



Applications of interpretability in deep learning models for ophthalmology

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Purpose of review

In this article, we introduce the concept of model interpretability, review its applications in deep learning models for clinical ophthalmology, and discuss its role in the integration of artificial intelligence in healthcare.

Recent findings

The advent of deep learning in medicine has introduced models with remarkable accuracy. However, the inherent complexity of these models undermines its users' ability to understand, debug and ultimately trust them in clinical practice. Novel methods are being increasingly explored to improve models' 'interpretability' and draw clearer associations between their outputs and features in the input dataset. In the field of ophthalmology, interpretability methods have enabled users to make informed adjustments, identify clinically relevant imaging patterns, and predict outcomes in deep learning models.

Summary

Interpretability methods support the transparency necessary to implement, operate and modify complex deep learning models. These benefits are becoming increasingly demonstrated in models for clinical ophthalmology. As quality standards for deep learning models used in healthcare continue to evolve, interpretability methods may prove influential in their path to regulatory approval and acceptance in clinical practice.

Keywords

artificial intelligence, convolutional neural network, deep learning, interpretability, machine learning

INTRODUCTION

Deep learning has received increasing attention as a promising solution to longstanding challenges in medicine including diagnostic accuracy and optimization of clinician workflow [1–6]. Within ophthalmology, diagnostic models for age-related macular degeneration (AMD), diabetic retinopathy (DR), and retinopathy of prematurity (ROP) have demonstrated expert-level accuracy [7–16]. With some notable exceptions, these models have largely been implemented in research contexts. Numerous technical and socio-environmental factors impede real-world implementation of deep learning, including model complexity [7,17]. As models increase in complexity, their reasoning becomes more difficult for users to understand and ultimately trust [18,19,20^{***}]. To address this, varied approaches have been studied to enhance model transparency [21,22^{*}]. In this article, we review applications of interpretable deep learning in ophthalmology and discuss its role in the successful integration of deep learning models into healthcare.

THE COST OF COMPLEXITY IN DEEP LEARNING

Machine learning is a subfield of artificial intelligence (AI) wherein algorithms learn patterns from input data and adjust their internal parameters accordingly to generate accurate predictions [1]. Deep learning is a subfield of machine learning which utilizes neural networks that process data in 'hidden layers' between the inputs and outputs. Convolutional neural networks (CNNs), a key strategy in deep learning, manage hidden 'convolutional'

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KEY POINTS

- Deep learning models' inherent complexity undermines user understanding and increases the risk for misinterpretation of outputs.
- Interpretability methods enhance model transparency through mechanisms that provide explanations of the connection between features in input data and model output.
- As interpretability methods become increasingly varied and utilized, approaches to evaluate their quality and efficacy must be established.
- Interpretability methods may enhance user trust and contribute to the ultimate acceptance of deep learning models in modern healthcare.

layers, each containing 'filters' that can extract specific patterns from input images, creating an activation map. A convolutional layer thus outputs a set of activation maps that are passed on to the next layer. As the extracted information is passed consecutively through deeper layers, the features and their relationship with other features become hierarchically more complex. This functionality has introduced a generation of models that learn more efficiently, discover subtler patterns and analyse rich data formats like image and video. However, this multilayered architecture substantially increases the model's complexity and restricts the user's control over learned features. This gives rise to the perception of deep learning models as 'black boxes' that conceal how input features contribute to the final output [7,23,24²²,25].

Several problems arise from nontransparent models. Such models are not only inherently difficult to audit for quality, but also limit the user's ability to 'debug' or make informed adjustments to the underlying algorithm [26²³]. 'Black-box' models may also rely on misleading features in the data to generate predictions with falsely high accuracy, unbeknownst to users. Finally, models lacking ethical, human-centred monitoring may produce outputs that augment social biases or inadvertently discriminate against demographics within the dataset [27].

