optimizes for Stage 3.

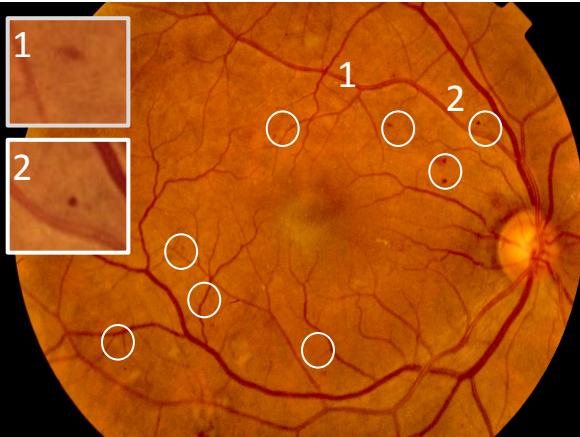
Further Exploration of Image Processing for Stage 1 DR

	Misdiagnosis of Mild NPDR (1) as Normal(0)	Overall/System			0 - Normal			1 - Mild NPDR			2- Moderate NPDR			3- Severe NPDR			4- PDR		
		Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity
	Baseline	6.58%	83.4%	71.2%	97.6%	97.9%	97.6%	98.2%	93.0%	63.2%	96.5%	87.8%	80.5%	90.9%	93.7%	57.9%	95.7%	94.4%	55.9%
Median filtering 3x3	2.60%	84.2%	72.0%	98.5%	97.9%	97.6%	98.2%	93.0%	63.2%	96.5%	87.8%	80.5%	90.9%	93.7%	57.9%	95.7%	94.4%	55.9%	97.8%
Median Filtering 5x5	5.26%	84.3%	72.3%	98.5%	97.8%	97.6%	98.0%	91.9%	60.5%	95.6%	86.8%	82.3%	88.8%	93.1%	60.5%	94.9%	93.5%	28.8%	99.3%
Media Filtering 7x7	5.26%	83.2%	70.0%	98.8%	98.5%	98.5%	98.5%	93.7%	61.8%	97.4%	88.5%	89.1%	88.2%	94.9%	34.2%	98.3%	95.1%	59.3%	98.2%
Median Filtering 11x11	5.26%	84.3%	72.3%	98.5%	98.5%	98.5%	98.5%	93.8%	65.8%	97.1%	87.2%	90.5%	85.8%	94.6%	7.9%	99.4%	94.5%	54.2%	98.1%
Grayscale->CLAHE 2	3.95%	85.7%	74.6%	98.8%	98.8%	98.8%	98.7%	93.3%	61.8%	96.9%	88.9%	87.7%	89.4%	94.9%	42.1%	97.8%	95.6%	62.7%	98.5%
LAB->CLAHE 5	2.63%	82.6%	69.5%	97.9%	98.5%	98.2%	98.7%	92.2%	65.8%	95.2%	86.7%	86.4%	86.8%	94.1%	31.6%	97.5%	93.7%	35.6%	98.8%
RGB -> CLAHE	2.63%	84.8%	73.8%	97.6%	98.2%	98.2%	98.2%	90.9%	50.0%	95.7%	83.2%	84.1%	82.9%	92.7%	21.1%	96.7%	92.3%	22.0%	98.5%
Grayscale->CLAHE 3	1.92%	85.0%	73.8%	98.2%	98.2%	97.3%	99.0%	91.5%	64.5%	94.6%	85.6%	81.8%	87.2%	95.7%	36.8%	99.0%	95.3%	59.3%	98.5%



- Median blur replaces the center pixel with the median value in the window
- Using a smaller kernel produces optimal results because using a large window may remove detail relevant to the features of DR
- While the difference in images using different kernel sizes is difficult to detect through a human eye, it can improve the model's classification in some cases. This ability to discern minute details is the advantage of deep learning and image processing.
- CLAHE with various thresholds was applied to various components.
- In conclusion, CLAHE is most effective in terms of early diagnosis when applied to intensity of a grayscale image directly, and optimal thresholds are 2-3, an unexpected value considering the maximum threshold is 64.

Analysis of Additional Image Processing Techniques for Stage 1 DR



Microaneurysms (MA), which are capillary dilations, are the only features present in stage 1 DR. They are the first indicator of the disease. In a fundus photo, microaneurysms appear as small red dots.

