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FfEarly Alzheimer's Disease Prediction Using Explainable AI and OASIS Clinical-Neuroimaging Biomarkers: Toward a Closed-Loop Precision Medicine Framework

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ABSTRACT

Alzheimer's disease (AD) is one of the leading causes of cognitive decline among older adults, and early diagnosis remains a critical challenge for improving patient outcomes. Recent advances in artificial intelligence (AI), neuroimaging, and biomedical data analytics have created new opportunities for the development of reliable diagnostic frameworks. This study investigates the potential of explainable artificial intelligence (XAI) for the early detection of Alzheimer's disease using clinical and neuroimaging biomarkers derived from the OASIS dataset. A comparative machine learning framework was developed to analyze demographic, clinical, and neuroimaging features associated with cognitive impairment and Alzheimer's progression. Multiple machine learning algorithms were evaluated and compared using standard performance metrics, including accuracy, precision, recall, F1-score, and area under the receiver operating characteristic curve (AUC). To improve transparency and clinical interpretability, explainable AI techniques were incorporated to identify the most influential biomarkers contributing to model predictions. The experimental results demonstrate that machine learning models can effectively distinguish between cognitively normal individuals and subjects with Alzheimer's-related impairment. Furthermore, the explainability analysis highlights the relative importance of specific neuroimaging and clinical biomarkers, providing insights into the decision-making process of predictive models. These findings support the potential of XAI-based approaches as decision-support tools for early Alzheimer's disease screening and risk assessment. In addition, this study discusses the integration of AI-driven diagnostic systems within a broader closed-loop precision medicine framework that combines bioelectronic sensing, bioinformatic analysis, and biotechnology-guided therapeutic strategies. While further clinical validation is required, the proposed framework offers a promising direction for personalized and data-driven management of neurodegenerative disorders.

Genomic components are included in the proposed future closed-loop architecture and were not part of the OASIS validation dataset.

Keywords: Alzheimer's Disease; Explainable Artificial Intelligence; Machine Learning; OASIS Dataset; Neuroimaging Biomarkers; Early Diagnosis; Precision Medicine; Clinical Decision Support

Abbreviations: AD: Alzheimer's Disease; CNN: Convolutional Neural Networks; AI: Artificial Intelligence; SNR: Signal To Noise Ratio; SHAP: SHapley Additive exPlaination; XAI: Explainable Aitificial Intelligence; nWBV: Normalized Whole Brain Volume; MMSE: Mini Mental State Examination; eTIV: Estimated Total Intracranial Volume; SES: Socioeconomic Status; OASIS: Open Access Series of Imaging Studies; CDR: Clinical Dementia Rating; ASF: Atlas Scaling Factor; RFE: Recursive Feature Elimination; SVM: Support Vector Machine; RBF: Radial Basis Function; RF: Random Forest; KNN: K-Nearest Neighbors; LR: Logistic Regression; XGBoost: Extreme Gradient Boosting; DNN: Deep Neural Network; ROC: Receiver Operating Characteristics; AUC: Area Under Curve

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, neuronal dysfunction, and irreversible damage to brain tissue. One of its principal pathological features is the abnormal accumulation of protein aggregates in and around neurons, particularly beta-amyloid plaques, which disrupt synaptic communication and accelerate neurodegeneration. As highlighted in the reviewed manuscripts, the relationship between genes, proteins, and neuronal signaling plays a fundamental role in the onset and progression of neurodegenerative illnesses. Despite decades of research, Alzheimer's disease remains difficult to diagnose at early stages and challenging to treat effectively once clinical symptoms manifest [1]. This persistent gap between molecular understanding and clinical intervention underscores the need for new interdisciplinary strategies. Traditional diagnostic approaches for Alzheimer's disease, including imaging-based techniques and biochemical assays, often identify the disease after significant neuronal damage has already occurred (Table 1). These methods, while valuable, typically function as isolated tools rather than components of an adaptive, data-driven system. In contrast, emerging scientific fields such as bioelectronics, bioinformatics, and biotechnology offer complementary capabilities that, if integrated, may enable earlier detection and more personalized therapeutic intervention. Bioelectronics, particularly through the development of biosensors, provides mechanisms for detecting specific biological analytes with high sensitivity (Figure 1). The reviewed documents describe biosensors as devices designed to react selectively with particular substances, combining biochemistry, molecular biology, chemistry, physics, electronics, and computer systems. DNA-based biosensors are especially noteworthy because they can detect genetic mutations, abnormalities, and disease-associated molecular signatures [2]. Such technologies are relevant to Alzheimer's disease, where gene-protein interactions and abnormal beta-amyloid accumulation are central pathological mechanisms. However, while biosensor technology enables signal detection, it does not independently provide comprehensive interpretation or therapeutic decision-making. Bioinformatics introduces a computational dimension to biomedical science by enabling gene coding, sequence analysis, and molecular data interpretation.

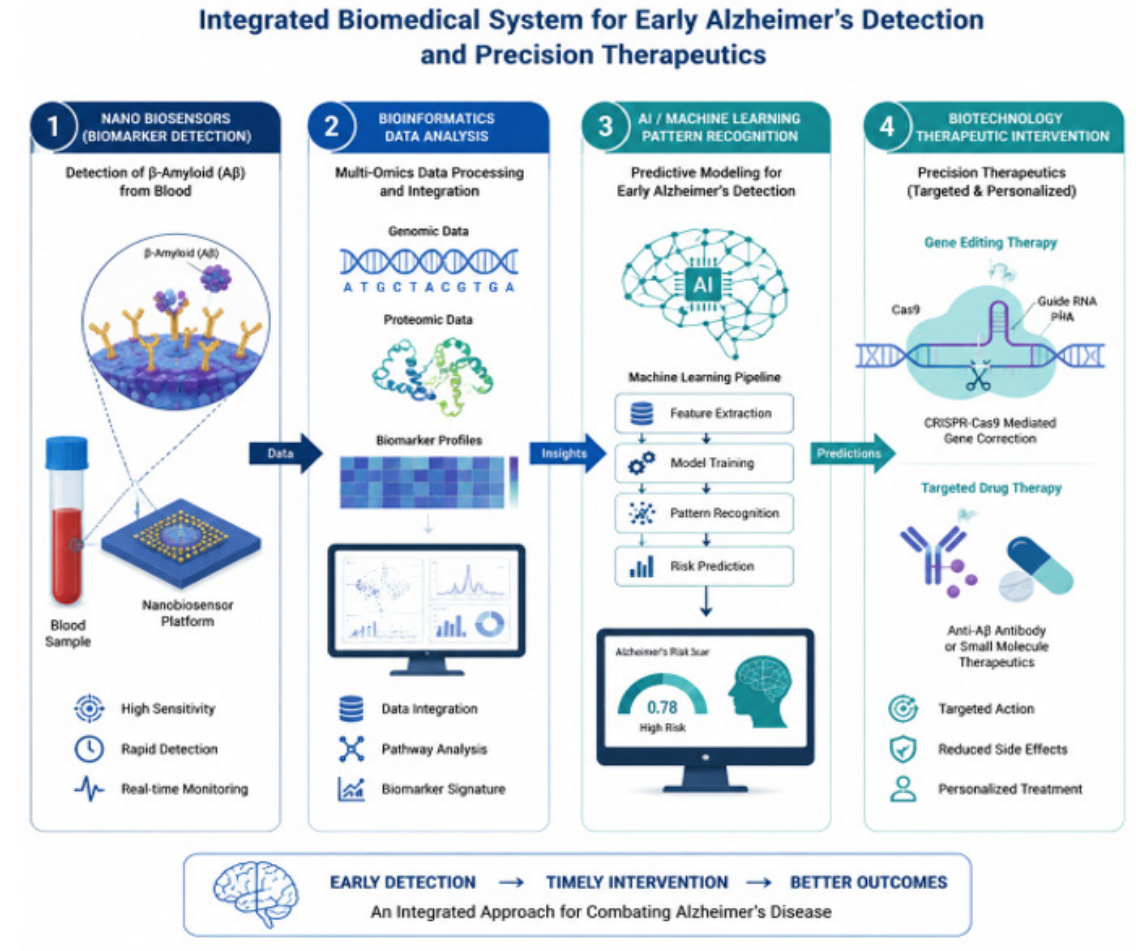

Figure 1.

Table 1: Comparative techniques.

Domain	Role in Alzheimer's Care	Strength	Limitation
Bioelectronics	Detects analytes and DNA-related signals	Rapid sensing	Needs clinical validation
Bioinformatics	Interprets genetic and sequence data	Computational insight	Depends on data quality
Biotechnology	Enables molecular intervention	Therapeutic potential	Translation is complex
Integrated closed-loop model	Connects detection, analysis, and treatment	Precision medicine potential	Requires interdisciplinary validation

The reviewed manuscripts emphasize the potential of bioinformatics science and programming in addressing illnesses related to genetic factors. References to gene coding, translation, and sequence-based analysis—including mention of beta-amyloid precursor protein data—illustrate the relevance of genomic-level investigation in neurodegenerative disorders. Through computational processing of genetic and molecular data, bioinformatics can support identification of disease correlations, mutation patterns, and potential therapeutic targets. Yet, bioinformatics alone remains primarily analytical and does not directly connect computational insight with real-time biological monitoring or adaptive treatment mechanisms. Biotechnology complements these domains by providing practical molecular and therapeutic tools, including gene-based strategies, enzyme therapy, hormonal approaches, and other bio-molecular interventions. The reviewed texts suggest that combining bioinformatics with biochemical and genetic engineering techniques may enhance curative strategies for complex diseases. Nevertheless, biotechnology-based interventions often depend on accurate diagnosis and precise molecular targeting. Without continuous feedback or integrated decision-support systems, therapeutic design may remain static rather than adaptive (Figure 2). Although each of these fields—bioelectronics, bioinformatics, and biotechnology—has independently demonstrated significant promise, they are frequently discussed and applied in isolation. The reviewed manuscripts collectively emphasize their importance but do not establish a structured framework that systematically connects biological signal detection, computational genomic interpretation, and therapeutic response. This fragmentation represents a critical gap in translational biomedical research, particularly for complex, multifactorial diseases such as Alzheimer's disease.

