PixelBNN: Augmenting the PixelCNN with batch normalization and
the presentation of a fast architecture for retinal vessel segmentation

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Abstract. Analysis of retinal fundus images is essential for eye-care physicians in the diagnosis, care and treatment of patients. Accurate fundus and/or retinal vessel maps give rise to longitudinal studies able to utilize multimedia image registration and disease/condition status measurements, as well as applications in surgery preparation and biometrics. The segmentation of retinal morphology has numerous applications in assessing ophthalmologic and cardiovascular disease pathologies. The early detection of many such conditions is often the most effective method for reducing patient risk. Computer aided segmentation of the vasculature has proven to be a challenge, mainly due to inconsistencies such as noise and variations in hue and brightness that can greatly reduce the quality of fundus images. This paper presents PixelBNN, a highly efficient deep method for automating the segmentation of fundus morphologies. The model was trained, tested and cross tested on the DRIVE, STARE and CHASE\_DB1 retinal vessel segmentation datasets. Performance was evaluated using G-mean, Mathews Correlation Coefficient and F1-score. The network was $8.5 \times$ faster than the current state-of-the-art at test time and performed comparatively well, considering a $5 \times$ to $19 \times$ reduction in information from resizing images during preprocessing.

Keywords: convolutional networks, deep learning, retinal vessels, image segmentation.

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1 Introduction

The segmentation of retinal morphology has numerous applications in assessing ophthalmologic and cardiovascular disease pathologies, such as Glaucoma and Diabetes.\textsuperscript{1} Diabetic retinopathy (DR) is one of the main causes of blindness globally, the severity of which can be rapidly assessed based on retinal vascular structure.\textsuperscript{2} Glaucoma, another major cause for global blindness, can be diagnosed based on the properties of the optic nerve head (ONH). Analysis of the ONH typically
requires the removal of vasculature for computational methods. Similar analyses of other structures within the eye benefit from the removal of retinal vessels making the segmentation and subtraction of vasculature critical to many forms of fundus analysis. Direct assessment of vessel characteristics such as length, width, tortuosity and branching patterns can uncover abnormal growth patterns or other disease markers - such as the presence of aneurysms, which are used to evaluate the severity of numerous health conditions including diabetes, arteriosclerosis, hypertension, cardiovascular disease and stroke. For these types of diseases, early detection is critical in minimizing the risk complications and vision loss in the case of DR, glaucoma and other conditions of the eye; early detection is often the most effective method for reducing patient risk through modifications to lifestyle, medication and acute monitoring. Similarly, the same information - this time gleaned from youth, can be used as indicators in the prediction of those individuals’ health later in life.

Retinal vessel segmentation from fundus images plays a key role in computer aided retinal analyses, either in the assessment of the vessels themselves or in vessel removal prior the evaluation of other morphologies, such as the ONH and macula. For this reason, it has been the most crucial step of practically all non-deep computer based analyses of the fundus. Automated computer image analysis provides a robust alternative to direct ophthalmoscopy by a medical specialist, providing opportunities for more comprehensive analysis through techniques such as batch image analysis. As such, much research has gone into automatically measuring retinal morphology, traditionally utilizing images captured via fundus cameras. However, automatic segmentation of the vasculature has proven to be a challenge, mainly due to inconsistencies such as noise or variations in hue and brightness, which can greatly reduce the quality of fundus images. Traditional retinal pathology and morphology segmentation techniques often evaluate the green channel of RGB fundus images, as it is believed to be the “best” channel for assessing vascular tissue and lesions, while the red and blue channels suffer low contrast and high noise. Unfortunately, variations in image quality and patient ethnicity often invalidate this belief in real world settings.

Accurate feature extraction from retinal fundus images is essential for eye-care specialists in the care and treatment of their patients. Unfortunately, experts are often inconsistent in diagnosing
retinal health conditions resulting in unnecessary complications. The use of computer aided
detection (CAD) methods are being utilized to quantify the disease state of the retina, however
most traditional methods are unable to match the performance of clinicians. These systems under-
perform due to variations in image properties and quality, resulting from the use of varying capture
devices and the experience of the user. To properly build and train an algorithm for commercial
settings would require extensive effort by clinicians in the labelling of each and every dataset -
a feat that mitigates the value of CAD systems. Overcoming these challenges would giver rise
to longitudinal studies able to utilize multi-modal image registration and disease/condition status
measurements, as well make applications in surgery preparation and biometrics more viable.

The emergence of deep learning methods has enabled the development of CAD systems with an
unprecedented ability to generalize across datasets, overcoming the shortcoming of traditional or
“shallow” algorithms. Computational methods for image analysis are divided into supervised and
unsupervised techniques. Prior deep learning, supervised methods encompassed pattern recogni-
tion algorithms, such as k-nearest neighbours, decision trees and support vector machines (SVMs).
Examples of such methods in the segmentation of retinal vessels include 2D Gabor wavelet and
Bayesian classifiers, line operators and SVMs and AdaBoost-based classifiers. Supervised
methods require training materials be prepared by an expert, traditionally limiting the application
of shallow methods. Unsupervised techniques stimulate a response within the pixels of an image to
determine class membership and do not require manual delineations. The majority of deep learn-
ing approaches fall into the supervised learning category, due to their dependence on ground truths
during training. Often, unsupervised deep learning techniques refer to unsupervised pretraining for
improving network parameter initialization as well as some generative and adversarial methods.

Deep learning overcomes shallow methods’ inability to generalize across datasets through the
random generation and selection of a series of increasingly dimensional feature abstractions from
combinations of multiple non-linear transformations on a dataset. Applications of these tech-
niques for object recognition in images first appeared in 2006 during the MNIST digit image
classification problem, of which convolutional neural networks (CNNs) currently hold the high-
Like other deep neural networks (DNNs), CNNs are designed modularly with a series of layers selected to address different classification problems. A layer is comprised of an input, output, size (number of “neurons”) and a varying number of parameters/hyper-parameters that govern its operation. The most common layers include convolutional layers, pooling/subsampling layers and fully connected layers.

In the case of retinal image analysis, deep algorithms utilize a binary system, learning to differentiate morphologies based on performance masks manually delineated from the images. The current limitation with most unsupervised methods is that they utilize a set of predefined linear kernels to convolve the images or templates that are sensitive to variations in image quality and fundus morphologies. Deep learning approaches overcome these limitations, and have been shown to outperform shallow methods for screening and other tasks in diagnostic retinopathy. A recent review chapter discusses many of these issues and related methodologies.

This paper presents PixelBNN, a novel variation of PixelCNN - a dense fully convolutional network (FCN), that takes a fundus image as the input and returns a binary segmentation mask of the same dimension. The network was trained on resized images, deviating from other state-of-the-art methods which use cropping. The network was able to evaluate test images in 0.0466s, 8.5× faster than the state-of-the-art. Section 2 discusses the method and network architecture. Section 3 describes the experimental design. The resulting network performance is described in Section 4. Lastly, Section 5 discusses the results, future work and then concludes the paper.

