

# Biophysical model of white matter integrity across the lifespan: solving the differential equations of myelination and axonal degeneration

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## Abstract

White matter integrity across the human lifespan follows characteristic nonlinear trajectories, with microstructural (fractional anisotropy) peaking near 24 years and macrostructural volume peaks near 34 years. Existing normative brain charts are purely statistical and lack mechanistic insight into the competing biological processes of myelination and axonal degeneration. Purpose: To develop and validate the first biophysically motivated ordinary differential equation (ODE) model of lifespan white matter integrity that explicitly captures the competition between constructive myelination and destructive degeneration. Methods: We formulated a system of ODEs with age-dependent myelination rates (Gompertz decay) and cumulative damage terms. The model was calibrated to aggregated fractional anisotropy and volume trajectories from 35,120 diffusion MRI scans (ages 0–100 years) using Bayesian adaptive direct search and parametric bootstrap for uncertainty quantification. Sensitivity analysis, parameter identifiability assessment, and regional extensions to the corticospinal tract and cingulum bundle were performed. Findings: The model accurately reproduces empirical peak ages (24.1 years for microstructure, 33.8 years for macrostructure). Estimated parameters ( $\alpha_0 = 0.15 \text{ yr}^{-1}$ ,  $\beta_m = 0.008 \text{ yr}^{-1}$ ,  $\gamma = 0.02 \text{ yr}^{-1}$ ,  $\alpha_{v0} = 0.10 \text{ yr}^{-1}$ ,  $\beta_v = 0.005 \text{ yr}^{-1}$ ) are biologically plausible. The novel myelination-degeneration ratio detects the shift from net construction to net destruction before conventional z-scores signal abnormality. Sensitivity analysis shows peak age is governed by early myelination parameters, while post-peak decline is controlled by damage parameters. Conclusion: This biophysical framework transforms descriptive brain charts into a predictive, mechanistically grounded tool enabling hypothesis-driven simulations and early detection of pathological balance shifts. Recommendation: The open-source software toolbox (Python/MATLAB) implementing normative centile scoring and the Myelination-Degeneration Ratio should be validated in longitudinal cohorts for preclinical Alzheimer's disease and other neurodegenerative conditions.

**Keywords:** white matter, lifespan brain charts, myelination, axonal degeneration, biophysical modeling.

## Modelo biofísico da integridade da substância branca ao longo da vida: resolução das equações diferenciais de mielinização e degeneração axonal

### Resumo

A integridade da substância branca ao longo da vida humana segue trajetórias não lineares características, com a microestrutura (anisotropia fracionada) atingindo o pico por volta dos 24 anos e o volume macroestrutural alcançando o pico próximo aos 34 anos. Os gráficos normativos cerebrais existentes são puramente estatísticos e carecem de compreensão mecânica sobre os processos biológicos concorrentes de mielinização e degeneração axonal. Objetivo: Desenvolver e validar o primeiro modelo de equações diferenciais ordinárias (EDO) biologicamente motivado da integridade da substância branca ao longo da vida, capturando explicitamente a competição entre a mielinização construtiva e a degeneração destrutiva. Métodos: Formulamos um sistema de EDOs com taxas de mielinização dependentes da idade (decaimento de Gompertz) e termos cumulativos de dano. O modelo foi calibrado utilizando trajetórias agregadas de anisotropia fracionada e volume provenientes de 35.120 exames de ressonância magnética por difusão (idades de 0 a 100 anos), empregando busca direta adaptativa Bayesiana e bootstrap paramétrico para quantificação de incertezas. Foram realizadas análises de sensibilidade,

