Memory-Inspired Modeling of Alzheimer's Progression: A KG-Driven Approach

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Motivation & The Memory Paradox

Alzheimer's disease is fundamentally characterized by progressive memory loss, yet standard machine learning models evaluate clinical visits as isolated "snapshots." They are temporally blind, lacking the longitudinal memory required to accurately track and forecast disease progression over a patient's lifetime. *[5]*

- **The Solution:** This research proposes a Distributed Multi-Agent System (C3) that resolves this paradox by grounding LLMs in a high-fidelity **Neo4j Knowledge Graph**. By transforming static tabular visits into a continuous longitudinal patient mesh, the system references historical **'Clinical Twins'** to enforce strictly deterministic medication safety guardrails and forecast 36-month disease trajectories with high-order stability.

Dual Knowledge Graph Architecture

- **Macro-KG (Global Statistics):** Wires AI in mathematical truths derived from 1,730 patient timelines
- **Micro-KG (The Patient Mesh):** Connects patients via *[:SIMILAR_TO]* edges to find Clinical Twins, grounding predictions in real historical outcomes.

Calibration Error Constraint Loss:

$$\mathcal{L}_{ECE} = \sum_m \frac{|B_m|}{N} |acc(B_m) - conf(B_m)|$$

$$d(v_{active}, \ ) = \sqrt{\sum_i (w_i(v_{a,i} - v_{h,i}))^2}$$

↓

$$d \leq \tau$$

↓

Add [:SIMILAR_TO] edge when $d \leq \tau$

Graph-anchored decision

$$\frac{\sum_{k \in Twins} \mathbb{1}(S^k_{t+36} = AD)}{|Twins|}$$

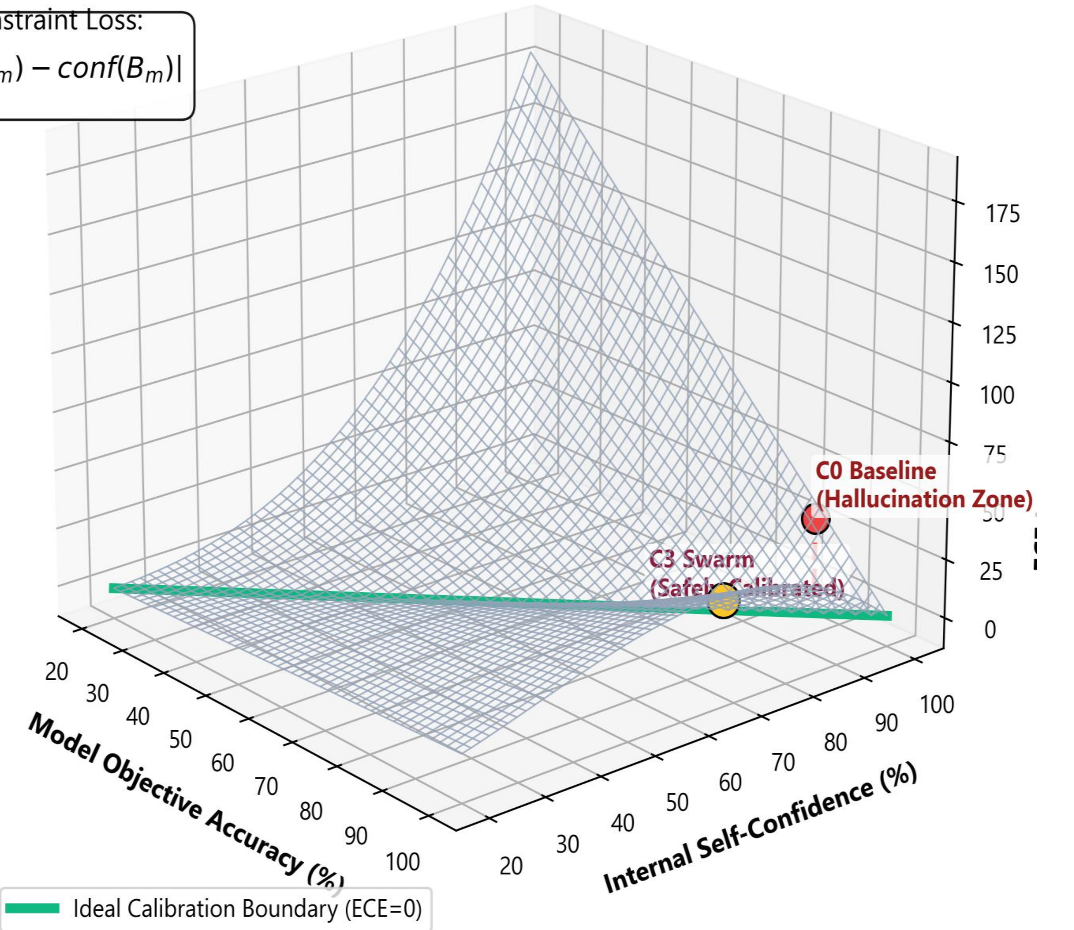
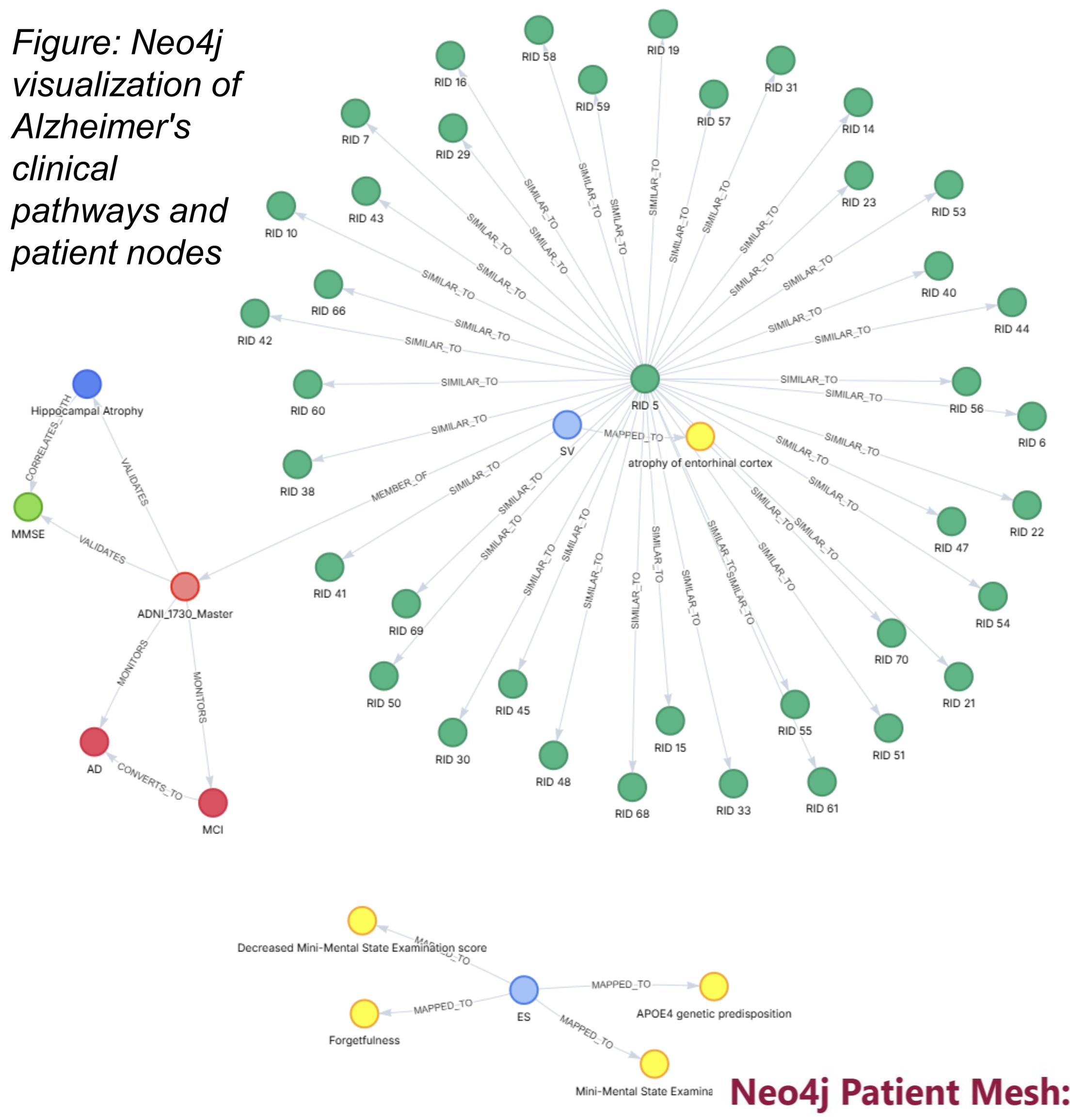


