UniCas for Medicine and Healthcare

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Abstract

With over twenty years of experience, our research group, affiliated with the Artificial Intelligence and Data Analysis Laboratory (AIDA), which belongs to the University of Cassino and Southern Lazio (UniCas), has been deeply engaged in artificial intelligence. The specific focus on Machine Learning, Pattern Recognition, and Deep Learning has evolved theoretically, with the development of specialized skills in model optimization, and practically, through application to real-world problems, particularly in the healthcare domain. In particular, attention is paid to designing and implementing Computer-Aided Diagnosis systems to support the prevention, diagnosis, and monitoring of Neurodegenerative diseases, Specific Learning Disorders, breast cancer, diabetic retinopathy, and movement-related disorders. Different data is utilized to reach the objectives of the AIDA Lab, and many approaches are implemented. Handwriting analysis is exploited to support the diagnosis of neurodegenerative diseases and specific learning disorders and to monitor them over time. Handwriting analysis encompasses two distinct approaches: examining dynamic features and scrutinizing handwriting sample images. This comprehensive approach allows a more thorough understanding of the individual's writing characteristics. Additionally, in Neurodegenerative Diseases, advancements include the utilization of 3D image analysis of MRI scans to aid in the detection of Alzheimer's disease, further enhancing diagnostic capabilities in this field. Mammograms are used for breast cancer prevention and diagnosis, while retinal images are used for diabetic retinopathy detection, particularly focusing on detecting small lesions. Detecting small lesions is a crucial step in diagnosis, as is identifying microcalcifications in digital mammograms and microaneurysms in digital fundus images. To address this challenge, we propose a novel architecture called GravityNet. Another field of study in the research conducted by the AIDA Lab is movement analysis, focusing on gait analysis, enabling precise evaluations in real-world settings and potential applications in Parkinson's disease assessment. To this end, Machine and advanced Deep Learning techniques are employed, such as deep cascades of boosting classifiers and Deep Convolutional and Attentional Neural Networks.

Keywords

Neurodegenerative Diseases, Handwriting, 3D Image Analysis, Breast Cancer, Small Lesion, Movement Analysis, Retinopathy

1. Neurodegenerative Diseases and Brain Disorders

The prevalence of neurodegenerative diseases (NDs) has been steadily increasing in recent years, underscoring a concerning trend. Another aspect underscoring the importance of research in this field is that NDs currently lack a cure. They can cause cognitive impairments manifesting as difficulties in memory, language, thinking, judgment, and motor skills. Individuals exhibiting a combination of these symptoms face a significantly heightened risk of developing dementia and, in more severe cases, Alzheimer's Disease (AD) or Parkinson's Disease (PD). Given the progressive nature of these conditions, early detection becomes crucial to initiate therapies to mitigate their effects.

Concerning other brain-related disorders, the prevalence of specific learning disorders (SLD) presents a significant and persistent challenge in educational and developmental psychology. These disorders encompass a range of

Ital-IA 2024: 4th National Conference on Artificial Intelligence, organized by CINI, May 29-30, 2024, Naples, Italy
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conditions affecting an individual's ability to acquire and apply foundational academic skills, such as reading, writing, and mathematics, despite adequate intelligence and opportunities for learning. Unlike NDs, which primarily affect cognitive functioning in adulthood, specific learning disorders often manifest during childhood and can persist into adolescence and adulthood if left untreated. Given the chronic nature of specific learning disorders and their potential to impact multiple domains of functioning, early identification and intervention are paramount.

1.1. Handwriting

Handwriting analysis has emerged as a valuable tool in the early detection of NDs like AD. This method's significance lies in its ability to provide insights into various cognitive, memory, and motor functions integral to writing. The complexity of writing, which encompasses language proficiency, executive skills, and attention span, can reveal changes in linguistic complexity, word choice, and syntactic structures. Such alterations are pivotal for early AD diagnosis as they reflect the underlying cognitive changes. Additionally, the link between writing and memory offers a window into the patient's ability to associate names with concepts, identify temporal relationships, and recall previously seen words, highlighting declines in episodic memory. Moreover, the analysis of fine motor control through handwriting, such as changes in pressure, speed, and stroke patterns, can indicate early declines in motor functions. These aspects of handwriting analysis serve as critical markers for the early identification and intervention of AD, aiming to delay its progression and improve patient outcomes.