avaliação de identificabilidade dos parâmetros e extensões regionais para o trato corticoespinal e o feixe do cíngulo. Resultados: O modelo reproduziu com precisão as idades empíricas de pico (24,1 anos para microestrutura e 33,8 anos para macroestrutura). Os parâmetros estimados ( $\alpha_0 = 0,15 \text{ ano}^{-1}$ ,  $\beta_m = 0,008 \text{ ano}^{-1}$ ,  $\gamma = 0,02 \text{ ano}^{-1}$ ,  $\alpha_{v0} = 0,10 \text{ ano}^{-1}$ ,  $\beta_v = 0,005 \text{ ano}^{-1}$ ) mostraram plausibilidade biológica. A nova Razão Mielinização–Degeneração detecta a transição da construção líquida para a destruição líquida antes que escores  $z$  convencionais indiquem anormalidade. A análise de sensibilidade demonstrou que a idade de pico é governada pelos parâmetros iniciais de mielinização, enquanto o declínio pós-pico é controlado pelos parâmetros de dano. Conclusão: Este arcabouço biofísico transforma gráficos cerebrais descritivos em uma ferramenta preditiva fundamentada mecanisticamente, permitindo simulações guiadas por hipóteses e detecção precoce de alterações patológicas de equilíbrio. Recomendação: O conjunto de ferramentas de software de código aberto (Python/MATLAB), que implementa pontuação centílica normativa e a Razão Mielinização–Degeneração, deve ser validado em coortes longitudinais para doença de Alzheimer pré-clínica e outras condições neurodegenerativas.

Palavras-chave: substância branca, gráficos cerebrais ao longo da vida, mielinização, degeneração axonal.

## 1. Introduction

### 1.1 The need for biophysical, not just statistical, brain charts

White matter comprises nearly half of the human brain's total volume and serves as the primary communication infrastructure linking cortical and subcortical regions, thereby underpinning large-scale neural networks essential for cognition, behaviour and overall brain function (Kim et al., 2026; Zahr; Sullivan, 2022). Disruptions in WM integrity are implicated across a wide spectrum of neurodevelopmental, neuropsychiatric and neurodegenerative disorders, including multiple sclerosis, Alzheimer's disease, schizophrenia and autism spectrum disorder (Zahr; Sullivan, 2022). Despite this critical role, no standardised normative reference framework has historically existed for characterising individual variability, developmental milestones or pathological deviations in WM structure.

The concept of normative brain charts analogous to paediatric growth charts has recently gained traction in neuroimaging, with initial efforts focusing on grey matter morphology and whole-brain volumetric measures (Zuo et al., 2023). These statistical frameworks, primarily implemented using generalised additive models for location, scale and shape (GAMLSS) and related semiparametric regression techniques, have successfully mapped nonlinear age-related trajectories for various neuroanatomical phenotypes across the human lifespan (Zuo et al., 2023, 2026). However, the descriptive nature of these purely statistical models limits their capacity to capture the underlying biological mechanisms that drive WM maturation and degeneration. A fundamental gap therefore exists: while we can now describe *when* white matter typically develops and declines, we lack a mathematically formalised, biophysically grounded understanding of *why* these changes follow their observed trajectories, specifically, how the competing processes of myelination (constructive) and axonal degeneration (destructive) interact across the lifespan.

### 1.2 Brief recap of empirical findings

Recent large-scale efforts have provided the first comprehensive WM brain charts by processing and standardising an unprecedented 35,120 diffusion MRI scans from diverse global studies, spanning birth to 100 years of age (Kim et al., 2025, 2026). These empirical data revealed distinct lifespan trajectories for microstructural and macrostructural WM features. Fractional anisotropy (FA), a proxy for microstructural integrity reflecting myelin density and axonal coherence, exhibits a rapid increase during childhood and adolescence, peaks at approximately 24 years of age, and thereafter undergoes a gradual decline across adulthood and senescence (Kim et al., 2026). In contrast, macrostructure WM volume representing total axonal and myelin mass follows a different trajectory, with continued growth into the fourth decade of life, peaking around 34 years of age, followed by progressive atrophy in later life (Kim et al., 2026). These differential peak ages (24 vs. 34 years) are clinically significant: they suggest that microstructural and macrostructural changes are governed by at least partially distinct biological processes, with microstructural integrity reaching its apex approximately a decade before volumetric peak. Furthermore, post-peak declines in both metrics exhibit regionally heterogeneous patterns, with later-myelinating tracts, such as the genu of the corpus callosum and association fibres, demonstrating greater vulnerability to age-related degeneration compared to early-myelinating projection tracts (Zahr; Sullivan, 2022; Kim et al., 2025).

