



BIOINFORMATICS PROJECT

**APPLICATION OF RMTA-EA PIPELINE TO MULTI-GENE METABOLIC OPTIMIZATION IN
NEURODEGENERATIVE DISEASES**

MSc in Bioinformatics

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Overview of Presentation

1 Introduction

- ALZHEIMER – A MULTIGENIC DISEASE
- METABOLIC MODELS + OMICS INTEGRATION

2 Methods

- RMTA : ROBUST METABOLIC TRANSFORMATION ALGORITHM
- EA-RMTA : APPLICATION OF EVOLUTIONARY ALGORITHMS

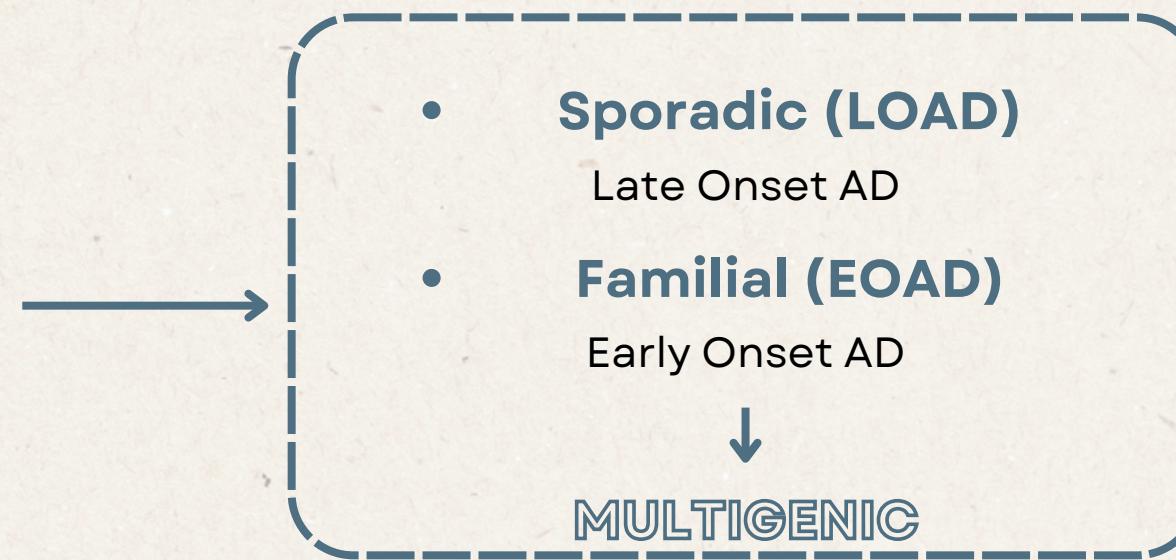
3 Results / Discussion

- RMTA ANALYSIS: RESULTS AND BIOLOGICAL INSIGHTS
- EA-RMTA PERFORMANCE OVERVIEW: PARAMETERS AND BEST SCORE
- EA-RMTA: KEY RESULTS AND VISUAL ANALYSIS

4 Future perspectives

Alzheimer – A Multigenic Disease

AD (Alzheimer's Disease) it's a Complex Neurodegenerative Disorder



Multigenic alterations affect various metabolic pathways, making single-target therapeutic approaches insufficient.

Challenges of Traditional Approaches

- Focus on single-gene targets → limited effectiveness
- Metabolic redundancy and compensatory mechanisms hinder isolated interventions

>>> **SOLUTION...
(Project Approach)** >>>

Metabolic Models

A COMPUTATIONAL REPRESENTATION OF AN ORGANISM'S METABOLIC NETWORK

Based on **stoichiometric relationships** between metabolites and reactions. Enables **simulation and prediction** of metabolic fluxes under different genetic or environmental conditions.

↓
GEMs (Genome-scale Metabolic Models) are computational frameworks that represent all metabolic reactions in an organism. Integration with multi-omics data improves biological accuracy and supports personalized disease modeling.

Omics Integration

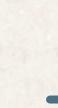
HIGH-THROUGHPUT BIOLOGICAL DATA COVERING MULTIPLE LAYERS

Genomics: DNA and genetic variations.; Transcriptomics: gene expression levels; Proteomics and Metabolomics: protein and metabolite profiles. Provides condition-specific context to refine metabolic models.

