

MEMENTO: Modeling Myelin Energy Failure in Alzheimer's Disease

A coupled ODE model grounded in cable theory and the TIER framework

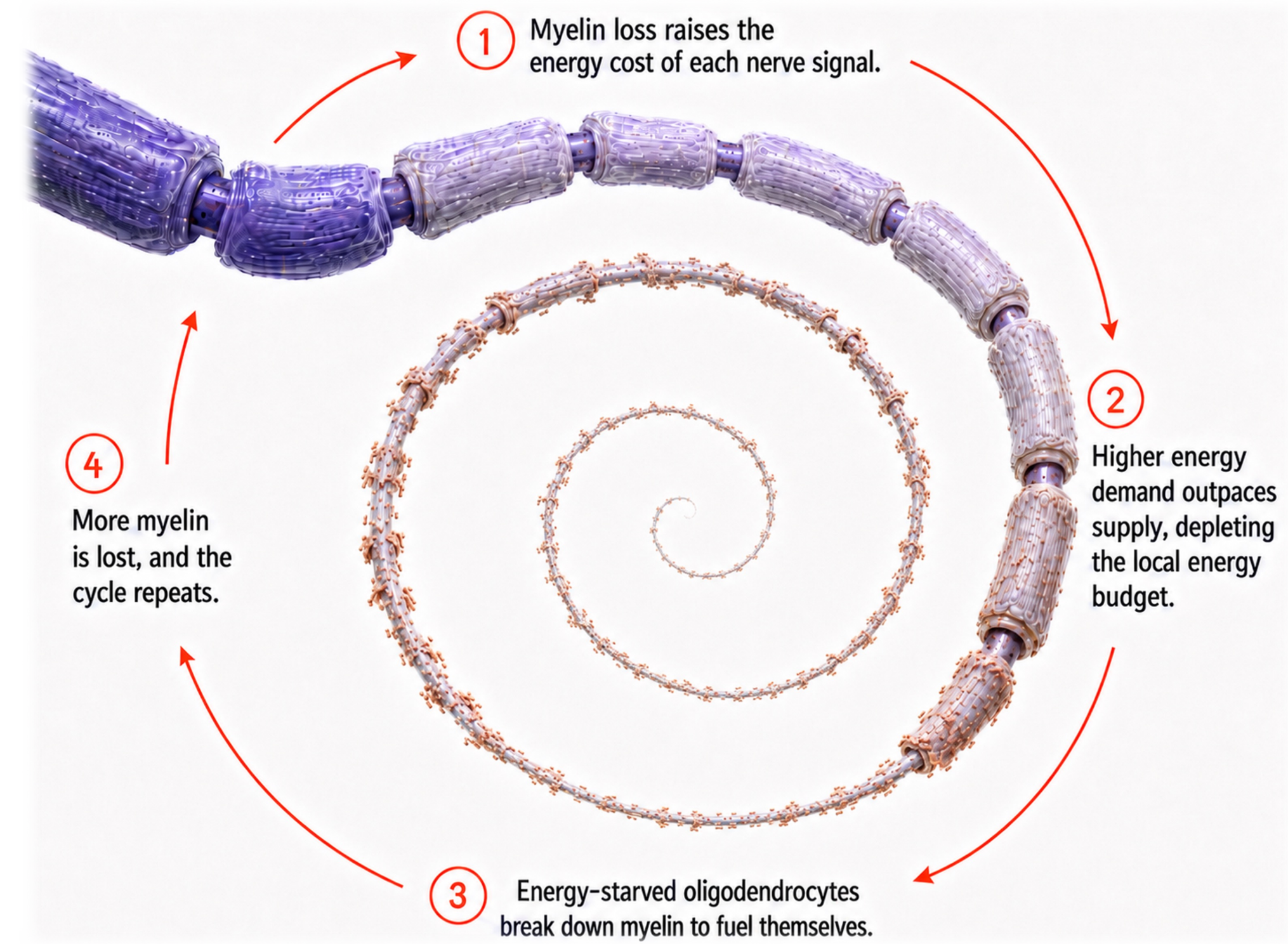
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BACKGROUND