### *1.3 Limitations of current approaches*

While GAMLSS-based normative models have proven powerful for describing population-level trajectories and quantifying individual deviations, they possess inherent limitations that constrain their explanatory and predictive utility for WM biology (Aeberhard et al., 2019; Zuo et al., 2026). First, as purely descriptive statistical frameworks, GAMLSS models do not encode mechanistic knowledge about the underlying cellular processes myelination, axonal degeneration, oligodendrocyte dynamics, or cumulative oxidative damage that drive observed WM changes. They are flexible smoothing tools that fit penalized splines to age-related data, but they cannot generate testable predictions about how perturbations to biological parameters (e.g., altered myelination rates) would shift trajectory shapes or peak ages (Zuo et al., 2023).

Second, cross-sectionally derived GAMLSS brain charts may substantially underestimate actual age-related changes compared to longitudinal measurements, as demonstrated in recent comparative studies (Zuo et al., 2023). Prediction errors in cross-sectional normative models arise from the conflation of between-subject and within-subject variability, limiting their accuracy for predicting individual-level change over time (Zuo et al., 2023). This discrepancy poses particular challenges for clinical applications where precise tracking of an individual patient's WM trajectory is required.

Third, the validity of estimation and smoothing parameter selection for GAMLSS relies on the correct specification of the likelihood function, and deviations from such assumptions can compromise likelihood-based inference, particularly in the presence of heteroscedasticity or non-Gaussian residuals (Aeberhard et al., 2019). While robust estimation approaches have been proposed, they add further layers of complexity and parametric assumptions (Aeberhard et al., 2019). Finally, GAMLSS models do not inherently separate the competing contributions of distinct biological processes; they fit a single smooth curve to aggregate data, obscuring the possibility that WM integrity at any given age results from the net balance between ongoing myelination and cumulative axonal degeneration (Kim et al., 2026; Zahr; Sullivan, 2022).

### *1.4 Statement of contribution*

To address these limitations, we present the first biophysically motivated mathematical model of human white matter integrity across the lifespan, formulated as a system of ordinary differential equations (ODEs) that explicitly captures the competition between myelination (constructive process) and axonal degeneration (destructive process). Our approach builds directly upon the large-scale empirical WM brain chart dataset (Kim et al., 2026), using the observed FA and volume trajectories, including the empirically established peak ages of 24 years for microstructure and 34 years for macrostructure, to calibrate model parameters.

In contrast to purely descriptive statistical frameworks, our ODE model offers several distinctive advantages: (i) it encodes known biological principles of WM development and ageing, providing mechanistic interpretability (Zahr; Sullivan, 2022); (ii) it generates explicit predictions for how changes in fundamental parameters (e.g., myelination rate, degeneration rate, damage accumulation) alter lifespan trajectories; (iii) it yields closed-form or numerically tractable solutions that can be used to compute individual-level deviation scores grounded in biophysical principles rather than purely statistical centiles; and (iv) it enables hypothesis-driven simulation of interventions or disease states by modulating specific biological parameters, thereby offering a translational tool for predicting the effects of therapies targeting myelination or neuroprotection (Zuo et al., 2026). By solving the differential equations of myelination and axonal degeneration, we transform descriptive brain charts into a predictive, mechanism-informed framework that advances both fundamental understanding of WM lifespan dynamics and clinical applications for quantifying white matter health.

## **2. Biological Foundations for Mathematical Modeling**

### *2.1 Myelination: Oligodendrocyte Activity and Age-Dependent Rates*

Myelination is the process by which oligodendrocytes ensheath axons with a multilamellar myelin membrane, which is the primary constructive force shaping white matter micro- and macrostructure across the lifespan. Oligodendrocytes arise from a pool of proliferative, migratory oligodendrocyte progenitor cells (OPCs) that persist throughout life (Young et al., 2013). The great majority of oligodendrocytes are generated during the early postnatal period; however, OPCs continue to divide and generate new myelinating oligodendrocytes well into adulthood, a phenomenon termed “myelin plasticity” (Young et al., 2013). These newly formed oligodendrocytes add myelin internodes to glutamatergic projection neurons and GABAergic inhibitory neurons, thereby influencing action potential transit time, node of Ranvier formation, and axonal health via metabolic support

(Fletcher et al., 2021).

