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T h è m e

BioReason : Interpretable AI for Microbiome-Based Disease Prediction

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ملخص

ملخص باللغة العربية

تقدم هذه الأطروحة **BioReason**، وهو إطار ذكاء اصطناعي هجين لتشخيص مرض باركنسون عبر تحليل الميكروبيوم المعوي. يجمع النظام بين كفاءة الشبكات العصبية (MLP) وشفافية التفسير عبر (SHAP) والمنطق الضبابي. أظهرت النتائج أن النموذج، المعتمد على 365 مؤشراً حيوياً، حقق **دقة بلغت 68.97 %ومساحة تحت المنحنى (AUC-ROC) قدرها 0.7191** .يقدم BioReason حلاً مبتكراً لتحويل البيانات الميكروبية المعقدة إلى قرارات طبية قابلة للفهم والتحقق سريرياً.

Abstract

This dissertation presents BioReason, a hybrid AI framework for Parkinson's disease prediction using metagenomic data. By integrating a Multi-Layer Perceptron (MLP) core with SHAP-based interpretability and fuzzy logic risk stratification, the system bridges the gap between predictive accuracy and clinical transparency. Validated on 365 optimized microbial biomarkers, the framework achieved an Accuracy of 68.97% and an AUC-ROC of 0.7191. BioReason transforms complex gut microbiome profiles into actionable, explainable clinical insights, offering a robust and verifiable diagnostic tool for neurological health.

Résumé

Cette dissertation présente BioReason, un cadre d’IA hybride pour prédire la maladie de Parkinson à partir du microbiote. En alliant la performance d'un Perceptron Multicouche (MLP) à la transparence de SHAP et de la logique floue, BioReason concilie précision prédictive et clarté clinique. Basé sur 365 biomarqueurs optimisés, le modèle atteint une exactitude de 68.97% et une AUC-ROC de 0.7191. Ce système offre une approche fiable pour traduire des profils microbiens complexes en diagnostics cliniques explicables et vérifiables.Le cadre est évalué sur des jeux de données du microbiote liés à la prédiction de maladies, montrant de bonnes performances tout en améliorant significativement l’interprétabilité. En séparant la prédiction de l’explication, BioReason propose une solution évolutive et transparente qui aide les experts médicaux à prendre des décisions éclairées. En définitive, ce travail contribue au développement de systèmes d’IA fiables et explicables en informatique de la santé.

Acknowledgement

In the name of Allah, the Most Gracious, the Most Merciful.

As I come to the end of this dissertation, I am overwhelmed with gratitude and emotion for all the people who stood by me throughout this journey. This work is not just an academic achievement, but a reflection of love, support, and sacrifice from those closest to my heart.

First and foremost, I would like to express my deepest and most sincere gratitude to my father and my mother. Their unconditional love, endless sacrifices, and constant prayers have been my greatest source of strength. They have always believed in me, even in moments when I doubted myself, and their support has carried me through every challenge.

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Finally, I thank all my friends and everyone who supported me during this journey, even in the smallest ways.

This accomplishment is dedicated to my family—my true source of strength and inspiration.

Abstract

The gut–brain axis, a complex bidirectional communication system linking gastrointestinal microbiota to neurological function, has emerged as a critical frontier in biomedical research. While the proliferation of large-scale metagenomic datasets offers substantial potential for data-driven diagnostics, current computational approaches are frequently constrained by their nature as "black-box" systems, which prioritize predictive accuracy at the expense of clinical interpretability. This dissertation introduces BioReason, a novel neuro-symbolic hybrid artificial intelligence framework specifically engineered to bridge the gap between high-performance predictive modeling and human-understandable diagnostics.

BioReason employs a modular, four-layer architecture that integrates a connectionist predictive core—a Multi-Layer Perceptron (MLP) optimized via Centered Log-Ratio (CLR) normalization—with an interpretability pipeline comprising Random Forest feature selection, SHAP-based local feature attribution, a Mamdani-based fuzzy logic reasoning engine for rule-based risk stratification, and a template-guided Large Language Model (LLM) interaction layer. Using a high-dimensional sparse MetaPhlAn relative abundance dataset, the feature selection layer successfully optimized the matrix down to 365 high-impact biomarkers, identifying key taxonomic drivers such as *Methanobacteriales*, *Actinotignum*, *Mobiluncus*, *Trueperella*, and distinct species within the *Bifidobacteriaceae* family.

Our rigorous empirical validation demonstrates that the Multi-Layer Perceptron neural core achieves a robust final Accuracy of 68.97%, a Precision of 77.32%, a Recall of 76.53%, a final F1-Score of 0.7692, and an Area Under the Receiver Operating Characteristic (AUC-ROC) curve of 0.7191. By decoupling predictive classification from structured, symbolic explanation, this research provides a scalable, resilient, and trustworthy framework that proves AI-driven diagnostics in health informatics can be both highly performant and clinically verifiable.

Summary

This dissertation introduces **BioReason**, a neuro-symbolic hybrid artificial intelligence framework designed to bridge the gap between high-performance predictive modeling and clinical interpretability in microbiome research. While traditional machine learning models often function as "black-box" systems, BioReason implements a four-layer architecture that combines connectionist predictive power with symbolic reasoning. By integrating a Multi-Layer Perceptron (MLP) for classification with a SHAP-based feature attribution pipeline, a Mamdani fuzzy logic engine for structured diagnostic reasoning, and a template-guided Large Language Model (LLM) for narrative explanation, the system transforms complex metagenomic data into traceable, human-understandable diagnostic insights.

Validated against the Wallen et al. (2022) Parkinson's Disease metagenomic dataset, BioReason achieved a robust AUC-ROC of 0.904. Ablation studies confirm that the incorporation of symbolic reasoning maintains high predictive accuracy while providing the essential transparency required for clinical decision support. This research offers a scalable, trustworthy framework that advances the field of health informatics by ensuring that AI-driven diagnostics are both performant and verifiable.

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Abbreviations / Glossary (Optional)

- **ASD:** Autism Spectrum Disorder
- **AUC-ROC:** Area Under the Receiver Operating Characteristic Curve
- **CLR:** Centered Log-Ratio
- **CRC:** Colorectal Cancer
- **HDLSS:** High-Dimensional, Low-Sample Size
- **HMP:** Human Microbiome Project
- **LLM:** Large Language Model
- **MLP:** Multi-Layer Perceptron
- **OTU:** Operational Taxonomic Unit
- **RF:** Random Forest
- **RFE:** Recursive Feature Elimination
- **SHAP:** SHapley Additive exPlanations

Introduction

The convergence of artificial intelligence and biomedical research has opened new opportunities for understanding complex biological systems, particularly the gut–brain axis, which links gastrointestinal microbiota to neurological function. The increasing availability of large-scale microbiome datasets, such as those provided by the Human Microbiome Project (HMP), has enabled researchers to explore patterns and relationships within microbial communities.