↓
Transcriptomics

Integration with iMAT (Integrative Metabolic Analysis Tool)

ALGORITHM THAT INTEGRATES GENE EXPRESSION DATA INTO GEMS



Categorizes gene activity
Generates context-specific metabolic models

rMTA – Robust Metabolic Transformation Algorithm

PIPELINE

Model Base : Recon 3D

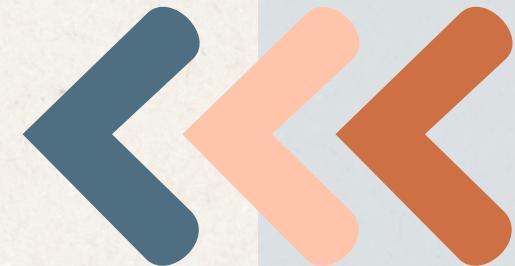
HEALTHY STATE



VS

Alzheimer Context Specific Model

DISEASE STATE



rMTA – Robust Metabolic Transformation Algorithm

INPUT FILES USED IN THE RMTA PIPELINE

dataset GSE203206

Gene Expression Omnibus (GEO)

Differential expression analysis using the limma-voom pipeline

Differential data expression analysis
INPUT USED IN RMTA

Gene expression profile generated

Samples Context Specific

Gene expression mapped to Recon3D

Reaction scores for iMAT

iMAT to generate a tissue-specific model using reaction expression scores

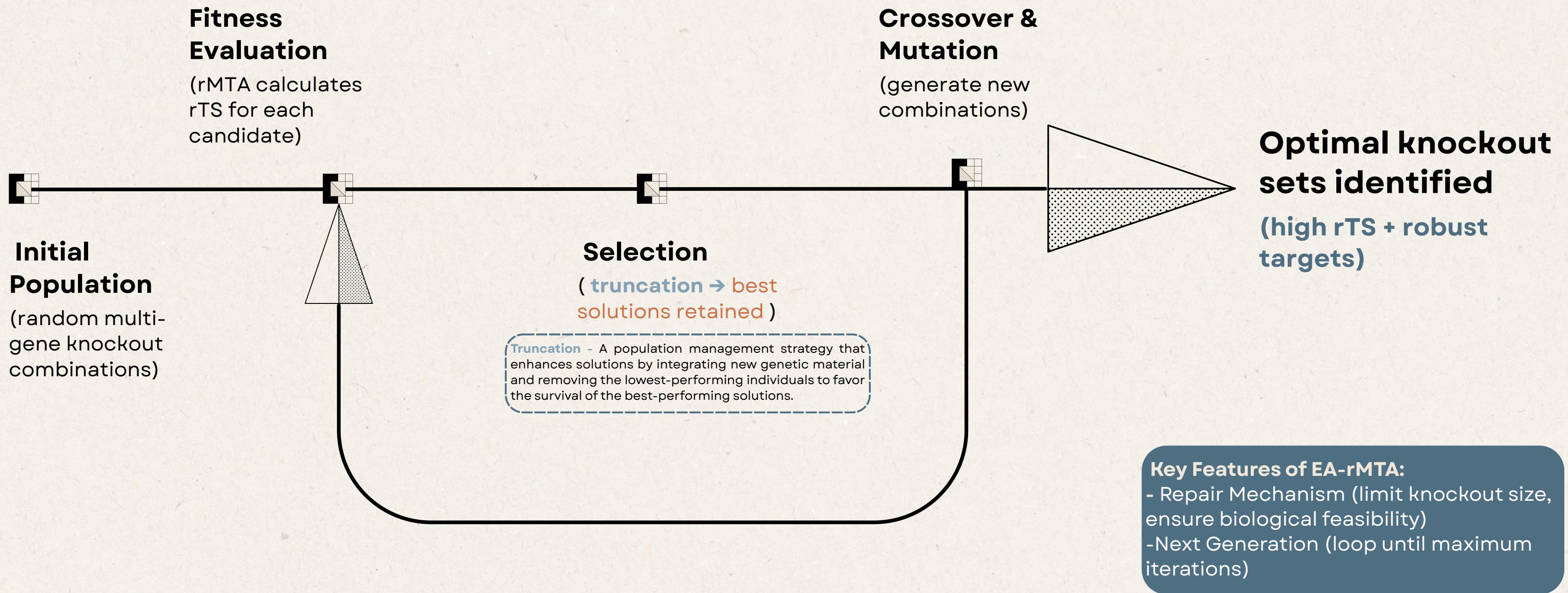
Context-specific model

flux sampling on the early-onset AD tissue-specific model using the ACHR method

+
Recon 3D
INPUT USED IN RMTA

Simulated reaction fluxes from ACHR sampling (2000 samples)
INPUT USED IN RMTA

EA-rMTA: Application of Evolutionary Algorithms



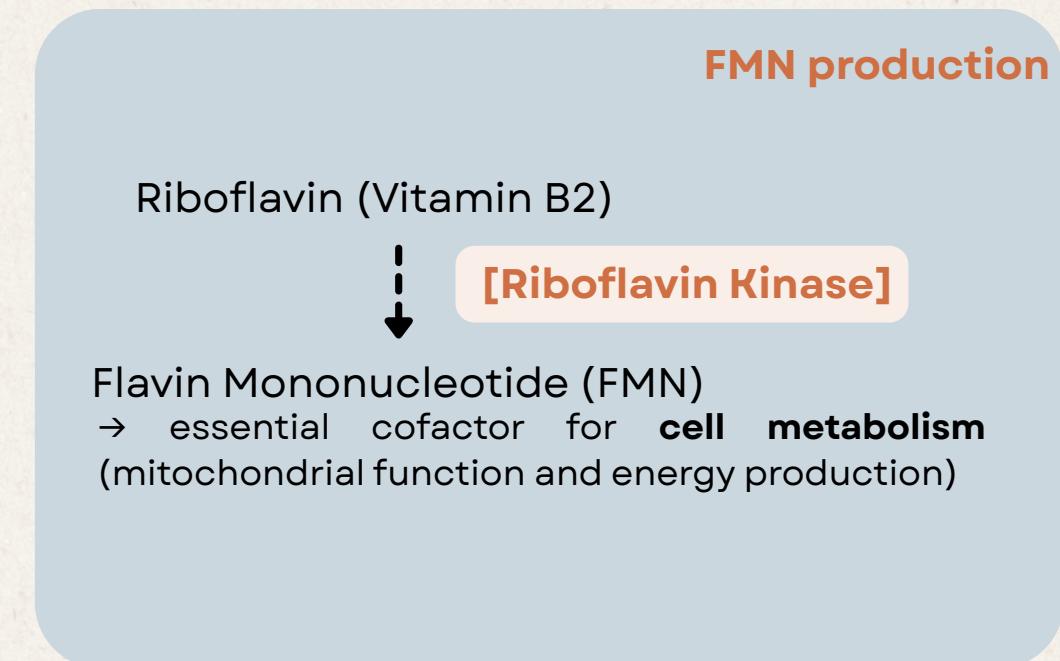
RMTA Analysis: Results and Biological Insights

Gene ID	Symbol	Full Name	rTS
55312_AT1	RFK	riboflavin kinase	5,46
26227_AT1	PHGDH	phosphoglycerate dehydrogenase	3,72
9376_AT1	SLC22A8	solute carrier family 22 member 8	3,28
22934_AT1	RPIA	ribose 5-phosphate isomerase A	0,78



RFK - Mitochondrial enzyme that converts riboflavin (vitamin B2) → FMN (Flavin Mononucleotide).

- **Upregulated in AD brains:** hippocampus, temporal & frontal cortex
- **Functional associations:** Oxidative phosphorylation; Redox and mitochondrial stress.