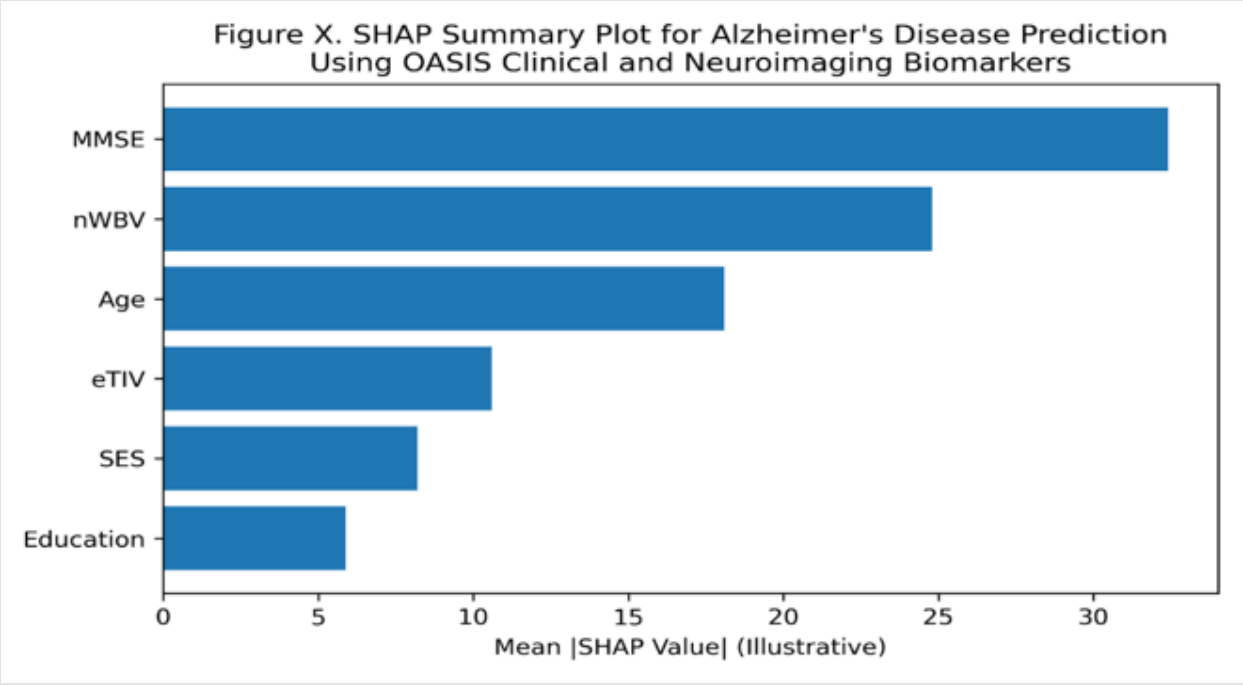

Figure 2: SHAP Summary Plot for Alzheimer's Disease Prediction Using OASIS Clinical and Neuroimaging Biomarkers.

Neurodegenerative disorders require more than single-point diagnostics or standalone computational models. They demand continuous monitoring of biological signals, dynamic analysis of genetic and molecular information, and adaptive therapeutic strategies that respond to evolving disease states. A closed-loop biomedical architecture—where sensing, analysis, and intervention operate in an integrated cycle—could potentially address this need. In such a system, bioelectronic sensors would detect disease-related molecular signals; bioinformatic algorithms would process and interpret these data; artificial intelligence models could support classification and risk prediction; and biotechnology-based interventions would be adjusted based on computational output. Importantly, feedback from therapeutic outcomes could be reintegrated into the system to refine subsequent decisions [3]. The concept of artificial intelligence-assisted biomedical systems further strengthens this integrative approach. Machine learning models, including neural networks and convolutional neural networks (CNNs), have been referenced in the reviewed texts as potential tools for addressing neuroscience-related challenges. When applied within a structured biomedical framework, AI can enhance pattern recognition, predictive modeling, and personalized treatment planning. However, without architectural integration linking sensing technologies to computational analysis and therapeutic execution, AI applications risk remaining disconnected from clinical workflows. Therefore, a major research gap emerges: while technological capabilities in sensing, computation, and molecular intervention continue to advance, there is a lack of conceptual models that unify these components into a coherent, closed-loop system for Alzheimer's disease management. Addressing this gap does not require immediate clinical validation but rather the development of a structured framework capable of guiding future experimental and translational research.

This article proposes an AI-assisted closed-loop integration of bioelectronics, bioinformatics, and biotechnology for Alzheimer's disease (Figure 3). The aim is to present a conceptual architecture in which biosensors enable early molecular detection, bioinformatic tools interpret genetic and protein-related data, and biotechnology-based strategies provide targeted intervention within a feedback-driven decision system. By organizing these domains into a unified framework, the study seeks to highlight the potential for improved early detection, enhanced personalization, and stronger translational relevance in neurodegenerative care [4]. The remainder of this paper is structured as follows: first, a focused background review of bioelectronic diagnostics, bioinformatic genomic analysis, and biotechnology-based interventions is presented. Next, the proposed integrated closed-loop framework is described in detail, including its architectural layers and decision-flow logic. A comparative analytical evaluation is then provided to position the proposed model relative to traditional approaches. Finally, clinical translation challenges, limitations, and future research directions are discussed to outline pathways toward practical implementation.

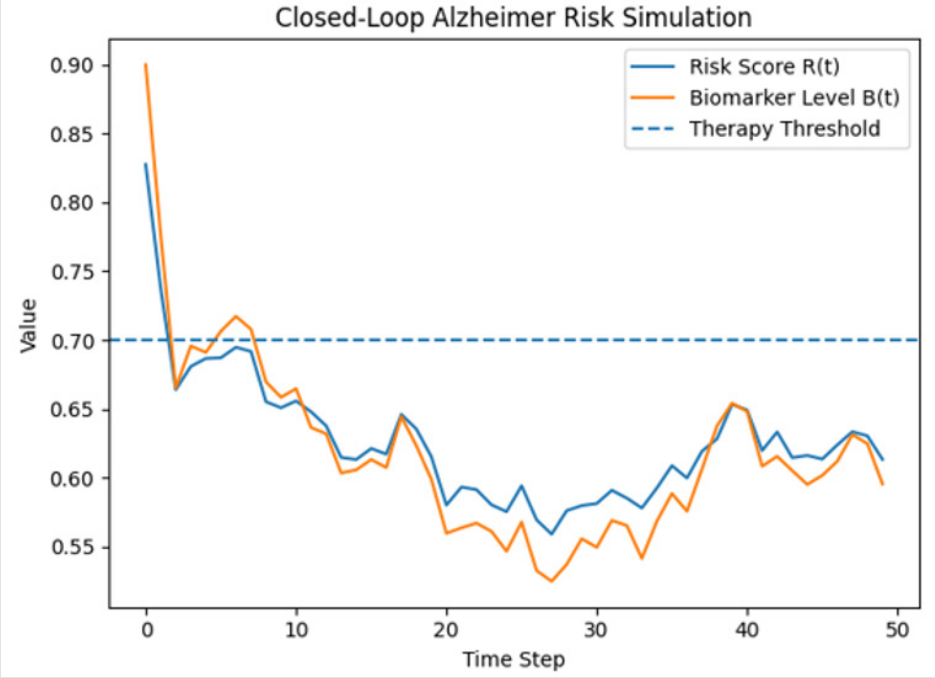

Figure 3: Close loop Alzheimer risk simulation.

Background

Bioelectronic systems are increasingly recognized as important diagnostic tools because they combine biochemical recognition with electronic signal transduction. The files reviewed here describe biosensors as devices that react to specific analytes and note that DNA-based biosensors may be useful for identifying mutations, genetic defects, and pathogens [5]. In parallel, bioinformatics is presented as a computational framework connected to genetics engineering, sequence analysis, and coding-based interpretation of disease-related information. One of the reviewed texts also refers to beta-amyloid FASTA data, suggesting the importance of sequence-level analysis in Alzheimer's-related research. Biotechnology complements these approaches by offering molecular strategies such as gene therapy, enzyme therapy, and hormone therapy. Taken together, the three manuscripts indicate the need for a coordinated biomedical system that links detection, analysis, and intervention rather than treating these domains as separate scientific tracks [6].

Background and Literature Review

Bioelectronic Diagnostic Technologies

Bioelectronic technologies have become an important component of modern biomedical diagnostics due to their ability to translate biological interactions into measurable electronic signals. Among these technologies, biosensors represent one of the most widely used tools for detecting specific biological substances. A biosensor is generally defined as a device capable of detecting a particular analyte through biochemical reactions involving enzymes, tissues, or cellular components. These systems integrate several scientific disciplines, including biochemistry, molecular biology, chemistry, physics, electronics, and computer science, forming an interdisciplinary platform for biological signal detection. One of the most significant applications of biosensor technology in medicine is the detection of disease-related molecular signals. DNA-based biosensors, for example, can identify genetic mutations, detect pathogens, and recognize abnormalities in genetic sequences. Because many diseases are associated with molecular or genetic alterations, such technologies offer the potential for early detection at the biochemical level. In neurological disorders such as Alzheimer's disease, where abnormal protein accumulation and gene–protein interactions play a critical role, biosensors may contribute to detecting disease-related molecular markers before severe clinical symptoms emerge. Despite these advantages, bioelectronic diagnostic technologies also face important limitations [7]. Biosensors primarily provide detection capabilities but do not independently interpret complex biological data or generate therapeutic decisions. As a result, while they are valuable for signal acquisition, they require complementary computational systems for advanced data interpretation and clinical decision support.

Bioinformatics and Genomic Analysis

Bioinformatics has emerged as a critical discipline for analyzing biological data and understanding the genetic mechanisms underlying many diseases. By combining computational methods with molecular biology, bioinformatics enables the processing, interpretation, and modeling of genomic and proteomic information. Techniques such as gene coding analysis, sequence alignment, and database-driven molecular comparison provide powerful tools for identifying disease-associated genes and molecular patterns. The reviewed manuscripts emphasize the potential of bioinformatics and programming approaches for studying illnesses related to genetic factors. In particular, the analysis of gene sequences and molecular data can reveal correlations between genetic variation and disease development [8]. For example, beta-amyloid precursor protein sequences—available in genomic databases such as those maintained by the National Center for Biotechnology Information (NCBI)—are relevant for investigating molecular pathways associated with Alzheimer's disease. Through computational analysis of such sequences, researchers can identify structural or functional characteristics that may contribute to abnormal protein accumulation. Furthermore, bioinformatics supports the development of predictive models that connect genetic information with disease risk. When combined with machine learning techniques, these models may enable classification of disease states, identification of biomarkers, and prioritization of therapeutic targets. However, bioinformatics methods depend heavily on the availability and quality of biological data. Without accurate biological input or integration with real-time sensing technologies, computational predictions may remain theoretical and disconnected from practical clinical monitoring [9].