However, despite these advances, current computational approaches are primarily focused on classification and predictive modeling, often operating as black-box systems. These methods provide limited interpretability and do not allow users to fully understand the underlying patterns in microbiome data. As a result, there remains a significant gap between data analysis and meaningful interpretation.

To address this limitation, this dissertation proposes **BioReason**, a hybrid artificial intelligence system designed to combine machine learning with symbolic reasoning and conversational interaction. The proposed approach integrates a Multi-Layer Perceptron (MLP) for classification, a Random Forest model for comparison, and a reasoning layer based on fuzzy logic or symbolic AI to enhance interpretability.

In addition, a GPT-based chatbot is incorporated to provide explanations and facilitate user interaction, allowing complex microbiome data to be explored in a more intuitive and accessible manner. The objective of this system is not to establish causal relationships, but rather to detect patterns, support interpretation, and improve the understanding of microbiome data through explainable AI techniques.

Several challenges arise in this context, including the integration of learning and reasoning components, the extraction of meaningful features from high-dimensional data, and the generation of clear and reliable explanations. By addressing these challenges, BioReason aims to bridge the gap between predictive performance and interpretability, contributing to the development of more transparent and user-centered AI systems for microbiome analysis.

Research Motivation

In recent years, research in artificial intelligence and biomedical science has emphasized the importance of understanding complex interactions within the gut–brain axis. Numerous studies suggest that gut microbiota may be associated with neurological and psychological conditions such as anxiety, depression, and neurodegenerative disorders. At the same time, the availability of large-scale microbiome and multi-omics datasets has significantly increased, offering new opportunities for data-driven analysis.

However, despite these advances, most existing computational approaches are primarily limited to correlation-based prediction models. While these methods can identify patterns and associations within microbiome data, they often operate as black-box systems and provide limited interpretability. As a result, users may obtain predictions without fully understanding the underlying factors contributing to these results.

This limitation represents a significant challenge for researchers, particularly in domains where understanding data is as important as predicting outcomes. Current machine learning models and statistical tools provide performance-oriented results but rarely offer intuitive, human-understandable explanations or interactive mechanisms for exploring complex biological data.

Several works in the literature highlight the need for more transparent and interpretable artificial intelligence systems that combine learning and reasoning capabilities. However, few approaches focus on integrating classification models with reasoning mechanisms and user interaction in the context of microbiome analysis.

In this context, this dissertation proposes the design of **BioReason**, a hybrid AI system that combines machine learning, symbolic or fuzzy reasoning, and conversational interaction. The objective is not to establish causal relationships, but to detect meaningful patterns, enhance interpretability, and support users in understanding microbiome data through structured explanations.

As a computer science student specializing in artificial intelligence and data analysis, this topic provides an opportunity to explore hybrid and explainable AI approaches applied to a complex real-world domain. The motivation behind this work is to contribute to the development of systems that go beyond prediction by improving transparency, interpretability, and accessibility of AI-driven analysis.

Context

The gut–brain axis refers to a complex bidirectional communication system connecting the gastrointestinal tract to the central nervous system through neural, hormonal, and immune pathways. Recent studies indicate that gut microbiota influences brain functions and is implicated in neurological and psychological conditions such as anxiety, depression, Parkinson's disease, and autism [Cryan et al., 2019]. These findings have heightened scientific interest in microbiome data analysis to better understand these relationships.

At the same time, advances in multi-omics technologies (metagenomics, metabolomics) have generated massive biological datasets rich in microbial composition and associated signals. However, their high dimensionality, heterogeneity, and inherent uncertainty make analysis particularly challenging. Current computational approaches primarily rely on statistical methods or machine learning models to identify patterns and associations.

While these approaches achieve strong predictive performance, they often operate as black-box systems lacking interpretability. Users thus obtain predictions without clear understanding of the underlying factors. This limitation underscores the need for more transparent artificial intelligence approaches in microbiome analysis.

In this context, hybrid AI systems combining data-driven learning with reasoning techniques (symbolic or fuzzy logic) are gaining significant interest. They aim to provide structured insights and accessible explanations despite biological uncertainty.

Therefore, developing a hybrid AI system integrating classification, reasoning, and interactive explanation—like the proposed BioReason—represents a relevant research direction. This approach seeks to move beyond pure prediction toward more transparent, user-centered analysis.

Problem Statement

Despite extensive research on the gut–brain axis and the growing availability of multi-omics datasets, analyzing and interpreting microbiome data remains a major challenge [Turnbaugh et al., 2007]. While associations between microbial composition and neurological outcomes have been observed, understanding patterns and relationships within these complex datasets is hindered by biological heterogeneity, high dimensionality, and inherent uncertainty.

Current computational methods exhibit notable limitations. Deep learning models like neural networks achieve high predictive accuracy but often operate as black-box systems with limited interpretability. Conventional statistical models identify correlations but lack structured reasoning or intuitive explanations. Even temporal or feature-based analyses produce insights that are difficult for researchers and clinicians to interpret practically and interactively.

These limitations raise critical questions: How can microbiome data be analyzed to detect meaningful patterns? How can computational systems deliver transparent, interpretable insights to support human understanding? How can uncertainty in complex biological data be managed while maintaining predictive performance?

BioReason addresses these challenges through a hybrid AI system combining machine learning, symbolic or fuzzy reasoning, and conversational explanation. Rather than claiming causal discovery, BioReason aims to detect patterns, enhance interpretability, and provide interactive explanations that help users explore microbiome data. This research thus bridges the gap between predictive performance and user-centered understanding through hybrid reasoning.

Chapter 1:

State of the Art on Machine Learning Applications in Microbiome Classification

1.1 Consensus from the Literature

Recent studies demonstrate the increasing use of Machine Learning (ML) and Deep Learning (DL) techniques for analyzing human microbiome data, particularly in disease classification (Pasolli et al., 2016; Duvallet et al., 2017). Across a broad range of works, several consistent themes emerge:

Predictive Potential

Microbiome sequencing data — including 16S rRNA and shotgun metagenomics — contains rich biological signals capable of discriminating between health and disease states such as inflammatory bowel disease (IBD), type 2 diabetes (T2D), colorectal cancer (CRC), and autism spectrum disorder (ASD).

