

CO-EVOLVING VIRTUAL CELL MODELS AND PERTURBATION PLANNERS FOR ALZHEIMER'S DISEASE DRUG DISCOVERY

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KEY TAKEAWAY: Co-evolutionary AI enables the discovery of complex, **multi-target combination therapies** *in silico* for AD reversal, surpassing single-target strategies and refining cellular disease simulators.

INTRODUCTION

Current *in silico* models:
Static, lacking interventions



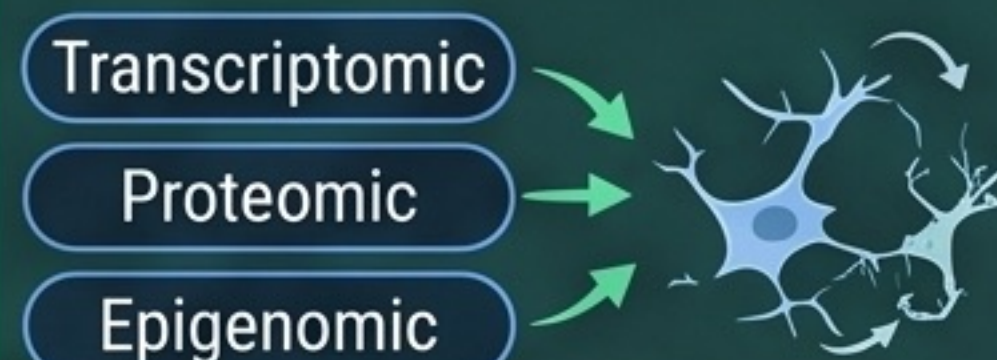
Unlinked AD complexities:



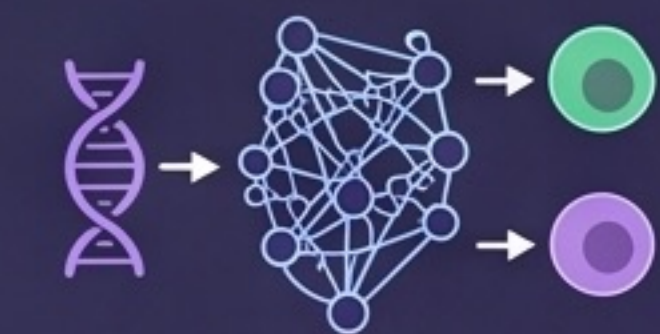
Optimized multi-target multi-target perturbation strategies for AD state reversal.
VCM+Planner

METHODS

Virtual Cell Model (VCM)
(Multimodal Latent Diffusion)



Perturbation Planner
(RL-Based)