- White matter damage can begin roughly 10 years before cognitive symptoms appear in aging and Alzheimer's disease (Silbert 2012). The brain regions that develop last are often the first to degenerate (Bartzokis 2011), also mapping developmental myelination.
- The TIER (thermodynamic-informational entropic relationship) framework proposes that the tissue doing the most work wears out fastest over time like any other system in engineering. While there are many routes to thermodynamic entropic damage, hubs of vulnerability can often be recognized. Myelin increases efficiency of information integration, and when damaged, the work of that processing increases, resulting in increased degeneration. When energy supply falls short of demand, the system triggers a self-amplifying cycle.
- Maintaining myelin costs more energy than it saves at typical firing rates, a fragile arrangement (Harris and Attwell 2012) When energy supplies dwindle, oligodendrocytes burn their own myelin for fuel (Asadollahi 2024). APOE4 disrupts myelin repair at four separate steps: cholesterol delivery, lipid transport, precursor cell function, and debris clearance (Blanchard 2022).
- We integrate this into a model of Myelin Energy Model of Entropic Neural Tissue Outcomes (MEMENTO).

The vicious cycle



METHODS

In cable theory (Kelvin 1850s; Hodgkin-Huxley 1952), insulation loss raises energetic cost and entropy generation. The model tracks two state variables: myelin integrity $M(t)$ and cumulative structural damage $S(t)$, both governed by Φ , the ratio of local energy supply to demand. When $\Phi < 1$, oligodendrocytes catabolize myelin for ATP. This raises conduction costs, which lowers Φ further, closing the feedback loop. A single exponent α determines whether the resulting decline is gradual or catastrophic.

MEMENTO equations and symbols
Energy balance
 $\Phi(t) = E_{\text{supply}}(t) / E_{\text{demand}}(t)$
Myelin dynamics (one closed loop)
 $dM/dt = \text{repair} - \text{catabolism}$
 $C_{\text{AP}}(t) = C_{\text{AP}_0} \cdot (1/M)^\alpha$ (cost rises as insulation falls)
Entropy (same α , second law)
 $dS/dt = \sigma_{\text{inefficiency}} + \sigma_{\text{deficit}}$
Symbols
 M myelin integrity (0 to 1)
 S cumulative entropy
 Φ energy supply / demand ratio
 α cost-rise exponent
 R APOE-modulated repair capacity
 C_{AP} per-action-potential energetic cost

RESULTS

Figure 1. Vicious cycle dynamics ($\epsilon 3/\epsilon 3$ reference, $\alpha = 1.0$)