Figure: Similarity rule, graph decision function, and ECE surface [3]

Neuro-Symbolic Framework

Figure: Neo4j visualization of Alzheimer's clinical pathways and patient nodes



Model C0 (Stateless Baseline): Evaluates single clinical visits in isolation. It simulates standard AI, acting as a "temporally blind" control group.

Model C1 (Semantic RAG): Injected with the patient's full longitudinal vector timeline. It possesses memory but lacks strict biological guardrails. *[4]*

Model C3 (Hybrid Graph-RAG): The ultimate proposed architecture. It merges episodic vector memory with the hard biological rules of the Knowledge

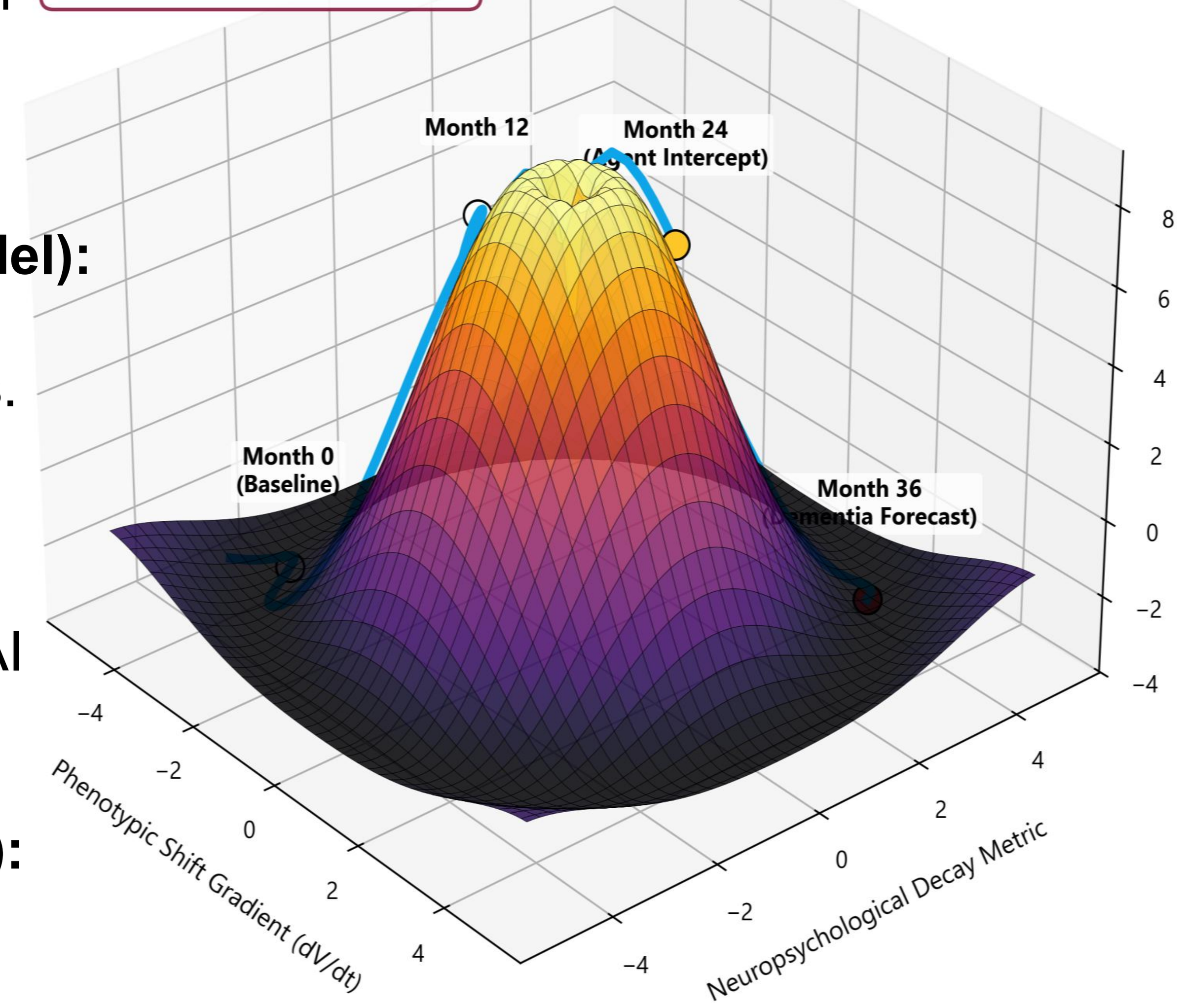
Neo4j Patient Mesh: 3D Latent Space Convergence Mapping