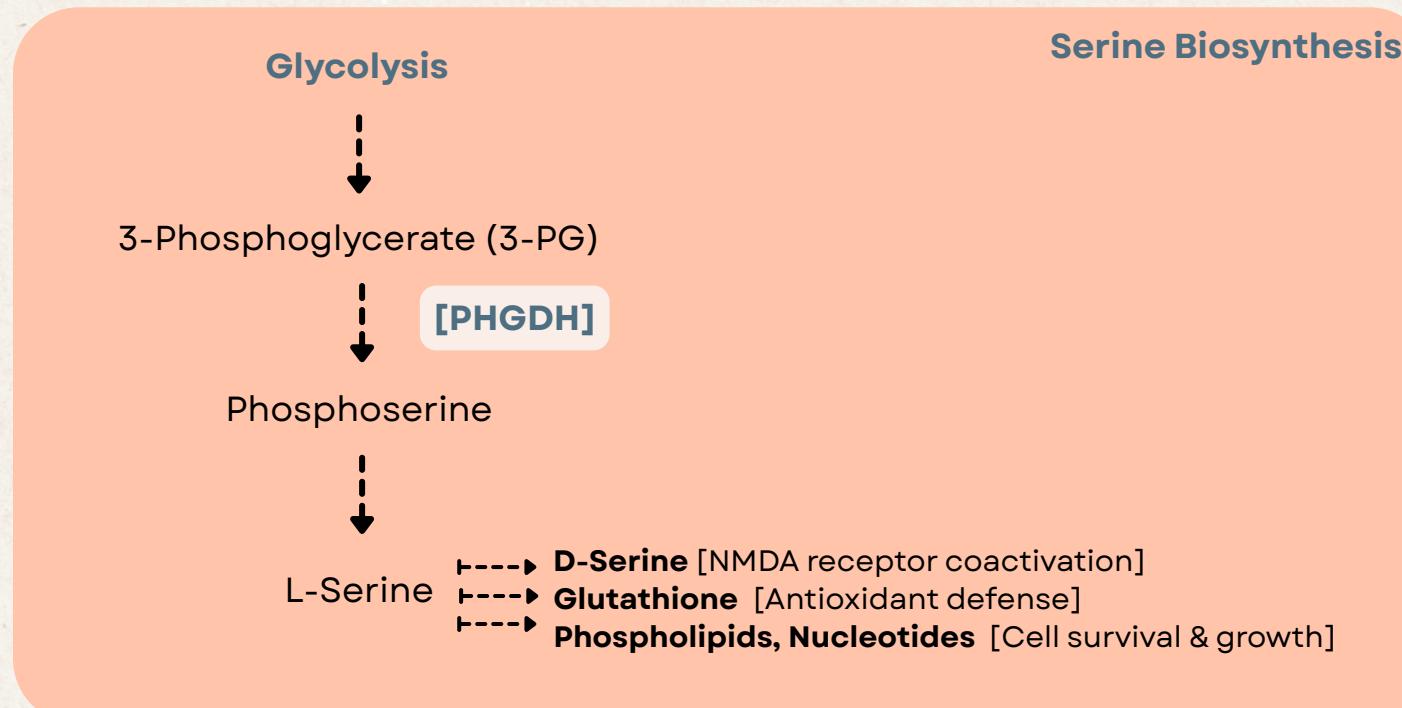
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PHGDH - Initiates serine biosynthesis

- **Elevated in AD brain** and correlates with cognitive decline;
- Targeted by neuroprotective peptides.



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SLC22A8 - Organic anion transporter (OAT3)

- **Decreased** in rat hippocampus under cholinergic injury (AD model);
- Implicated in **neurovascular inflammation** and blood-brain barrier dysfunction.

EA-rMTA Performance Overview: Parameters and Best Score

Best rMTA Score:
5.46



EA-rMTA outperforms rMTA as Alzheimer's is a polygenic disease, where analyzing multiple genes jointly captures more relevant biological signals than single-gene assessments.