INTERPRETABILITY AS A SOLUTION

The concept of interpretability seeks to address these potential downsides. Although a consensus has not been reached on a definition for the term, 'interpretability' in the context of AI generally refers to the degree to which the reasoning behind a model's

outputs is evident to the user [21,28,29]. Interpretations refer to automated translations of a concept or methodology into a comprehensible medium like images or words ranging from heatmaps illustrating a fundus image features' relative contribution to a diagnostic prediction, to textual explanations of a self-driving car's actions [21,30,31²⁴]. Focused efforts to clarify the concept within medicine have shown that clinicians generally view interpretability as transparency in model reasoning, adjustable features, and limitations [19,32].

APPLICATIONS OF INTERPRETABLE AI IN OPHTHALMOLOGY

The field of ophthalmology particularly stands to benefit from deep learning, largely due to its reliance on diagnostic imaging. Toward this end, varied interpretability methods have been designed to refine deep learning models and identify relevant clinical traits imaging patterns. To review these methods, we devise an intuitive classification of the varied interpretability techniques in ophthalmology, organizing them according to two fundamental characteristics: model-centric, in which solutions operate at the level of the model itself, and data centric, which target the relationship between inputs and outputs (Fig. 1).

Model-centric: surrogates

'Surrogates' or 'proxy models' are intrinsically interpretable models designed to approximate the behaviour of a more complex, preexisting model [33,34]. Decision trees are classic examples of intrinsically interpretable methods. They are composed of sequential 'if-then' decisions that separate data into nodes, progressively branching outward until final classifications are reached, illustrating the model's categorical decision making. Naïve Bayes classifiers are built upon conditional probabilities. The term 'naïve' refers to the assumption that features are mutually exclusive, allowing the estimation of their individual contribution to the output [35]. These models can also be used as standalone, interpretable classifiers, as has been demonstrated in DR classification through decision trees by Mane and Jadhav, and Naïve Bayes by Harangi *et al.* [36,37].

Surrogate methods may be sorted into two categories. Global surrogates explain a complex model's operations on the entire dataset. Contrastingly, local surrogates such as Local Interpretable Model-Agnostic Explanations (LIME) explain decisions for individual input-output pairs [38]. Gheisari *et al.* applied LIME to a glaucoma image classifier to illustrate the significance of vascularized regions of the