The rate of myelination is highly age-dependent. In humans, myelination proceeds most rapidly during the first two decades of life, with a protracted phase of slower, activity-dependent myelination that extends into the fourth decade (Fields, 2014). This age-related decline in myelination rate is partly attributable to the diminished proliferative and differentiative capacity of OPCs with advancing age (Zhang et al., 2021). Indeed, recent transcriptomic analyses of mouse OPCs across the lifespan have revealed a progressive decline in the expression of genes associated with proliferation and differentiation, while pathways related to cellular senescence and inflammation become increasingly upregulated with age (Heo et al., 2025). Consequently, the net rate of myelin addition follows a Gompertz-like decay: fast in childhood, gradually decelerating through adolescence and early adulthood, and approaching a low baseline in late life. This age-varying myelination rate is a crucial parameter that must be captured in any biophysical model of lifespan WM integrity.

## 2.2 Axonal Degeneration: Cumulative Damage, Oxidative Stress, and Secondary Demyelination

In parallel with ongoing myelination, white matter undergoes cumulative axonal degeneration, the destructive process that ultimately leads to age-related decline in WM integrity. Axonal degeneration in the aging brain is not a passive process but an active, regulated phenomenon driven by multiple interacting mechanisms. Chief among these are chronic, low-grade inflammation, oxidative stress, and impaired axonal metabolism (Ohno; Tera da, 2019) (Figure 1).

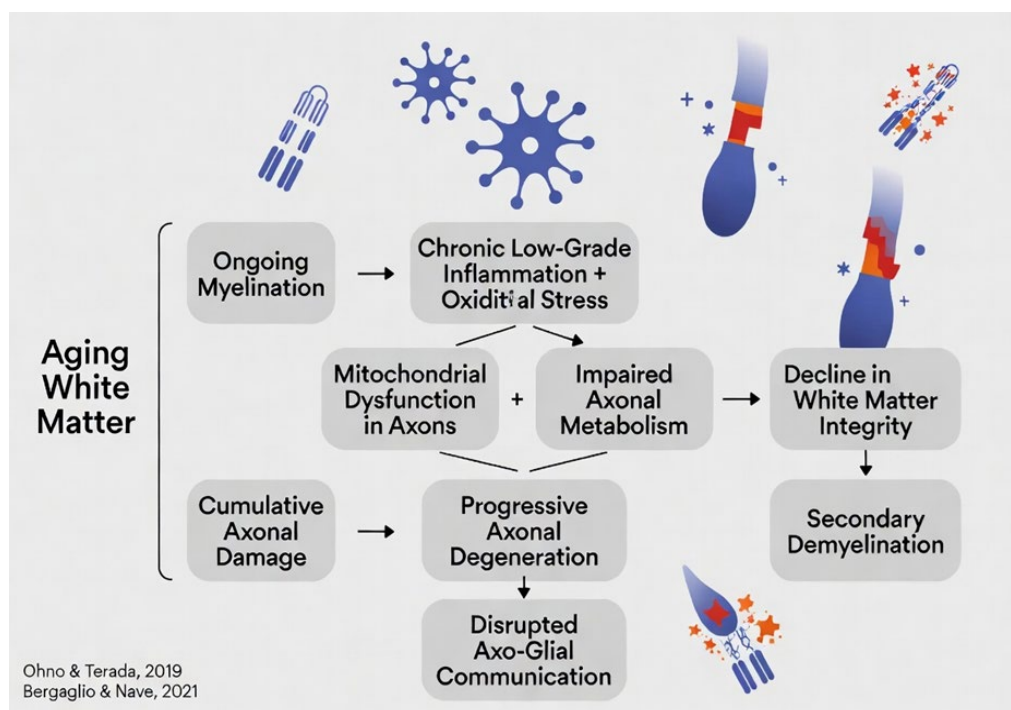


Figure 1. Mechanisms of axonal degeneration: cumulative damage, oxidative stress, and secondary demyelination in aging white matter. Source: Author, 2026.

