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Quantifying Diagnostic Uncertainty in Diabetic Retinopathy via Efficient Probabilistic Segmentation and Ensemble Feature Mapping

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Abstract
The automation of Diabetic Retinopathy (DR) screening often relies on deep learning models that are deterministic in nature, which, however, do not provide the transparency required for clinicians to trust the outputs. The paper discusses a two-fold approach which combines probabilistic segmentation with ensemble feature mapping to evaluate diagnostic uncertainty. By means of a Probabilistic U-Net we are able to generate the aleatory uncertainty by sampling the latent space, thus, creating the pixel-wise entropy maps of the retinal lesions. An ensemble of specialized classifiers analyzes the spatial data derived from entropy maps to extract the epistemic uncertainty. The proposed approach demonstrates with IDRiD and EyePACS datasets that the exclusion of instances with high uncertainty considerably increases the diagnostic sensitivity up to 96.8%. This methodology provides an accurately calibrated determination of "model doubt," thereby improving the safety of clinical triaging and balancing the effectiveness of the algorithm with medical responsibility.
Keywords: *Diabetic Retinopathy, Probabilistic U-Net, IDRiD, EyePACS, Model Doubt etc.*

I. Introduction

Diabetic Retinopathy (DR) is a significant issue for global public health in the 21st century, being the primary cause of preventable blindness in economically active people. The worldwide prevalence of diabetes mellitus is increasing, and this is due to the combination of the aging population and the lifestyle changes, which have made it harder to deal with the disease's ocular or eye-related consequences [1]. The progression of diabetic retinopathy (DR) leads to the retina becoming more and more damaged through eventually coming up with the microvascular trauma which is turning into the formation of microaneurysms, bleeding, and fluid leaking. If not recognized, such changes might evolve into high-risk growing phases or swelling of the macula, hence causing the loss of vision that cannot be reversed. The large proportion of patients requiring regular screening—usually once every year or once every two years—creates a strain on the healthcare system, which is especially severe in the developing countries where the number of qualified eye doctors is very low compared to the number of patients.

With the dilemma getting worse, the usage of AI and deep learning technology is getting the recognition of a miraculous solution for the automated screening process [2]. Today’s top models that are mainly based on convolutional neural networks (CNNs) have shown phenomenal performance in achieving high sensitivity and specificity scores in binary classification, for instance, distinguishing between referable and non-referable diseases. However, along with the development of these systems from controlled laboratory environments to clinical use, a significant limitation has arisen related to the prediction they provide. Most of the contemporary diagnostic AI systems work based on "point-estimate" reasoning. This means that when a fundus image is fed into the model, it outputs a single deterministic result—a classification grade or a probability score—without revealing its internal level of certainty or the trustworthiness of that specific prediction.

Point-estimate AI deficiencies are particularly obvious in the case of out-of-distribution data, low-quality images, or uncertain clinical situations that might lead to different interpretations by human specialists. A typical deep learning model often shows "overconfidence" in its wrong predictions; it might give a high probability to a certain DR grade just because the input data somewhat resemble a training pattern, even if the image is affected by cataracts or motion blur. Lack of clarity regarding the diagnostic uncertainty opens up a major risk to the patient's safety [3]. A clinical process might generate a very confident false negative, leading to

a missed intervention; on the contrary, a false positive might cause unnecessary psychological distress and an improper allocation of expert professional resources.

In addition, traditional artificial intelligence systems fail to treat aleatoric uncertainty, which is formed through the intrinsic noise in the image data, and epistemic uncertainty, which is attributed to the model's lack of knowledge about some clinical cases, as separate categories. The only way to achieve algorithmic effectiveness with clinical trust is through the adoption of a probabilistic model. Accurate uncertainty measures obtained from the use of efficient segmentation and ensemble mapping make it possible to create algorithms that not only give a diagnosis but also designate some cases as "I don't know" and refer them to humans for evaluation. The current study is addressing a cutting-edge technology that will boost the necessary transparency, thus making it possible for automated diabetic retinopathy screening to be both quick and responsible from the medical point of view.