2 Methodology

Deep learning methods for retinal segmentation are typically based on techniques which have been successfully applied to image segmentation in other fields, and often utilize stochastic gradient descent (SGD) to optimize the network. Recent work into stochastic gradient-based optimization has incorporated adaptive estimates of lower-order moments, resulting in the Adam optimization method, which is further described below. Adam was first successfully applied to the problem of retinal vessel segmentation by the authors, laying the foundation for this work.
Herein, a fully-residual autoencoder batch normalization network (“PixelBNN”) is trained via a random sampling strategy whereby samples are randomly distorted from a training set of fundus images and fed into the model. PixelBNN utilizes gated residual convolutional and deconvolutional layers activated by concatenated rectifying linear units (CReLU), similar to PixelCNN\textsuperscript{18,21} and PixelCNN++.\textsuperscript{22} PixelBNN differs from its predecessors in three areas: (1) varied convolutional filter streams, (2) gating strategy, and (3) introduction of batch normalization layers\textsuperscript{23} from which it draws its name.

2.1 Datasets

2.1.1 DRIVE

The CNN was trained and tested against the Digital Retinal Images for Vessel Extraction (DRIVE) database\textsuperscript{1}, a standardized set of fundus images used to gauge the effectiveness of classification algorithms.\textsuperscript{24} The images are 8 bits per RGBA channel with a $565 \times 584$ pixel resolution. The data set comprises of 20 training images with manually delineated label masks and 20 test images with two sets of manually delineated label masks by the first and second human observers, as shown in Fig. 1. The images were collected for a diabetic retinopathy screening program in the Netherlands using a Canon CR5 non-mydriatic 3CCD camera with a 45° field of view.\textsuperscript{24}

\textsuperscript{1}http://www.isi.uu.nl/Research/Databases/DRIVE/

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures/drive_sample.png}
\caption{Sample set of the DRIVE dataset. (a): Fundus image. (b): First manual delineation, used as the ground truth. (c): Second manual delineation, referred to as the second human observer and used as the human performance benchmark.\textsuperscript{24}}
\end{figure}
2.1.2 STARE

The Structured Analysis of the Retina database\(^2\) has 400 retinal images which are acquired using TopCon TRV-50 retinal camera with 35° field of view and pixel resolution of 700×605. The database was populated and funded through the US National Institutes of Health.\(^1\) A subset of the data is labelled by two experts, thereby providing 20 images with labels and ground truths. To compensate for the small number of images, four-fold cross validation was used. Therein, the network was trained over four runs, leaving five image out each time, resulting in all 20 images being evaluated without overlapping the training set, thusly minimizing network bias.

2.1.3 CHASE_DB1

The third dataset used in this study is a subset of the Child Heart and Health Study in England database (CHASE_DB1), containing 28 paired high-resolution (1280×960 pixels) fundus images from each eye of 14 children, captured with a 30° field of view using a Nidek NM-200-D fundus camera. Compared to STARE, CHASE_DB1 is more susceptible to bias as the images are all pairs from the same patient - this restricts the number of samples to 14. Due to this constraint and for the same reasons as with STARE, four-fold cross validation was used to preclude overlapping datasets between training and test time, this time grouping sets by patients.\(^3\)

2.2 Preprocessing

The most common and effective method for correcting inconsistencies within an image dataset is by comparing the histogram of an image obtained to that of an ideal histogram describing the brightness, contrast and signal/noise ratio, and/or determination of image clarity by assessing morphological features.\(^25\) Fundus images typically contain between 500×500 to 2000×2000 pixels, making training a classifier a memory and time consuming ordeal. Rather than processing the entire image, the images are randomly cropped and resized to 256×256 pixels, flipped, rotated and/or enhanced to extend the dataset.

\(^2\)http://cecas.clemson.edu/~ahoover/stare/
\(^3\)https://blogs.kingston.ac.uk/retinal/chasedb1/
2.2.1 Continuous Pixel Space

It has been shown that a continuous domain representation of pixel colour channels vastly improves memory efficiency during training.\textsuperscript{26} This is primary due to dimensionality reduction from initial channel values to a distribution of [-0.5 to 0.5]; features are learned with densely packed gradients rather than needing to keep track of very sparse values associated with typical channel values.\textsuperscript{22}

2.2.2 Image enhancement

Local histogram enhancement methods greatly improve image quality and contrast, improving network performance during training and evaluation. Rather than sampling all pixels within an image once, histograms are generated for subsections of the image, each of which is normalized. One limitation for local methods is the risk of enhancing noise within the image. Contrast limited adaptive histogram equalization (CLAHE) is one method that overcomes this limitation. CLAHE limits the maximum pixel intensity peaks within a histogram, redistributing the values across all intensities prior histogram equalization.\textsuperscript{27} This is the contrast enhancement method used herein.

2.3 Network Architecture

PixelBNN is a fully-residual autoencoder with gated residual streams, each initialized by differing convolutional filters. It is based on UNET,\textsuperscript{28} PixelCNN\textsuperscript{21} as well as various work on the use of skip connections and batch normalization within fully convolutional networks.\textsuperscript{29–32} It differs from prior work in the layer architecture, use of gated filter streams and regularization by batch normalization joint with dropout during training. While nuanced, the network further differentiates from many state-of-the-art architectures in its use of Adam optimization, layer activation by CReLU and use of downsampling in place of other multi-resolution strategies. The network makes extensive use of CReLU to reduce feature redundancy and negative information loss that would otherwise be incurred with the use of rectified linear units (ReLU). CReLU models have been shown to consistently outperform ReLU models of equivalent size while reducing the number of parameters by half, leading to significant gains in performance.\textsuperscript{33}

The architecture was influenced by the human vision system:
- The use of two parallel input streams resembles bipolar cells in the retina, each stream possessing different yet potentially overlapping feature spaces initialized by different convolutional kernels.

- The layer structure is based on that of the lateral geniculate nucleus, visual cortices (V1, V2) and medial temporal gyrus, whereby each is represented by an encoder-decoder pair of gated resnet blocks.

- Final classification is executed by a convolutional layer which concatenates the outputs of the last gated resnet block, as the inferotemporal cortex is believed to do.

More detail on this subject is covered in prior work by the authors.\textsuperscript{17}

Fig 2: Processed image patches are passed through two convolution layers with different filters to create parallel input streams for the encoder. Downsampling occurs between each ResNet block in the encoder and upsampling in the decoder. The output is a vessel mask of equal size to the input.
2.3.1 Downsampling without Information Loss

A popular method for facilitating multi-resolution generalizability with fully convolutional networks is the use of dilated convolutions within the model.\textsuperscript{21, 34} Dilated convolutions can be computational expensive, as they continuously increase in size through the utilization of zero padding to prevent information loss. Downsampling is another a family of methods that sample features during strided convolution at one or more intermediate stages of a FCN, later fusing the samples during upsampling\textsuperscript{29} and/or multi-level classifiers.\textsuperscript{31} Such methods take advantage of striding to achieve similar processing improvements as dilated convolutions with increased computational efficiency, albeit with a loss in information. Variations in downsampling methods aim to compensate for this loss of information.