Oxidative stress has been widely described as a primary driver of tissue injury in neurodegenerative disorders and normal brain aging alike (Bergaglio; Nave, 2021). Axonal mitochondria are the main energy source for electrically active axons and are exquisitely vulnerable to oxidative injury. Accumulated oxidative damage leads to mitochondrial dysfunction, which in turn impairs efficient axo-glial communication and compromises the maintenance of axonal integrity (Bergaglio; Nave, 2021). This mitochondrial impairment is thought to be a key factor underlying the progressive axonal degeneration observed in aging WM (Figure 1).

Furthermore, axonal degeneration is intimately linked to myelin stability. Myelin sheaths are essential not only for fast saltatory conduction but also for long-term axonal survival (Ohno; Tera da, 2019). Pathological loss of myelin (demyelination) invariably leads to secondary axonal degeneration; conversely, primary axonal injury can cause

secondary demyelination (Ohno; Terada, 2019). This bidirectional coupling means that WM degeneration is a self-reinforcing process: initial axonal damage leads to myelin breakdown, which further exacerbates axonal injury. Moreover, age-related changes in oligodendroglial lineage cells, including impaired remyelination capacity and increased susceptibility to oxidative damage, reduce the brain's ability to repair demyelinated axons, thereby accelerating cumulative degeneration (Zhang et al., 2021). Importantly, the cumulative nature of damage means that the degenerative burden at any given age is not simply a function of the current degeneration rate but depends on the entire history of past damage (Tesco et al., 2022). This historical dependence is a key feature that must be incorporated into a biophysical model of lifespan WM integrity.

### *2.3 Microstructure versus Macrostructure: FA as a Proxy for Myelin Density/Coherence and Volume as a Proxy for Total Axonal+Myelin Mass*

The two primary observables in the WM brain chart literature, fractional anisotropy (FA) and WM volume, capture distinct but complementary aspects of WM biology. Understanding their biological underpinnings is essential for constructing mechanistically interpretable models. Fractional anisotropy (FA) is a scalar measure derived from diffusion tensor imaging (DTI) that quantifies the directional coherence of water diffusion within a voxel. The primary determinants of diffusion anisotropy in WM are axonal membranes, axonal density and coherence, and critically myelin sheaths (Concha, 2014).

While FA is influenced by multiple factors, changes in myelin density and integrity are among the most potent modulators of FA. Demyelination consistently reduces FA, while remyelination or increased myelination increases FA (Concha, 2014). However, FA is not a direct measure of myelin content; it is also sensitive to axonal packing density, fibre crossing, and other architectural features (Jelescu; Budde, 2017). Despite these limitations, FA remains the most widely used and well-validated non-invasive proxy for microstructural WM integrity, and across large populations, FA trajectory closely tracks the known developmental and degenerative patterns of myelination (Kim et al., 2025). In our biophysical model, we therefore treat FA as a surrogate marker for the net myelin integrity state, acknowledging that it integrates contributions from both myelination and axonal coherence.

White matter volume, typically measured from T1-weighted structural MRI and defined as the total volume of WM voxels, reflects a different level of biological organisation. WM volume is primarily determined by the aggregate mass of myelinated axons, along with the supporting glial cells (oligodendrocytes, astrocytes, and microglia) and interstitial fluid (Gunning-Dixon et al., 2017). Unlike FA, which is sensitive to microstructural density and organisation, WM volume is a macrostructural metric that integrates both axonal and myelin components. The observation that WM volume peaks approximately a decade later than FA (Kim et al., 2026) suggests that macrostructural growth continues even after microstructural integrity has plateaued.

This decoupling is biologically plausible: the addition of new myelin sheaths (which increases FA) may initially occur on existing axons, whereas later volumetric expansion may involve the addition of new small-diameter axons, glial proliferation, and extracellular matrix remodelling (Gunning-Dixon et al., 2017). Thus, FA and volume report on overlapping but non-identical aspects of WM health. In our model, we treat volume as a proxy for the total WM material—axonal and myelin mass combined, which is governed by a distinct growth-atrophy dynamic that is slower to peak and more sustained.