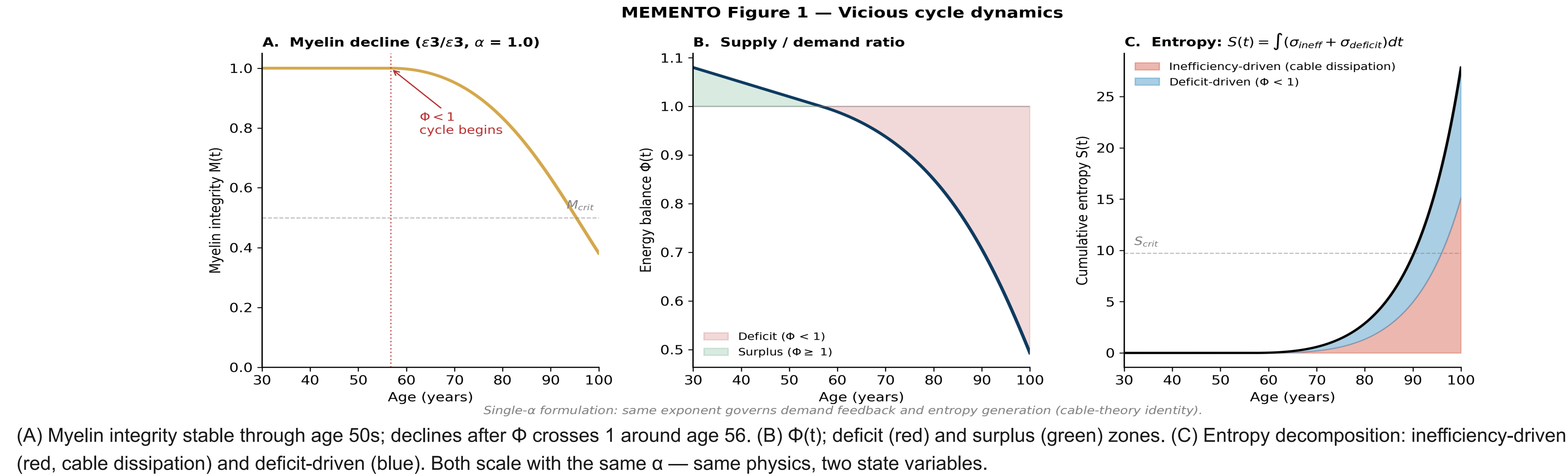


Figure 2. APOE dose-dependent onset

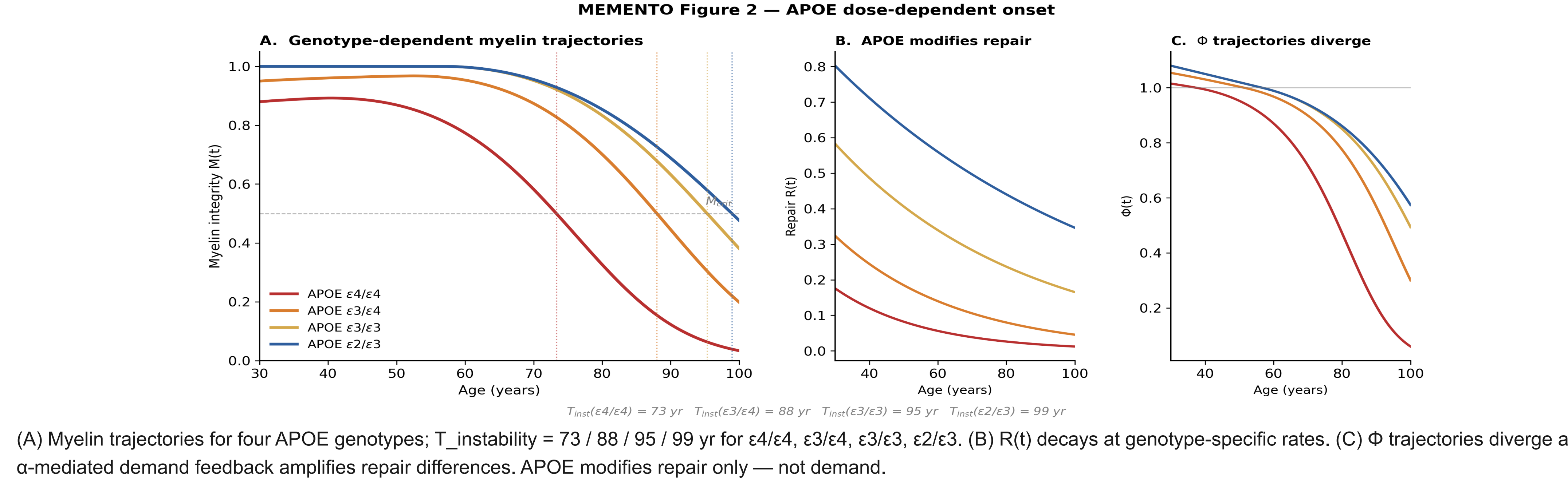


Figure 3. Marathon validation (Ramos-Cabrer 2025)