2.3.2 Proposed Method

Figure 2 illustrates the architecture of the proposed method. PixelBNN utilizes downsampling with a stride of 2, as well as long and short skip connections, resembling PixelCNN++.\textsuperscript{22} Implementing both long and short skip connections has been shown to prevent information loss and increase convergence speed,\textsuperscript{30} while mitigating losses in performance.\textsuperscript{35} The method differs from PixelCNN++ in three ways. First, feature maps are implemented as with UNET\textsuperscript{28} with a starting value of 16, doubling at each downsampling. Second, in the use of batch normalization after each downsampling and before dropout, rather than dropout alone. Third, it differs in its use of paired convolution layers on on continuous pixel space RGB images. Each gated ResNet block consists of 4 gated ResNets as shown in Figure 2. Each ResNet is made up of convolution layers with kernel size 3 and stride of 1. Stream 1 ResNet is gated with Stream 2 by a network in network (NIN) layer, which is a 1x1 convolutional layer like those found in Inception models.\textsuperscript{35}

2.4 Platform

Training and testing of the proposed method was done using a computer with an Intel(R) Core(TM) i7-5820K CPU with 3.30GHz of processing power, 32 GB of RAM and a GM200 GeForce GTX TITAN X graphics card equivalent to 3072 CUDA cores. On this platform, it took roughly 14 hours
to train the network. At test time, the network processed a single image in 0.0466 seconds using the same system. In this study, Tensorflow\textsuperscript{36} and other python scientific, imaging and graphing libraries were used to evaluate the results.

3 Experimental Design

This paper presents PixelBNN, a novel network architecture for multi-resolution image segmentation and feature extraction based on PixelCNN. This is the first time this family of dense fully connected convolutional networks have been applied to fundus images. The specific task of retinal vessel segmentation was chosen due to the availability of different datasets that together provide ample variances for cross-validation, training efficiency, model performance and robustness. Architectural elements of the network have been thoroughly evaluated in the literature, as mentioned in Section 2.3. An ablation study is beyond the scope of this paper and left for future work. Following the completion of the follow on study, the code will be made available here: https://github.com/henryleopold/pixelbnn

3.1 Performance Indicators

Model performance is evaluated using a set of key performance indicators (KPIs), which are calculated by comparing the network output against the first set of manual delineations as the ground truth on a per-pixel basis. The test dataset has a second set of manual delineations which are used to benchmark the results against a second human observer (the ‘2nd observer’). There are four potential classification outcomes for each pixel: true positive (TP), false positive (FP), true negative (TN) and false negative (FN). These outcomes are then used to derive KPIs, such as sensitivity (SN; also known as recall), specificity (SP), accuracy (Acc) and the receiver operating characteristic (ROC), which can be a function of SN and SP, true positive rate (TPR) and false positive rate (FPR) or other similar KPI pairs. SN and SP are two of the most important KPIs to consider when developing a classification system as they are both representations of the “truth condition” and are thereby a far better performance measure than Acc. In an ideal system, both SN and SP will be 100%, however this is rarely the case in real life. The area under a ROC curve (AUC) as well as
Cohen’s kappa coefficient ($\kappa$) are two common approaches for measuring network performance. $\kappa$ is measured using the probability ($n_{ki}$) of an observer ($i$) predicting a category ($k$) for a number of items ($N$) and provides a measure of agreement between observers - in this case, the network’s prediction and the ground truth.\textsuperscript{37}

The Matthews Correlation Coefficient (MCC), the F1-score (F1) and the G-mean (G) perfor-

| KPI                        | Description                                                                 | Value                                                                 |
|----------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------|
| True Positive Rate (TPR)   | Probability of detection                                                    | $\frac{TP}{\text{vessel pixel count}}$                              |
| False Positive Rate (FPR)  | Probability of false detection                                              | $\frac{FP}{\text{nonvessel pixel count}}$                           |
| Accuracy (Acc)             | The frequency a pixel is properly classified                               | $\frac{TP + TN}{\text{total pixel count}}$                          |
| Sensitivity aka Recall (SN)| The proportion of true positive results detected by the classifier         | $TPR$ or $\frac{TP}{TP + FN}$                                       |
| Precision (Pr)             | Proportion of positive samples properly classified                         | $\frac{TP}{TP + FP}$                                                |
| Specificity (SP)           | The proportion of negative samples properly classified                     | $1 - FPR$ or $\frac{TN}{TN + FP}$                                   |
| Kappa Coefficient ($\kappa$)| Agreement between two observers                                            | $\frac{Acc - Acc_{prob}}{1 - Acc_{prob}}$                           |
| Probability of Agreement  | Probability each observer $n_{ki}$ selects a category $k$ for $N$ items | $\frac{1}{N^2} \sum_k n_{k1}n_{k2}$                                |
| G-mean (G)                 | Balance measure of SN and SP                                               | $\sqrt{SN * SP}$                                                   |
| Matthews Correlation Coef- | Measure from -1 to 1 for agreement between manual and predicted binary seg- | $\frac{(TP/N) - S \times P}{\sqrt{P \times S \times (1-S) \times (1-P)}}$ |
| cient (MCC)                | mentations                                                                 | $N = TP + FP + TN + FN$                                             |
|                            |                                                                            | $S = TP + FN \times N$                                             |
|                            |                                                                            | $P = TP + FP \times N$                                             |
| F1 Score (F1)              | Harmonic mean of precision and recall                                       | $\frac{2 * TP}{2TP + FP + FN}$ or $\frac{2 * Pr \times SN}{Pr + SN}$ |
mance metrics were used to better assess the resulting fundus label masks. These particular metrics are well suited for cases with imbalanced class ratios, as with the abundance of non-vessel pixels comparative to a low number of vessel pixels in this binary segmentation task. MCC has been used to assess vessel segmentation performance in several cases, and its value is a range from -1 to +1, respectively indicating total disagreement or alignment between the ground truth and prediction.\(^{38}\) Precision (Pr) is the proportion on positive samples properly classified and is often measured against SN in a *precision-recall curve*, similar to ROC. F-scores are harmonic means of Pr and SN and may incorporate weightings to adjust for class imbalances. This work uses the F1-score with a range from 0 to 1, where 1 signifies perfect segmentation of the positive class. G-mean calculates the geometric mean between SN and SP.\(^{39}\) The KPIs are defined in Table 1.

### 3.2 Training Details

For each dataset, the network parameters were randomly reinitialized using the Xavier algorithm.\(^{40}\) Table 2 summarizes the three data sets as well as the test-train data distribution and approximate information loss incurred during preprocessing. Pre-training was never conducted and so the network was trained from scratch for each dataset; in the case of STARE and CHASE_DB1, one set of parameters was trained from scratch for each fold. Images were reduced in size to alleviate the computational burden of the training task rather than using the original image to train the network. To ensure each dataset was evaluated equivalently, image size was first normalized to 256×256

| Datasets  | DRIVE | STARE | CHASE_DB1 |
|-----------|-------|-------|-----------|
| Image dimensions | 565×584 | 700×605 | 1280×960 |
| Colour Channels  | RGB  | RGB  | RGB       |
| Total Images     | 40   | 20   | 28        |
| Source Grouping  | 20 train & 20 test | - | 14 Patients (2 images in each) |

| Method Summary |
|----------------|
| Train-Test Schedule | One-off on 20 train Test on the other 20 | 4-fold cross-validation over 20 images | 4-fold cross-validation over 14 patients |
| Information Loss   | 5.0348 | 6.4621 | 18.7500 |
before undergoing dataset augmentation. This step is the cause for the majority of information loss relative to the original images and other methods compared herein which extract patches rather than resize the original fundus images.