Temporal Sequencing Function:

$$Loss = \arg\min_{\pi} \sum_t \| v_{\pi(t)} - v_{\pi(t+1)} \|_2$$

Bayesian Guardrail Probability:

$$P_{AD} = \frac{\sum_k \mathbb{1}(S^k_{t+36} = 1)}{N_{twins}} \propto P(AD) \prod P(v|AD)$$



The Multi-Agentic Model C3 To prevent cognitive overload when processing massive amounts of Graph and Vector data, Model C3 separates prediction into 3 modules:

Agent 1 (C2 Diagnosis Model): Queries Neo4j for "Twins" to forecast Month 36 diagnoses.

Agent 2 (Temporal Sequencing): Sequences clinical events to overcome AI blindness.

Agent 3 (Safety Constraint): Blocks contraindicated drugs using strict biological rules.

Quantitative Results

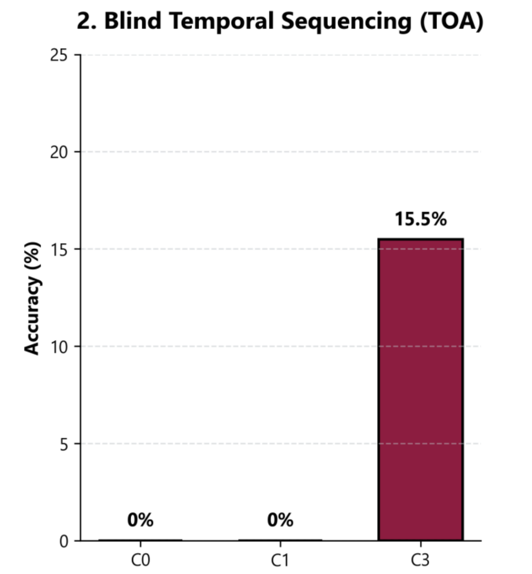
1. KG Validation (Global Benchmarking)

- **CI-to-Dementia: 46.0%** conversion over 4.1 years. *(Validates Skogholt 2022 pan-ADNI baseline of 47.3%) [1].*
- **Hippocampal Atrophy: 3.9%** annual volume loss *(Validated within 3.6–4.6% expected window) [2].*
- **Clinical Correlation:** Strong link between brain volume and MMSE decline (r = 0.73).