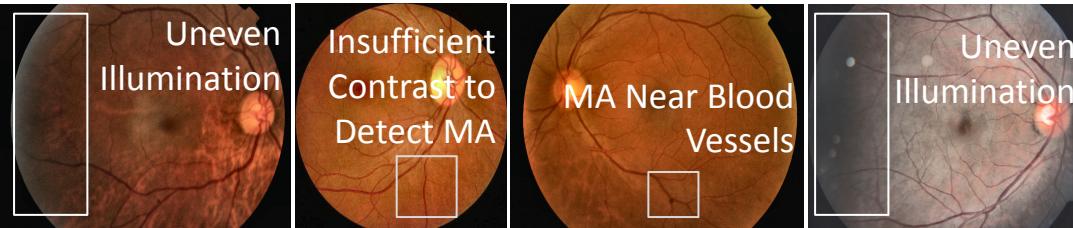


Figure 4: 4 images of stage 1 DR misclassified by my model as stage 0 DR

- To further investigate how to limit the misdiagnosis of stage 1 DR, I pulled images of stage 1 DR that were classified as stage 0 by my model
- Based on these images, I predicted that the misdiagnosis may have been caused by (1) uneven illumination (2) excess noise (3) low contrast
- I conducted a deeper study of image processing algorithms that could be particularly applicable to stage 1 DR, summarized in the table to the right.

Algorithm	Purpose	Advantages	Disadvantages
Shade Correction	Equalize lighting throughout an image	Combats uneven illumination in fundus photos	Could potentially remove DR related features
Extended Minima Transform	Create a binary image to emphasize extended minimas	Draws attention to a specific feature (MA in this case)	Identifying an appropriate threshold can be challenging
Morphological Reconstruction	Dilate an image to exaggerate peaks and valleys	Emphasizes extremes in an image	Could draw attention to features unrelated to DR

- I explored the effects of morphological transformations on microaneurysm detection
- I used thresholding to create a mask image (C) which highlights areas of concern, then layered it over the original image (D)
- This technique could be used for both deep learning and clinical applications , because it is can help detect microaneurysms less noticeable to the eye. Image (D) identifies suspect regions in the fundus image



Figure 5: (A) Original image (B) Image after CLAHE (C) Mask Image (D) Original image with mask image overlaid

Conclusions, Achievements, & Future Work

Conclusions

- My results indicate using stage optimized image processing can produce higher accuracy (88.9%-98.8%), sensitivity (60.5%-98.8%), and specificity (90.1%-98.8%) for each stage.
- My results clearly demonstrate there is not one model that produces the best results for all stages: this makes sense as different stages of DR have different features - instead, using my proposed stage specific analysis provides the highest metrics. The optimal models by stage are below:
 - Stage 0: LAB/CLAHE
 - Stage 1: Median Filtering
 - Stage 2: LAB/CLAHE
 - Stage 3: Green Component → Grayscale
 - Stage 4: LAB/CLAHE
- Additional image processing algorithms targeted specifically towards stage 1 DR have been explored in order to further reduce missed early diagnosis

Achievements

- Misdiagnosis of Mild NPDR (Stage 1) as Normal (Stage 0), the most devastating type of misdiagnosis, can be dramatically **reduced ~80%** from 6.58% to 1.32% with grayscale/CLAHE image processing
 - This result is significant, as currently ~50% of DR patients are diagnosed too late to prevent vision impairment, yet early diagnosis and treatment **decrease the risks of vision impairment by 95%.**²
- Metrics in other stages can be improved by using my proposed stage optimized image processing methods by up to **12%.**
- I optimized ideal image processing algorithms for diagnosing each stage. This is the first report so far.

Future Work

- Continuously optimize my model through testing on additional larger datasets (EYEPACS¹⁷) and datasets to test identification of particular DR features (e-ophtha_MA²¹, DRIVE²²)
- Utilize clinical datasets to validate my model for further improvement. Current progress is ongoing in terms of accessing a database.
- The preliminary results of my research are very promising in terms of identifying small sized microaneurysms and hemorrhages, so I plan to further explore and develop new image processing techniques with a focus on early stage diagnosis with high sensitivity
- **I will be presenting my research at the 2021 Association for Research in Vision and Ophthalmology (ARVO) Imaging in the Eye Conference 2021 May 13-14.**
- **A paper based on this research is under review for publication by Translational Vision Science & Technology journal.**

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