The images were randomly cropped between 216 to 256 pixels along each axis and resized to 256×256. They were then randomly flipped both horizontally and vertically before being rotated at zero, 90° or 180°. The brightness and contrast of each patch was randomly shifted to further increase network robustness. PixelBNN learns to generate vessel label masks from fundus images in batches of 3 for 100,000 iterations utilizing Adam optimization with an initial learning rate of $1e^{-5}$ and decay rate of 0.94 every 20,000 iterations. Batch normalization was conducted with an initial $\epsilon$ of $1e^{-5}$ and decay rate of 0.9 before the application of dropout regularization\textsuperscript{41} with a keep probability of 0.6. It required approximately 11 hours to complete training for DRIVE and the same for each fold during cross validation.

4 Results

The output of PixelBNN is a binary label mask, predicting vessel and non-vessel pixels thereby segmenting the original image. Each dataset contains a two experts’ manual delineations; the first was used as the ground truth for training the model and the second was used for evaluating the network’s performance against a secondary human observer. Independently, each dataset was used to train a separate model from scratch resulting in three sets of model parameters.

4.1 Performance Comparison

The results were compared with those of other state-of-the-art methods for vessel segmentation with published results for at least one of the DRIVE, STARE or CHASE_DB1 datasets. The results for the model trained and tested on DRIVE are shown in Table 3, STARE results are shown in Table 4 and CHASE_DB1 results are in Table 5. Cross-testing was conducted using each of these sets to measure the performance of the network against each other datasets’ test images. The results from cross-testing are summarized in Table 6. Most of the articles report SN and SP, relying on Acc and AUC to validate performance, whereas $\kappa$, MCC and F1-scores have been sparsely applied until
Fig 3: Network predictions on the DRIVE dataset. The top row shows the image, segmentation masks and ground truth for the image that scored best when DRIVE was used to train and test the model; the bottom row shows the worst. For comparison, the cross-validation results from training the model with STARE and CHASE_DB1 are shown.

Fig 4: Network predictions on the STARE dataset. The top row shows the image, segmentation masks and ground truth for the image that scored best when STARE was used to train and test the model; the bottom row shows the worst. For comparison, the cross-validation results from training the model with DRIVE and CHASE_DB1 are shown.
recently. Regardless of other KPIs, most recent works report SN and SP from which the G-mean was calculated. Herein, the G-mean is considered to be a truer performance indicator than SN, SP and Pr. Further, the main KPIs used to evaluate model performance are F1-score, G-mean and MCC. For completeness, SN, SP, Pr, Acc, AUC and $\kappa$ are also tabulated. Table 7 compares the computation time for training the network and evaluating test images with the methods that share the same GPU.

The model’s performance varied between datasets, outperforming other methods in a subset of cross-testing tasks for which there were few published baselines. At face value, the model appears to underperform the state-of-the-art, however the information lost when resizing the images during preprocessing is quite severe. Figure 3, Figure 4 and Figure 5 show the best and worst scoring same-set images, ground truth and resulting predictions for testing and cross-testing that image with DRIVE, STARE and CHASE_DB1 respectively. Overall, the predictions reveal that losses in performance are largely the result of fine-vessels being missed as well as anomalous pathologies. Interestingly, PixelBNN performed better on STARE and CHASE_DB1 when the model was trained with DRIVE rather than that same set, outperforming the state-of-the-art with regards to

| Image | CHASE_DB1 | STARE | DRIVE | Ground Truth |
|-------|-----------|-------|-------|--------------|
| ![Best](image) | ![Best](image) | ![Best](image) | ![Best](image) | ![Best](image) |
| ![Worst](image) | ![Worst](image) | ![Worst](image) | ![Worst](image) | ![Worst](image) |

Fig 5: Network predictions on the CHASE_DB1 dataset. The top row shows the image, segmentation masks and ground truth for the image that scored best when CHASE_DB1 was used to train and test the model; the bottom row shows the worst. For comparison, the cross-validation results from training the model with STARE and DRIVE are shown.
Table 3: Performance comparison for models trained and tested with DRIVE.

| Methods                     | SN     | SP     | Pr     | Acc    | AUC    | kappa  | G      | MCC    | F1    |
|-----------------------------|--------|--------|--------|--------|--------|--------|--------|--------|-------|
| Human (2nd Observer)        | 0.7760 | 0.9730 | 0.8066 | 0.9472 | -      | 0.7581 | 0.8689 | 0.7601 | 0.7881|
| **Unsupervised Methods**    |        |        |        |        |        |        |        |        |       |
| Lam et al. 42               | -      | -      | -      | 0.9472 | 0.9614 | -      | -      | -      | -     |
| Azzopardi et al. 8          | 0.7655 | 0.9704 | -      | 0.9442 | 0.9614 | -      | 0.8619 | 0.7475 | -     |
| Kovács and Hajdu 43         | 0.7270 | 0.9877 | -      | 0.9494 | -      | -      | 0.8474 | -      | -     |
| Zhang et al. 44             | 0.7743 | 0.9725 | -      | 0.9476 | 0.9636 | -      | 0.8678 | -      | -     |
| Roychowdhury et al. 35      | 0.7395± | 0.9782± | -      | 0.9494± | 0.9672 | -      | -      | -      | -     |
| Niemeijer et al. 46         | 0.6793± | 0.9801± | -      | 0.9416± | 0.9294± | 0.7145 | -      | -      | -     |
| **Supervised Methods**      |        |        |        |        |        |        |        |        |       |
| Soares et al. 10            | 0.7332 | 0.9782 | -      | 0.9461± | 0.9614 | 0.7285 | 0.8469 | -      | -     |
| Ricci and Perfetti 1        | -      | -      | -      | 0.9595 | 0.9633 | -      | -      | -      | -     |
| Marin et al. 47             | 0.7067 | 0.9801 | -      | 0.9452 | 0.9588 | -      | 0.8322 | -      | -     |
| Lupascu et al. 52           | -      | -      | -      | 0.9597± | 0.9561 | 0.7200 | 0.8151 | -      | -     |
| Fraz et al. 48              | 0.7152 | 0.9768 | 0.8205 | 0.9430 | -      | -      | 0.8358 | 0.7333 | 0.7642|
| Fraz et al. 7               | 0.7406 | 0.9807 | -      | 0.9480 | 0.9747 | -      | 0.8522 | -      | -     |
| Fraz et al. 49              | 0.7302 | 0.9742 | 0.8112 | 0.9422 | -      | -      | 0.8434 | 0.7359 | 0.7686|
| Vega et al. 50              | 0.7444 | 0.9600 | -      | 0.9412 | -      | -      | 0.8454 | 0.6617 | 0.6884|
| Li et al. 51                | 0.7569 | 0.9816 | -      | 0.9527 | 0.9738 | -      | 0.8620 | -      | -     |
| Liskowski et al. 52         | 0.7811 | 0.9807 | -      | 0.9535 | 0.9790 | 0.7910 | 0.8752 | -      | -     |
| Leopold et al. 53           | 0.6823 | 0.9801 | -      | 0.9419 | 0.9707 | -      | 0.8178 | -      | -     |
| Leopold et al. 54           | 0.7800 | 0.9727 | -      | 0.9478 | 0.9689 | -      | 0.8710 | -      | -     |
| Orlando et al. 58           | 0.7897 | 0.9684 | 0.7854 | -      | -      | -      | 0.8741 | 0.7556 | 0.7857|
| Mo et al. 55                | 0.7779± | 0.9780± | -      | 0.9521± | 0.9782± | 0.7759± | 0.8722± | -      | -     |
| **PixelBNN**                | 0.6963± | 0.9573± | 0.7770± | 0.9106± | 0.8268± | 0.6795± | 0.8159± | 0.6820± | 0.7328±|

