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Use of supervised machine learning algorithm in Diabetic retinopathy classification

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Abstract

Artificial intelligence provides unparalleled analytic accuracy, transmission capacity, risk stratification, and workflow optimization. Diabetic retinopathy is an important cause of preventable blindness worldwide, and artificial intelligence technology provides precocious diagnosis, monitoring, and guide treatment. High-quality exams are fundamental in supervised artificial intelligence algorithms.

In this article, ETDRS, NHS, ICDR, SDGS diabetic retinopathy grading, and manual annotation are described and compared in publicly available datasets. The various DR labeling systems generate a fundamental problem for AI datasets.

Keywords: Diabetic retinopathy classifications, Artificial intelligence, Datasets

Background

Computers executing automated functions were firstdescribed in 1950, with the first publication in 1943. Since then, Artificial Intelligence capacity has evolved into deep learning and neural networks, technologies that could simulate interconnected neurons and provideoutputs after multiple information layers [1, 2].

Automated technology provides unprecedented diag- nostic accuracy, screening capacity, risk stratification, and workflow optimization with accuracy equivalent to healthcare professionals [3] and more cost-effective dis- eases screening [4].

In Machine Learning, supervised learning is the most applied method in disease screening and classificationalgorithms, corroborating the importance of data labe- ling quality [5, 6].

Diabetic retinopathy (DR) is the leading cause of pre- ventable blindness in working-age adults worldwide[7, 8], responsible for more than 24,000 annual cases of blindness [9] and the main focus in Ophthalmological AI screening algorithms [10]. There is an increased blind- ness risk in patients with chronic diabetes mellitus, espe- cially those with poor clinical control [11].

Telemedicine and automated screening programs could diagnose, monitor, and guide treatment. Precocious diag- nosis and therapy could avoid severe vision loss in 90%of cases, but only 60% of diabetic patients have recom- mended yearly examinations [12].

There are many Diabetic Retinopathy classifications applied in distinct countries and screening programs, with the International Council of Ophthalmology Dia- betic Retinopathy (ICDR) classification as the most applied in open-access ophthalmological datasets [13].

High-quality retinal exams are fundamental in thedevelopment of AI algorithms, but also standards in labe- ling protocols, classifications, and quality control. This article describes and compares the most commonly dia-betic retinopathy classifications, referencing criteria, and their applications in datasets.

Main text

This study compared the most often-applied DR clas- sification scales: Scottish Diabetic Retinopathy Grading [14], Early Treatment Diabetic Retinopathy Grading [15], International Clinic Diabetic Retinopathy [16], National Health Service Diabetic Retinopathy Classification grad- ing [17], Modified Davis Retinopathy staging [18], and direct findings

identification.

The Early Treatment Diabetic Retinopathy Study

At an international consortium of ophthalmologists at Airlie House in 1968, internists and neurosurgeons standardized a diabetic retinopathy classification applied in the landmark Early Treatment Diabetic Retinopathy Study [15], designed to generate a more precise stagingfor DR and macular edema. The study screened for the presence of microaneurysms (MA), retinal hemorrhages, cotton-wool spots, intraretinal microvascular abnormali-ties (IRMA), venous beading, and neovessels in 35-mmphotographs. The consortium provided standard photos of microaneurysms, hemorrhages, and neovessels.

The ETDRS defined microaneurysms as red spots of less than 125 microns in its longest dimension with well-delimited margins and defined hemorrhage as a red spotwith irregular margins with more than 125 microns. Punctate lesions, blots, linear hemorrhages, and microa-neurysms were classified as red spots when they were not distinguished in ETDRS charts [19].

ETDRS defined clinically significant macular edemaas retinal edema seen in retinal stereo photographs at or within 500 microns of the center of the macula or hard exudates at or within 500 microns of the foveal centerand retina thickening or retinal thickening larger than one disc diameter area within one disc diameter of the center of the macula. In 2006, Rudnisky compared modi- fied ETDRS protocols with one or two fields and 16:1 JPEG images and showed good reproducibility compared to standard ETDRS stereoscopic photos [20]. (Table 1).

National Health Service diabetic retinopathy classification The National Health Service (NHS) was a diabetic retin-opathy classification system applied In England, Scot-land, Wales, and Northern Ireland between 2002 and2007. It applied an ETDRS modified diabetic retinopathyscale classified in four severity stages [17, 21]. This pro-gram evaluated and classified DR using macula-centeredand optic disc-centered images [22]. The NHS screening program provided guidelines for grading and lesions clas- sifications [23].