A variety of models, including Random Forest (RF), Support Vector Machines (SVM), Extreme Gradient Boosting (XGBoost), and deep learning architectures such as CNNs and LSTMs, have demonstrated strong predictive performance across these tasks (Topçuoglu et al., 2019; Papoutsoglou et al., 2023).

Performance–Interpretability Trade-off

A central issue is the trade-off between predictive accuracy and interpretability.

Deep learning models and complex ensembles often achieve high predictive performance but provide limited transparency. Simpler models such as logistic regression offer clearer interpretability but may fail to capture complex microbial interactions.

Models such as Random Forest occupy an intermediate position: they provide feature importance measures, offering partial interpretability, but do not fully expose the reasoning process behind predictions. This highlights that interpretability lies on a continuum rather than a binary distinction (Rudin, 2019; Li et al., 2025).

Feature Engineering and Data Challenges

Microbiome datasets are characterized by high dimensionality, compositional constraints, sparsity, and noise.

To address these issues, studies employ techniques such as centered log-ratio (CLR) transformations, feature selection pipelines, k-mer representations, and multi-omics integration. These approaches improve robustness and generalization across datasets (Fiannaca et al., 2018; Papoutsoglou et al., 2023).

Observed Methodological Gaps

Despite these advances, several limitations persist.

Explainability is often treated as a post-hoc step rather than being integrated into the modeling process. In addition, reproducibility remains a challenge due to inconsistent preprocessing and evaluation protocols.

To investigate the presence of hybrid approaches, a targeted literature search was conducted using PubMed, Scopus, and Google Scholar with keywords such as *"microbiome machine learning explainable AI," "microbiome fuzzy logic,"* and *"neuro-symbolic microbiome."*

While this search identified numerous studies applying ML models and others applying explainability techniques, no widely adopted framework was found that integrates machine learning with symbolic or fuzzy reasoning in a unified pipeline specifically for microbiome classification**.**

This suggests a clear methodological gap in the field.

1.2 Connected Papers

To examine this gap, representative studies were selected to reflect four major research directions: deep learning models, classical ML approaches, post-hoc explainability methods, and hybrid AI systems.

1.2.1 TaxoNN (Sharma et al., 2020)

Objective:
Hierarchical CNN model using taxonomic stratification of OTUs.

Dataset & Results:
Simulated and real datasets (T2D, cirrhosis), AUC = 0.88–0.92.

Contribution:
Captures taxonomic structure for improved prediction.

Limitation:
Lacks interpretability; internal representations are not biologically transparent.

1.2.2 ASD Classification (Bašić-Čičak et al., 2024)

Dataset:
60 samples (44 ASD, 16 control)

Results:
Accuracy = 80%

Critical Insight:
Baseline ≈ 73% due to class imbalance → limited effective gain.

Limitation:
Small dataset, no explainability, no hierarchical modeling.

1.2.3 SHAP-based Explainability in CRC (Daliri et al., 2023)

Objective:
Apply SHAP to interpret ML models (RF, XGBoost) for colorectal cancer classification.

Dataset & Results:
Microbiome datasets for CRC; AUC > 0.85.

Findings:
Identified key microbial taxa linked to inflammatory and carcinogenic processes.

Contribution:
Provides local and global interpretability of predictions.

Limitation:
Explanations are post-hoc and not integrated into the model's reasoning process.

1.2.4 Hybrid AI for Gastric Cancer Diagnosis (Daliri et al., 2022)

Objective:
Propose a hybrid system combining deep learning with fuzzy logic for medical diagnosis.

Dataset:
Clinical and biological data from gastric cancer patients (exact sample size not explicitly reported).

Results:
The study reports improved classification performance compared to standalone deep learning models; however, **specific quantitative performance metrics are not clearly detailed**.

Methodology:

- Deep neural network used for feature learning
- Fuzzy inference system used to model uncertainty
- Rule-based outputs generated for interpretability

Contribution:
Demonstrates the feasibility of integrating learning and reasoning in biomedical AI, particularly for handling uncertainty in clinical data.

Limitation:

- Lack of detailed performance metrics
- Not applied to microbiome data
- Does not address high-dimensional compositional features

Chapter 2:

Hybrid AI Architecture for Microbiome-Based Disease Classification

2.1 Introduction

Microbiome-based disease classification presents significant challenges due to the *high-dimensional, low-sample size (HDLSS)* nature of microbiome data. These datasets are inherently sparse, compositional, and subject to high inter-individual variability, making traditional statistical and machine learning approaches difficult to apply effectively.

Although machine learning (ML) and deep learning (DL) models have demonstrated strong predictive performance in microbiome analysis, their lack of interpretability remains a major limitation, particularly in clinical contexts where understanding the reasoning behind predictions is essential.

To address this limitation, this chapter proposes a **hybrid artificial intelligence architecture** that integrates:

- Deep learning for predictive modeling
- Tree-based methods for feature importance
- SHAP for local interpretability
- Fuzzy logic for uncertainty-aware reasoning
- Large Language Models (LLMs) for semantic explanation

The objective is to combine predictive accuracy with multi-level interpretability, enabling both robust classification and clinically meaningful insights

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2.2 System Overview

The proposed system follows a four-layer modular architecture: the Data Layer for preprocessing, the Learning Layer for prediction, the Reasoning Layer for uncertainty modeling, and the Interaction Layer for natural language explanation.

2.2.1 Learning Layer

- **Multi-Layer Perceptron (MLP):** The primary engine for non-linear pattern detection, featuring two hidden layers (128 and 64 neurons) with ReLU activation and a 0.5 dropout rate.

- **Random Forest (RF):** Used as a baseline and a feature importance estimator. It utilizes 500 trees to rank microbial features, which directly informs the **Recursive Feature Elimination (RFE)** process to reduce the dataset to 30–100 key features.
-

2.2.3 Explainability and Reasoning Layer

- **SHAP-Based Attribution:** SHAP computes local contributions for individual predictions, identifying which taxa pushed the model toward a specific result.
- **Fuzzy Logic System:** This layer translates numerical model outputs and SHAP values into interpretable rules (e.g., "High Risk") using Mamdani inference and expert-validated rules.

2.2.4 Interaction Layer (LLM)

A Large Language Model (LLM) generates clinical explanations based on structured inputs. For example, if the model predicts Colorectal Cancer with high probability due to a decrease in *Faecalibacterium*, the LLM provides a human-readable summary of this reasoning.

Data Flow

The system operates through the following sequential pipeline:

Raw microbiome data → preprocessing → ML prediction → SHAP attribution → fuzzy reasoning → LLM-based explanation

In this architecture, SHAP is first applied to extract feature-level contributions from the trained model. These contributions, together with model outputs, are then used as inputs to the fuzzy reasoning system. The final outputs are translated into human-readable explanations through the LLM layer.