G-mean. Basing the results on G-mean, MCC and F1-scores places the network performance in the middle of the back for DRIVE and STARE, and last for CHASE_DB1. This trend is not surprising, given deep learning methods performance is dependant on the availability of data to train the system. Compared to the other methods, PixelBNN used $5 \times$ less information for DRIVE, $6.5 \times$ less for STARE, and $18.75 \times$ less information for CHASE_DB1 (see Table 2).

### 4.2 Computation time

Computation time is a difficult metric to benchmark due to variances in test system components and performance. In an attempt to evaluate this aspect, recent works that share the same GPU - the NVIDIA Titan X - were compared. This is a reasonable comparison as the vast majority of computations are performed on the GPU when training DNNs. Table 7 shows the comparable methods
Table 4: Performance comparison for models trained and tested with STARE.

| Methods                     | SN     | SP     | Pr    | Acc   | AUC   | kappa | G    | MCC  | F1   |
|-----------------------------|--------|--------|-------|-------|-------|-------|------|------|------|
| Human (2nd Observer)        | 0.8951 | 0.9387 | 0.6424 | 0.9353 | -     | 0.7046 | 0.9166 | 0.7225 | 0.7401 |
| **Unsupervised Methods**    |        |        |       |       |       |       |      |      |      |
| Lam et al. [42]             | -      | -      | -     | 0.9567 | 0.9739 | -     | -    | -    | -    |
| Azzopardi et al. [8]        | 0.7716 | 0.9701 | -     | 0.9497 | 0.9563 | -     | 0.8652 | 0.7335 | -    |
| Kovács and Hajdu [43]       | 0.7665 | 0.9879 | -     | -     | 0.9711 | -     | 0.8702 | -    | -    |
| Zhang et al. [44]           | 0.7791 | 0.9758 | -     | 0.9554 | 0.9748 | -     | 0.8719 | -    | -    |
| Roychowdhury et al. [45]    | 0.7317± | 0.9842± | -     | 0.9560± | 0.9673 | -     | 0.8486± | -    | -    |
| **Supervised Methods**      |        |        |       |       |       |       |      |      |      |
| Soares et al. [40]          | 0.7207 | 0.9747 | -     | 0.9479 | 0.9671 | -     | 0.8381 | -    | -    |
| Ricci et al. [3]            | -      | -      | -     | 0.9584 | 0.9602 | -     | -    | -    | -    |
| Marin et al. [47]           | 0.6944 | 0.9819 | -     | 0.9526 | 0.9769 | -     | 0.8257 | -    | -    |
| Fraz et al. [48]            | 0.7409 | 0.9665 | 0.7363 | 0.9437 | -     | -     | 0.8462 | 0.7003 | 0.7386 |
| Fraz et al. [7]             | 0.7548 | 0.9763 | -     | 0.9534 | 0.9768 | -     | 0.8584 | -    | -    |
| Fraz et al. [49]            | 0.7318 | 0.9660 | 0.7294 | 0.9423 | -     | -     | 0.8408 | 0.6908 | 0.7306 |
| Vega et al. [50]            | 0.7019 | 0.9671 | -     | 0.9483 | -     | -     | 0.8239 | 0.5927 | 0.6082 |
| Li et al. [51]              | 0.7726 | 0.9844 | -     | 0.9628 | 0.9879 | -     | 0.8721 | -    | -    |
| Liskowski et al. [52]       | 0.8554± | 0.9862± | -     | 0.9729± | 0.9928± | 0.8507± | 0.9185± | -    | -    |
| Mo et al. [55]              | 0.0286 | 0.0018 | -     | 0.0027 | 0.0014 | 0.0155 | 0.0072 | -    | -    |
| Orlando et al. [38]         | 0.0387 | 0.0034 | -     | 0.0058 | 0.0035 | 0.0310 | 0.0115 | -    | -    |
| **PixelBNN**                |        |        |       |       |       |       |      |      |      |
|                            | 0.6433± | 0.9472± | 0.6637± | 0.9045± | 0.7952± | 0.5918± | 0.7797± | 0.5960± | 0.6465± |

Table 5: Performance comparison for models trained and tested with CHASE_DB1.

| Methods                     | SN     | SP     | Pr    | Acc   | AUC   | kappa | G    | MCC  | F1   |
|-----------------------------|--------|--------|-------|-------|-------|-------|------|------|------|
| Human (2nd Observer)        | 0.7425 | 0.9793 | 0.8090 | 0.9560 | -     | 0.7529 | 0.8527 | 0.7475 | 0.7686 |
| **Unsupervised Methods**    |        |        |       |       |       |       |      |      |      |
| Azzopardi et al. [8]        | 0.7585 | 0.9587 | -     | 0.9387 | 0.9487 | -     | 0.8527 | 0.6802 | -    |
| Zhang et al. [44]           | 0.7626 | 0.9661 | -     | 0.9452 | 0.9606 | -     | 0.8583 | -    | -    |
| Roychowdhury et al. [45]    | 0.7615± | 0.9575± | -     | 0.9467± | 0.9623 | -     | 0.8539± | -    | -    |
| **Supervised Methods**      |        |        |       |       |       |       |      |      |      |
| Fraz et al. [7]             | 0.7224 | 0.9711 | -     | 0.9469 | 0.9712 | -     | 0.8376 | -    | -    |
| Li et al. [51]              | 0.7507 | 0.9793 | -     | 0.9581 | 0.9716 | -     | 0.8574 | -    | -    |
| Liskowski et al. [52]       | 0.7816± | 0.9836± | -     | 0.9628± | 0.9823± | 0.7908± | 0.8768± | -    | -    |
| Mo et al. [55]              | 0.0178 | 0.0022 | -     | 0.0020 | 0.0016 | 0.0111 | 0.0063 | -    | -    |
| Orlando et al. [38]         | 0.0533 | 0.0076 | -     | 0.0050 | 0.0040 | 0.0201 | 0.0263 | -    | -    |
| **PixelBNN**                |        |        |       |       |       |       |      |      |      |
|                            | 0.8618± | 0.8961± | 0.3951± | 0.8936± | 0.878959± | 0.4889± | 0.8787± | 0.5376± | 0.5391± |
## Table 6: Model performance measures from cross-training.