This DR classification considered macular exudates sign of macular edema because the images were non-ste-reoscopic; it also added a photocoagulation classification (Table 1).

International Clinic Diabetic Retinopathy

The International Clinic Diabetic Retinopathy (ICDR) classification was published in 2003 after a consensus of 31 retina specialists, endocrinologists, and epidemiolo-gists from 16 countries and sponsored by the American Academy of Ophthalmology [16]. The ICDR classified DRon a five-stage severity scale and classified diabetic macu-lar edema as apparently absent or present. The classifi- cation was created to simplify the ETDR and Wisconsin Epidemiologic Study scale and make it more applicable indaily practice studies [16].

ICDR is applied in the EYEPACS dataset [24], Asian Pacific Tele-Ophthalmology Society dataset [25], Indian Diabetic Retinopathy Image Dataset [26], Messidor 1 and 2 datasets [27] (Table 1).

The Scottish Diabetic Retinopathy Grading Scheme, 2004 In 2003, the National Scotland Eye Screening for Dia-betic Retinopathy Program was created [28]. This grad-ing system classified DR in all patients aged 12 years andolder. Retinal digital photos were analyzed, and the re-screening period or ophthalmologist referral was estab-lished. The Scottish diabetic retinopathy grade (SDRG)is divided into four DR severities in a single fovea-cen-tered image with at least two disc diameters temporalto the fovea and one disc diameter nasal to the disc [14](Table 1).

Modified Davis retinopathy staging

The ICDR score simplifies DR in three stages: simple diabetic retinopathy, pre-proliferative retinopathy, and proliferative retinopathy using 45-degree photographsof the posterior pole applied in the Jichi DR dataset [18] (Table 1).

Direct findings identification

In AI datasets, findings such as microaneurysms, hemor- rhages, hard exudates, and retinal detachment could be identified through direct identification. Applications such as SuperAnnotate [29], VGG Image annotation Tool [30], Supervise.ly [31], Labelbox [32], and Visual Object Tag- ging Tool [33] are available as labeling tools.

In ODIR [34], DIARETDB 0 and 1 [35], DR 1 and 2 [36], E-Ophtha [37], and HEI-MED [38], retinal findingsare manually annotated (Fig. 1).

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Table 1 Comparison of ETDRS, NHS, ICDR, SDRGS, Modified Davis diabetic retinopathy scales

		ETDRS	NHS	ICDR	Scottish Diabetic Retinopathy Grading Scheme	Modified Davis
Diabetic Retinopathy	Non proliferative DR	Grade 0 - No red dot	R0 - One or more isolated Cotton Wool Spots in the absence of microaneurysms or hemorrhage	No disease	No disease	No disease
		Grade 1 - Questionable red dots	R1 - Any number of Cotton Wool Spots and other non-referable features (IRMA, venous beading) Venous loops	Mild NPDR - microaneurysms only	Mild Background - At least one microaneurysm, flame exudate, blot hemorrhages with or without HE	Simple DR - microaneurysm, retinal hemorrhage, hard exudate, retinal edema, and more than three small soft exudates
		Grade 2 - Definitive red dots less than photograph 1				
		Grade 3 - Definitive red dots greater than photograph 1 and less than photograph 2A		Moderate NPDR - More than just microaneurysm and less than severe NPDR	Moderate background - more than 4 blot hemorrhages in one hemifield	
		Grade 4 - Definitive red dots greater than photograph 2A and less than photograph 2B				
		Grade 5 - Definitive red dots greater than 2B	R2 - Preproliferative Venous beading Venous reduplication Multiple blot hemorrhages Intraretinal microvascular abnormality	Severe NPDR - More than 20 intraretinal hemorrhages in each of 4 quadrants or Venous Beading in 2+ quadrants or Prominent IRMA in 1+ quadrant	Severe non-proliferative or pre proliferative DR - >4 blot hemorrhage in both hemifields, intraretinal microvascular anomalies, venous beading	Pre Proliferative DR - soft exudate, varicose veins, intraretinal microvascular abnormality, and non-perfusion area over on disc area
	Proliferative DR	Early PDR - Neovessels and less than high-risk proliferative DR	R3 A - Proliferative - active Newly present proliferative retinopathy New findings indicating reactivation of proliferation	PDR - Neovascularization or Vitreous and or pre-retinal hemorrhage	Proliferative retinopathy - NVD, NVE, vitreous hemorrhage, retinal detachment	Proliferative DR - neovascularization, pre retinal hemorrhage, vitreous hemorrhage, fibrovascular proliferative membrane, and tractional retinal detachment
		High-risk PDR- disc neovessels greater than photograph 10A or disc neovessels and vitreous hemorrhage / pre retinal hemorrhage or neovessels elsewhere with more than 1/2 disc area with vitreous hemorrhage / pre retinal hemorrhage	R3 B - Proliferative - stable Evidence of peripheral retinal laser treatment and stable retina			
Macular edema		Edema at or within 500 micra of the center of the macula or hard exudates at or within 500 micra of the foveal center and retina thickening or retinal thickening larger than one disc diameter area within one disc diameter of the center of the macula	Presence of exudates greater or equal to half-disc area in the macular region.	Exudates or apparent thickening within one disc diameter from the fovea	M1 - Hard exudates within 1-2 DD of the fovea	
					M2 - blot hemorrhage or hard exudates within 1 DD of the fovea	