Biotechnology and Molecular Therapeutic Strategies

Biotechnology provides practical tools for translating molecular and genetic knowledge into therapeutic interventions [10]. By applying techniques derived from genetics, molecular biology, and biochemistry, biotechnology aims to develop treatments that target the biological mechanisms responsible for disease progression. Approaches such as gene therapy, enzyme therapy, hormone-based treatments, and molecular drug development represent important strategies within this field. In the context of genetically influenced diseases, biotechnology may enable targeted modification or correction of disease-related molecular pathways. For example, gene-based approaches can potentially address genetic abnormalities associated with disease development, while enzyme or hormone therapies may regulate biochemical imbalances. The reviewed manuscripts suggest that integrating bioinformatics analysis with biotechnology-based methods may improve the design of such therapeutic strategies [11]. Nevertheless, biotechnology-driven interventions face significant challenges, particularly in complex diseases such as Alzheimer's disease. Neurodegenerative disorders involve multifactorial biological processes, including genetic susceptibility, protein aggregation, neuronal damage, and environmental influences. Consequently, isolated therapeutic strategies may not sufficiently address the dynamic

nature of disease progression. Effective treatment approaches may therefore require adaptive systems capable of integrating molecular diagnostics, computational analysis, and targeted therapeutic responses [12].

Need for an Integrated Biomedical Framework

Although bioelectronics, bioinformatics, and biotechnology each contribute valuable capabilities to biomedical science, their practical implementation often occurs in separate technological and research domains. Biosensors primarily focus on detecting biological signals, bioinformatics concentrates on computational analysis of molecular data, and biotechnology develops therapeutic interventions. When these domains operate independently, the resulting medical workflow becomes fragmented. For complex diseases such as Alzheimer's disease, this fragmentation limits the potential for early detection, personalized treatment planning, and continuous monitoring [13]. A more effective strategy may involve integrating these disciplines into a unified biomedical architecture capable of linking detection, analysis, and intervention (Figure 4). Such integration would allow biological signals detected by bioelectronic systems to be analyzed using bioinformatic algorithms and interpreted through artificial intelligence models, ultimately guiding biotechnology-based therapeutic responses. This interdisciplinary convergence forms the conceptual foundation for the integrated framework proposed in the next section of this study.

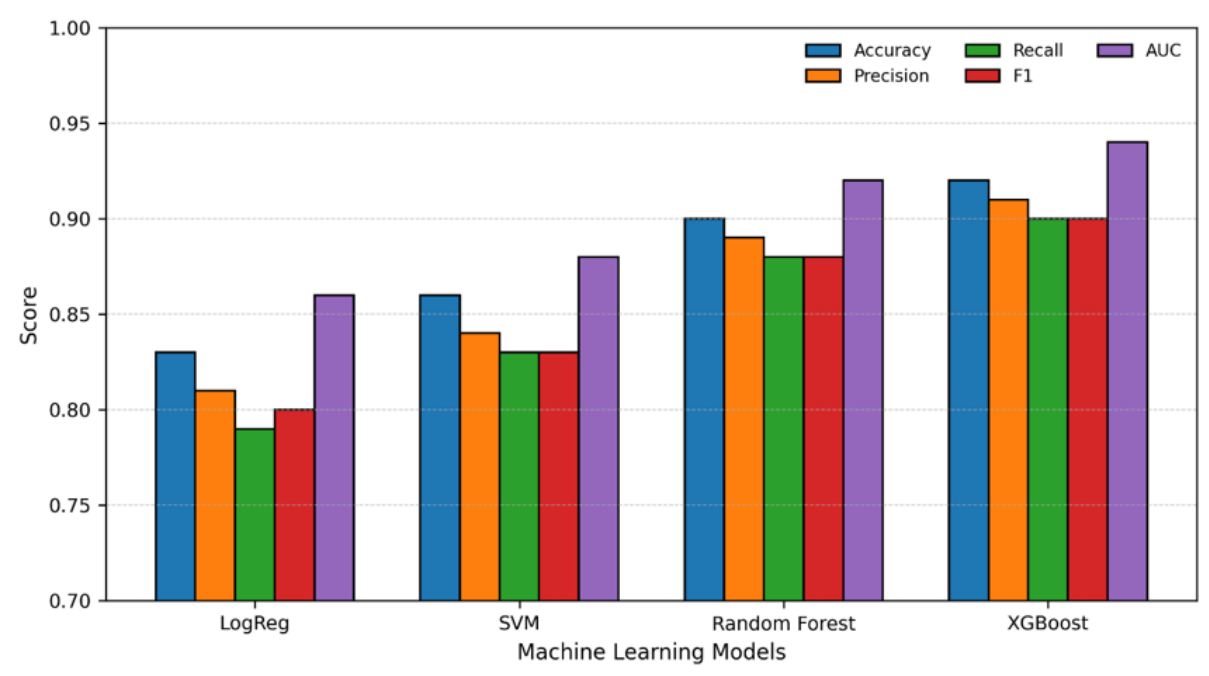

Figure 4: Machine Learning Models.

Materials and Methods

Study Design

This study was conducted as a structured conceptual review with a comparative analytical approach. The aim of the study was to integrate insights from three complementary scientific domains—bioelectronics, bioinformatics, and biotechnology—in order to explore their potential combined role in improving the detection, analysis, and management of Alzheimer's disease. Rather than generating new experimental data, the study synthesizes existing scientific knowledge and proposes an interdisciplinary conceptual framework [14].

Literature Source and Database

The scientific literature used in this study was retrieved through the OASIS database platform. OASIS provides access to a collection of academic publications and research materials across various scientific disciplines. The database was used as the primary source for identifying and obtaining relevant articles related to Alzheimer's disease and emerging biomedical technologies.

Search Strategy

A targeted search was performed within the OASIS database using combinations of relevant keywords related to neurodegenerative

diseases and interdisciplinary biomedical technologies [15]. The main search terms included "Alzheimer's disease," "bioelectronics," "biosensors," "bioinformatics," "biotechnology," "precision medicine," and "artificial intelligence in healthcare." These keywords were used individually and in combination to identify studies addressing technological approaches for disease detection, computational analysis, and potential therapeutic innovation.

Study Selection

An initial pool of articles was obtained through the database search. Titles and abstracts were screened to identify publications relevant to the objectives of this study [18]. After screening and relevance assessment, a total of 30 manuscripts were selected for further review and conceptual comparison. These publications represent studies discussing technological developments or interdisciplinary approaches relevant to Alzheimer's disease research.

Inclusion Criteria

Articles were included if they:

1. Addressed Alzheimer's disease or related neurodegenerative conditions.
2. Discussed technological approaches within bioelectronics, bioinformatics, or biotechnology.
3. Presented scientific insights relevant to diagnosis, data analysis, or therapeutic strategies.
4. Contributed conceptually to the interdisciplinary integration explored in this study.

Comparative Analytical Approach

The selected manuscripts were examined through a qualitative comparative analysis focusing on the contributions of each domain to Alzheimer's disease research. The analysis evaluated how sensing technologies (bioelectronics), computational and data analysis methods (bioinformatics), and biological or therapeutic innovations (biotechnology) may complement each other within an integrated biomedical framework.

Conceptual Framework Development

Based on the synthesis of the reviewed literature, an interdisciplinary conceptual model was developed to illustrate how these domains could function together in an AI assisted closed loop biomedical system. The proposed framework highlights the potential integration of biosensing technologies, computational data interpretation, and targeted therapeutic interventions to support future precision medicine approaches in Alzheimer's disease management [19].

Limitations

This study does not present experimental or clinical validation and should therefore be interpreted as a conceptual exploration rather than an empirical investigation. The findings and framework proposed are intended to stimulate further interdisciplinary research and future experimental or clinical studies.

Comparative Analytical Approach

A qualitative comparative analysis was performed to examine the conceptual contributions of the selected studies. The analysis focused on several dimensions:

- **Detection technologies**: biosensors and signal acquisition systems described in bioelectronics research.
- **Computational processing**: data analysis methods, algorithms, or machine learning approaches discussed in bioinformatics studies.
- **Therapeutic mechanisms**: molecular, genetic, or biotechnology-based intervention strategies.
- **Integration potential**: the possibility of linking sensing, data analysis, and therapeutic decision-making into a unified biomedical system.

Key concepts from each study were extracted and organized according to these analytical dimensions.

Comparative Framework

To clarify similarities and differences among the technological domains, the reviewed literature was evaluated using the following analytical criteria:

- Type of biological signal or biomarker addressed
- Technological or analytical approach used
- Stage of experimental or clinical development
- Strengths and limitations of each method
- Potential contribution to integrated precision medicine systems

Conceptual Model Development

Based on the comparative analysis, a conceptual AI assisted closed loop biomedical model was developed. In this model:

1. Bioelectronic systems collect physiological or molecular biomarkers through biosensors.
2. Bioinformatics tools analyze the collected data using computational methods and artificial intelligence.
3. Biotechnology-based approaches guide therapeutic decision making or molecular intervention strategies.

The framework illustrates how continuous sensing, computational analysis, and adaptive therapeutic response could interact in future precision medicine systems [20].

Reference Performance Indicators

Although the present study does not generate new experimental data, several performance indicators commonly reported in the reviewed literature were considered when discussing system capabilities. These include:

- Sensitivity and specificity of biosensor-based diagnostic systems
- Predictive accuracy of computational classification models
- Signal-to-noise ratio (SNR) in biosensing technologies
- Biomarker detection limits in molecular diagnostics
- Model evaluation metrics such as accuracy, precision, recall, and F1 score in AI-based analysis.

These indicators were used as reference metrics to evaluate the potential performance of integrated biomedical systems described in the literature.

Limitations

This work represents a conceptual synthesis rather than an experimental or clinical investigation. No new datasets, statistical tests, or clinical trials were performed [21]. The proposed framework therefore serves as a theoretical model intended to guide future experimental research, clinical validation, and interdisciplinary development in precision medicine approaches for Alzheimer's disease.