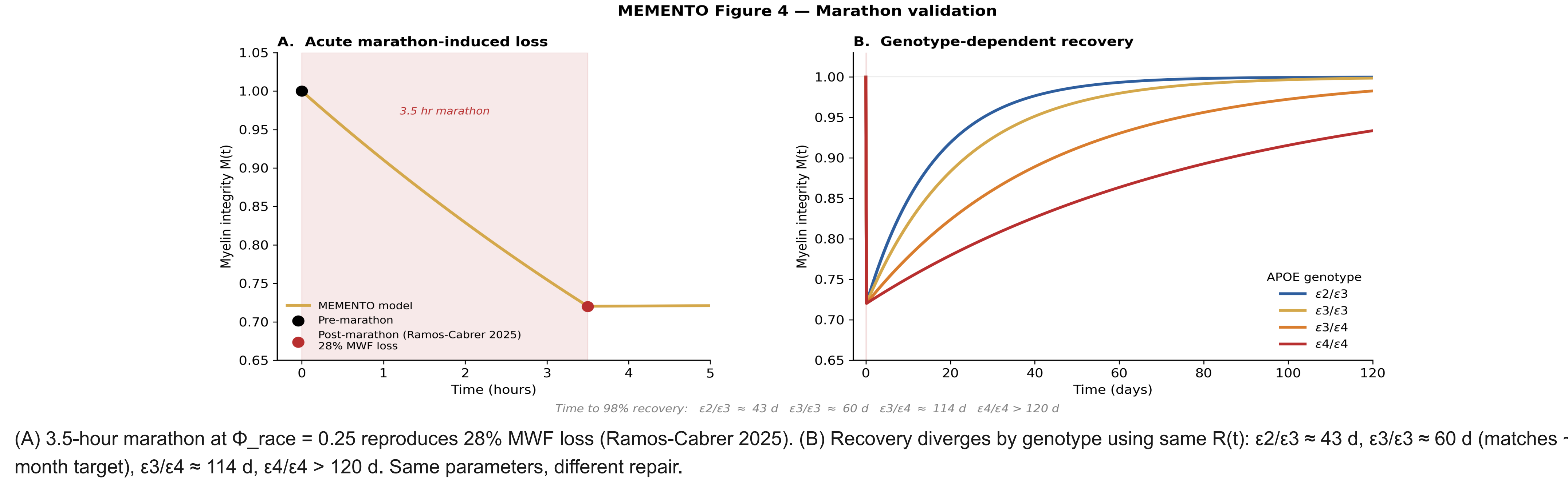
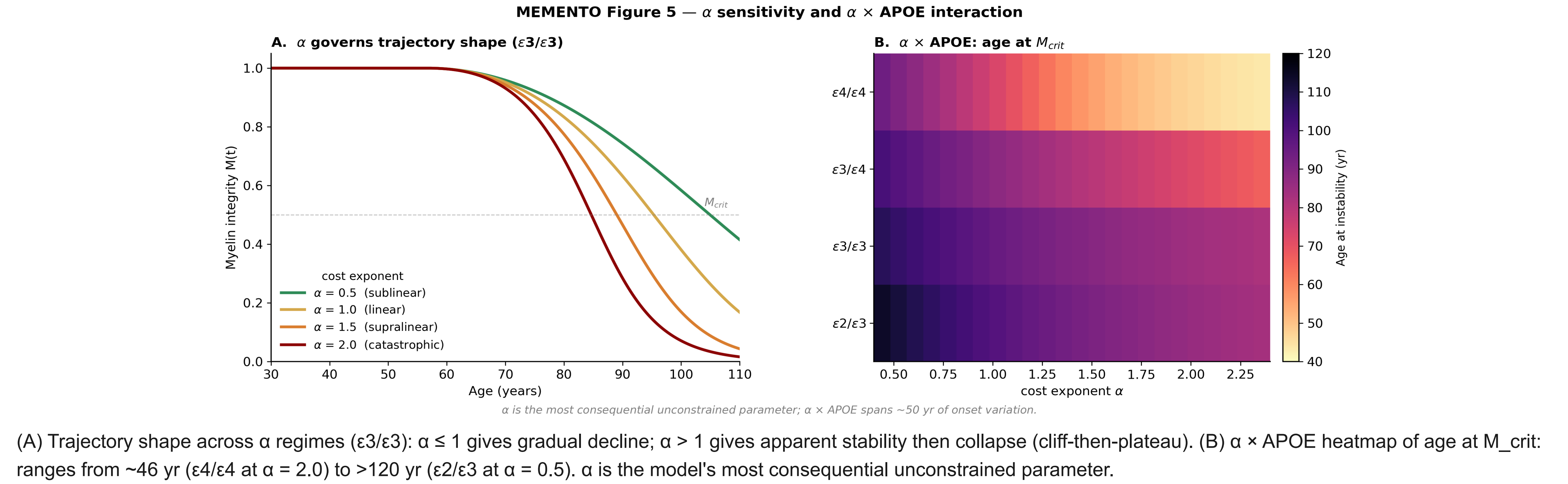