1.1.1. Task Images Analysis

In the context of AD, alterations in handwriting are often observable due to the cognitive and motor changes associated with the condition. In the 2000s, researchers began to recognize the potential of handwriting analysis as a non-invasive and accessible tool for early detection. In 2018, researchers from the AIDA LAb started a meticulous data acquisition campaign by administering an experimental protocol [1] of 25 handwriting tasks. The research included a total of 174 participants, with 89 patients diagnosed with AD and 85 healthy control subjects. Each participant was invited to perform the experimental protocol by using the WACOM Bamboo Folio graphic tablet, enabling participants to write on standard A4 white paper sheets using a pen that appears typical. This pen not only produced ink traces on the sheet but also generated digital information recorded by the tablet in the form of spatial coordinates and pressure for each point (x, y, and z). The tablet additionally captured in-air movements up to a maximum height of $3cm$ from its surface. After the acquisition step, many images of the handwritten traces were collected or generated. Paper sheets were scanned to generate the offline image dataset [2], while the raw data, expressed as coordinates, were used to generate synthetic images by interpolating consecutive points. In this way, we generated the binary dataset [3] and the RGB one [4], which encoded dynamic information in the three color channels. Figure 1 illustrates the various images examined and produced within this research path. In particular, they refer to the Clock Drawing Test.

Figure 1: Samples of different kinds of Handwriting images acquired and generated, specifically focusing on the Clock Drawing Test.

These datasets were used to feed a system that exploited the ability of Convolutional Neural Networks (CNNs) to extract features automatically. Various experiments were conducted using different task configurations and datasets. Despite deploying numerous experimental settings, they all shared a common baseline architecture, facilitating comparative analysis and yielding insightful results. The baseline experimental architecture comprises four key steps: data acquisition, feature extraction/engineering, Machine Learning (ML) and Deep Learning (DL) classification, and combining rule application. The outcomes of this research revealed interesting trends. Across various tasks, CNN-extracted deep features consistently outperformed other approaches, emphasizing the advantage of DL. Experimentation with offline images suggests their potential in diagnosing NDs, underscoring the importance of considering shape details in distinguishing patients from healthy individuals, especially in medical applications where sensitivity is crucial. Finally, this research highlighted that some handwriting tasks were more significant in supporting AD diagnosis, and combining them improved the final prediction.

1.1.2. Dynamic Analysis

Our research also focused on handwriting analysis by capturing raw data through digital devices, which track intricate handwriting details like pressure, tilt, and motion. This data was meticulously organized and analyzed to extract critical dynamic and static features, such as velocity, acceleration, and stroke pressure, providing a rich dataset for examination. Before the ML algorithms, we conducted thorough preprocessing to normalize and clean the data, followed by feature selection processes

[5] to highlight the most indicative characteristics of the handwriting. This preparation phase also included hyperparameter tuning to refine our ML models for optimal performance. Our methodology incorporated two distinct ML approaches: a Statistical Approach, analyzing overall handwriting patterns to detect deviations indicative of diseases, and a Stroke Approach, focusing on the detailed analysis of individual handwriting strokes. This dual perspective enabled us to capture both the broad characteristics and the fine-grained patterns in handwriting that may signal the early stages of conditions like Alzheimer's disease. By leveraging digital technology for data acquisition and applying a nuanced ML analysis, our study aims to enhance the early diagnosis and understanding of NDs, offering the potential for timely intervention and improved patient outcomes.