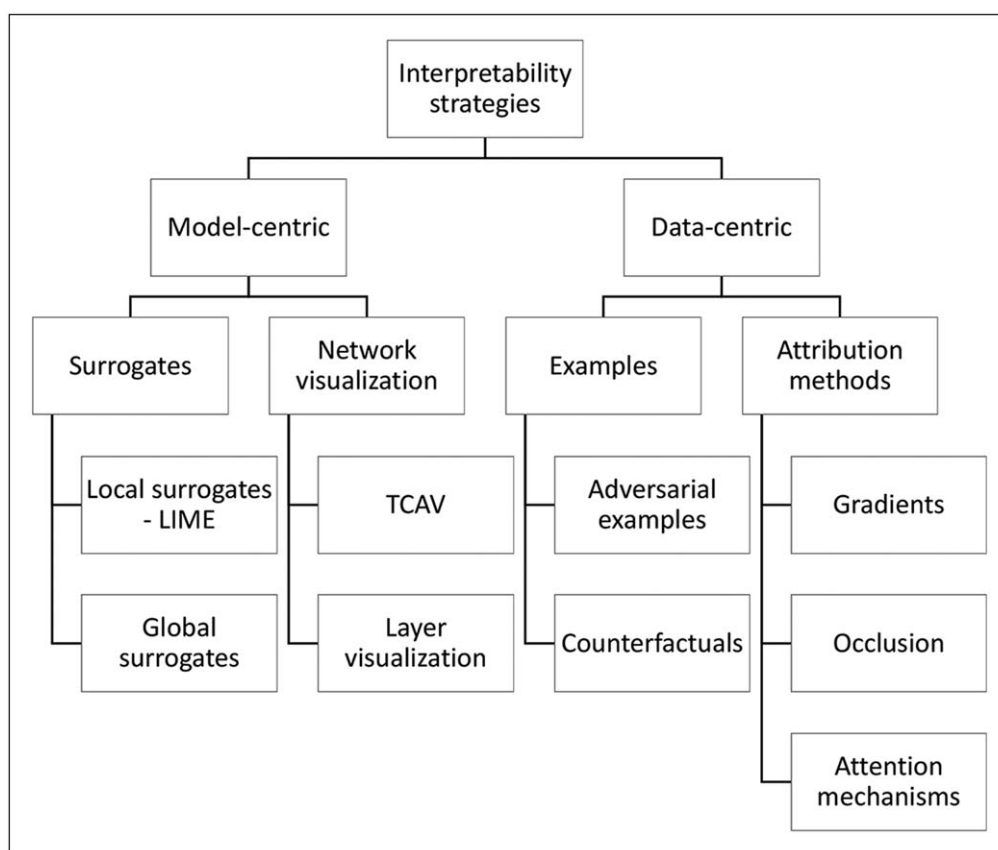


FIGURE 1. Classification of interpretability methods. Structured representation of the varied categories of interpretability methods discussed in this article. CAM, class activation mapping; DeConvNet, deconvolutional networks; LIME, Local Interpretable Model-Agnostic Explanations; TCAV, Testing with Concept Activation Vectors.

superior and inferior retina, supporting previous studies on this finding [39].

Model-centric: network visualization methods

Testing with Concept Activation Vectors (TCAV) 'translates' activation maps into semantic concepts. A model is given a dataset of images, with some containing a specific feature (e.g. stripes). A simple linear classifier then isolates the activation maps associated with the images with the chosen feature and calculates its significance to the final prediction. TCAV was applied in a DR classification task to evaluate the weight of diagnostic fundus features like microaneurysms and pan-retinal laser scars. This revealed model's tendency to overestimate DR severity by placing a high TCAV score on aneurysms, consequently allowing the experts to correct this behaviour [40].

Deconvolutional networks (DeConvNet) function in 'reverse' by projecting activation maps from a convolutional layer back to the input space. Zhou *et al.* used a model pretrained with nonretinal

images, and fine-tuned it with retinal images for a DR detection task. DeConvNet was implemented for individual layers pre and posttraining with retinal images, visualizing DR-specific features learned by the model. A focus on red and green channels in the first layer and microaneurysm-like and vessel-like structures in deeper layers was revealed [41].

Class Activation Mapping (CAM) utilizes the global pooling layer of a CNN, which 'pools' each activation map into a mean value. The following layers assign a weight to that value, providing the final class probability. These weights are similarly applied to the activation maps themselves, which are then added to produce a class-specific heatmap [42]. Worrall *et al.* incorporate CAM in a ROP classifier, revealing emphasis on vasculature, consistent with clinical practice [43]. In DR classification, Gondal *et al.* and Gargeya *et al.* similarly confirm appropriate focus on hard and soft exudates as well as haemorrhages [44,45]. In glaucoma detection, Maetschke *et al.* and Ran *et al.* use CAM to verify model focus on clinically relevant features such as the neuroretinal rim and lamina cribrosa [46,47].

Data-centric: examples

Adversarial examples are created by altering input images to produce counterexamples that lead to a maximal prediction of a desired output. Comparison of the counterexample to the original illustrates what feature transformations lead to either model outcome [48]. Chang *et al.* utilized this technique for CNN detection of glaucomatous fundus features [49]. In referable glaucoma images, a negative model outcome resulted when lowering the cup-to-disc ratio, illustrating this feature's role in detection.