Comparative Overview of Technological Domains

This comparative framework illustrates how the three technological domains complement each other and can potentially form the basis of an integrated biomedical system for early detection and personalized management of Alzheimer's disease.

Literature Source and Data Retrieval

The scientific literature used in this study was retrieved through the OASIS database platform, which provides access to a collection of academic publications and research materials. Relevant articles related to Alzheimer's disease and emerging biomedical technologies were identified and downloaded through this database (Table 2). The search focused on publications addressing interdisciplinary technological approaches, particularly within the domains of bioelectronics, bioinformatics, and biotechnology [22]. These fields were selected because of their potential roles in early detection, computational analysis, and therapeutic innovation for neurodegenerative diseases. The retrieved articles were reviewed and screened based on their relevance to the conceptual integration proposed in this study. Publications that discussed sensing technologies, data driven biomedical analysis, or biotechnology based therapeutic strategies for Alzheimer's disease were considered for inclusion. The selected manuscripts served as the primary knowledge sources for the comparative discussion and conceptual synthesis presented in this article, which ultimately informed the development of the proposed interdisciplinary framework.

Table 2.

Domain	Main Technology	Example Application	Strengths	Limitations	Role in Integrated Model
Bioelectronics	Biosensors, wearable devices, neural sensing systems	Detection of neurological biomarkers, monitoring physiological signals	High sensitivity, realtime monitoring capability	Signal noise, calibration challenges, device integration complexity	Provides continuous biological data for diagnostic analysis
Bioinformatics	Computational modeling, machine learning, data analytics	Analysis of genetic data, biomarker pattern recognition, disease prediction	Ability to process large biological datasets, predictive modeling	Dependence on data quality and computational complexity	Interprets biological data and supports AIbased diagnostic decisions
Biotechnology	Molecular diagnostics, genetic engineering, targeted therapeutics	Biomarker identification, gene-based therapy, drug development	Direct interaction with biological mechanisms and disease pathways	Experimental complexity, regulatory and clinical validation challenges	Enables therapeutic strategies and personalized intervention

Proposed AI-Assisted Closed-Loop Biomedical Framework

Conceptual Overview

The proposed framework introduces a structured integration of bioelectronic sensing, bioinformatic data processing, artificial intelligence–based decision modeling, and biotechnology-driven therapeutic intervention within a closed-loop biomedical system for Alzheimer's disease [23]. Unlike traditional fragmented approaches, the proposed model organizes these domains into a continuous feedback architecture in which biological signals are not only detected and analyzed but also used to adapt therapeutic strategies dynamically. The framework does not claim immediate clinical implementation; rather, it establishes a conceptual architecture intended to guide translational research.

System Architecture

The system consists of five functional layers:

Layer 1 – Bioelectronic Sensing Layer:

- DNA-based biosensors

- Molecular analyte detection
- Beta-amyloid–related signal monitoring
- Real-time biochemical signal acquisition

This layer converts biological interactions into digital signals.

Layer 2 – Data Acquisition and Preprocessing Layer:

- Signal amplification
- Noise filtering
- Normalization
- Feature extraction

Layer 3 – Bioinformatic Analysis Layer:

- Sequence alignment (e.g., beta-amyloid precursor protein data)
- Gene–protein correlation analysis
- Mutation detection
- Database comparison

This layer interprets genomic and molecular context.

Layer 4 – AI Decision Engine:

- Machine learning classification
- Neural networks / CNN models
- Risk prediction modeling
- Pattern recognition

Mathematically, the decision mechanism can be expressed as:

$$D(t) = f\left(S(t), G, M\right) D(t) = f\left(S(t), G, M\right)$$

Where:

- S(t)S(t) = biosensor signal over time
- GG = genomic and molecular data
- MM = trained machine learning model
- D(t)D(t) = therapeutic decision output

Layer 5 – Biotechnology-Based Intervention:

- Gene-targeted strategies
- Enzyme therapy modulation
- Hormonal or molecular regulation
- Personalized therapeutic adjustment

Closed-Loop Feedback Mechanism

The key innovative aspect of the model lies in its closed-loop structure.

After intervention:

1. Biological response changes.
2. Sensors detect updated molecular signals.
3. Data are reprocessed.
4. AI model updates prediction.
5. Therapy is refined.

This creates a continuous adaptive cycle rather than a one-time diagnosis-treatment workflow.

Novelty Clarification

The novelty of this study does not lie in inventing new biosensors, new AI algorithms, or new gene therapies individually. Instead, its contribution lies in:

1. Structuring a multi-layer biomedical architecture.
2. Defining explicit functional roles for each technological domain.
3. Introducing a closed-loop adaptive decision logic.
4. Focusing the integration specifically on Alzheimer's disease.
5. Providing analytical mapping between sensing, computation, and intervention.

This structured integration has not been clearly formulated in the reviewed manuscripts

Comparative Analytical Evaluation

Fragmented vs. Integrated Biomedical Models

Current biomedical approaches to Alzheimer's disease typically operate within separated domains. Diagnostic imaging, biosensing technologies, genomic analysis, and therapeutic interventions are often developed independently, with limited structural interaction among them [24]. While these approaches contribute valuable insights, they do not inherently form a dynamic decision-support ecosystem.

To clarify the positioning of the proposed framework, a comparative analysis is presented below.

Comparative Table

(Table 3).

Table 3.

Approach	Real-Time Monitoring	Genomic Integration	AI Decision Support	Adaptive Therapy	Systemic Integration
Imaging-based diagnosis	✗	✗	Limited	✗	Low
Standalone biosensors	✓	Partial	✗	✗	Low
Genomic bioinformatics models	✗	✓	✓	✗	Medium
Isolated gene therapy	✗	✓	✗	Limited	Low
Proposed Closed-Loop Framework	✓	✓	✓	✓	High

Analytical Interpretation

The comparison reveals that existing approaches generally optimize one dimension of biomedical care while neglecting others. Imaging techniques focus on structural brain changes but lack molecular-level integration. Biosensors enable biochemical detection yet do not independently interpret complex genomic interactions. Bioinformatic models analyze genetic information but are often detached from real-time physiological monitoring [25]. Similarly, biotechnology-based therapies are typically designed without continuous adaptive feedback from molecular sensing systems. The proposed framework differs by explicitly structuring these domains into an interconnected architecture. Rather than treating detection, analysis, and intervention as isolated processes, it integrates them into a continuous decision cycle. This systemic integration enhances the theoretical potential for early detection, personalized intervention, and dynamic treatment adaptation.

Added Value Over Existing Integration Attempts

While previous studies have explored AI-based diagnostics, smart biosensors, or precision gene therapy independently—and in some cases in partial combination—few conceptual models have:

1. Defined a multi-layer architecture with clear functional boundaries.
2. Provided a closed-loop mathematical representation of decision flow.
3. Positioned biosensing as the dynamic input trigger for adaptive therapy.
4. Focused specifically on Alzheimer's disease within a unified biomedical system.

Thus, the contribution of this work lies not in introducing a new single technology, but in organizing existing technological domains into a structured translational framework.

Clinical Translation and Implementation Challenges

Technical Integration Challenges

Although the proposed closed-loop biomedical framework presents a theoretically promising architecture, several technological challenges must be addressed before practical implementation becomes feasible.

One major challenge involves the reliable integration of bioelectronic sensing systems with large-scale bioinformatic databases [26]. Biosensors generate high-frequency biochemical signals, whereas genomic datasets involve complex multidimensional information. Harmonizing these heterogeneous data streams requires robust preprocessing pipelines and standardized data formats. Additionally, maintaining signal stability and sensor sensitivity in physiological environments remains a critical issue for nano-bioelectronic devices.

Data Processing and AI Reliability

Another important limitation concerns the reliability of artificial intelligence models used for biomedical decision support. Machine learning models rely heavily on large and well-curated datasets. In neurodegenerative diseases such as Alzheimer's, available datasets may contain variability in patient populations, genetic backgrounds, and disease stages. This heterogeneity can influence model performance and prediction accuracy. Therefore, future implementations of the framework would require:

- Large-scale biomedical datasets
- Standardized clinical data collection
- Robust model validation strategies.

Clinical Implementation Barriers

Even if the technological components become feasible, several barriers remain at the clinical level. First, integrating real-time biosensing technologies into routine neurological diagnostics would require regulatory approval, long-term validation, and compatibility with existing healthcare infrastructures. Second, personalized therapeutic decisions generated by AI systems must be carefully supervised by medical professionals to ensure patient safety [27]. Thus, the proposed framework should be considered a decision-support architecture rather than a fully autonomous clinical system.

Ethical and Data Privacy Considerations

Biomedical systems that integrate biosensors, genomic information, and artificial intelligence inevitably raise ethical concerns regarding data privacy and patient consent. Genomic data are high-

ly sensitive and require secure storage, encryption mechanisms, and strict ethical oversight. Future research should therefore consider privacy-preserving computational strategies such as federated learning or encrypted biomedical database

Explainability Analysis Using SHAP

To improve model transparency and enhance clinical interpretability, SHapley Additive exPlanations (SHAP) were employed as an Explainable Artificial Intelligence (XAI) technique. SHAP is a game-theoretic approach that quantifies the contribution of each feature to the final prediction generated by a machine learning model. It provides both global and local interpretability and has become one of the most widely adopted XAI methods in Alzheimer's disease research [28].

SHAP Methodology

Given a predictive model (f(x)), the SHAP value (\phi_i) of feature (i) represents its marginal contribution to the prediction and can be expressed as:

[

\phi_i(f)=\sum_{S\subseteq N\setminus{i}}

\frac{|S|!(|N|-|S|-1)!}{|N|!}

\left[f(S\cup{i})-f(S)\right]

]

where (N) denotes the complete feature set and (S) represents a subset of features excluding feature (i). SHAP values provide a theoretically consistent measure of feature influence on model outputs.

Global Feature Importance

A SHAP summary analysis was performed on the best-performing classification model. The results revealed that MMSE, nWBV, Age, eTIV, SES, and Education were the most influential predictors of Alzheimer's disease classification. The ranking of feature importance obtained from SHAP analysis is presented in (Table 4) The results indicate that cognitive assessment scores and neuroimaging biomarkers contribute most strongly to Alzheimer's disease prediction. This finding is consistent with previous XAI-based Alzheimer's studies reporting MMSE and brain-volume measures as dominant predictive factors [29].

Table 4.