1.2. Specific Learning Disorder

Handwriting and drawing are essential for preschool and school-age children's cognitive and motor development. Studies indicate that a significant portion of the school day, ranging from 30-60%, is dedicated to fine motor activities, primarily handwriting. Graphomotor tasks, crucial for academic success and personal expression, account for about 40% of a primary school student's activities. In this age group, 20% of children are at risk of experiencing graphomotor difficulties, with 27% displaying subpar graphomotor abilities. It is essential to note the role of *Specific Learning Disorders* (SLDs), such as dysgraphia, which are closely associated with graphomotor challenges. Early detection and intervention are crucial in addressing these disorders. Our research aims to develop innovative ML solutions that promptly identify and address handwriting issues early in a child's academic journey. Timely intervention is crucial, as the window for effective rehabilitation narrows over time. ML is essential for identifying subtle yet vital changes in the graphomotor cycle that experienced specialists may miss. The study started with creating an experimental protocol to reveal the fundamental features of handwriting. The handwriting was digitized using graphic tablets, generating a comprehensive dataset for training ML models to accurately differentiate between various learning impairments. The investigation will be longitudinal, spanning four years of data collection. This will increase the depth of the dataset and allow for a detailed exploration of the evolution of graphomotor skills and associated challenges. The monitoring will enable the study to identify graphomotor problem trends and indicators, enhancing ML algorithms' capacity to classify handwriting issues and lead to accurate early interventions.

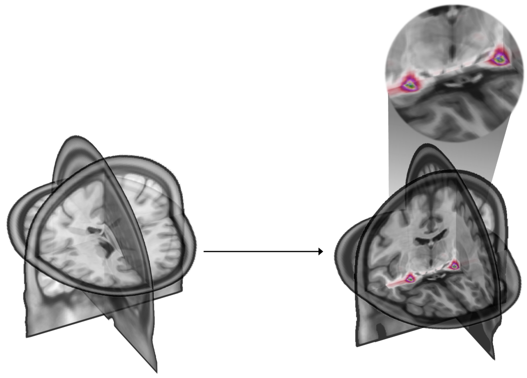

Figure 2: From a 3D MRI image, the network can highlight the AD-related brain regions.

1.3. 3D Images Analysis

3D imaging is a widely used technique in diagnostic procedures for brain disorders. Magnetic resonance imaging (MRI) provides a non-invasive means to observe and analyze in vivo pathological changes in the brain related to Brain Disorders, facilitating the study of disease evolution. MRI analysis is significant in AD diagnosis since it is identified by structural and functional changes in dynamically changing morphological patterns, which are appropriately captured with high-resolution MRI. It is also noteworthy that brain atrophy, a distinctive AD symptom, can be identified through MRI. This form of atrophy serves as a reliable marker of the disease. It is indicative of its progression, as well as being associated with tau deposition and neuropsychological impairments, essential factors in the clinical manifestation of AD.

In recent years, CNNs and Vision Transformers have transformed neuroimaging data analysis for AD, moving beyond the traditional ML that focuses on approaches that rely on handcrafted features and classifiers. Recent works have proven promising in diagnosing and predicting Alzheimer's; however, at the same time, presenting different limitations mainly linked to the use of 3D CNN networks. Training these networks requires many samples, often unavailable in the medical field. One way to mitigate this problem is to use 3D volume slicing approaches. The volume is divided into 2D slices by slicing from one of the three anatomical body planes. This solution partially solves the problem but involves the loss of learning global patterns of the entire volume.

Another key aspect of DL models in the medical field is the interpretability of their results. It is crucial for clinical applications and remains a significant challenge that hinders the deployment of DL-aided diagnostic systems in real-world scenarios.

Our research aims to develop models that compensate for current limitations. We are developing approaches that allow us to be effective with few training samples and are explainable at the same time. Radiologists typically examine 3D images as a series of 2D images and base their diagnosis by focusing on specific brain parts from different views. Inspired by this, we have developed a diagnosis and XAI approach that allows us to diagnose AD and, at the same time, highlight the areas predominantly affected by the disease. From a series of 2D slices extracted from the volume, the network can reconstruct a three-dimensional saliency map highlighting the areas affected by AD with voxel-level precision (see Figure 2). Preliminary results show effectiveness in highlighting areas commonly associated with the disease, suggesting that these approaches are promising for diagnosing and predicting brain disorders.

2. Medical Image Analysis

2.1. Breast cancer detection

Breast cancer ranks as the most prevalent form of cancer among women and stands as the second leading cause of death. Detecting breast cancer at an early stage is crucial for increasing survival rates, prompting the implementation of mammography screening programs in numerous countries. Mammograms can reveal various abnormalities, including calcifications, masses, architectural distortions, and focal asymmetry.