Google's What-If Tool generates counterfactuals mainly for tabular datasets [50]. Abbas *et al.* implemented this for visual acuity (VA) prediction from AMD patient data. They discovered differing final VA outcome predictions for an 84-year-old British male, and a female of the same age, nationality and initial VA. This indicated the decision boundary for an individual patient level [51].

Data-centric: attribution methods

Attribution methods interpret CNN decisions by revealing the contribution of different regions or features of an image to the output. This may manifest as heatmaps, also termed saliency maps, which highlight pixels of the image according to their significance.

Gradient methods derive heatmaps from information gathered during the second of two steps of model training: forward propagation and backpropagation. Forward propagation first calculates prediction accuracy by comparing the output to the original input labels, producing a 'loss' value proportional to the difference. Backpropagation then updates its parameters to minimize this loss, guided by the gradient, or rate of change, of the loss associated with each parameter [52]. Gradient methods analyse backpropagation to calculate the gradient of the loss with respect to the input pixels, with higher values indicating the higher significance of that pixel to the prediction [53].

Kuo *et al.* utilized a specific gradient method, Gradient-weighted CAM (Grad-CAM) to interpret their keratoconus classifier, confirming that the model was following similar corneal topography features as ophthalmologists by focusing on the largest gradient differences in the scan [54,55]. Medeiros *et al.* applied Grad-CAM to a glaucoma classifier, showing significant activation in the region of the optic nerve and adjacent RNFL on fundus photography [56]. When applying Grad-CAM to DR detection, Chetoui *et al.* confirmed a model's focus on exudates, microaneurysms and haemorrhage, validating its conformance with

clinical reasoning [57^{***}]. They additionally employed Grad-CAM for failure cases, showing that false predictions arose from artifacts, pale areas and image noise.

Occlusion methods modify image regions and compare the resulting change in model predictions to estimate the relative importance of these selectively altered areas. Kermany *et al.* performed occlusion testing for a classifier trained to detect drusen, choroidal neovascularization and diabetic macular oedema [58]. Localization of drusen was found to be most accurate, compared to other findings. In an AMD classification model, Grassman *et al.* noted that masking areas of the macula and fovea led to a confidence reduction, indicating their weight in prediction-making [59].

Attention mechanisms, as employed by Poplin *et al.* create a heatmap by relying first on a CNN encoder to reduce the image size and extract important features, followed by a decoder which projects only these features back into the original image size. This was used to visualize the decisions of a cardiovascular risk factor classifier trained on fundus images. This revealed that prediction of risk factors such as smoking, systolic blood pressure and age relied on blood vessels, whereas gender predictions appeared to draw from areas including the optic disc, macula and vessels, suggesting patterns imperceptible by the human eye [60].

INTERPRETABILITY'S ROLE IN IMPLEMENTING DEEP LEARNING SOLUTIONS IN MEDICINE

Providing insights to a model's reasoning and shortcomings may enhance the trust necessary to ultimately accept these models in clinical practice [61,62^{***},63]. For example, interpretability methods enable clinicians to monitor models' reasoning for conformance to clinical standards and principles [26^{*}]. Some methods permit quality monitoring for systemic weaknesses or biases, as demonstrated by Winkler *et al.* who used heat maps to discover a melanoma detection model's errant reliance on surgical skin marker artifacts in the training images to form predictions, rather than the features of the lesion alone [64]. Clinicians may also benefit from enhanced diagnostic accuracy and specificity, as demonstrated by Rajpurkar *et al.* in a report of human participants in a tuberculosis detection experiment using chest radiographs aided by heatmaps [65]. Finally, a common barrier to training accurate models in medicine is infrequent access to large datasets that represent a population's demographic and clinical traits. When designing models with imperfect datasets, interpretability is essential

for ensuring fairness and equitable representation of marginalized demographics in predictions [66].