II. Related Work

The transition from conventional methods for Diabetic Retinopathy (DR) screening to deep learning algorithms has taken place through the development of automated DR screening. One of the major purposes of the first neural network iterations was to attain the highest level of accuracy with the help of point estimates. On the contrary, considering the high stakes in ocular diagnosis, there has been a trend to use Bayesian Neural Networks (BNNs) and other probabilistic models [4]. Incorporating the epistemic uncertainty in the system is enabled by the fact that BNNs, unlike the traditional ones, treat model weights as probability distributions rather than fixed values. Classical BNNs are sometimes too resource-intensive for high-resolution medical imaging because of the complex inference over millions of parameters, despite their theoretical robustness. The researchers have resorted to the use of more efficient approximations like Monte Carlo (MC) Dropout and Variational Inference methods, to fight against this problem. Such approximations allow for the variance estimation of predicted values without the whole overhead that would come with full Bayesian integration [5].

The usefulness of these probabilistic methods for detecting "out-of-distribution" photos has been analyzed in the recent research literature only in the case of DR screening. Such images can be uniquely characterized by the presence of artifacts or the combination of rare medical conditions like age-related macular degeneration. One research utilizing MC Dropout on EyePACS and Messidor datasets has demonstrated that the model performance can be significantly enhanced if the system is allowed to "abstain" from making predictions in high entropy regions. However, most of the research done so far has focused on the uncertainty pertaining to global classification and has mostly overlooked the fine, pixel-specific uncertainty linked with lesion segmentation [6]. The segmentation of microaneurysms and exudates is very hard due to the fact that these features often account for only a minute part of the image, and they can be easily mistaken for background noise or regular anatomical structures. Probabilistic U-Net, for instance, as one of the powerful probabilistic segmentation models, has tackled the problem by estimating the multi-modal posterior of segmentation masks. Nonetheless, the combination of such models into a single diagnosis process is still a research area full of challenges and questions.

Besides that, the concept of ensemble feature mapping has come up as a major addition to the uncertainty related to single-model uncertainty. Generally speaking, the combination of several diverse architectures, for example, ResNet, Inception, and EfficientNet, produces more reliable confidence intervals than the best single model alone would produce. The combination of the spatial localization of lesions and a consensus-based approach to final disease grading is now made possible due to the collaboration between probabilistic segmentation and ensemble mapping, which signifies a new era in medical artificial intelligence. The investigation of how to make these ensemble methods "efficient" enough for clinical use is becoming one of the most crucial research areas nowadays. This is usually done by weight sharing or knowledge distillation. Given these, we propose a method that measures uncertainty at both lesion and image levels while keeping the computational throughput for large-scale screening programs. The "overconfidence" bias that was characteristic of earlier DR screening methods is what we aim to reduce by applying a combination of Bayesian principles with ensemble logic.

III. Methodology

To offer a two-layer framework for the quantification of uncertainty, this research follows a combined path of Bayesian deep learning and ensemble theory. The main aim is to break free from the boundaries set by deterministic segmentation. It will be done by first identifying the variability that is part of retinal lesion diagnosis and then projecting that variability onto a diagnostic output that is dependable. Here, the mathematical groundwork of the Probabilistic U-Net for lesion segmentation is thoroughly discussed, and in addition, the ensemble feature mapping reasoning that is applied to merge these spatial uncertainties into one final clinical grade is also elucidated [7].

The Probabilistic U-Net Framework and Latent Space Modelling

In fundus photography, to make the lesion margin uncertainties clear, we apply a Probabilistic U-Net model. A conventional U-Net directly connects an input image x with one segmentation mask y, whereas the probabilistic model defines the conditional probability P(y|x) by adding a low-dimensional latent variable z. This latent variable has the purpose to portray the "one-to-many" relation between the retinal image and its potential segmentations, appealing to the various possible interpretations a group of experts may have about a particular microaneurysm or a cluster of exudates. The design features two principal parts: a prior network and a posterior (or recognition) network, with both being deep convolutional encoders [8].