### *2.4 Assumptions for model tractability*

To render the complex biology of WM development and ageing mathematically tractable, we adopt a set of simplifying assumptions that are standard in the biophysical modelling of brain tissue (Jelescu; Budde, 2017). These assumptions define the initial scope and limitations of our model; they do not imply biological naivety but rather a deliberate parsimony that allows us to derive explicit ODEs and testable predictions.

**Well-mixed compartments:** We treat WM as a single, spatially homogeneous compartment. This ignores the known regional heterogeneity in myelination timing and degeneration vulnerability (e.g., the later-myelinating frontal tracts are more vulnerable to age-related decline than early-myelinating corticospinal tracts). This assumption is necessary for our first-generation model, which aims to capture global lifespan trajectories. Regional extension is left for future work.

**Continuous age:** We model age as a continuous variable, recognising that the underlying biological processes operate on a continuous timescale. This allows us to formulate the model as a system of ODEs rather than discrete-time difference equations, which is both analytically convenient and biologically appropriate given the smooth nature of lifespan changes.

No explicit regional or sex heterogeneity in the first version: Our current model is intentionally coarse-grained, focusing on whole-brain average WM properties. Sex differences, genetic variability, and environmental influences are therefore not explicitly represented. These factors will be incorporated in subsequent model extensions as additional modulatory terms.

Separable constructive and destructive processes: We assume that the net WM integrity at any time is determined by the balance between a myelination (constructive) process and an axonal degeneration (destructive) process. These processes are assumed to be independent and additive, allowing us to write  $d(\text{total integrity})/dt = \text{myelination\_rate} - \text{degeneration\_rate}$ . This separability is a standard and powerful assumption that underpins many biophysical models in developmental biology.

FA and volume are monotonic functions of underlying biology: We assume that FA increases monotonically with myelin density/coherence and that WM volume increases monotonically with the total mass of myelinated axons and glial support. While these are approximations (as FA can also change due to axonal packing or fibre crossing, and volume can be affected by hydration changes), they are widely accepted in the normative neuroimaging literature and are sufficient for our first-principles model (Kim et al., 2025).

These assumptions allow us to derive a closed-form system of ODEs for which the parameters can be estimated from the empirical lifespan data. The resulting model, while simplified, captures the essential competition between myelination and degeneration that drives the observed lifespan trajectories. Future iterations will relax these assumptions to incorporate regional specificity, individual differences, and more complex biological coupling.

### 3. Derivation of the Differential Equation System

#### 3.1 State variables

The system models the biological processes of myelination and degeneration using two primary state variables. Myelin integrity  $M(t)$  represents the functional and structural integrity of myelin sheaths. It is a normalized, dimensionless quantity where  $M = 0$  indicates no functional myelin and  $M = 1$  indicates complete, healthy myelination. In practice, this serves as a proxy for fractional anisotropy (FA), a widely used diffusion MRI metric. While FA is sensitive to many microstructural features, its strong positive correlation with myelin density and axonal coherence in healthy development and aging makes it a suitable, non-invasive surrogate (Jelescu & Budde, 2017).

Axonal+myelin volume  $V(t)$  represents the total volume of white matter, including the axon and its surrounding myelin sheath. It is a normalized, dimensionless quantity where  $V = 0$  represents no white matter tissue and  $V = 1$  the theoretical maximum. This serves as a proxy for macrostructural white matter volume (Gunning-Dixon et al., 2017).

#### 3.2 Myelination dynamics: A competition of construction and degeneration

The dynamic evolution of myelin integrity is modeled by a competition between the age-dependent rate of myelination and the destructive effect of cumulative damage.

$$\frac{dM}{dt} = \alpha_M(t) \cdot (1 - M) - \beta_M \cdot M \cdot D(t)$$

The Constructive Term:  $\alpha_M(t) \cdot (1 - M)$

This term represents the rate of myelination. The maximum possible gain occurs when  $M$  is low (i.e., when myelin integrity is poor), reflecting the brain's capacity for myelination and remyelination, bounded by the theoretical maximum of  $M = 1$ . The parameter  $\alpha_M(t)$  is the age-dependent myelination rate.