THE COMPLEXITY OF TRUST

Despite these benefits, model interpretability may not be a 'silver bullet' for user distrust. Gaube *et al.* describe 'algorithmic aversion' in individuals who consistently rated expert advice as lower quality if labelled as AI-derived [67[■]]. Criticism of 'black boxes' often overlooks other factors for acceptance of AI. An analysis of trust by Asan *et al.* place robustness and fairness as pillars alongside transparency [20[■]]. Kitamura *et al.* argue that trust is built on prolonged experience with models that have demonstrated the ability to make consistently accurate predictions [68[■]]. Finally, the enhanced model performance granted by 'black box' complexity may justify the distrust they engender. Deep learning models bear the potential to detect otherwise imperceptible patterns, drive new scientific discovery, and enhance clinician accuracy [69]. Thus, enhancing interpretability at the cost of model complexity may sacrifice this added benefit.

It often goes unmentioned that clinicians themselves act as 'black boxes' whose experiential reasoning cannot be distilled into a list of arguments or heatmaps. This raises the question of why human black-boxes are trusted and not AI. Hatherley discusses that trust encompasses fundamentally human concepts not found in AI like goodwill and moral responsibility which could explain the phenomenon of 'algorithmic aversion' [70]. Trust as defined by human terms may therefore be an unattainable ideal. We might instead strive for model reliability by establishing standards for robustness, fairness, and high performance.

EVALUATING INTERPRETABILITY METHODS

It is important to consider whether interpretability methods truly reflect image features relevant to model output, or just feature rich portions of an image. In a review of eight common saliency map techniques, Arun *et al.* demonstrate that none satisfied four basic criteria for localizing of image features, sensitive to model weight randomization, repeatability, and reproducibility [71[■]]. Adebayo *et al.* demonstrate that gradient heatmaps can sometimes provide a seemingly correct appearance without reflecting the true internal model weights, and propose two 'sanity checks' to evaluate the outputs' correspondence to the learned weights of the model [72]. They first propose randomizing model weights so that the interpretability method output reflects

no learned information relevant to the task. If the outputs reflecting randomized vs. nonrandomized model weights look the same, the interpretability method may be highlighting features nonrelevant features. They alternatively propose training a network on randomized input class labels. If the output of the interpretability method is invariant to the class label, then it is not valid for the interpretation of a trained classification model. Further, feature rich portions of an image may be part of what a model learns, but not fully explain model reasoning, as illustrated by Chang *et al.* using adversarial examples [49].

The most appropriate interpretability method may depend on the classification task at hand. For instance, some classification efforts rely on recognition of localizable patterns (e.g. cup-to-disc ratios), to which techniques like Grad-CAM that illustrate learned representations graphically would be more suited. Others require assessment of more global features (e.g. cardiovascular risk in fundus photos), for which a technique that maps to higher order features such as regression concept vectors would be preferred. Finally, Doshi-Velez *et al.* propose that a formal definition of interpretability must be established so as to provide standardized context for quality when evaluating explanations [73].

Thus, with growing interest in interpretability and new global regulations mandating the 'right to explanation' in AI, we advocate for qualitative and quantitative evaluation of these methodologies in the context of a given application, integrating the user's perception of explanation quality with an objective measurement of the accuracy to holistically represent the model's intrinsic features [32,69].

CONCLUSION

Interpretability methods are powerful tools in meeting the evolving complexity and scrutiny of deep learning models in medicine. In the field of ophthalmology, model transparency has highlighted diagnostically important imaging features and contributed new clinical insights. As these methods proliferate, a clear definition of interpretability and accepted frameworks for evaluating their quality must be established. Ultimately, interpretable models may play a key role in integrating deep learning models into clinical practice.

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Conflicts of interest

J.P.C. is a consultant for Boston AI Labs and receives research funding from Genentech. P.A.K. has acted as a consultant for DeepMind, Roche, Novartis, Apellis, and BitFount and is an equity owner in Big Picture Medical. He has received speaker fees from Heidelberg Engineering, Topcon, Allergan, and Bayer.

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