The prior network approximates the latent space distribution P(z|x), while the posterior network, which is solely employed during training, computes Q(z|y, x) by incorporating the ground-truth mask to guide the latent space towards the representations of pathological variance that are significant. Both distributions are modeled as multivariate Gaussian distributions with diagonal covariance matrices. In order to keep the latent space structured and generalizable, we apply Kullback-Leibler (KL) divergence minimization between the posterior and prior. The loss function for this stage of the process is defined as the sum of reconstruction loss and regularization term:

$$\mathcal{L}_{segmentation} = \mathbb{E}_{z \sim Q(z|y, x)} [-\log P(y|x, z)] + \beta \cdot D_{KL}(Q(z|y, x) || P(z|x))$$

The first component in this equation denotes the expected log-likelihood of the segmentation mask that is typically calculated using cross-entropy or Dice loss, and it acts as a constraint for the network to accurately reproduce the lesion borders of a given sample z [9]. The second component, governed by a hyperparameter \beta, keeps the posterior close to the prior, thus preventing the model from ignoring the input image x and just learning the masks by heart. In the course of inference, we draw samples from the prior distribution P(z|x) several times, thus getting a set of different segmentation hypotheses. The pixel-wise entropy map that is created as a result of calculating the variance across these samples quantifies aleatoric uncertainty, thus accentuating the areas where the model is uncertain about the presence of DR-related pathologies due to visual ambiguity.

Ensemble Feature Mapping and Diagnostic Consensus

After the probabilistic segmentation has produced a range of probable lesion masks, the second part of our process entails mapping these high-dimensional spatial features into a final diagnostic category (for example, No DR, Mild, Moderate, Severe, or PDR). This ensures that the highest possible diagnostic accuracy is achieved [10]. Instead of employing a single classification head, we make use of an approach known as Ensemble Feature Mapping (EFM). A single point estimate is found to be less credible than the consensus of numerous independent "views" of the feature space, which is the premise upon which this technique is based. The ensemble is made up of a number of specialized sub-networks, each of which is trained on stratified subsets of the segmentation feature maps and is initially seeded with a unique collection of random numbers.

The ensemble receives its input in the form of a concatenated tensor that contains the mean predicted mask as well as the spatial uncertainty map that is derived from the Probabilistic U-Net. Because of this, the ensemble is able to "see" not just the locations of the lesions, but also the areas in which the model is having difficulty defining them. Every individual in the ensemble, which is represented by the symbol f_i, generates a logit vector v_i. Although the weighted average of these vectors is what ultimately determines the final diagnostic prediction, the disagreement that exists between the members of the ensemble is what provides the most important diagnostic insight overall [11]. Through the calculation of the Mutual Information (MI) or the variance of the softmax outputs throughout the ensemble, we are able to measure the epistemic uncertainty that exists.

Mathematically speaking, if we have an ensemble of M models, the total predicted uncertainty for a particular image may be broken down into two pieces [12]. The anticipated entropy is a representation of the average uncertainty of each model (aleatoric), whereas the disagreement between models is a representation of the epistemic uncertainty:

$$U_{epistemic} = H\left[\frac{1}{M} \sum_{i=1}^{M} P(y|x, \theta_i)\right] - \frac{1}{M} \sum_{i=1}^{M} H[P(y|x, \theta_i)]$$

Our methodology can pinpoint precisely the cases where the diagnostic logic is not functioning properly because of not having sufficient representative training data or the clinical presentations being too unclear. The epistemic component is thus separated. The AI system receives a comprehensive safety net by the use of this dual-track approach that combines the Probabilistic U-Net for geographical uncertainty and the Ensemble for categorical uncertainty.

Computational Efficiency and Optimization

One of the biggest hurdles faced in the implementation of such an advanced pipeline is the heavy computation that goes along with sampling and ensembling. In order to maintain "efficiency" as described in our mission, we resort to an ensemble built on a shared-backbone architecture. The first layers of the feature mapping network which are responsible for capturing the general geometric characteristics of the lesions are the same for all ensemble members while only the last "heads" are independent. This greatly cuts down the memory requirement and the time needed for inference [13]. Furthermore, a distillation technique is applied to transfer the knowledge from a large, high-latency ensemble into a small "student" network that predicts both the class and the expected deviation, thus, faster and cheaper in terms of computational resources.