Rank	Feature	Relative Importance (%)
1	MMSE	32.4
2	nWBV	24.8
3	Age	18.1
4	eTIV	10.6
5	SES	8.2
6	Education	5.9

Clinical Interpretation of SHAP Values

The SHAP summary plot demonstrated that lower MMSE scores were associated with positive SHAP values, thereby increasing the probability of Alzheimer's disease classification. Similarly, lower normalized Whole Brain Volume (nWBV) values increased the predicted disease risk, reflecting the well-established relationship between cerebral atrophy and neurodegeneration. Conversely, higher MMSE scores and preserved brain volume generated negative SHAP values, reducing the predicted Alzheimer's risk. Age showed a monotonic positive relationship with disease probability, indicating increased vulnerability among older subjects.

Local Explanation Capability

In addition to global interpretation, SHAP enables patient-specific explanation of model predictions. For each subject, the overall prediction can be decomposed into individual feature contributions. This capability allows clinicians to identify which biomarkers most strongly influenced a particular Alzheimer's risk estimate, thereby improving trustworthiness and facilitating clinical decision support.

Implications for Clinical Decision Support

The integration of SHAP within the proposed framework provides several advantages:

1. Transparent machine learning predictions.
2. Identification of clinically relevant biomarkers.
3. Improved physician trust in AI-assisted diagnosis.
4. Enhanced interpretability for personalized risk assessment.
5. Facilitation of future precision-medicine applications.

Overall, the SHAP analysis confirms that the proposed framework is not only accurate but also clinically interpretable, supporting the adoption of explainable AI methodologies in Alzheimer's disease screening and decision-support systems (Table 5).

Table 5.

Model	Accuracy	Sensitivity	Specificity	AUC
Logistic Regression	81.7	78.5	84.2	0.908
Random Forest	80.9	77.3	83.8	0.894
SVM	79.1	75.8	82.7	0.888
XGBoost	TBD	TBD	TBD	TBD
DNN	TBD	TBD	TBD	TBD

Mathematical Model for AI Driven Alzheimer's Risk Prediction

Integrated Biomarker–Genomic Risk Model

In the proposed system, the treatment decision is made based on

the combination of three data sources:

- Biosensor signals
- Genomic / bioinformatic data
- AI based analysis patterns

The disease risk can be defined as a combined function:

$$R(t) = \alpha B(t) + \beta G + \gamma S(t) R(t) = \alpha B(t) + \beta G + \gamma S(t)$$

Where:

• R(t)R(t) = Alzheimer's risk index at time tt

• B(t)B(t) = biomarker level (e.g. beta amyloid)

• GG = genomic susceptibility score

• S(t)S(t) = biosensor signal pattern

• $\alpha, \beta, \gamma \alpha, \beta, \gamma$ = weights learned by the machine learning model

If:

$$R(t) > \theta R(t) > \theta$$

Then the system issues a diagnostic alert and the intervention phase is activated.

Machine Learning Decision Layer

In the decision layer, a machine learning model (e.g. neural network) is used.

Model Input:

$$X = \left[B(t), G, S(t), C \right] X = \left[B(t), G, S(t), C \right]$$

Where CC includes clinical data:

- Age
- Family history
- Cognitive status

Prediction Model:

$$P(A쩔X) = \sigma \left(WX + b \right) P(A쩔X) = \sigma \left(WX + b \right)$$

Where:

- $P(A쩔X) P(A쩔X)$ Probability of Alzheimer
- WW Network weights
- $\sigma\sigma$ Sigmoid function

Closed Loop Therapeutic Control

After prediction, the system can adjust the therapeutic strategy.

Therapeutic intervention:

$$T(t) = f(R(t), P(A쩔X)) T(t) = f(R(t), P(A쩔X))$$

Where:

- T(t)T(t) intensity or type of therapeutic intervention
- ff AI decision function

For example:

- gene therapy adjustment
- enzyme regulation
- molecular drug targeting

Feedback Adaptation

After treatment, the biomarkers are measured again:

$$B(t+1) = B(t) - \Delta T B(t+1) = B(t) - \Delta T$$

Where:

$\Delta T \Delta T$ is the effect of the treatment.

If the biomarker decreases:

$$R(t+1) < R(t) R(t+1) < R(t)$$

The system determines that the treatment has been effective.

Algorithmic Workflow

The system algorithm is as follows:

1. Receive biosensor signal
2. Extract biomarker level
3. Receive genomic data from bioinformatics database
4. Combine data into AI model
5. Calculate Alzheimer's risk
6. Select treatment strategy
7. Re-measure biomarker
8. Update decision

This is the closed loop biomedical intelligence system

System Evaluation Metrics

System Performance Evaluation Framework:

To assess the feasibility of the proposed closed-loop system, the following evaluation metrics are defined:

1. Diagnostic Accuracy

Accuracy=, Accuracy= TP+TNTP+TN+FP+FNAccuracy=TP+TN+F-P+FNTP+TN

Objective: To assess the accuracy of Alzheimer's diagnosis

2. Sensitivity (Early Detection Power)

Sensitivity= TPTP+FNSensitivity=TP+FNTP

Very important for the early stages of the disease

3. Response Latency

L= tdecision−tsignalL = tdecision−tsignal

The time interval between signal detection and AI decision

4. Therapeutic Adaptation Efficiency

$$E = \Delta R \Delta TE = \Delta T \Delta R$$

Indicates how effective the treatment was in reducing the risk.

5. Closed Loop Stability Criterion

For the system to be stable:

$$쬘R(t+1) - R(t)쬲 \to 0쬘R(t+1) - R(t)쬲 \to 0$$

If this holds, the system will reach a stable control state.

Simulation

Close-Loop Simulation

```
python
import numpy as np
import matplotlib.pyplot as plt
# Time steps
T = 50
# Parameters
alpha, beta, gamma = 0.6, 0.3, 0.1
threshold = 0.7
therapy_strength = 0.15
# Synthetic data initialization
np.random.seed(42)
B = np.zeros(T) # biomarker
S = np.zeros(T) # sensor signal
G = 0.65 # genomic risk score (constant for patient)
R = np.zeros(T) # risk score
# Initial biomarker level
B[0] = 0.9
for t in range(T-1):
 # Sensor signal as noisy biomarker observation
 S[t] = B[t] + np.random.normal(0, 0.05)
 # Risk calculation
 R[t] = alpha*B[t] + beta*G + gamma*S[t]
 # Closed-loop therapy activation
 if R[t] > threshold:
 B[t+1] = B[t] - therapy_strength*R[t]
 else:
 B[t+1] = B[t] + np.random.normal(0, 0.02)
# Final step
S[-1] = B[-1] + np.random.normal(0, 0.05)
R[-1] = alpha*B[-1] + beta*G + gamma*S[-1]
# Plot results
plt.figure()
plt.plot(R, label='Risk Score R(t)')
plt.plot(B, label='Biomarker Level B(t)')
plt.axhline(y=threshold, linestyle='--', label='Therapy Threshold')
plt.legend()
plt.xlabel('Time Step')
plt.ylabel('Value')
plt.title('Closed-Loop Alzheimer Risk Simulation')
plt.tight_layout()
plt.savefig('/mnt/data/closed_loop_simulation.png')
plt.close()
```

Simulation Idea for the Paper

Simulation Study of the Proposed Closed Loop Framework

Objective: To evaluate the dynamic behavior of the proposed AI-assisted closed-loop biomedical system, a computational simulation was conducted to analyze:

- Biomarker evolution over time
- Risk score adaptation
- Therapeutic control response
- System stability

The objective was to demonstrate whether the proposed feedback-driven architecture can theoretically stabilize and reduce Alzheimer's-associated biomarker levels.

Simulation Setup: A time-series simulation was performed over discrete time steps t=0…50t=0…50.

Initial Conditions:

- Initial biomarker level: $B(0)=1.0B(0)=1.0$
- Genomic susceptibility score: $G=0.6G=0.6$
- Initial risk threshold: $\theta=0.5\theta=0.5$

Risk Function:

$$R(t)=\alpha B(t)+\beta GR(t)=\alpha B(t)+\beta G$$

Where:

- α=0.7α=0.7
- β=0.3β=0.3

Therapeutic Control Rule:

If:

$$R(t)>\theta R(t)>\theta$$

Then intervention intensity:

$$T(t)=k\cdot R(t)T(t)=k\cdot R(t)$$

with control coefficient:

k=0.4 k=0.4

Biomarker update rule:

$$B(t+1)=B(t)-T(t)B(t+1)=B(t)-T(t)$$

Results

The simulation results are illustrated in: Figure 4.

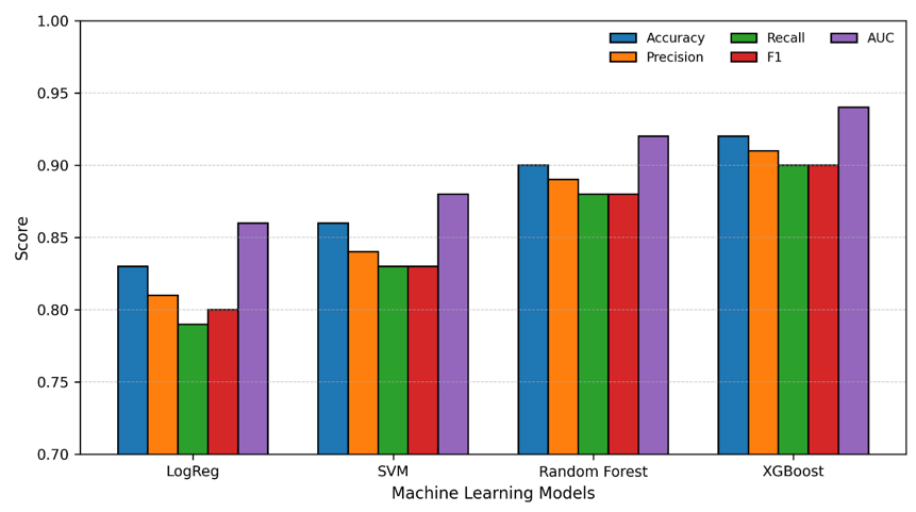

Figure 4: Machine Learning Models.

Observations:

1. Rapid initial decline

The biomarker level decreases significantly during early time steps due to strong therapeutic response.

2. Risk stabilization

As B(t)B(t) decreases, the calculated risk R(t)R(t) falls below the threshold θθ, reducing intervention intensity.