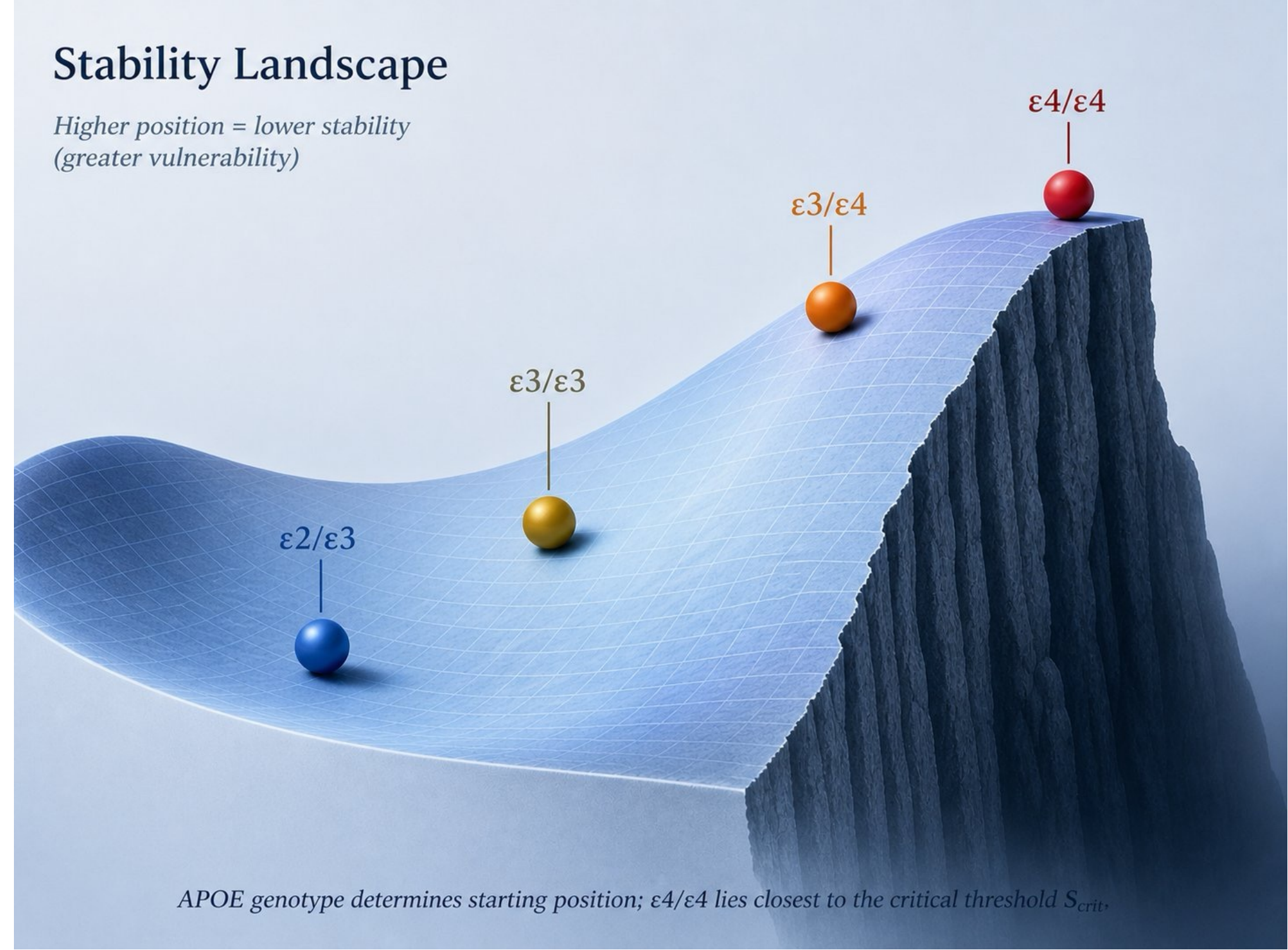
Figure 4. α sensitivity and $\alpha \times$ APOE interaction



DISCUSSION

- The physics here is over 150 years old. Kelvin and Heaviside worked out how electrical signals decay in imperfectly insulated cables. Hodgkin and Huxley applied the same equations to nerve fibers in 1952. Myelin is the insulating layer. When it breaks down, signals leak, cost more energy, and generate more entropy. Rising inefficiency and rising entropy are the same problem in two different units.
- There is also a direct consequence for memory and learning. The strength of a new synaptic connection depends on how strongly the arriving signal depolarizes the receiving neuron. Weaker, slower signals from demyelinated fibers produce weaker connections, so the brain compensates by firing more often to get the same effect (Cabeza 2018). But firing more is more expensive, and the compensation is never complete. The result is that fluid intelligence, the kind that depends on fast and flexible integration across long-range circuits, declines first. Crystallized intelligence, built on older and better-myelinated pathways, holds on much longer. Cable physics explains this without any additional assumptions.

Where genotypes sit on the basin



CONCLUSION

The model illustrates neurodegeneration based on oligodendrocyte-neuronal interactions. When a brain region works too hard for too long without adequate fuel, oligodendrocytes begin catabolizing their own myelin to survive. This may initiate a feedback loop. Less insulation means slower, costlier signals, less efficient energy use per informational unit. Increasing inefficiency is entropy by definition.

APOE4 carriers in this model exhaust their repair capacity faster at every step of the process. Once the cycle starts, recovery becomes increasingly unlikely. The regions doing the most integration, the same ones that developed last and were left least insulated to begin with, enter this cycle first and have the least capacity to recover from it.

The model predicts that targeting myelin repair capacity, as well as related metabolism, directly may be effective in reducing neurodegeneration in vulnerable patients.

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