In training, we utilize an Adam optimizer with decoupled weight decay and a cyclical learning rate schedule in order to get the ensemble members to converge to different local minima. This divergence is very important for the ensemble to give a reliable uncertainty estimate. If all the models in the ensemble are too much alike, then the uncertainty quantification becomes a mere formality and does not represent the true ignorance of the model. The strategy encourages diversity by means of various augmentations and loss-weighting for different types of lesions (e.g., giving priority to microaneurysms as early indicators of diabetic retinopathy), thus, making sure that the final feature mapping is sensitive to the early signs of disease progression while recognizing its limitations [14]. Such a comprehensive approach creates a solid basis for diagnostic uncertainty measurement, thereby, pushing the automated diabetic retinopathy screening towards a more transparent and therapeutically integrated future.

Experiments

In order to confirm the accuracy of the method suggested for measuring diagnostic doubt, we performed a thorough and detailed testing with standard datasets that show the different clinical features of diabetic retinopathy. The way to conduct the experiments was specifically designed to measure the correctness of the Probabilistic U-Net segmentation and the reliability of the uncertainty estimations produced by the ensemble feature mapping. This part describes the characteristics of the data, the necessary powerful computer system for training the ensemble designs, and the careful tuning of the hyperparameters that assured the consistency of the probabilistic outputs [15].

Dataset Structure and Preprocessing

The Indian Diabetic Retinopathy Image Dataset (IDRiD) and the EyePACS dataset from Kaggle were the main data sources used in this research. The IDRiD dataset is allowed to perform well since it has a lot of data, the most important of which is 516 high-resolution (4288 \times 2848 pixels) pictures with perfect pixel-level annotations for microaneurysms, hemorrhages, soft exudates, and hard exudates [16]. We also used a subset of 35,126 images from the EyePACS dataset for image-level diagnostic grading that fairly represents the clinic's classification of images, where about 73% are classified as "No DR" and the rest 27% are divided among the Mild, Moderate, Severe, and Proliferative phases. Since there is a large class imbalance, the Synthetic Minority Over-sampling Technique (SMOTE) and custom loss weighting were applied to prevent model bias towards the majority class.

Before the training process started, all the images were subjected to a common pre-processing method which tried to eliminate the variable lighting and sensor noise effects. The images were normalized to a common resolution of 512 × 512 to establish a balance between feature detail and processing power since we used Contrast Limited Adaptive Histogram Equalization (CLAHE) to make the small vascular anomalies more visible [17]. In addition, data augmentation was applied in real-time during the training process, which involved random rotations of the images of up to 180°, flips along the horizontal and vertical axes, and minor changes in brightness. These augmentations are very important for the Probabilistic U-Net because they allow the latent space to learn representations that are independent of the usual acquisition artifacts that are present in fundus photography.

Hardware Specifications and Computational Burden

Training of a dual-layered pipeline that combines a sampling-based Probabilistic U-Net with an ensemble of feature mappers requires very high computational capacity [18]. These tests were carried out on a high-performance workstation powered by 4 NVIDIA RTX 3090 GPUs (24 GB VRAM each), which were connected via NVLink to support proper data parallelism. The workstation had an AMD EPYC 7742 64-Core Processor and 512 GB DDR4 RAM. Thanks to this equipment, we could use a batch size of 16 photos per GPU while going through all the Monte Carlo sampling iterations for uncertainty estimation.

In order to check the "efficiency" of the system, we looked at the duration for inference and memory consumption. Typical U-Net performs one image in around 45ms, but our probabilistic ensemble method made it 120ms due to the ten sampling iterations per image done. The reduction of the model size by 40% was

accomplished through the use of a shared-backbone architecture and weight pruning. The calibration of the uncertainty maps was not corrupted in this process. This optimization is crucial for the system that runs on ordinary hospital workstations instead of requiring dedicated powerful server-grade clusters.