Computer-aided diagnosis (CAD) systems have been devised to aid radiologists in analyzing mammographic images for diagnostic and screening purposes. Incorporating ML and DL techniques has led to significant progress in numerous tasks, such as image classification, lesion detection, and segmentation. CNNs stand as the de facto standard in many image analysis applications, demonstrating the ability to detect microcalcifications and other types of lesions accurately. Our research revolves around utilizing CNNs and transformer models to address various challenges in mammogram analysis. Transformer-based models, such as the Vision Transformer, promise to capture a broader context in breast imaging tasks. Ongoing research on transformer-based models in mammography indicates their efficacy in tasks like multi-view mammogram classification.

One of our research interests involves the classification of entire mammograms as malignant or normal, assessing their performance based on the type of lesion present and at different input resolutions [6]. Mammographic images exhibit lesions with diverse characteristics in size, shape, texture, and sparsity, which may align better with local convolutional paradigms or self-attention capable of capturing long-range features. We also propose a method for single calcification detection in mammograms involving a specialized convolution layer operating in the frequency domain as the first layer of a CNN [7]. This layer automatically learns a bank of Difference of Gaussians (DoG) band-pass filters parameterized by their associated pairs of standard deviations inversely proportional to the filter's bandwidth. Additionally, we explore the potential of transformer models in backbone-head architecture for lesion detection [8].

Amalgamating traditional image processing techniques with ML and DL methodologies has significantly advanced cancer detection in breast imaging. Ongoing exploration of innovative approaches, such as frequency-filter-integrated CNNs and transformer-based models, offers promise for further enhancing detection accuracy.

2.2. Small lesion detection

There has been significant interest in utilizing DL techniques for medical image analysis in recent years. These methods, employing advanced neural network architectures, have greatly improved the ability to extract valuable information from complex medical images. This advancement holds promise for more accurate diagnostics and tailored healthcare solutions. While current object detection models have shown impressive success, the increasing resolution of medical images presents a unique challenge, requiring greater attention to detail and identifying smaller objects within the images. Small lesions can be critical indicators of various medical conditions, making their accurate detection crucial for diagnosis and treatment planning.

To address this, a novel DL model, called GravityNet [9], is proposed to enhance the detection of small objects, employing innovative anchoring techniques known as *gravity points*, that appear to be 'attracted' to lesions. The architecture comprises a backbone network and two subnets dedicated to regression and classification tasks. This proposed approach notably enhances detection accuracy, leading to earlier diagnoses and improved patient outcomes. The results underscore the significance of this innovative approach, demonstrating its broad implications across various clinical applications.

For instance, GravityNet is applied to identify calcifications in digital mammograms, which are crucial for the early detection of breast cancer. Furthermore, its effectiveness in detecting microaneurysms in retinal images could significantly aid the early diagnosis and management of diabetic retinopathy, a leading cause of blindness worldwide.

In addition, GravityNet shows promise in cytology imaging, particularly in the analysis of whole slide images to detect cell nuclei, which is crucial for cervical cancer identification. Accurate identification of cell nuclei in cytology images helps pathologists identify morphology and abnormal cell patterns indicative of cervical cancer. This capability has significant potential to improve the efficiency and accuracy of cervical cancer screening programs, enabling earlier diagnosis and intervention to reduce the morbidity and mortality associated with this prevalent cancer.

Finally, GravityNet extends to the identification of large vessel occlusions (LVOs), a crucial task in stroke diagnosis and treatment planning. LVOs are obstructions in the brain's main arteries, and their early detection is essential to determine appropriate treatment strategies to minimize neurological damage and improve patient outcomes. Leveraging its advanced DL algorithms, GravityNet can accurately detect and localize LVOs in volumetric space within computed tomographic angiography (CTA) scans. This capability allows healthcare professionals to quickly identify patients at risk of a severe stroke and promptly initiate interventions such as thrombectomy or thrombolysis, which can significantly reduce disability and mortality rates.