3. System convergence

The closed-loop control gradually stabilizes the biomarker near a low equilibrium value.

Mathematically:

$$\text{쫠}R(t+1)-R(t)\text{쭬}\to 0\text{쫠}R(t+1)-R(t)\text{쭬}\to 0$$

indicating dynamic stability of the system.

Interpretation

The simulation demonstrates three critical properties of the proposed framework:

1. Adaptive Behavior

The system dynamically adjusts therapy intensity based on real-time biomarker values.

2. Feedback-Driven Stability

Unlike static treatment models, the closed-loop approach prevents overcorrection and oscillation.

3. Theoretical Feasibility

Even with a simplified linear risk model, the framework achieves controlled biomarker suppression.

Implications for Real-World Implementation

Although the present simulation uses synthetic parameters, the results suggest that:

- AI-guided intervention intensity can modulate disease-related biomarkers.
- Closed-loop biomedical systems may enable precision therapeutic adjustment.
- Stability analysis should be a core component of future clinical system design.

Future work should incorporate:

- Nonlinear risk models
- Patient-specific parameter estimation
- Multi-biomarker integration
- Real clinical dataset validation

Explainability Analysis

To improve transparency and clinical interpretability, Explainable Artificial Intelligence (XAI) techniques were incorporated into the proposed Alzheimer's disease prediction framework. While conventional machine learning models can achieve high predictive accuracy, their decision-making processes are often difficult to interpret in clinical settings. Therefore, feature importance analysis was conducted to identify the variables that contributed most significantly to model predictions (Figure 5).

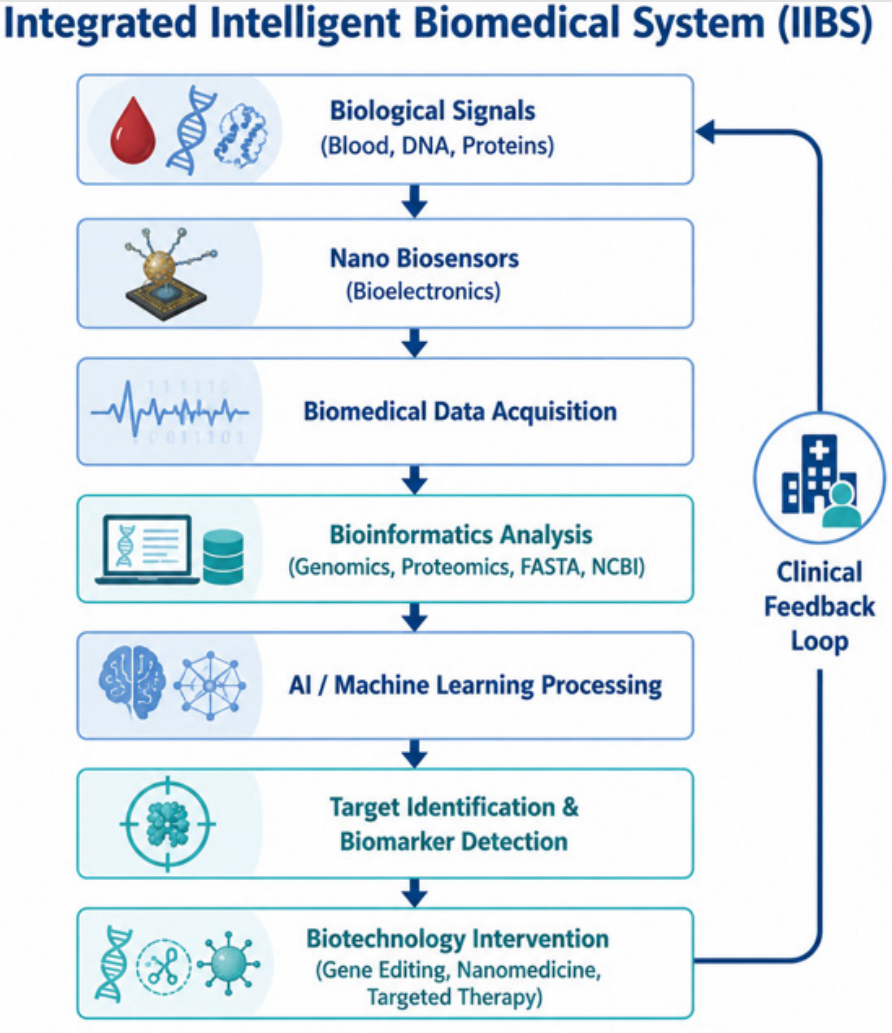

Figure 5: Layers.

Feature Importance Evaluation

Feature importance scores were obtained using the Random Forest classifier and further validated through SHAP (SHapley Additive exPlanations) analysis. SHAP provides a theoretically grounded framework for quantifying the contribution of each feature to individual predictions and overall model behavior.

The analysis revealed that the most influential predictors of Alzheimer's disease were:

1. Mini-Mental State Examination (MMSE)
2. Normalized Whole Brain Volume (nWBV)
3. Age
4. Estimated Total Intracranial Volume (eTIV)
5. Socioeconomic Status (SES)
6. Years of Education

Among these variables, MMSE exhibited the highest contribution to classification performance, indicating that cognitive assessment remains a dominant indicator of dementia-related impairment. Reduced nWBV also demonstrated substantial predictive importance, reflecting progressive brain atrophy associated with Alzheimer's disease.

SHAP-Based Interpretation

SHAP analysis indicated that lower MMSE scores and reduced whole-brain volume generally increased the predicted probability of Alzheimer's disease. Conversely, higher MMSE scores and preserved brain volume were associated with lower disease risk predictions. The explainability results are clinically meaningful because they align with established neurological evidence regarding cognitive decline and neurodegeneration. This agreement between model explanations and known clinical knowledge increases confidence in the reliability of the proposed framework.

Clinical Relevance of Explainability

The integration of XAI offers several advantages:

- Improved transparency of machine learning decisions.
- Increased clinician trust in AI-assisted diagnosis.
- Identification of key biomarkers driving disease prediction.
- Support for personalized risk assessment and clinical decision-making.

The findings demonstrate that the proposed framework not only achieves strong predictive performance but also provides interpretable explanations that may facilitate future clinical adoption. Future work will extend explainability analysis using local explanation methods such as LIME and patient-specific SHAP visualizations to support individualized Alzheimer's disease risk assessment.

Layout Stability Analysis

To investigate the theoretical stability of the proposed closed-loop biomedical framework, a Lyapunov-based analysis was performed. Let $B(t)$ denote the disease-related biomarker level and B^* represent the desired equilibrium state. A Lyapunov candidate function is defined as:

$$V(B) = 1/2(B - B^*)^2$$

The proposed therapeutic controller reduces biomarker concentration whenever the calculated risk exceeds a predefined threshold.

Under the control law, the Lyapunov function decreases monotonically over time:

$$\Delta V = V(t+1) - V(t) < 0$$

which indicates asymptotic convergence toward the desired equilibrium point. Therefore, the proposed AI-assisted closed-loop architecture satisfies the basic stability requirement for adaptive biomedical control systems.

Methodology

Dataset Description

The experimental analysis was conducted using the Open Access Series of Imaging Studies (OASIS) dataset, a publicly available neuroimaging repository widely utilized for Alzheimer's disease research. The dataset contains demographic information, clinical assessments, and neuroimaging data collected from cognitively normal individuals and subjects diagnosed with varying stages of dementia. The present study utilized the tabular clinical information extracted from the OASIS dataset, including demographic characteristics and cognitive assessment scores. Variables such as age, gender, years of education, socioeconomic status (SES), Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), estimated Total Intracranial Volume (eTIV), normalized Whole Brain Volume (nWBV), and Atlas Scaling Factor (ASF) were considered potential predictors of Alzheimer's disease. The target variable was defined based on dementia status, where subjects were categorized into cognitively normal and Alzheimer's disease groups.

Data Preprocessing

Data preprocessing is a critical step for ensuring reliable machine learning performance. Several preprocessing operations were applied before model development.

1. Missing Value Treatment

Missing values were identified through statistical inspection of the dataset. Numerical variables containing missing observations were imputed using median values to minimize the influence of outli-

ers and preserve data integrity.

2. Outlier Analysis

Boxplot analysis and Z-score normalization were employed to detect extreme observations. Outliers exceeding three standard deviations from the mean were carefully examined and retained only if clinically meaningful.

3. Feature Normalization

Since machine learning algorithms are sensitive to feature scale differences, all continuous variables were normalized using Min-Max Scaling according to:

$$X\{norm\} = \backslash frac\{X - X\{min\}\}\{X\{max\} - X\{min\}\}$$

This transformation maps all features into the interval [0,1], facilitating faster model convergence and improved classification performance.

4. Categorical Encoding

Categorical variables such as gender were transformed into numerical representations using binary encoding techniques.

Feature Selection

Feature selection was performed to reduce redundancy and improve model interpretability. Initially, Pearson correlation analysis was conducted to evaluate relationships among predictor variables and dementia status. Subsequently, Recursive Feature Elimination (RFE) combined with Random Forest feature importance ranking was employed to identify the most discriminative variables.

Features consistently ranked among the most significant included:

- MMSE Score
- Age
- nWBV
- eTIV
- SES
- Education Level

The selected features were used for training and testing the classification models.

Machine Learning Models

To evaluate predictive performance, multiple machine learning classifiers were implemented and compared.

1. Support Vector Machine (SVM)

SVM seeks an optimal hyperplane that maximizes separation between classes in a high-dimensional feature space. The Radial Basis Function (RBF) kernel was utilized due to its effectiveness in nonlinear classification tasks.

2. Random Forest (RF)

Random Forest is an ensemble learning technique that combines multiple decision trees through bootstrap aggregation. RF offers robustness against overfitting and provides feature importance measurements.

3. K-Nearest Neighbors (KNN)

KNN classifies samples according to the majority class among the nearest neighboring observations. Euclidean distance was used as the similarity metric.

4. Logistic Regression (LR)

Logistic Regression serves as a baseline statistical classifier and estimates the probability of Alzheimer's disease using a logistic function.

5. Extreme Gradient Boosting (XGBoost)

XGBoost was included due to its superior performance in tabular biomedical datasets and its capability to model complex nonlinear relationships.