Immediate referable classifications are in grey color, when available criteria

Referencing criteria comparison

The NHS, ICDR, and SDRGS establish referencing criteria. In NHS and SDRGS, the criteria are similar, with multiple retinal hemorrhages, intraretinal microvascular anomalies, or venous beading. In the ICDR, should be referenced patients with more than just microaneurysm, a criterion with greater sensitivity [14, 16, 17].

Considering macular edema, the NHS, SDRGS, and ICDR recommend referencing patients with exudates or apparent thickening in the macular area. The NHS recommends exudates distance within half-disc diameter from the fovea and ICDR and SDRGS within one disc diameter [14, 16, 17] (Table 1).

Conclusions

Artificial intelligence and automated technology were first reported more than 70 years ago and nowadays pro- vide unprecedented diagnostic accuracy, screening, risk stratification, and workflow optimization [3].

Reliable datasets are fundamental in supervised Machine Learning development; however, labeling process standardization, quality control, and homogenization remain challenging [39].

In diabetic retinopathy, there are distinct DR classifications, with different numbers of DR gradings and methods such as the Scottish Diabetic Retinopathy Grading [14], Early Treatment Diabetic Retinopathy Grading [15], ICDR [16], NHS Diabetic Retinopathy Classification grading [17], and Modified Davis Retinopathy staging [18] that are described in this review. Still, direct retinal findings annotation is valuable in neural networks training.

The Scottish Diabetic Retinopathy Grading is a valuable classification through retinal photographs due to a single macular centered retinal evaluation and is more sensi-tive for grading moderate and severe cases than ICDR classification.

When choosing the classification method applied in the dataset, the image field of view and the number of images must be considered. Classical ETDRS and ICDR classifications tend to underestimate DR classification in retinal photographic images due to limited image view areas compared to retinal fundus examinations.

The various DR labeling systems generate a fundamental problem for AI datasets, and it is fundamentable to standardize DR grading in datasets to develop algorithms and ensure proper patient referral. Reliable labeling methods also need to be considered in datasets with

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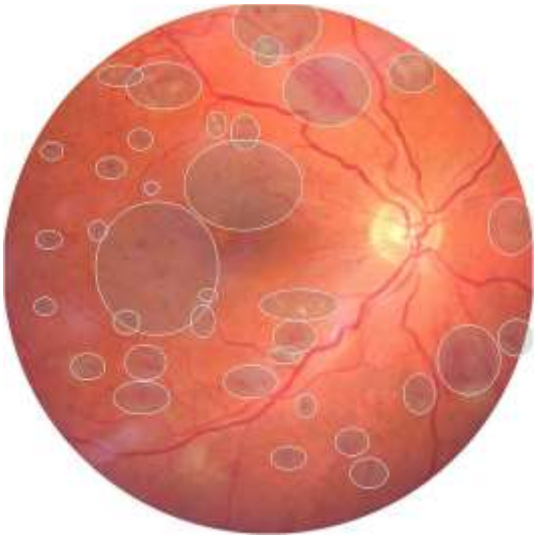

Fig. 1 Direct retinal findings manual annotation example, inLabelbox software

Abbreviations
ETDRS: Early Treatment Diabetic Retinopathy Grading; NHS: National HealthService Diabetic Retinopathy Classification grading; ICDR: International Council of Ophthalmology Diabetic Retinopathy; SDRGS: Scottish DiabeticRetinopathy Grading; AI: Artificial intelligence.

Competing interests
The authors declare that they have no competing interests.

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