Simulate cell state transitions

Propose/Genetic/Pharmacologic combinations

Driver, VCM generalization

Refine proposals

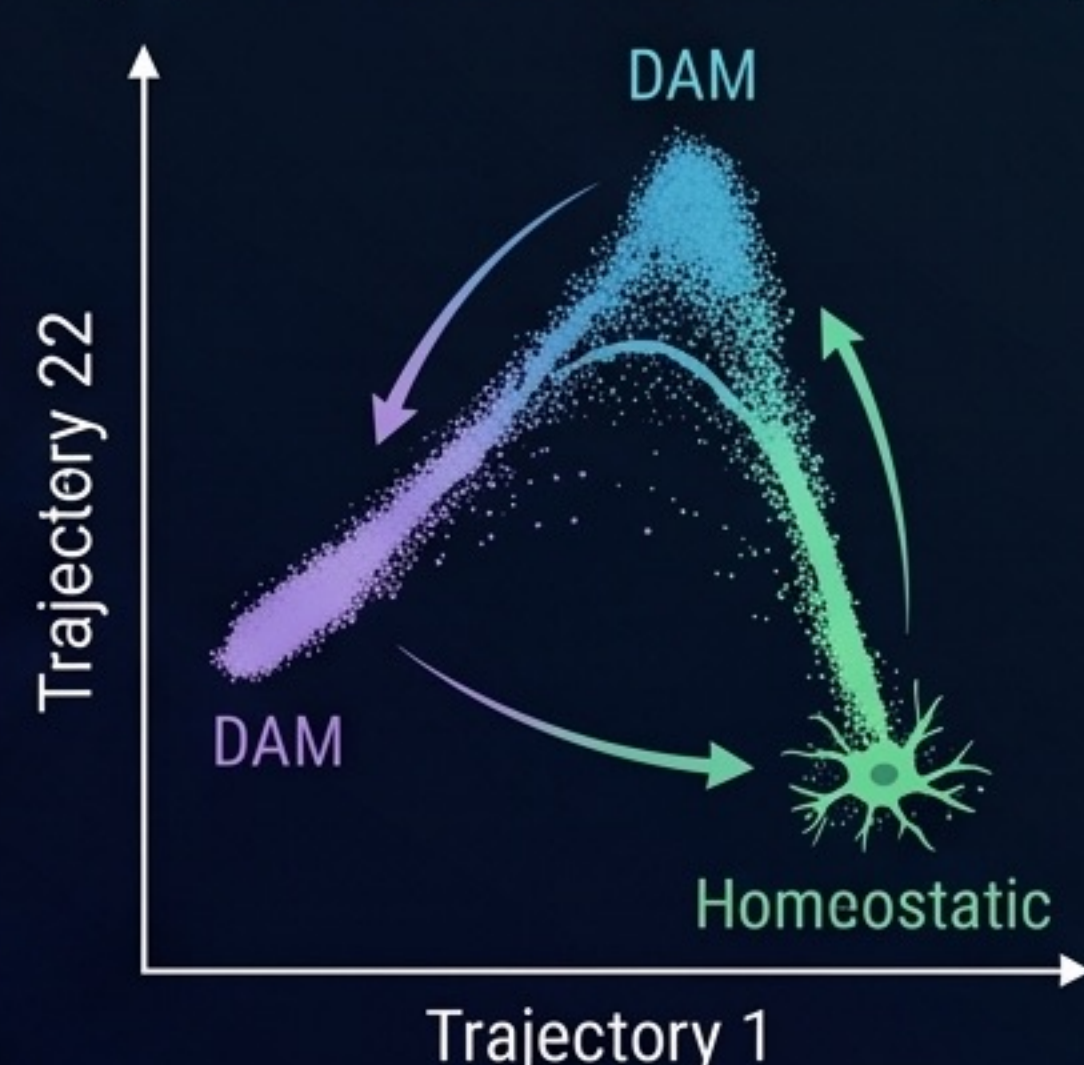
Co-Evolution Cycle



Validation for synthetic single-cell AD datasets modeling DAM transitions

RESULTS

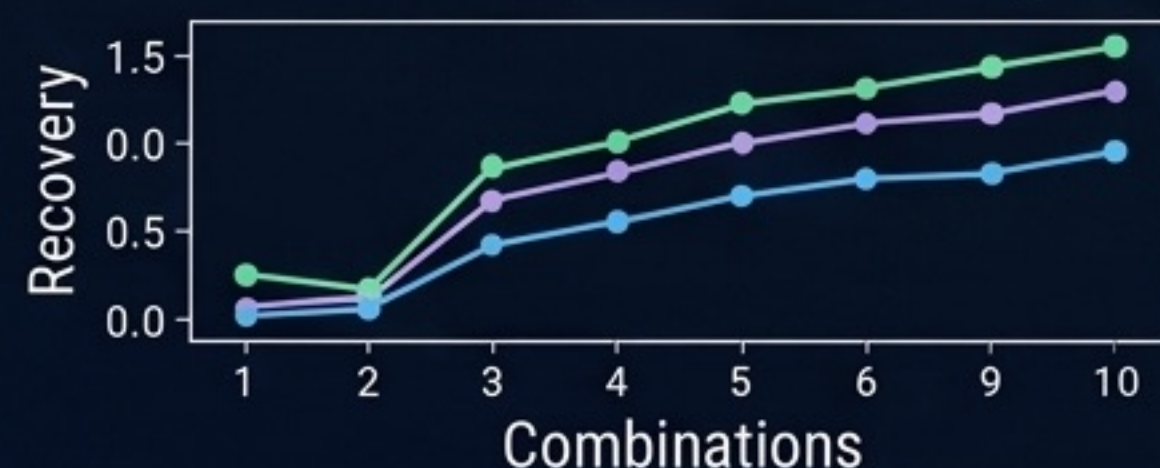
AD State Transition Reversal
(e.g. DAM to Homeostatic microglia)



Pathological Attractor Reversal Score
(outperformed single targets by 38%)



Predicted Transcriptomic Recovery Score



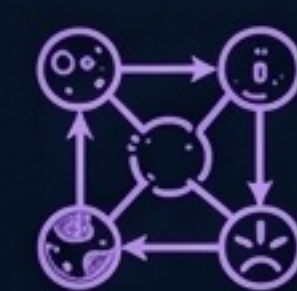
CONCLUSIONS



Powerful New Paradigm for *in silico* AD Drug Discovery.



Iterative Refinement (Co-Evolution) of Cell Simulator & Planner.



Enables Discovery of Complex Combination Therapies.



Validate before Costly *In Vitro* or *In Vivo* Trials.