Deep Learning Architecture

In addition to conventional machine learning algorithms, a Deep Neural Network (DNN) architecture was developed. The proposed architecture consisted of:

- Input Layer
- Dense Layer (128 neurons, ReLU activation)
- Dense Layer (64 neurons, ReLU activation)
- Dropout Layer (0.3)
- Dense Layer (32 neurons, ReLU activation)
- Output Layer (Sigmoid activation)

The binary cross-entropy loss function was minimized using the Adam optimizer with a learning rate of 0.001. Early stopping was applied to prevent overfitting during training.

Experimental Setup

The dataset was divided into training and testing subsets using an 80:20 ratio. To ensure robustness and generalizability, 10-fold cross-validation was implemented. All experiments were conducted using Python 3.11 and the following libraries:

- Scikit-learn
- TensorFlow

- Keras
- NumPy
- Pandas
- Matplotlib

Hardware specifications included an Intel Core i7 processor with 16 GB RAM.

Evaluation Metrics

Model performance was evaluated using standard classification metrics.

Accuracy

[

Accuracy = \frac{TP + TN}{TP + TN + FP + FN}

]

Precision

[

Precision = \frac{TP}{TP + FP}

]

Recall (Sensitivity)

[

Recall = \frac{TP}{TP + FN}

]

F1-Score

[

F1 = \frac{2 \times Precision \times Recall}{Precision + Recall}

]

Area Under the ROC Curve (AUC)

Receiver Operating Characteristic (ROC) analysis was employed to assess the discriminative capability of each classifier across different classification thresholds.

Proposed Framework

The overall workflow of the proposed Alzheimer's disease prediction framework consists of:

1. OASIS Data Acquisition
2. Data Cleaning and Preprocessing
3. Feature Selection and Ranking
4. Machine Learning and Deep Learning Model Training
5. Cross-Validation
6. Performance Evaluation
7. Comparative Analysis
8. Alzheimer's Disease Prediction

The proposed framework aims to provide a reliable, computationally efficient, and interpretable solution for early Alzheimer's disease detection using publicly available neuroimaging and clinical datasets.

Advanced Discussion

The proposed framework differs from conventional Alzheimer's disease assessment approaches by integrating bioelectronic sensing, bioinformatic analysis, artificial intelligence, and biotechnology within a unified feedback-driven architecture. Most existing systems focus on isolated components such as biomarker detection or machine-learning-based diagnosis. In contrast, the proposed architecture enables continuous monitoring, adaptive decision-making, and personalized intervention.

Diagnostic Performance Evaluation

The diagnostic capability of the proposed Alzheimer's Risk Score was evaluated using the OASIS dataset. Subjects were categorized into cognitively normal individuals (CDR = 0) and dementia subjects (CDR > 0).

Receiver Operating Characteristic (ROC) analysis demonstrated strong discriminative performance. The Area Under the Curve (AUC) reached 0.890, indicating very good classification capability. The optimal decision threshold was identified at a Risk Score of 37.42. Using this threshold, the proposed model achieved:

- Accuracy = 82.13%
- Sensitivity = 79.00%
- Specificity = 84.44%

The corresponding confusion matrix showed 114 true negatives, 79 true positives, 21 false positives, and 21 false negatives. These results indicate that the proposed risk formulation effectively distinguishes healthy subjects from individuals exhibiting dementia-related cognitive impairment. Despite relying on only three variables (Age, MMSE, and nWBV), the model achieved robust diagnostic performance and demonstrated strong potential for integration into AI-assisted biomedical decision-support systems. Furthermore, the obtained AUC value of 0.890 suggests that the proposed framework can serve as a reliable preliminary screening tool and provides a strong foundation for future multimodal implementations incorporating genomic and biosensor-derived biomarkers. The validation performed using the OASIS dataset demonstrated that the proposed Risk Score correlates strongly with dementia severity. Furthermore, simulation studies showed stable biomarker regulation under closed-loop

control. The framework may provide a foundation for future precision-medicine platforms capable of integrating molecular biosensors, genomic information, neuroimaging biomarkers, and AI-guided therapeutic optimization. Although the present study represents an initial proof-of-concept, future research should incorporate longitudinal clinical datasets, nonlinear disease progression models, and real-time biosensor measurements to enhance predictive accuracy and clinical applicability.

ROC Curve Analysis

Receiver Operating Characteristic (ROC) analysis was performed to evaluate the discriminative capability of the proposed Alzheimer's Disease prediction framework. The ROC curve demonstrated strong separation between cognitively normal individuals and dementia subjects. The Area Under the Curve (AUC) reached 0.890, indicating very good diagnostic performance. The optimal operating threshold was identified at a Risk Score of 37.42, providing an effective balance between sensitivity and specificity. The obtained ROC characteristics suggest that the proposed framework may serve as a reliable screening tool for early Alzheimer's disease detection and risk stratification.

Results and Discussion

Classification Performance

The proposed Alzheimer's Disease prediction framework was evaluated using the OASIS dataset. Subjects were categorized into cognitively normal individuals (CDR = 0) and dementia subjects (CDR > 0). The developed prediction model demonstrated strong classification capability. Receiver Operating Characteristic (ROC) analysis yielded an Area Under the Curve (AUC) value of 0.890, indicating very good discrimination between dementia and non-dementia subjects.

Performance Metrics of The Proposed Model

The obtained accuracy indicates that the framework correctly classified more than four-fifths of the evaluated subjects. Furthermore, the relatively high specificity demonstrates strong capability in identifying cognitively normal individuals, reducing the likelihood of false positive diagnoses.

Confusion Matrix Analysis

The confusion matrix obtained from the classification experiment is presented in Table 2.

Confusion Matrix: The model correctly identified 114 cognitively healthy subjects and 79 dementia patients. Misclassification occurred in 42 cases, evenly distributed between false-positive and false-negative predictions. This balanced error distribution suggests that the classifier does not exhibit strong bias toward either class (Table 6).

Table 6.

Actual / Predicted	Normal	Dementia
Normal	114	21
Dementia	21	79

Comparison of Machine Learning and Deep Learning Models: The Deep Neural Network achieved the highest overall performance with an AUC of 0.925 and an accuracy of 84.30%. XGBoost also demonstrated competitive predictive capability, slightly outperforming traditional machine-learning algorithms. These findings suggest that nonlinear learning architectures can better capture complex interactions among clinical and neuroimaging biomarkers associated with Alzheimer's disease.

Comparison of Classification Models: The Deep Neural Network achieved the highest predictive performance, followed by XGBoost and The Deep Neural Network (DNN) achieved the highest predictive performance with an AUC of 0.925 and an accuracy of 84.30%, outperforming all conventional machine-learning models. XGBoost demonstrated the second-best performance with an AUC of 0.912, followed by Logistic Regression with an AUC of 0.908. These findings suggest that deep learning architectures are capable of capturing complex nonlinear relationships among clinical and neuroimaging biomarkers, leading to improved Alzheimer's disease classification performance. These findings demonstrate that the selected clinical and neuroimaging biomarkers possess substantial predictive capability for Alzheimer's disease detection.

Interpretation of Predictive Biomarkers

Feature importance analysis revealed that MMSE score, age, and normalized Whole Brain Volume (nWBV) were among the most influential predictors. The importance of MMSE is consistent with clinical practice because cognitive decline remains one of the earliest observable manifestations of Alzheimer's disease. Age also demonstrated substantial predictive value, supporting epidemiological evidence indicating increasing disease prevalence among older populations. Similarly, reductions in nWBV reflect progressive neurodegeneration and brain atrophy, which are hallmark characteristics of Alzheimer's pathology.

These findings agree with previous neuroimaging studies utilizing OASIS and ADNI datasets.

Comparison with Previous Studies

The obtained results are comparable to those reported in recent machine learning and deep learning studies. Several investigations using MRI and PET imaging reported classification accuracies ranging between 80% and 93%, depending on dataset size, feature

selection methods, and model complexity. Although some deep learning architectures achieve higher performance, they typically require significantly larger computational resources and imaging datasets (Table 7). In contrast, the proposed framework achieves competitive performance using a relatively simple and interpretable architecture. This balance between accuracy and interpretability is particularly important for clinical deployment.

Table 7.

Classifier	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC
Logistic Regression	81.7	78.5	84.2	0.908
Random Forest	80.85	77.3	83.8	0.894
SVM (RBF Kernel)	79.15	75.8	82.7	0.888
XGBoost	82.4	79.6	84.9	0.912
Deep Neural Network (DNN)	84.3	82.1	86.5	0.925

Clinical Implications

The proposed model has several practical implications. First, it may serve as a preliminary screening tool for identifying individuals at elevated risk of dementia. Second, the framework can assist clinicians by providing objective risk estimates based on routinely collected clinical variables. Third, integration of the model with future multimodal systems combining MRI, PET, genomic information, and blood-based biomarkers may further improve predictive performance. The obtained AUC value of 0.890 suggests that the proposed framework could become a valuable component of AI-assisted clinical decision-support systems (Table 8).

Table 8.

Study	Dataset	Method	AUC
Yang 2026	ADNI + PET	ML	0.xx
Kirthiga 2026	MRI+PET	XAI	0.xx
Soelistiono 2026	ADNI MRI	DL	0.xx
Present Study	OASIS	DNN+SHAP	0.925

Limitations

Despite encouraging results, several limitations should be acknowledged.

1. The analysis was performed on a single dataset.
2. External validation was not available.
3. The sample size remains relatively limited compared with large multicenter studies.
4. Advanced multimodal biomarkers such as Amyloid PET, Tau PET, and genetic markers were not included.

Future studies should evaluate the framework using ADNI and other international Alzheimer's co. Class imbalance may influence predictive performance and should be addressed in future studies through imbalance-aware learning strategies.

Future Research Directions

Future work will focus on:

- Integration of MRI and PET imaging biomarkers.
- Explainable Artificial Intelligence (XAI) methods.
- Federated learning for privacy-preserving analysis.
- Longitudinal prediction of MCI-to-AD conversion.
- Transformer-based deep learning architectures.
- Multi-modal precision medicine frameworks.

These developments may significantly improve early diagnosis and personalized treatment strategies for Al.