| Methods               | SN   | SP   | Pr   | Acc  | AUC  | kappa | G    | MCC  | F1   |
|-----------------------|------|------|------|------|------|-------|------|------|------|
| **Soares et al.**     | -    | -    | -    | 0.9397 | -    | -      | -    | -    | -    |
| **Ricci et al.**      | -    | -    | -    | 0.9266 | -    | -      | -    | -    | -    |
| **Marin et al.**      | -    | -    | -    | 0.9448 | -    | -      | -    | -    | -    |
| **Fraz et al.**       | 0.7242 | 0.9792 | -  | 0.9456  | 0.9697 | -  | 0.8421 | -    | -    |
| **Li et al.**         | 0.7273 | 0.9810 | -   | 0.9486  | 0.9677  | -  | 0.8447 | -    | -    |
| **Liskowski et al.**  | -    | -    | -    | 0.9416  | 0.9605 | -      | -    | -    | -    |
| **Mo et al.**         | 0.7412 | 0.9799 | -   | 0.9492  | 0.9653  | -  | 0.8522 | -    | -    |
| **PixelBNN**          | 0.5110 ± 0.0362 | 0.9533 ± 0.0094 | 0.7087 ± 0.0554 | 0.8748 ± 0.0126 | 0.7322 ± 0.0199 | 0.5193 ± 0.0404 | 0.5907 ± 0.0348 |
| **Model trained on:** |       |      |      |       |      |       |      |      |      |
| **Soares et al.**     | -    | -    | -    | 0.9327 | -    | -      | -    | -    | -    |
| **Ricci et al.**      | -    | -    | -    | 0.9464 | -    | -      | -    | -    | -    |
| **Marin et al.**      | -    | -    | -    | 0.9528 | -    | -      | -    | -    | -    |
| **Fraz et al.**       | 0.7010 | 0.9770 | -  | 0.9493  | 0.9660  | -  | 0.8276 | -    | -    |
| **Li et al.**         | 0.7027 | 0.9828 | -   | 0.9545  | 0.9671  | -  | 0.8310 | -    | -    |
| **Liskowski et al.**  | -    | -    | -    | 0.9505  | 0.9595 | -      | -    | -    | -    |
| **Mo et al.**         | 0.7009 | 0.9843 | -   | 0.9570  | 0.9751  | -  | 0.8306 | -    | -    |
| **PixelBNN**          | 0.7842 ± 0.0255 | 0.9265 ± 0.0113 | 0.9070 ± 0.0181 | 0.8553 ± 0.0323 | 0.6383 ± 0.0942 | 0.8519 ± 0.0204 | 0.6465 ± 0.0303 |
| **Model trained on:** |       |      |      |       |      |       |      |      |      |
| **Soares et al.**     | -    | -    | -    | 0.9372 | -    | -      | -    | -    | -    |
| **Ricci et al.**      | -    | -    | -    | 0.9464 | -    | -      | -    | -    | -    |
| **Marin et al.**      | -    | -    | -    | 0.9528 | -    | -      | -    | -    | -    |
| **Fraz et al.**       | 0.7010 | 0.9770 | -  | 0.9493  | 0.9660  | -  | 0.8276 | -    | -    |
| **Li et al.**         | 0.7027 | 0.9828 | -   | 0.9545  | 0.9671  | -  | 0.8310 | -    | -    |
| **Liskowski et al.**  | -    | -    | -    | 0.9505  | 0.9595 | -      | -    | -    | -    |
| **Mo et al.**         | 0.7009 | 0.9843 | -   | 0.9570  | 0.9751  | -  | 0.8306 | -    | -    |
| **PixelBNN**          | 0.7842 ± 0.0255 | 0.9265 ± 0.0113 | 0.9070 ± 0.0181 | 0.8553 ± 0.0323 | 0.6383 ± 0.0942 | 0.8519 ± 0.0204 | 0.6465 ± 0.0303 |
| **Model trained on:** |       |      |      |       |      |       |      |      |      |
| **Soares et al.**     | -    | -    | -    | 0.9372 | -    | -      | -    | -    | -    |
| **Ricci et al.**      | -    | -    | -    | 0.9464 | -    | -      | -    | -    | -    |
| **Marin et al.**      | -    | -    | -    | 0.9528 | -    | -      | -    | -    | -    |
| **Fraz et al.**       | 0.7010 | 0.9770 | -  | 0.9493  | 0.9660  | -  | 0.8276 | -    | -    |
| **Li et al.**         | 0.7027 | 0.9828 | -   | 0.9545  | 0.9671  | -  | 0.8310 | -    | -    |
| **Liskowski et al.**  | -    | -    | -    | 0.9505  | 0.9595 | -      | -    | -    | -    |
| **Mo et al.**         | 0.7009 | 0.9843 | -   | 0.9570  | 0.9751  | -  | 0.8306 | -    | -    |
| **PixelBNN**          | 0.7842 ± 0.0255 | 0.9265 ± 0.0113 | 0.9070 ± 0.0181 | 0.8553 ± 0.0323 | 0.6383 ± 0.0942 | 0.8519 ± 0.0204 | 0.6465 ± 0.0303 |

## Table 7: Computation time for different networks using an NVIDIA Titan X.

| Method               | Description               | Training time (s/iteration) | Test time (s/image) |
|----------------------|---------------------------|-----------------------------|--------------------|
| Liskowski et al.     | Repurposed MNIST LeNet    | 0.96                        | 92                 |
| Mo et al.            | Pre-trained Multi-classifier | N/A                        | 0.4                |
| PixelBNN             | Proposed Method           | 0.52                        | 0.0466             |

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approximate training and test speeds. Training time was evaluated by normalizing the total time for training the network by the number of training iterations. The total number of iterations was not provided in the multi-classifier article. Test time is the duration required for evaluating one image at test time. The network evaluated test images in 0.0466s, 8.6× faster than the state-of-the-art.

5 Discussion

Herein, the baseline results for the first known application of PixelBNN, a variant of PixelCNN - a family of FCNs which has never before been applied to fundus images - was evaluated on the task of image segmentation against DRIVE, STARE and CHASE_DB1 retinal fundus image datasets. Different from the works in the literature, which use cropping and patch segmentation strategies, the proposed method instead resizes the fundus images, shrinking them to 256×256. This incurs a loss of information as many pixels and details are discarded in the process, proportionately reducing the feature space by which the model can learn this task. The decision to use this strategy was primarily driven by computational efficiency, as the methods are intended for use in real time within CAD systems. The cross-testing demonstrates the model’s ability to learn generalizable features from each dataset, making it a viable architecture for automated delineation of morphological features within CAD systems. The drop in model performances compared to the state-of-the-art is believed to be caused by the loss of information incurred during preprocessing and will be investigated in future work that also delves into an ablation study.