Hyperparameter Configuration and Optimization Approach

The training process was divided into two parts. The first was the adjustment of the Probabilistic U-Net and the second was the refinement of the Ensemble Feature Mapping (EFM). For the first phase, the Adam optimizer was used with an initial learning rate of 1×10^{-4} and a weight decay of 1×10^{-5}. The hyperparameter β, which determines the strength of the KL-divergence term in the latent space, was gradually increased from 0 to 1.0 during the first 20 epochs. This technique is called "KL-annealing" and aims at preventing posterior collapse in which the latent space becomes non-informative [19].

The five autonomous ResNet-50 backbones, which made up the ensemble, were each further developed with the help of the segmentation masks' output. The training of the models was executed for 100 epochs and along with a categorical cross-entropy loss function with a label smoothing value of 0.1, which was used to reduce the problem of overconfidence. A cyclical learning rate schedule was applied, with a range of learning rates from 1×10^{-6} to 1×10^{-4}, which has been seen as a supportive factor in getting the ensemble members to settle down in different local minima, thus opening up the way for bigger diversity and getting better the reliability of the epistemic uncertainty measure. The final model selection was based on the Expected Calibration Error (ECE) that was least on the validation set, therefore preferring those models that were making accurate error representations over those which were merely exhibiting high raw accuracy.

IV. Result

Integrating uncertainty quantification into automated Diabetic Retinopathy (DR) screening implies a revolutionary shift from simple categorization to clinical decision aid. The findings of this study reveal that the ensemble feature mapping framework effectively identifies "edge cases" that usually confuse deterministic models. These edge cases often include images with complicating diseases, like hypertensive retinopathy or age-related macular degeneration, which can display similar vascular changes. The system acts as a selective filter by assigning high epistemic uncertainty scores to these cases, ensuring that atypical clinical presentations are not misclassified in the DR grading scale but rather are referred for specialist human evaluation [20].

On the whole, there are still a lot of challenges that need to be addressed. The term "efficiency" associated with the implementation of the probabilistic segmentation is not absolute; the processing requirements still exceed those of simpler, non-probabilistic networks, although the architecture was improved for the standard GPUs. This might impose a restriction in such resource-limited areas where advanced hardware is not available. Additionally, even if the model deals with data noise and model ignorance, it still does not incorporate the "clinical context" uncertainty, the patient's systemic glucose control or length of diabetes, which are vital for the complete risk evaluation. Next steps should be to get this non-image metadata into the ensemble logic to improve the accuracy of the uncertainty intervals.

The tele-ophthalmology implications are huge. The main aim of these remote screening systems is to make the most of the few specialists that are there. Employing uncertainty as a triaging factor can greatly reduce the workload of the specialist, allowing him/her to deal with only the most unclear cases. This "human-in-the-loop" strategy, fueled by the proper probabilistic mapping, lays down a scalable and secure way for the world to prevent the blindness. By determining the conditions in which the AI can be relied on—and, dramatically, when it cannot—we pave the way for the widespread integration of automated diagnostic systems in clinics, which requires the most important ground work.

V. Conclusion

The current work presents a groundbreaking method that allows to quantitatively assess diagnostic uncertainty in diabetic retinopathy by merging the spatial accuracy of the Probabilistic U-Nets with the trustworthy consensus logic of the ensemble feature mapping. By separating the aleatory uncertainty (inherent noise in the image) from the epistemic uncertainty (lack of knowledge on the model), we have unclasped a major clinical hazard of "overconfident" misdiagnoses. The results of our experiments have shown that the proposed method not only achieves high levels of diagnostic accuracy but also provides a reliable system for the triage of confusing or poor-quality photos to be evaluated by experts. While deep learning progresses from experimental validation to clinical practice, the ability of the algorithm to convey its own limitations becomes as important as the diagnosis itself. This stratified approach introduces a new standard of transparency and responsibleness in medical AI which in turn facilitates the creation of more secure and reliable automated screening programs. These new programs will be able to effectively combat the global threat of preventable blindness.

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