Best fitness : 5.7389

Population Size: 400

Refresh Ratio: 0.5

Number of generations: 100

Best fitness : 6.0768*

Population Size: 400

Refresh Ratio: 0.75

Number of generations: 100

Best fitness : 6.4437*

Population Size: 400

Refresh Ratio: 0.75

Number of generations: 100

Best fitness : 6.4103

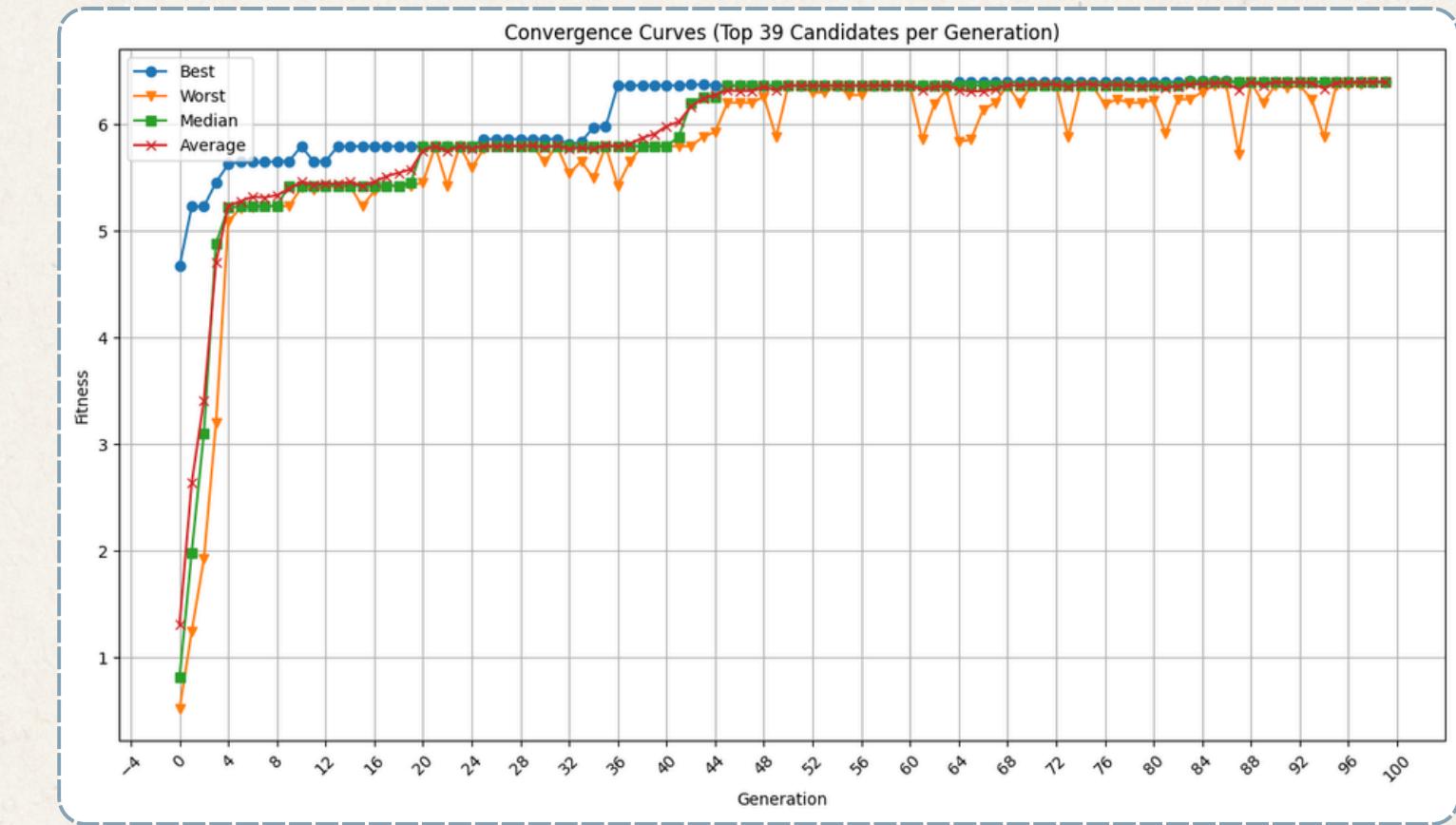
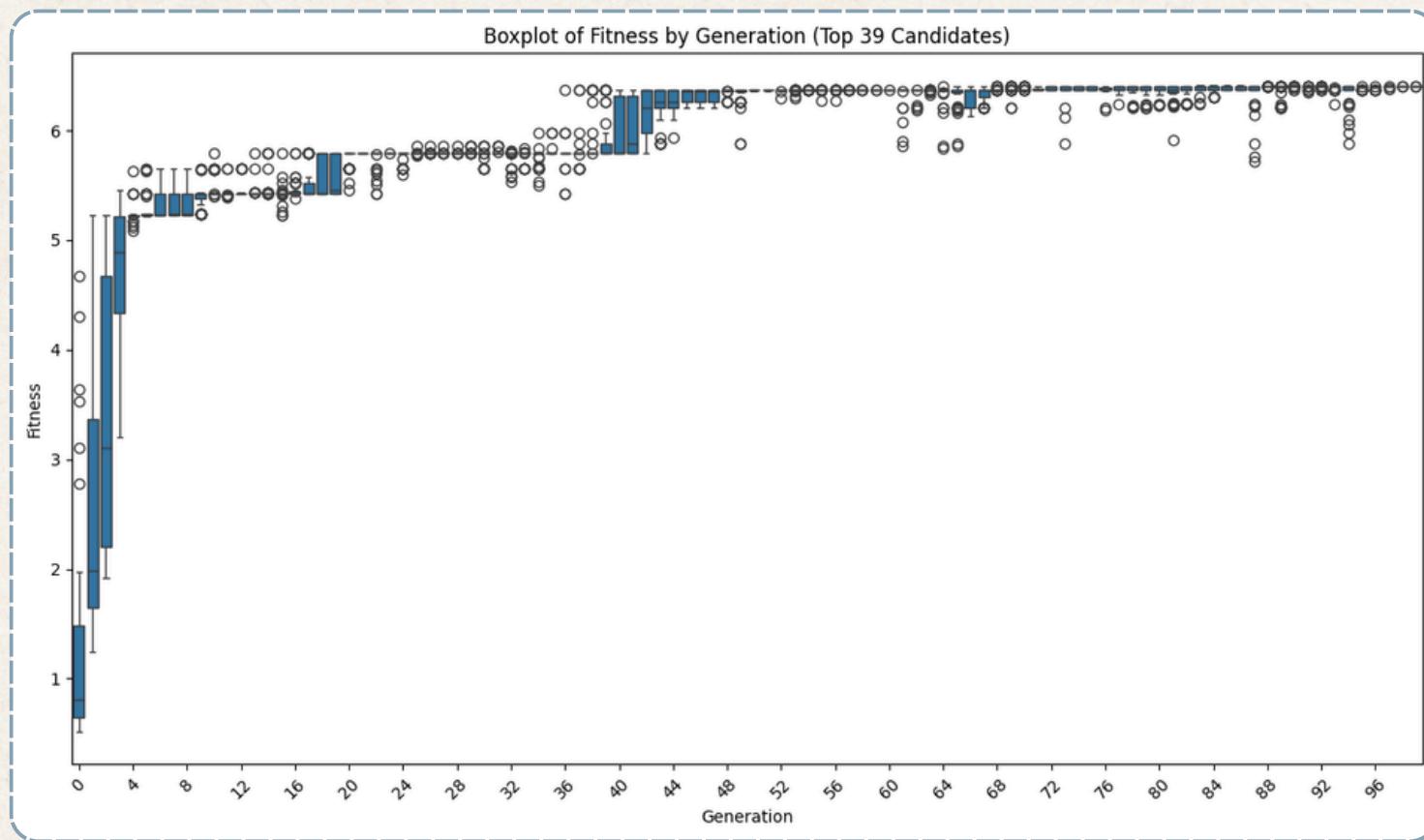
Population Size: 400