5.1 Conclusion

This paper proposed a method for segmenting retinal vessels using PixelBNN - a dense multi-stream FCN, using Adam optimization, batch normalization during downsampling and dropout regularization to generate a vessel segmentation mask by converting the feature space of retinal fundus images. F1-score, G-mean and MCC were used to measure network performance, rather than Acc, AUC and 𝜂. This novel architecture performed well, even after a severe loss of information, even outperforming state-of-the-art methods during cross-testing. This reduction in
information also allowed the system to perform $8.5 \times$ faster than the current state-of-the-art at test time, making it a viable candidate for application in real-world CAD systems.

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

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References

1. A. Hoover, V. Kouznetsova, and M. Goldbaum, “Locating blood vessels in retinal images by piecewise threshold probing of a matched filter response,” *IEEE Transactions on Medical Imaging* **19**, 203–210 (2000).

2. H. Jelinek and M. J. Cree, *Automated image detection of retinal pathology*, CRC Press (2009).

3. E. Ricci and R. Perfetti, “Retinal blood vessel segmentation using line operators and support vector classification,” *IEEE Transactions on Medical Imaging* **26**, 1357–1365 (2007).

4. M. J. Cree, “The Waikato Microaneurysm Detector,” *The University of Waikato, Tech. Rep* (2008).

5. M. Fraz, R. Welikala, A. Rudnicka, *et al.*, “Quartz: Quantitative analysis of retinal vessel topology and size – an automated system for quantification of retinal vessels morphology,” *Expert Systems with Applications* **42**(20), 7221 – 7234 (2015).

6. M. D. Abramoff, M. K. Garvin, and M. Sonka, “Retinal imaging and image analysis,” *IEEE Reviews in Biomedical Engineering* **3**, 169–208 (2010).

7. M. M. Fraz, P. Remagnino, A. Hoppe, *et al.*, “An ensemble classification-based approach applied to retinal blood vessel segmentation,” *IEEE Transactions on Biomedical Engineering* **59**, 2538–2548 (2012).

8. G. Azzopardi, N. Strisciuglio, M. Vento, *et al.*, “Trainable cosfire filters for vessel delineation with application to retinal images,” *Medical Image Analysis* **19**, 46–57 (2015).
9 M. Fraz, P. Remagnino, A. Hoppe, et al., “Blood vessel segmentation methodologies in retinal images – a survey,” *Computer Methods and Programs in Biomedicine* **108**(1), 407 – 433 (2012).

10 J. V. Soares, J. J. Leandro, R. M. Cesar, et al., “Retinal vessel segmentation using the 2-d gabor wavelet and supervised classification,” *IEEE Transactions on Medical Imaging* **25**, 1214–1222 (2006).

11 A. Almazroa, R. Burman, K. Raahemifar, et al., “Optic disc and optic cup segmentation methodologies for glaucoma image detection: A survey,” *Journal of Ophthalmology* **2015**, 180972 (2015).

12 C. A. Lupascu, D. Tegolo, and E. Trucco, “Fabc: Retinal vessel segmentation using adaboost,” *IEEE Transactions on Information Technology in Biomedicine* **14**, 1267–1274 (2010).

13 Y. Bengio, A. Courville, and P. Vincent, “Representation learning: A review and new perspectives,” *IEEE Transactions on Pattern Analysis and Machine Intelligence* **35**, 1798–1828 (2013).

14 G. E. Hinton, S. Osindero, and Y.-W. Teh, “A fast learning algorithm for deep belief nets,” *Neural Computation* **18**, 1527–1554 (2006).

15 Y. LeCun, Y. Bengio, and G. Hinton, “Deep learning,” *Nature* **521**, 436–444 (2015).

16 M. D. Abrámoff, Y. Lou, A. Erginay, et al., “Improved automated detection of diabetic retinopathy on a publicly available dataset through integration of deep learningdeep learning detection of diabetic retinopathy,” *Investigative Ophthalmology & Visual Science* **57**(13), 5200 (2016).

17 H. A. Leopold, J. Zelek, and V. Lakshminarayanan, “Deep learning for retinal analysis,” in *Biomedical Signal Processing in Big Data*, E. Sejdic and T. H. Falk, Eds., CRC Press (2017), In Press.
18 A. van den Oord, N. Kalchbrenner, L. Espeholt, et al., “Conditional image generation with pixelcnn decoders,” in Advances in Neural Information Processing Systems 29, D. D. Lee, M. Sugiyama, U. V. Luxburg, et al., Eds., 4790–4798, Curran Associates, Inc. (2016).

19 D. P. Kingma and J. Ba, “Adam: A method for stochastic optimization,” CoRR abs/1412.6980 (2014).

20 H. Leopold, J. Orchard, V. Lakshminarayanan, et al., “A deep learning network for segmenting retinal vessel morphology,” in 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 3144 (2016).

21 A. V. Oord, N. Kalchbrenner, and K. Kavukcuoglu, “Pixel recurrent neural networks,” in Proceedings of The 33rd International Conference on Machine Learning, M. F. Balcan and K. Q. Weinberger, Eds., Proceedings of Machine Learning Research 48, 1747–1756, PMLR, (New York, New York, USA) (2016).

22 T. Salimans, A. Karpathy, X. Chen, et al., “Pixelcnn++: A pixelcnn implementation with discretized logistic mixture likelihood and other modifications,” in Submitted to ICLR 2017, (2016).

23 S. Ioffe and C. Szegedy, “Batch normalization: Accelerating deep network training by reducing internal covariate shift,” in Proceedings of the 32nd International Conference on Machine Learning, F. Bach and D. Blei, Eds., Proceedings of Machine Learning Research 37, 448–456, PMLR, (Lille, France) (2015).

24 J. Staal, M. D. Abràmoff, M. Niemeijer, et al., “Ridge-based vessel segmentation in color images of the retina,” IEEE Transactions on Medical Imaging 23, 501–509 (2004).

25 A. D. Fleming, S. Philip, K. A. Goatman, et al., “Automated assessment of diabetic retinal image quality based on clarity and field definition,” Investigative Ophthalmology & Visual Science 47(3), 1120 (2006).

26 D. P. Kingma, T. Salimans, R. Jozefowicz, et al., “Improved variational inference with inverse autoregressive flow,” in Advances in Neural Information Processing Systems 29, D. D. Lee, M. Sugiyama, U. V. Luxburg, et al., Eds., 4743–4751, Curran Associates, Inc. (2016).
27 R. Szeliski, *Computer Vision: Algorithms and Applications*, Springer-Verlag New York, Inc., New York, NY, USA, 1st ed. (2010).

28 O. Ronneberger, P. Fischer, and T. Brox, “U-net: Convolutional networks for biomedical image segmentation,” in *Medical Image Computing and Computer-Assisted Intervention – MICCAI 2015: 18th International Conference, Munich, Germany, October 5-9, 2015, Proceedings, Part III*, N. Navab, J. Hornegger, W. M. Wells, *et al.*, Eds., 234–241, Springer International Publishing, (Cham) (2015).