2.Temporal Sequencing (TOA)

Standard LLMs proved temporally blind when stripped of explicit date tags.

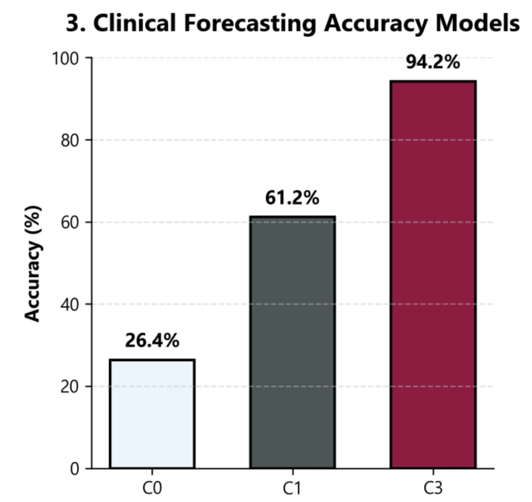
- **Baselines (C0/C1):** 0.0% (Failed double-blind test)
- **Graph-RAG (C3): 15.5%** (Successful progression)



3. Clinical Forecasting Accuracy

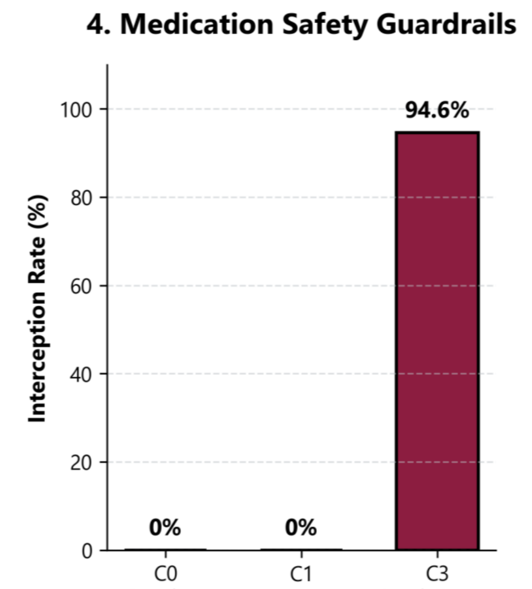
Models restricted to Month 12 data to forecast Month 36 conversion.

- **Baseline (C0):** 26.4%
- **Vector (C1):** 61.2%
- **Graph-RAG (C3): 94.2%** (Highest overall performance).



4. Medication Safety Guardrails

Active Interception: The C3 architecture actively queried the Neo4j graph to block contraindicated drugs (e.g., Memantine for MCI) with a **94.6% success rate**, enforcing hard biological rules over hallucinations.



Conclusion

This research demonstrates that grounding LLMs in **Graph Neural Ontologies** removes the critical safety barriers preventing AI from entering clinical workflows. By enforcing biological guardrails on longitudinal patient meshes, our **C3 framework** provides a scalable, explainable, and safe blueprint for next-gen Alzheimer's diagnostics.

REFERENCES:

[1] Marinescu, R. V., et al. (2018). TADPOLE Challenge: Prediction of Longitudinal Evolution in Alzheimer's Disease. arXiv preprint arXiv:1805.03909. Data provided by Alzheimer's Disease Neuroimaging Initiative (ADNI).

[2] Skogholt, A. H., et al. (2022). Pan-ADNI baseline for MCI-to-Dementia conversion and hippocampal atrophy.

[3] Lewis, P., et al. (2020). Retrieval-Augmented Generation for Knowledge-Intensive NLP Tasks. NeurIPS.

[4] Guo, C., et al. (2017). On Calibration of Modern Neural Networks. ICML.

[5] Jack Jr, C. R., et al. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia.

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