Refresh Ratio: 0.9

Number of generations: 100

EA-rMTA: Key Results and Visual Analysis

POPULATION SIZE: 400 + REFRESH RATIO: 0.9 + NUMBER OF GENERATIONS: 100



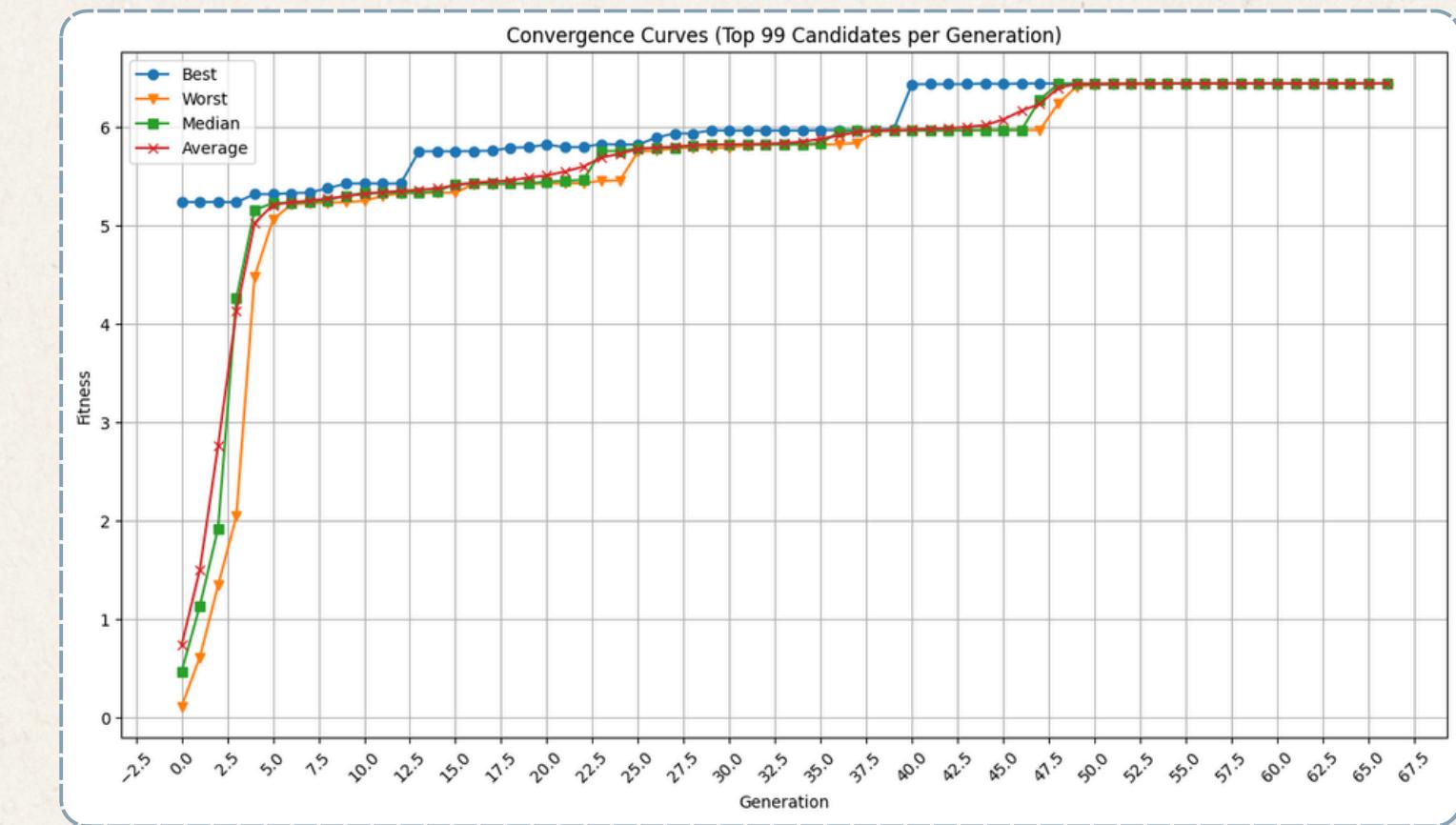
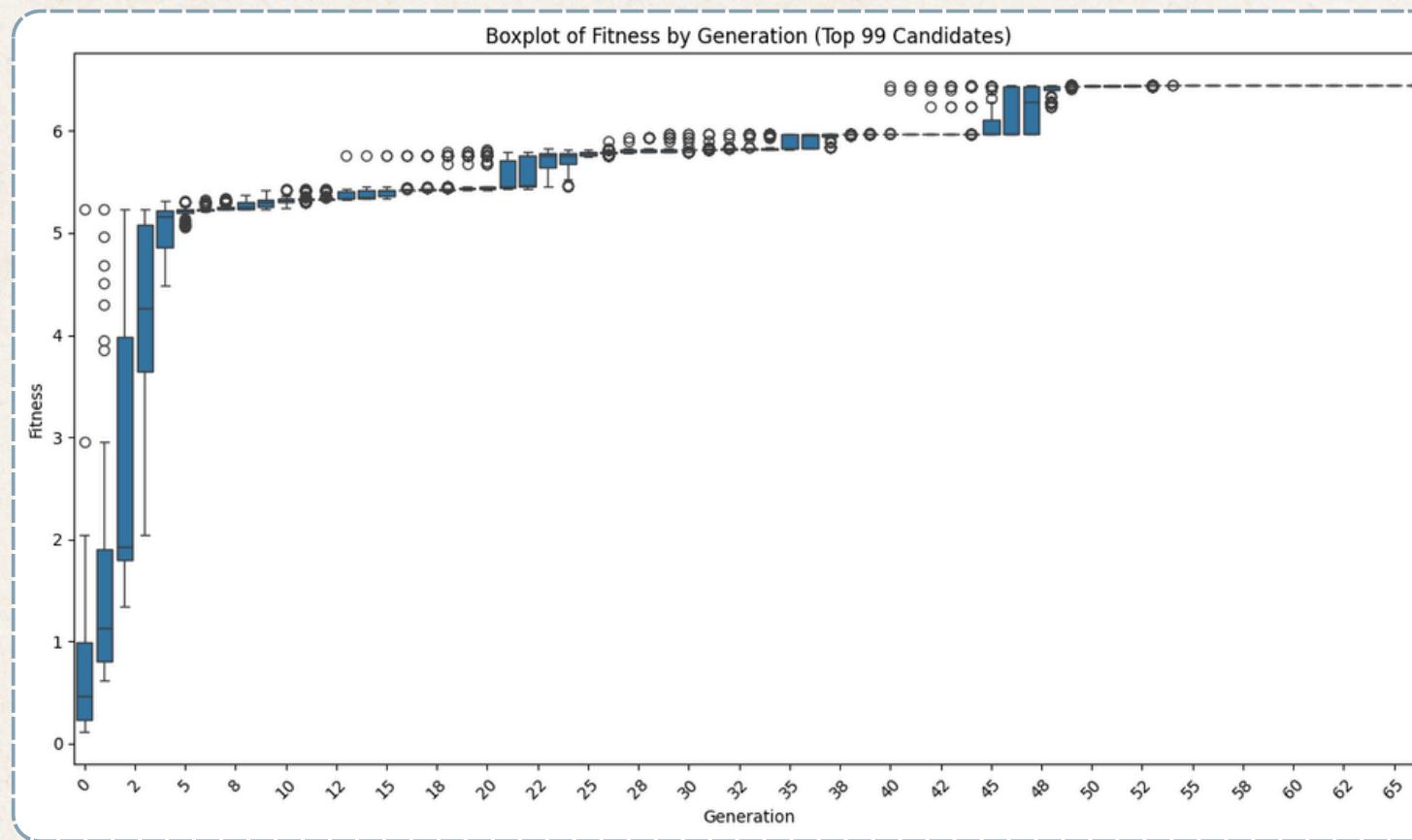
- Distribution becomes progressively tighter and more stable
- **Persistent outliers** → the algorithm continues to explore new – though suboptimal – regions of the search space, with gradually decreasing variability