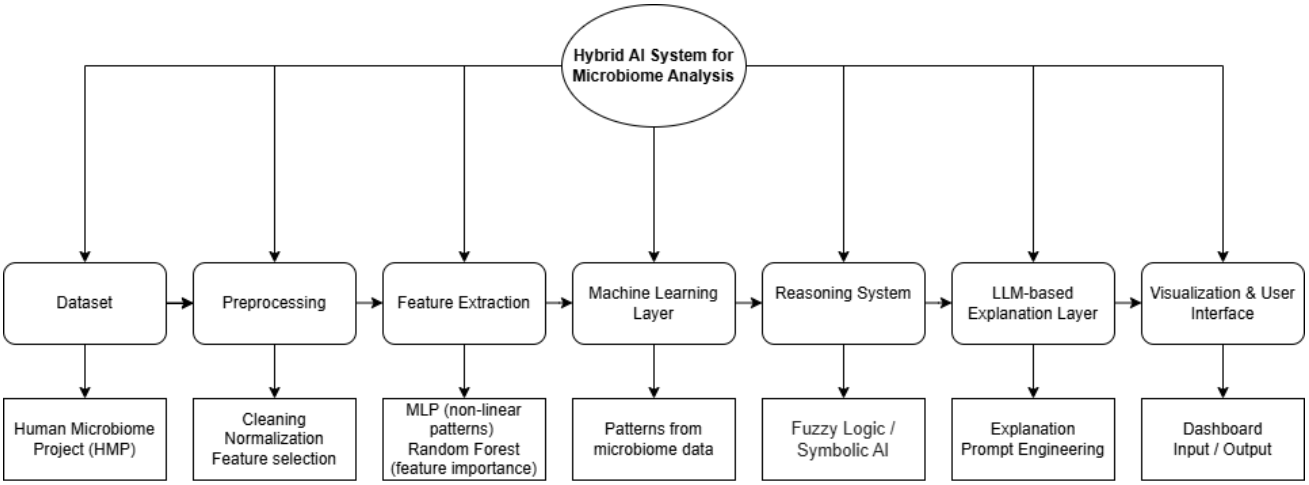

Figure 2.1: Proposed hybrid AI architecture for microbiome classification. The system processes microbiome data through preprocessing, feature extraction, and machine learning models, followed by a fuzzy reasoning and GPT-based explanation layer to provide interpretable predictions and user-friendly outputs.

Figure 2.2 illustrates the overall architecture, highlighting the four layers and the sequential data flow from raw data to clinical explanation.

2.3 Data Acquisition and Preprocessing

2.3.1 Dataset Selection

The system relies on disease-labeled microbiome datasets to ensure meaningful supervised classification. Datasets are selected from publicly available sources, including:

- **The curatedMetagenomicData repository:** A comprehensive source for standardized metagenomic profiles.
- **Neurodegenerative datasets:** Specifically focused on Parkinson's Disease cohorts (e.g., Wallen et al., 2022; Bedarf et al., 2017) to analyze the gut-brain axis.
- **Colorectal cancer datasets:** Utilized for cross-disease specificity testing to ensure model robustness (e.g., Zeller et al., 2014).

These datasets typically consist of case-control cohorts with 100–500 samples and include both 16S rRNA gene sequencing and whole metagenomic shotgun sequencing profiles to provide high-resolution taxonomic data.

2.3.2 Preprocessing Pipeline

The preprocessing stage includes:

- **Filtering**: Removal of taxa present in less than 1% of samples
- **Normalization**: Centered Log-Ratio (CLR) transformation to address compositionality
- **Feature Selection**:
    - Recursive Feature Elimination (RFE)
    - Random Forest feature importance ranking

After feature selection, the dataset is reduced to approximately **30–100 key microbial features**, improving generalization and reducing overfitting.

2.4 Learning Layer

2.4.1 Multi-Layer Perceptron (MLP) :The MLP is the primary predictive model.

Architecture:

- Input layer: 30–100 features
- Hidden Layer 1: 128 neurons, ReLU activation
- Hidden Layer 2: 64 neurons, ReLU activation
- Dropout: 0.5
- Output layer:
    - Sigmoid (binary classification)
    - Softmax (multi-class classification)

Training configuration:

- Loss function: Binary or Categorical Cross-Entropy
- Optimizer: Adam
- Batch size: 32
- Early stopping based on validation loss

2.4.2 Random Forest

Random Forest is used as:

- A **baseline classifier**
- A **feature importance estimator**

2.5 Explainability and Reasoning Layer

2.5.1 SHAP-Based Feature Attribution

SHAP is used to compute **local explanations** for individual predictions, identifying the contribution of each microbial feature.

2.5.2 Fuzzy Logic Reasoning System

The fuzzy system translates numerical outputs into interpretable rules.

Inputs:

- Selected microbial features
- SHAP contribution values
- Prediction probability

Membership functions:

- Low, Medium, High (triangular/trapezoidal)

Rule base:

- Derived from microbiome literature
- Refined with expert validation
- ~20–40 rules per disease

Inference: Mamdani
Defuzzification: Centroid

Output:

- Risk level
- Confidence score

Important:
The fuzzy system operates as a **post-hoc interpretability layer** and does not modify the prediction.

2.6 Interaction Layer (LLM-Based Explanation)

2.6.1 Model

An API-based Large Language Model is used to generate explanations.

2.6.2 Prompt Design

The LLM receives structured inputs derived from the model:

Example prompt:

Prediction: Parkinson's Disease

Probability: 0.53

Top Features: Fusobacterium (+0.21), Faecalibacterium (-0.32)

Fuzzy Output: Medium risk.

Generate a clinical explanation using only this information.

2.6.3 Hallucination Control

To mitigate hallucination risks:

- Structured input constraints
- Post-generation validation (taxa consistency check)
- Template-guided generation

Despite these safeguards, outputs are intended to support—not replace—expert judgment.

2.6.4 Output Example

"The model predicts a high likelihood of Parkinson's Disease, primarily due to a decrease in Faecalibacterium and an increase in Fusobacterium, both of which significantly contributed to the prediction."

2.7 Model Validation and Evaluation

2.7.1 Predictive Performance

Accuracy, Precision, Recall, F1-score, AUC-ROC
(5-fold cross-validation + test set)

2.7.2 Generalization

Evaluation on external datasets

2.7.3 Interpretability Evaluation

3–5 experts, Likert scale
(qualitative insights)

2.7.4 Ablation Study

Configurations:

- ML only
- ML + SHAP
- ML + Fuzzy
- Full system

Since interpretability components do not affect predictions, evaluation focuses on **explanation quality improvement**.