3. Movement Analysis

Gait Analysis (GAn) is an objective assessment of a person's walking abilities and is an essential part of motor assessment. It helps health professionals make informed clinical decisions and develop targeted rehabilitation strategies to improve gait functions. In clinical practice, GAn is performed by healthcare professionals via standardized questionnaires, functional tests, and visual observation of the patient's walking pattern. The identification of gait irregularities is based on the subjective quantification of spatio-temporal parameters and detailed kinematic and kinetic evaluations.

Various advanced technologies have completely changed the way of analyzing motion objectively. Optical motion capture systems are the most accurate and precise for joint kinematics assessment, making them the "gold standard" within laboratory settings. Such technologies enable the accurate acquisition of motion data using reflective markers placed at strategic joint locations and multiple cameras that track them. However, they are mainly restricted to specialized gait laboratories and research settings due to their limitations, which include high costs, technical expertise demands, and extensive setup durations, hampering widespread clinical adoption. ML approaches are increasingly used in GAn, developing from integrating computational intelligence with biomechanics to offer robust methods for analyzing complex movement patterns [10]. CNN are increasingly utilized for human pose estimation within marker-less motion analysis (MMA) systems, significantly augmenting their precision and reliability. In contrast to marker-based motion analysis systems, MMA systems eliminate the need for markers attached to the patient's skin, streamlining the experimental workflow and reducing preparation time. Moreover, these systems allow to perform GAn even outside gait laboratories. This makes them useful for biomechanical evaluations in sports settings and assessing ambulatory functions in patients with neuromotor impairments during routine activities. This approach combines movement and GAn with clinical precision and practical applicability, which allows for patient care and athletic performance enhancement in real-world settings. MMA systems bridge the gap between rigorous laboratory analysis and everyday assessment, representing a significant stride in precision medicine and rehabilitative care. Figure 3 shows the practical application of an innovative MMA framework developed to estimate joint and segment angles from 2D videos and images. It showcases real-time data acquisition and analysis during a treadmill gait assessment, proving the successful integration of technology and biomechanics in modern therapeutic and athletic environments. By delivering precise and dependable joint and segment dynamics measurements, such a solution can significantly augment human movement analysis, potentially elevating health outcomes and athletic performance.

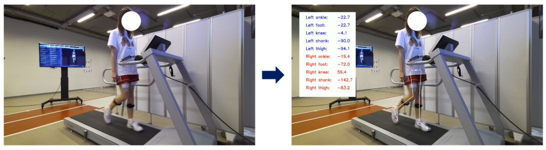

Figure 3: From 2D input video to marker-less joint and segment angles assessment

Moreover, in the context of Parkinson's Disease (PD), a common neurodegenerative disorder with progressive loss of dopaminergic and other sub-cortical neurons, GAn is an essential tool for the diagnosis and progression of the disease, which is characterized by motor symptoms such as tremors, rigidity, bradykinesia (slowness of movement), and postural instability. Through the utilization of GAn, clinicians can better understand how PD affects an individual's mobility in daily life, enabling the identification of specific gait patterns associated with PD progression. To achieve this aim, ML algorithms are used to classify diseases based on spatiotemporal and kinematic gait features extracted from MMA. An essential aspect of employing ML in medical diagnostics is explainability, particularly when understanding the impact of different features on the model's predictions. Understanding what features have a major impact on the outcome is essential in the medical field. The use of MMA systems presents a significant advancement in the management of PD, enabling continuous and real-time monitoring of patients' movements. This continual observation facilitates the development of highly personalized rehabilitation and therapy programs that can be adjusted daily to meet the evolving needs of each patient.

Acknowledgments

1. Part of these researches were funded by Italian Ministry of University, MIUR program “Dipartimenti di Eccellenza 2018-2022” Law 232/216 and by D.M. 351/2022 “Dottorati innovativi per la pubblica amministrazione”.
2. Project ECS 0000024 “Ecosistema dell’innovazione - Rome Technopole” financed by EU in NextGenerationEU plan through MUR Decree n. 1051 23.06.2022 PNRR Missione 4 Componente 2 Investimento 1.5 - CUP H33C22000420001.
3. Supported by Luxembourg National Research Fund (FNR) (**MEMENTO** – **M**achine l**E**arning-based **M**arker-l**E**ss gait analysis system for clinical assessment of huma**N** mo**T**i**O**n [16749075])

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