29 J. Long, E. Shelhamer, and T. Darrell, “Fully convolutional networks for semantic segmentation,” in *The IEEE Conference on Computer Vision and Pattern Recognition (CVPR)*, (2015).

30 M. Drozdzal, E. Vorontsov, G. Chartrand, *et al.*, *The Importance of Skip Connections in Biomedical Image Segmentation*, 179–187. Springer International Publishing, Cham (2016).

31 H. Chen, X. Qi, J.-Z. Cheng, *et al.*, “Deep contextual networks for neuronal structure segmentation,” in *Proceedings of the Thirtieth AAAI Conference on Artificial Intelligence, AAAI’16*, 1167–1173, AAAI Press (2016).

32 K. He, X. Zhang, S. Ren, *et al.*, “Deep residual learning for image recognition,” in *The IEEE Conference on Computer Vision and Pattern Recognition (CVPR)*, (2016).

33 W. Shang, K. Sohn, D. Almeida, *et al.*, “Understanding and improving convolutional neural networks via concatenated rectified linear units,” in *Proceedings of The 33rd International Conference on Machine Learning*, M. F. Balcan and K. Q. Weinberger, Eds., *Proceedings of Machine Learning Research* 48, 2217–2225, PMLR, (New York, New York, USA) (2016).

34 N. Kalchbrenner, A. van den Oord, K. Simonyan, *et al.*, “Video pixel networks,” *CoRR abs/1610.00527* (2016).

35 C. Szegedy, S. Ioffe, V. Vanhoucke, *et al.*, “Inception-v4, inception-resnet and the impact of residual connections on learning,” in *ICLR 2016 Workshop*, (2016).

36 M. Abadi, A. Agarwal, P. Barham, *et al.*, “Tensorflow: Large-scale machine learning on heterogeneous distributed systems,” *CoRR abs/1603.04467* (2016).
37 J. Cohen, “A coefficient of agreement for nominal scales,” *Educational and Psychological Measurement* **20**(1), 37–46 (1960).

38 J. I. Orlando, E. Prokofyeva, and M. B. Blaschko, “A discriminatively trained fully connected conditional random field model for blood vessel segmentation in fundus images,” *IEEE Transactions on Biomedical Engineering* **64**, 16–27 (2017).

39 H. He and E. A. Garcia, “Learning from imbalanced data,” *IEEE Transactions on Knowledge and Data Engineering* **21**, 1263–1284 (2009).

40 X. Glorot, A. Bordes, and Y. Bengio, “Deep sparse rectifier neural networks,” in *Proceedings of the Fourteenth International Conference on Artificial Intelligence and Statistics*, G. Gordon, D. Dunson, and M. Dudík, Eds., *Proceedings of Machine Learning Research* **15**, 315–323, PMLR, (Fort Lauderdale, FL, USA) (2011).

41 N. Srivastava, G. Hinton, A. Krizhevsky, *et al.*, “Dropout: A simple way to prevent neural networks from overfitting,” *Journal of Machine Learning Research* **15**, 1929–1958 (2014).

42 B. S. Y. Lam, Y. Gao, and A. W. C. Liew, “General retinal vessel segmentation using regularization-based multiconcavity modeling,” *IEEE Transactions on Medical Imaging* **29**, 1369–1381 (2010).

43 G. Kovács and A. Hajdu, “A self-calibrating approach for the segmentation of retinal vessels by template matching and contour reconstruction,” *Medical Image Analysis* **29**(3), 24–46 (2016).

44 J. Zhang, B. Dashtbozorg, E. Bekkers, *et al.*, “Robust retinal vessel segmentation via locally adaptive derivative frames in orientation scores,” *IEEE Transactions on Medical Imaging* **35**, 2631–2644 (2016).

45 S. Roychowdhury, D. D. Koozekanani, and K. K. Parhi, “Iterative vessel segmentation of fundus images,” *IEEE Transactions on Biomedical Engineering* **62**, 1738–1749 (2015).

46 *Comparative study of retinal vessel segmentation methods on a new publicly available database*, **5370** (2004).
47 D. Marín, A. Aquino, M. E. Gegúndez-Arias, et al., “A new supervised method for blood vessel segmentation in retinal images by using gray-level and moment invariants-based features,” *IEEE transactions on medical imaging* **30**(1), 146–158 (2011).

48 M. M. Fraz, P. Remagnino, A. Hoppe, et al., *Retinal Vessel Extraction Using First-Order Derivative of Gaussian and Morphological Processing*, 410–420. Springer Berlin Heidelberg, Berlin, Heidelberg (2011).

49 M. M. Fraz, A. Basit, and S. A. Barman, “Application of morphological bit planes in retinal blood vessel extraction,” *Journal of Digital Imaging* **26**, 274–286 (2013).

50 R. Vega, G. Sanchez-Ante, L. E. Falcon-Morales, et al., “Retinal vessel extraction using lattice neural networks with dendritic processing,” *Computers in Biology and Medicine* **58**(Supplement C), 20 – 30 (2015).

51 Q. Li, B. Feng, L. Xie, et al., “A cross-modality learning approach for vessel segmentation in retinal images,” *IEEE Transactions on Medical Imaging* **35**, 109–118 (2016).

52 P. Liskowski and K. Krawiec, “Segmenting retinal blood vessels with deep neural networks,” *IEEE Transactions on Medical Imaging* **35**, 2369–2380 (2016).

53 H. A. Leopold, J. Orchard, J. Zelek, et al., “Segmentation and feature extraction of retinal vascular morphology,” *Proc. SPIE Medical Imaging* **10133** (2017).

54 H. A. Leopold, J. Orchard, J. Zelek, et al., “Use of gabor filters and deep networks in the segmentation of retinal vessel morphology,” *Proc. SPIE Biomedical Optics* **10068** (2017).

55 J. Mo and L. Zhang, “Multi-level deep supervised networks for retinal vessel segmentation,” *International Journal of Computer Assisted Radiology and Surgery* (2017).

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1 Sample set of the DRIVE dataset. (a): Fundus image. (b): First manual delineation, used as the ground truth. (c): Second manual delineation, referred to as the second human observer and used as the human performance benchmark.24
Processed image patches are passed through two convolution layers with different filters to create parallel input streams for the encoder. Downsampling occurs between each ResNet block in the encoder and upsampling in the decoder. The output is a vessel mask of equal size to the input.

Network predictions on the DRIVE dataset. The top row shows the image, segmentation masks and ground truth for the image that scored best when DRIVE was used to train and test the model; the bottom row shows the worst. For comparison, the cross-validation results from training the model with STARE and CHASE_DB1 are shown.

Network predictions on the STARE dataset. The top row shows the image, segmentation masks and ground truth for the image that scored best when STARE was used to train and test the model; the bottom row shows the worst. For comparison, the cross-validation results from training the model with DRIVE and CHASE_DB1 are shown.

Network predictions on the CHASE_DB1 dataset. The top row shows the image, segmentation masks and ground truth for the image that scored best when CHASE_DB1 was used to train and test the model; the bottom row shows the worst. For comparison, the cross-validation results from training the model with STARE and DRIVE are shown.

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