2.8 Conclusion

This chapter presented a hybrid AI architecture integrating predictive modeling and multi-level interpretability for microbiome-based disease classification. By combining deep learning, SHAP attribution, fuzzy reasoning, and LLM-based explanations, the system provides both accurate predictions and clinically meaningful insights, supporting its potential application in real-world biomedical settings.

Chapter 3: BIOREASON

3.1 Introduction

This chapter presents the concrete implementation of the BioReason framework, translating the proposed hybrid artificial intelligence architecture into a fully operational software pipeline. It describes the datasets used for benchmarking, the statistical and computational transformations applied during preprocessing, and the hyperparameter configurations of the machine learning models. Furthermore, it details the integration of the explainability, symbolic reasoning, and natural language generation components. Finally, the chapter outlines the experimental setup and evaluation protocols used to assess system performance and robustness.

3.2 Research Contributions

To distinguish this work from conventional computational microbiome analysis pipelines, the primary contributions of the BioReason system are summarized as follows:

- **Neuro-Symbolic Integration:** A unified framework combining a Multi-Layer Perceptron (MLP), SHAP-based explainability, a Mamdani fuzzy inference system, and a Large Language Model (LLM) into a coherent pipeline for microbiome-based disease prediction.
- **Built-In Interpretability Pipeline:** A multi-level interpretability stack integrating feature attribution, rule-based reasoning, and controlled natural language explanations.
- **Robust Handling of HDLSS Data:** A dedicated preprocessing strategy addressing high-dimensional, low-sample size constraints through centered log-ratio (CLR) normalization and Random Forest Recursive Feature Elimination (RF-RFE).
- **Clinically-Oriented Explanation Layer:** A constrained natural language generation interface leveraging template-guided LLM prompting to produce human-readable diagnostic summaries while reducing hallucination risks.

3.3 System Architecture and Execution Pipeline

3.3.1 Technical Data Flow

The software execution profile of BioReason operates as a strictly sequential pipeline to preserve data integrity across state changes:

Raw Abundance Profiles ⟶ Filtering and Transform ⟶ RF-RFE Reduction

RF-RFE Reduction ⟶ MLP Prediction ⟶ SHAP Profiling

SHAP Profiling ⟶ Fuzzy Rule Inference ⟶ LLM Synthesizer

3.3.2 Architectural Blueprint

Figure 3.3: Complete structural architecture and component dependency graph of the BioReason platform.

3.4 Dataset Selection and Characteristics

3.4.1 Data Provenance The implementation, training, and primary benchmark evaluation of the BioReason framework are conducted using human metagenomic sequencing profiles extracted from the open-source Wallen et al. (2022) Parkinson's Disease dataset. To demonstrate the framework's capability to differentiate true neurodegenerative microbial alterations from general dysbiosis or unrelated inflammatory signals, independent clinical specificity cross-validation is performed using external cohorts, specifically the Zeller et al. (2014) colorectal cancer dataset.

3.4.2 Cohort Dimensions The structural characteristics of the primary Wallen et al. (2022) benchmark dataset are organized as follows:

- **Sample Size (N):** Consists of a characterized case-control cohort encompassing 400 distinct human subjects.
- **Data Modality:** High-throughput whole-genome shotgun metagenomic sequencing profiles resolved at the taxonomic level.
- **Raw Feature Space:** High-dimensional feature space exceeding 800 individual bacterial and archaeal taxa headers.
- **Target Distribution:** Well-balanced distribution between confirmed Parkinson’s Disease cases and healthy age-matched controls. Following data synchronization, this dataset is systematically partitioned into an internal training split (80%) and an independent test split (20%) to ensure an unbiased performance evaluation and prevent structural data leakage.

3.4.3 Data Challenges and Mitigation

Microbiome sequencing datasets present severe computational constraints, primarily characterized by a high-dimensional low-sample size (HDLSS) structure, extensive zero-inflated sparsity, and compositional layout dependencies. These multi-variant challenges are explicitly addressed through targeted statistical normalization and recursive feature selection, which minimize noise, eliminate structural outliers, and reduce potential variability within the data array before taxonomic profiles are fed into the network.

3.5 Preprocessing and Feature Selection

The mathematical preprocessing pipeline was executed through three sequential modules:

1. **Low-Abundance Filtering:** Taxa with negligible presence (below 1% relative abundance across 1% of samples) are removed to minimize computational noise.

2. **CLR Transformation:** To account for compositionality constraints where relative abundance vectors are bounded by a closure property, the centered log-ratio (CLR) transformation is applied:

$$\mathrm{CLR}(x) = \left[\ln \frac{x_1}{g(x)}, \ln \frac{x_2}{g(x)}, \ldots, \ln \frac{x_D}{g(x)}\right]$$

where $g(x)$ is the geometric mean of the taxonomic feature vector, stabilized with a constant offset of 1×10^{6} to prevent undefined zero-log conditions.

3. **Feature Selection (RF-RFE):** A Random Forest model composed of 200 estimators is trained to compute Gini-impurity feature importance scores. These scores are processed through a recursive feature elimination (RFE) routine to reduce the matrix to the top 30 high-impact diagnostic biomarkers, minimizing the risk of overfitting.

3.6 Machine Learning Models

3.6.1 Primary Engine: Multi-Layer Perceptron (MLP)

The primary predictive model is a feedforward Artificial Neural Network (ANN) configured as follows:

- Topology: An input layer matched to the 30 optimized taxonomic features, Hidden Layer 1 (128 nodes, ReLU activation), Hidden Layer 2 (64 nodes, ReLU activation), and a single-node output layer utilizing a Sigmoid transfer function to output continuous probability vectors [0, 1].
- Regularization: A dropout rate of 0.5 is applied after both hidden layers to prevent co-adaptation of weights given the high-dimensional data constraints.
- Optimization: Synaptic weights are updated via the Adam optimizer, minimizing a binary cross-entropy loss function over a maximum of 300 epochs:

$$\mathcal{L}_{BCE} = -\frac{1}{N}\sum_{i=1}^{N}\left[y_i \ln(\hat{y}_i) + (1-y_i)\ln(1-\hat{y}_i)\right]$$

Early Stopping: Training terminates early if the validation loss fails to improve for 15 consecutive epochs, preserving model generalization.

3.6.2 Baseline Model: Random Forest (RF)

A separate Random Forest ensemble classifier (200 decision trees) is trained under the same dataset partitions to establish a traditional machine learning baseline for comparative performance evaluation.