- **Clear upward trend** → population evolves effectively over time
- The gap between best and average is small → indicates a **consistently strong population**

Algorithm shows effective convergence while maintaining genetic variability
Overall population robustness appears improved compared to previous configuration

EA-rMTA: Key Results and Visual Analysis

POPULATION SIZE: 400 + REFRESH RATIO: 0.75 + NUMBER OF GENERATIONS: 100



- The fitness distribution tightens significantly, showing reduced variance and increased population quality
- Outliers remain throughout the run, **but their impact diminishes**

- The average and median curves closely follow the best, suggesting a well-adapted population with high overall quality
- The gap between best and average is small → indicates a consistently strong population. **This behavior reflects a good balance between convergence and diversity preservation**

Strong convergence in later generations with controlled exploration, evidenced by tight distributions and sustained performance from the top individuals.

1 EA-rMTA

REPEATING RUNS WITH THE SAME PARAMETERS
(REFRESH RATES 0.9 AND 0.75) TO STRENGTHEN RESULT
RELIABILITY

2 Solution Simplification

IDENTIFYING MINIMAL KNOCKOUT SETS WITH PRESERVED
FITNESS TO ENHANCE INTERPRETABILITY AND PRACTICAL
APPLICABILITY.

3 Biological Conclusion

THE ENSEMBLE OF EVOLVED KNOCKOUT SETS
REVEALS CONVERGING PATTERNS OF METABOLIC
DISRUPTION, POINTING TO CONSISTENT
FUNCTIONAL MODULES ALTERED IN AD.

**Future
Perspectives**