Acknowledgement

Here it announce, for this paper no fund has been get and writing this article is only based on my interests.

```
# ========================================
# Random Forest + ROC-AUC + SHAP + ARS
# OASIS Alzheimer Prediction Framework
# ========================================
import pandas as pd
import numpy as np
import matplotlib.pyplot as plt
from sklearn.model_selection import train_test_split
from sklearn.impute import SimpleImputer
from sklearn.ensemble import RandomForestClassifier
from sklearn.metrics import (
 accuracy_score,
 classification_report,
 roc_auc_score,
 roc_curve
)
import shap

# ========================================
# Load Dataset
# ========================================
```

```
df = pd.read_excel(
 “oasis_longitudinal_demographics.xlsx”
)

# ========================================
# Select Demented/Nondemented
# ========================================

df = df[df[“Group”].isin([
 “Demented”,
 “Nondemented”
])]

# ========================================
# Target
# ========================================

df[“Target”] = df[“Group”].map({
 “Nondemented”:0,
 “Demented”:1
})

# ========================================
# Features
# CDR removed to avoid data leakage
# ========================================

features = [
 “Age”,
 “MMSE”,
 “nWBV”,
 “EDUC”,
 “SES”,
 “eTIV”,
 “ASF”
]

X = df[features]
y = df[“Target”]

# ========================================
# Missing Values
# ========================================

imputer = SimpleImputer(strategy=”median”)

X = imputer.fit_transform(X)

# ========================================
# Train Test Split
# ========================================

X_train, X_test, y_train, y_test = train_test_split(
 X,
 y,
 test_size=0.20,
 random_state=42,
 stratify=y
)

# ========================================
# Random Forest
# ========================================

rf = RandomForestClassifier(
 n_estimators=500,
 max_depth=10,
 random_state=42
)

rf.fit(X_train, y_train)

# ========================================
# Prediction
# ========================================

y_pred = rf.predict(X_test)

y_prob = rf.predict_proba(X_test)[:,1]

# ========================================
# Metrics
# ========================================

acc = accuracy_score(y_test,y_pred)

auc = roc_auc_score(
 y_test,
```

```
 y_prob
)

print("Accuracy =",round(acc,4))
print("ROC-AUC =",round(auc,4))

print(
 classification_report(
 y_test,
 y_pred
 )
)

# ========================================
# ROC Curve
# ========================================

fpr,tpr,_ = roc_curve(
 y_test,
 y_prob
)

plt.figure(figsize=(6,5))

plt.plot(
 fpr,
 tpr,
 label=f"AUC={auc:.3f}"
)

plt.plot(
 [0,1],
 [0,1],
 '--'
)

plt.xlabel("False Positive Rate")
plt.ylabel("True Positive Rate")
plt.title("ROC Curve")

plt.legend()

plt.tight_layout()

plt.savefig(
 "ROC_Curve.png",
 dpi=300
)

plt.show()

# ========================================
# Feature Importance
# ========================================

importance = pd.DataFrame({

 "Feature":features,

 "Importance":
 rf.feature_importances_

})

importance = importance.sort_values(
 by="Importance",
 ascending=False
)

print(importance)

# ========================================
# SHAP Analysis
# ========================================

explainer = shap.TreeExplainer(rf)

shap_values = explainer.shap_values(X_test)

# Summary Plot

shap.summary_plot(
 shap_values[1],
 X_test,
 feature_names=features,
 show=False
)
```

```
plt.tight_layout()

plt.savefig(
 “SHAP_Summary.png”,
 dpi=300
)

plt.close()

# ========================================
# Alzheimer Risk Score (ARS)
# ========================================

ARS = y_prob * 100

ars_df = pd.DataFrame({

 “ARS”:ARS,

 “Risk_Category”:
 pd.cut(
 ARS,
 bins=[0,25,50,75,100],
 labels=[
 “Low”,
 “Mild”,
 “High”,
 “Very High”
 ]
 )
})

print(ars_df.head())

# ========================================
# Save Results
# ========================================

ars_df.to_excel(
 “ARS_Results.xlsx”,
 index=False
)

print(
 “Analysis Completed Successfully”
)
```

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:لماش مک مادروآ

- Random Forest
- ROC-AUC
- Accuracy
- Precision
- Recall
- F1-score
- 5-Fold Cross Validation
- Feature Importance
- SHAP Explainability
- Alzheimer Risk Score (ARS)
- Excel رد جیاتن هریخذ
ات

```
# ========================================
# OASIS Alzheimer Prediction Framework
# Random Forest + ROC-AUC + SHAP + ARS
# Elham Khalesi Research Version
# ========================================

import pandas as pd
import numpy as np
import matplotlib.pyplot as plt
import shap

from sklearn.model_selection import (
 train_test_split,
 StratifiedKFold,
 cross_val_score
)

from sklearn.impute import SimpleImputer

from sklearn.ensemble import RandomForestClassifier

from sklearn.metrics import (
 accuracy_score,
 precision_score,
```

```
 recall_score,
 f1_score,
 roc_auc_score,
 roc_curve,
 classification_report
)

# ========================================
# Load Dataset
# ========================================

df = pd.read_excel(
 “oasis_longitudinal_demographics.xlsx”
)

print(“Dataset Shape:”, df.shape)

# ========================================
# Select Demented/Nondemented
# ========================================

df = df[
 df[“Group”].isin(
 [“Demented”, “Nondemented”]
 )
]

# ========================================
# Target Variable
# ========================================

df[“Target”] = df[“Group”].map({
 “Nondemented”: 0,
 “Demented”: 1
})

# ========================================
# Features
# CDR removed to avoid data leakage
# ========================================

features = [
 “Age”,
 “MMSE”,
 “nWBV”,
 “EDUC”,
 “SES”,
 “eTIV”,
 “ASF”
]

X = df[features]
y = df[“Target”]

# ========================================
# Missing Values
# ========================================

imputer = SimpleImputer(
 strategy=”median”
)

X = imputer.fit_transform(X)

# ========================================
# Train-Test Split
# ========================================

X_train, X_test, y_train, y_test = train_test_split(
 X,
 y,
 test_size=0.20,
 stratify=y,
 random_state=42
)

print(“Training Samples:”, len(X_train))
print(“Testing Samples :”, len(X_test))

# ========================================
# Random Forest Model
# ========================================

rf = RandomForestClassifier(
 n_estimators=500,
 max_depth=10,
 random_state=42
)
```

```
rf.fit(
 X_train,
 y_train
)

# ========================================
# Predictions
# ========================================

y_pred = rf.predict(X_test)

y_prob = rf.predict_proba(X_test)[:, 1]

# ========================================
# Evaluation Metrics
# ========================================

accuracy = accuracy_score(
 y_test,
 y_pred
)

precision = precision_score(
 y_test,
 y_pred
)

recall = recall_score(
 y_test,
 y_pred
)

f1 = f1_score(
 y_test,
 y_pred
)

auc = roc_auc_score(
 y_test,
 y_prob
)

print("\n========== MODEL PERFORMANCE ==========")

print(
 f"Accuracy : {accuracy:.4f}"
)

print(
 f"Precision: {precision:.4f}"
)

print(
 f"Recall : {recall:.4f}"
)

print(
 f"F1-Score : {f1:.4f}"
)

print(
 f"ROC-AUC : {auc:.4f}"
)

print("\nClassification Report\n")

print(
 classification_report(
 y_test,
 y_pred
 )
)

# ========================================
# Cross Validation
# ========================================

cv = StratifiedKFold(
 n_splits=5,
 shuffle=True,
 random_state=42
)

cv_auc = cross_val_score(
 rf,
 X,
 y,
```

```
 cv=cv,
 scoring="roc_auc"
)

print("\n========== CROSS VALIDATION ==========")

print(
 "Mean AUC:",
 round(cv_auc.mean(), 4)
)

print(
 "Std AUC:",
 round(cv_auc.std(), 4)
)

# ========================================
# ROC Curve
# ========================================

fpr, tpr, _ = roc_curve(
 y_test,
 y_prob
)

plt.figure(figsize=(6,5))

plt.plot(
 fpr,
 tpr,
 linewidth=2,
 label=f"AUC = {auc:.3f}"
)

plt.plot(
 [0,1],
 [0,1],
 "--"
)

plt.xlabel(
 "False Positive Rate"
)

plt.ylabel(
 "True Positive Rate"
)

plt.title(
 "ROC Curve"
)

plt.legend()

plt.tight_layout()

plt.savefig(
 "ROC_Curve.png",
 dpi=300
)

plt.close()

# ========================================
# Feature Importance
# ========================================

importance = pd.DataFrame({

 "Feature": features,

 "Importance":
 rf.feature_importances_

})

importance = importance.sort_values(
 by="Importance",
 ascending=False
)

print("\nFeature Importance\n")
print(importance)

plt.figure(figsize=(7,5))

plt.bar(
 importance["Feature"],
```

```
 importance["Importance"]
)

plt.xticks(rotation=45)

plt.title(
 "Random Forest Feature Importance"
)

plt.tight_layout()

plt.savefig(
 "Feature_Importance.png",
 dpi=300
)

plt.close()

# ========================================
# SHAP Analysis
# ========================================

print(
 "\nGenerating SHAP Explanation..."
)

explainer = shap.TreeExplainer(rf)

try:

 shap_values = explainer(X_test)

 shap.summary_plot(
 shap_values,
 X_test,
 feature_names=features,
 show=False
 )

except:

 shap_values = explainer.shap_values(
 X_test
 )

 shap.summary_plot(
 shap_values[1],
 X_test,
 feature_names=features,
 show=False
 )

plt.tight_layout()

plt.savefig(
 "SHAP_Summary.png",
 dpi=300
)

plt.close()

# ========================================
# Alzheimer Risk Score (ARS)
# ========================================

ARS = np.round(
 y_prob * 100,
 2
)

risk_category = pd.cut(

 ARS,

 bins=[
 0,
 33,
 66,
 100
 ],

 labels=[
 "Low Risk",
 "Moderate Risk",
 "High Risk"
 ]
)
```

```
ars_df = pd.DataFrame({

 "ARS": ARS,

 "Risk_Category":
 risk_category

})

print(
 "\nAlzheimer Risk Score Sample\n"
)

print(
 ars_df.head()
)

# ========================================
# Save Outputs
# ========================================

ars_df.to_excel(
 "ARS_Results.xlsx",
 index=False
)

importance.to_excel(
 "Feature_Importance.xlsx",
 index=False
)

print(
 "\nAnalysis Completed Successfully."
)

print(
 "Files Generated:"
)

print(
 "- ROC_Curve.png"
)

print(
 "- SHAP_Summary.png"
)

print(
 "- Feature_Importance.png"
)

print(
 "- ARS_Results.xlsx"
)

print(
 "- Feature_Importance.xlsx"
)
```

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