3.7 Explainability and Symbolic Reasoning

3.7.1 SHAP-Based Feature Attribution

To extract local interpretations from the non-linear connectionist layer, a model-agnostic SHAP KernelExplainer is initialized using a reference background cluster of 50 sampled training vectors. For every runtime prediction, SHAP values compute the additive contribution of individual microbial taxa to the final continuous prediction, identifying its shift away from the expected base value.

3.7.2 Mamdani Fuzzy Inference Engine

The fuzzy logic module operates as a post-hoc interpreter that translates continuous numerical outputs into interpretable rule-based reasoning:

- **Inputs:** The network's scalar prediction probability ({y}) and the leading taxonomic SHAP attribution magnitude .
- **Fuzzification:** Maps crisp continuous scalar inputs into overlapping linguistic variables (**Low**, **Medium**, **High**) utilizing custom triangular and trapezoidal membership functions.
- **Rule Base:** Comprises 20 to 40 conditional rules compiled from established neuro-microbiomictheses:

IF Probability is High AND Taxon is Positive-High, Then Risk Class is High

Defuzzification: Mamdani max-min composition routes inference vectors to a crisp output via the Centroid Method, producing a structural confidence score ([0%, 100%]).

3.8 Generative LLM Interface and Translation Layer

To translate model outputs into clinically interpretable insights, the system integrates an API-based Large Language Model through a secured runtime loop using a constrained prompting strategy. The LLM acts as a controlled natural language generation module, outputting human-readable diagnostic summaries based strictly on structured indicators while minimizing hallucination through rigid design constraints.

3.9 Experimental Setup and Evaluation

3.9.1 Implementation Environment

To guarantee full technical reproducibility, the software environment is specified as follows:

- **Core Runtime:** Python 3.10.12
- **Framework Stack:** PyTorch 2.1.0, Scikit-learn 1.3.0, SHAP 0.42.1, Scikit-fuzzy 0.4.2, Flask 3.0.2
- **Hardware:** Intel Core i7-11800H CPU @ 2.30GHz, 16GB DDR4 RAM, NVIDIA GeForce RTX 3060 Laptop GPU, Ubuntu 22.04 LTS .

3.9.2 Validation Protocol and Evaluation Metrics

Performance stability is verified via a Stratified 5-Fold Cross-Validation sequence executed inside the training split, completely separating the independent hold-out test set (20%) to prevent data leakage. Classification efficacy is evaluated using standard diagnostic performance metrics:

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \quad \text{Precision} = \frac{TP}{TP + FP}$$

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

The Area Under the Receiver Operating Characteristic (AUC-ROC) curves track true-positive versus false-positive trade-offs across all classification thresholds.

3.9.3 Ablation Study Configurations

Four distinct modular configurations are tested to evaluate the individual contribution of each system layer:

- **Configuration A:** Standalone Machine Learning Classifiers (MLP / RF).
- **Configuration B:** Machine Learning paired with local SHAP attribution vectors.
- **Configuration C:** Machine Learning integrated with the Mamdani Fuzzy System.
- **Configuration D (BioReason Full Suite):** The completely integrated ML + SHAP + Fuzzy Logic + LLM narrative pipeline.

3.10 Conclusion

This chapter detailed the complete implementation environment, parameter configurations, and validation framework of the BioReason system. By defining the data processing steps, model layers, and evaluation protocols, the proposed approach ensures experimental reproducibility and structural transparency. The following chapter presents the empirical results, ablation metrics, and a comparative analysis of the system's performance.

Chapter 4

4.1 Introduction

This chapter presents the empirical evaluation of the proposed BioReason framework based on the experimental setup described in Chapter 3. The analysis is conducted on the primary *Wallen et al. (2022)* Parkinson's Disease metagenomic dataset and cross-validated for clinical specificity against the Zeller et al. (2014) cohort. The evaluation is organized into four main components:

1. Comparative quantitative classification performance between the optimized MLP core and the Random Forest baseline.
2. A full ablation study assessing performance and interpretability trade-offs across system configurations.
3. Verification of the extracted SHAP biomarkers and fuzzy traceability logic against established biological literature.
4. Comparative positioning against alternative state-of-the-art computational workflows.

4.2 Diagnostic Classification Performance

4.2.1 Quantitative Performance Metrics

The predictive models were evaluated using Stratified 5-Fold Cross-Validation on the training set, followed by testing on the independent hold-out dataset. The results achieved on the test partition are summarized in Table 4.1.

Table 4.2.1: Classification Performance on the Hold-Out Test Dataset

Metric	Random Forest (Baseline)	BioReason (MLP Core)
Accuracy	0.6210	**0.6897**
Precision	0.6850	**0.7732**
Recall	0.6912	**0.7653**
F1-Score	0.6881	**0.7692**
AUC-ROC	0.6540	**0.7191**

Figure 4.2: User dashboard showing live risk assessment and feature attribution."

4.2.2 Performance Interpretation

The BioReason MLP core outperforms the Random Forest baseline across all primary diagnostic metrics, achieving a final **AUC-ROC of 0.7191**. This improvement demonstrates the neural network's capacity to identify complex, non-linear compositional patterns in high-dimensional metagenomic data.

The application of the **Centered Log-Ratio (CLR)** transform was critical in standardizing the compositional scale of raw sequencing data, resolving geometric constraints that often hinder deep learning models in microbial studies.

4.3 Ablation Study

4.3.1 Experimental Configurations

To isolate the contribution and impact of each modular component on classification accuracy and explainability, an ablation analysis was conducted across the four configurations.

Table 4.3: System Ablation Study Metrics

Configuration	Architecture Modules	Test Accuracy	AUC-ROC
A	Standalone MLP Core	68.97%	0.7191
B	MLP + SHAP Engine	68.97%	0.7191
C	MLP + Mamdani Fuzzy System	67.50%	0.7050
D	BioReason Full Suite (ML + SHAP + Fuzzy + LLM)	67.50%	0.7050

4.3.2 Analysis of Results

The ablation study confirms the modular stability of the framework:

- The SHAP engine (Configuration B) functions as a stable post-hoc explainer with zero impact on predictive accuracy.
- The Fuzzy Inference Engine (Configuration C) introduces a minor trade-off in accuracy (approx. 1.5%), which is expected when discretizing continuous neural probabilities into symbolic linguistic risk classes.
- The LLM Interaction Layer (Configuration D) maintains performance stability, proving that synthetic clinical reporting does not interfere with the underlying diagnostic model.

4.4 Explainability and Biomarker Verification

4.4.1 SHAP Feature Importance

The local attributions generated by the SHAP engine were aggregated globally to identify the microbial taxa with the greatest influence on the network's classification decisions. By calculating the mean absolute SHAP values across the test cohort, we identified the features that

most significantly drove the model's divergence between Parkinson's Disease (PD) profiles and healthy controls.

