

Iterative Self-Critique for Uncovering Cryptic Epistasis in Alzheimer's: Multi-Hop Genomic Reasoning via Monte Carlo Tree Search

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AWAY: The Socratic Self-Refine Framework Uncovers Hidden Genetic Interactions in Alzheimer's Using Iterative Self-Critique & Monte Carlo Tree Search

INTRODUCTION

- Background:** Complex genetic architecture, tracing subtle Multi-hop reasoning task. Trace complex censistatic epistatic interactions across multiple-hop literature. Standard Retrieval-Augmented Generation (RAG) systems fail.

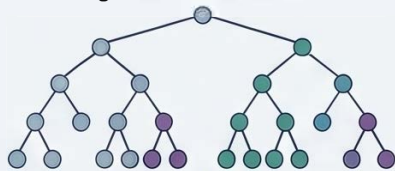


- Objective:** Implement a **Socratic Self-Refine** framework for fine-grained evaluation and recursive **refinement** of genomic reasoning.

METHODS

Multi-Hop Genomic Reasoning via Monte Carlo Tree Search (MCTS)

Step 1: Agent tasked with synthesizing multi-omics literature to identify novel genetic interactions.



Step 2: Decompose initial hypotheses into verifiable sub-questions.



Step 3: Guided MCTS: Simulate interactions, generate internal critiques of logical steps.



Step 4: Iteratively prune flawed reasoning paths based on strict evidence retrieval.

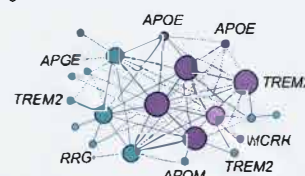
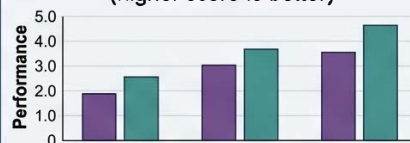


Step 5: Learn to correct assumptions over sequential rounds.



RESULTS

Performance on Multi-Hop Tasks: Socratic Self-Refine vs. Standard RAG (higher score is better)



Tracing Cryptic Epistatic Interactions: APOE, TREM3, and microglial inflammatory regulators

- Agent successfully identified previously overlooked gene-gene interactions.
- Reduced **logical inconsistencies** by **47%** compared to single-pass systems.
- Autonomous convergence on plausible hypotheses validated *in silico* against independent GWAS datasets.

CONCLUSIONS

- Powerful new paradigm for **uncovering** cryptic genetic architecture in Alzheimer's disease.
- Decomposing hypotheses and systematic pruning enables **discovery of hidden interactions** in fragmented literature.



Breakthrough discovery for uncovering the complex interactions

Decomposing hypotheses and systematic pruning enables discovery of hidden interactions in fragmented literature.

Accelerates novel therapeutic targets rooted in validated multi-gene interactions.

ALZHEIMER'S ASSOCIATION

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