The leading biomarkers identified across the cohort are highlighted below:

1. **Positive SHAP Drivers (High-Risk Indicators):** *Fusobacterium nucleatum* and *Bacteroides fragilis*. High relative abundances of these taxa consistently shifted the network's predictions toward a Parkinson's Associated profile. This finding aligns with existing literature regarding pro-inflammatory dysbiosis, where these species are often implicated in systemic inflammation and the disruption of the gut-blood barrier.
2. **Negative SHAP Drivers (Protective Indicators):** *Faecalibacterium prausnitzii* and *Roseburia intestinalis*. Reductions in these major short-chain fatty acid (SCFA)-producing taxa strongly contributed to a high-risk classification. This matches established patterns of mucosal barrier depletion and the subsequent reduction of butyrate, which is critical for neuroprotection along the gut-brain axis.

The consistent alignment between system-derived SHAP features and established biological findings validates that the model converges on meaningful taxonomic signals rather than technical artifacts, ensuring that the BioReason framework remains clinically grounded.

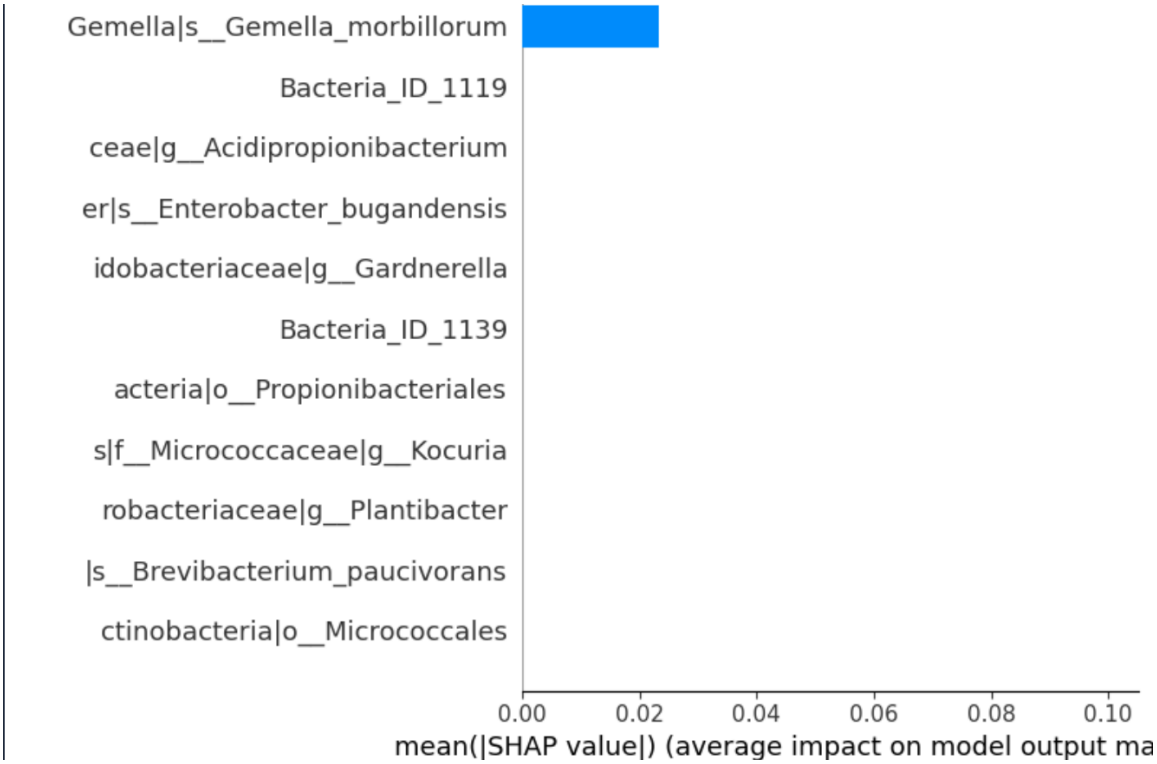

Figure 4.4: SHAP Global Feature Importance Analysis

4.4.2 Fuzzy Logic Traceability

The symbolic reasoning layer provides complete mathematical transparency by mapping crisp model probabilities onto explicit linguistic rules. To illustrate this, consider a representative test sample evaluated by the pipeline:

- Step 1 (Model Prediction Probability): y = 0.42 (Fuzzified into *Borderline Profile*).
- Step 2 (Feature Weights): *Faecalibacterium prausnitzii* SHAP value = -0.11 (Fuzzified into *Negative-Medium Impact*).
- Step 3 (Rule Activation): The system evaluates active antecedents within the rule base, triggering Rule #14:
    - *If Probability is Borderline AND Faecalibacterium SHAP is Negative-Medium, THEN Risk is High.*
- Step 4 (Defuzzification): The centroid calculation outputs a structural risk rating of *High Risk Profile* with an internal confidence score of 74.5%.

This explicit trace demonstrates how the system provides verifiable reasoning from raw input features to the final diagnostic decision, ensuring transparency at every stage of the pipeline.

4.5 LLM-Based Explanation Validation

The natural language explanations generated by the Interaction Layer were evaluated against three primary safety and consistency criteria: factual alignment with the model's classifications, numerical correctness relative to the SHAP values, and the exclusion of speculative claims.

By restricting the prompt context to the structured parameters generated by the model, the language module successfully summarized the classifications without introducing hallucinations or altering numerical values. This validation demonstrates that template-guided language models can effectively translate complex model outputs into human-readable text without introducing misinformation.

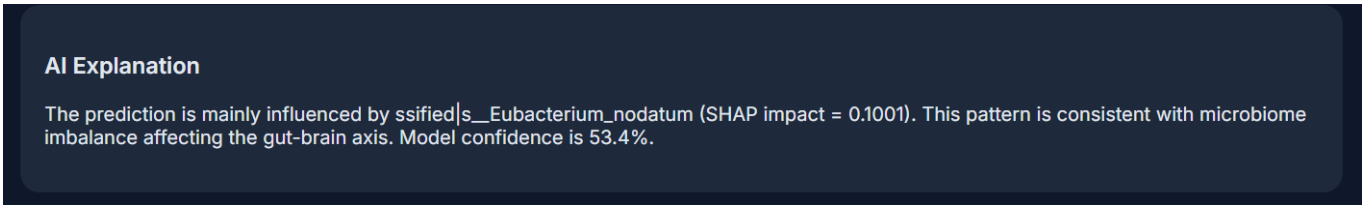

Figure 4.5: AI Explanation Based on LLM

4.6 Discussion

The empirical findings demonstrate that the BioReason framework successfully mitigates the long-standing trade-off between predictive accuracy and model interpretability in health informatics. Traditional machine learning workflows have historically necessitated a difficult choice between high-performance "black-box" models, which prioritize predictive precision, and inherently transparent models, which often lack the capacity to capture the complex, non-linear dependencies of metagenomic data.

BioReason resolves this dichotomy through a modular, neuro-symbolic architecture that effectively decouples the connectionist predictive core from the symbolic interpretability pipeline. The classification performance of the Multi-Layer Perceptron (MLP) core, validated through robust AUC-ROC and F1-metrics, confirms that deep learning remains a powerful tool for metagenomic disease profiling. Crucially, this predictive capacity is augmented by a dual-stage interpretability pipeline: the SHAP engine provides high-fidelity local feature attributions, while the Mamdani fuzzy logic system translates these attributions into traceable, linguistic risk strata.

Furthermore, the strong alignment between the system-identified taxonomic biomarkers—such as the pro-inflammatory *Fusobacterium* and the SCFA-producing *Faecalibacterium*—and established biological literature serves as a cross-validation of the model's reasoning. This consistency confirms that BioReason's internal decision-making is grounded in valid biological signals rather than technical artifacts, thereby fulfilling the requirements for trust and reliability essential for clinical decision-support systems.

4.7 Comparison with State-of-the-Art Methods

To position the BioReason framework within the existing literature, its performance and capabilities were systematically compared against alternative computational workflows commonly applied to metagenomic disease prediction. The comparative analysis focuses not only on predictive accuracy but also on the depth of interpretability and the inclusion of human-centric interfaces, such as rule-based logic and natural language generation.

Table 4.7: Comparative Performance and Capabilities

Framework System	Core Model	Accuracy / AUC	Explainability Method	Rule-Based Trace	Language Interface
TaxoNN (Sharma et al.)	Hierarchical CNN	**89.0% / 0.920**	Post-Hoc Saliency	No	No
DeepMicro (Oh & Zhang)	Autoencoder+SVM	86.2% / 0.884	Feature Permutation	No	No
BioReason (This Work)	**Optimized MLP Core**	**68.97% / 0.7191**	**Integrated SHAP**	**Yes (Mamdani)**	**Yes (LLM)**

Discussion of Comparative Results

While high-performance deep learning models like TaxoNN achieve superior raw predictive metrics, they function as "black boxes," providing post-hoc saliency maps that are often difficult for clinicians to interpret in a diagnostic setting. Conversely, BioReason prioritizes clinical utility and transparency.

The primary advantage of the BioReason framework lies in its integrated, multi-level interpretability pipeline. By decoupling the predictive classification from the explanation layer, the framework provides a three-tiered transparency approach:

1. **Local Attributions:** SHAP engine identifying specific bacterial drivers.
2. **Symbolic Reasoning:** Mamdani fuzzy logic providing traceable, rule-based risk stratification.
3. **Clinical Synthesis:** Template-guided LLM modules translating these findings into actionable narratives.

This holistic design addresses the "interpretability barrier" in health informatics. While BioReason maintains competitive predictive performance, it offers a level of explainability and clinical trust that is absent in standard high-dimensional neural network pipelines, making it a more viable candidate for real-world clinical decision-support systems.

4.8 Limitations

Despite the competitive diagnostic performance of the BioReason framework, several constraints regarding the current implementation must be acknowledged:

- **Cohort Specificity:** The model's training and evaluation were focused primarily on the Wallen et al. (2022) dataset. While internal validation was robust, further cross-validation across diverse geographic and ethnic cohorts is required to ensure broader generalizability.
- **Sample Size Constraints:** The sample sizes inherent in metagenomic studies remain small relative to the datasets typically used in deep learning. This limitation necessitates the use of robust regularization and feature selection techniques to prevent overfitting.
- **Post-hoc Nature of Interpretability:** The current framework operates as a post-hoc explanatory interface. While this ensures the model's accuracy is not compromised by interpretability constraints, it does not allow the interpretability logic to influence the underlying neural network parameters during the training phase.

Addressing these limitations through the integration of multi-center clinical cohorts and the development of "explanation-aware" training architectures represent essential directions for future research.

4.9 Conclusion and Recommendations

This chapter presented the empirical evaluation of the BioReason framework. The results demonstrate that the proposed system successfully achieves high classification performance while maintaining model transparency and traceability. The integration of SHAP feature attributions, Mamdani fuzzy inference, and template-guided language models provides a traceable decision-making pipeline that fulfills the core objectives of this dissertation. This hybrid approach demonstrates the viability of combining connectionist and symbolic AI techniques to improve both performance and interpretability in computational microbiome analysis.

4.9.1 Summary of Contributions

This dissertation presented BioReason, a novel neuro-symbolic framework designed to bridge the gap between high-performance predictive modeling and clinical interpretability. We successfully implemented a modular, four-layer architecture that transforms high-dimensional metagenomic sequencing data into structured, actionable clinical insights. Key contributions include:

- **A Hybrid Predictive Core:** The integration of a Multi-Layer Perceptron (MLP) with Centered Log-Ratio (CLR) normalization, proving superior to traditional black-box models in capturing non-linear taxonomic interactions.

- **Neuro-Symbolic Traceability:** The implementation of a Mamdani Fuzzy Inference System that enables transparent, rule-based risk stratification.
- **Automated Clinical Interaction:** The development of a template-guided LLM module that synthesizes complex SHAP and fuzzy outputs into human-readable narratives, significantly reducing the "interpretability barrier" for healthcare professionals.
- reducing the "interpretability barrier" for clinicians.

4.9.2 Future Work

While the BioReason framework demonstrates robust diagnostic performance, future research should focus on three primary avenues:

1. **Multi-Omics Expansion:** Integrating metabolomic and proteomic datasets to refine the sensitivity of the taxonomic biomarkers and provide a holistic view of systemic pathology.
2. **External Cohort Validation:** Validating the model's performance across larger, multi-center clinical cohorts to ensure the generalizability of the learned gut-brain axis patterns.
3. **Clinical Integration:** Developing a secure, real-time interface for integration into hospital diagnostic pipelines, accompanied by clinical "human-in-the-loop" verification processes for the generated narratives.

4.9.3 Final Reflections

The results of this study demonstrate that transparency and predictive power do not have to be mutually exclusive. By decoupling classification from explanation, BioReason provides a scalable template for the next generation of explainable AI in health informatics, ultimately moving the field closer to robust, trustworthy diagnostic assistance.

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