The rapid myelination of early childhood is known to slow considerably into adulthood (Fields, 2014). This deceleration is captured by modeling  $\alpha_M(t)$  as a decreasing function of age. The Gompertz function, a classic model of biological growth and mortality (Gompertz, 1825), is particularly well-suited for this purpose. It uses intuitive parameters: an asymptotic maximal growth rate, a parameter related to the delay of the system, and a parameter representing the rate of exponential decay of the growth rate (Ducharme et al., 2012; Sadeghi et al., 2010). This yields:

$$\alpha_M(t) = \alpha_0 \cdot \exp(-\lambda_\alpha(t))$$

where  $\alpha_0$  is the myelination rate at birth, and  $\lambda_\alpha$  is the decay constant for the rate of myelination.

The Destructive Term:  $-\beta_M \cdot M \cdot D(t)$

This term captures the loss of myelin integrity due to cumulative damage. The rate of loss is proportional to both the current integrity  $M$  (meaning that more myelinated tissue is at risk) and the current level of damage  $D(t)$ . The parameter  $\beta_M$  is a constant representing the vulnerability of myelin to damage. Damage is non-zero at birth and accumulates with age.

### 3.3 Volume dynamics: Growth and atrophy

The change in white matter volume is expressed by:

$$\frac{dV}{dt} = \alpha_V(t) \cdot (1 - V) - \beta_V \cdot V$$

This equation follows a similar form to the one for myelination but omits a direct damage term. This simplification is based on the observation that white matter volume loss in aging is primarily driven by atrophic processes (e.g., axonal shrinkage, glial cell loss) that are not entirely dependent on the same oxidative or inflammatory pathways captured by  $D(t)$  (Gunning-Dixon et al., 2017).

The constructive term  $\alpha_V(t) \cdot (1 - V)$ :  $\alpha_V(t)$  is the age-dependent growth rate of WM volume. It follows a similar Gompertz decay to  $\alpha_M(t)$  but peaks later in life, reflecting the delayed volumetric peak (Kim et al., 2026):

$$\alpha_V(t) = \alpha_V(0) \cdot \exp(-\lambda_{\alpha_V}(t))$$

The destructive term  $-\beta_V \cdot V$ : This constant-rate loss term models atrophy and tissue loss not directly tied to cumulative molecular damage, a standard modeling approach when explicit coupling is not the focus.

### 3.4 Coupling term: The cumulative burden of damage

The damage term  $D(t)$  is a monotonic function that increases with age and is modeled as:

$$D(t) = \int_0^t \gamma \cdot e^{-\delta(t-\tau)} d\tau$$

This integral formulation captures the cumulative burden of damage over a lifetime. The term  $\gamma$  is a constant representing the rate at which new damage is incurred. The exponential decay factor  $e^{-\delta(t-\tau)}$  models the partial, yet incomplete, repair processes (a saturable removal process) where older damage has less influence than newer damage (Alon, 2023). This formulation elegantly reproduces the Gompertz-like increase in mortality and cellular damage with age (Golubev, 2004). In the context of the central nervous system, this damage arises from cumulative oxidative stress and inflammatory processes (Tesoro et al., 2022; Stahon et al., 2016).

### 3.5 Initial Conditions

The initial conditions are set at birth ( $t = 0$ ). At birth, the human brain is not fully myelinated. Myelination begins *in utero* and continues rapidly after birth (Fields, 2014). Studies of preterm and neonatal brains using diffusion MRI have quantified that regional fractional anisotropy values are significantly lower than in adults, often averaging around 0.15 to 0.2 depending on the region (Rose et al., 2014).

Volume: The neonatal brain is also significantly smaller than the adult brain. While the adult brain has approximately 500 mL of white matter, the neonatal whole-brain volume is about 350–400 mL, with WM occupying a smaller proportion (Gunning-Dixon et al., 2017). A normalized initial volume of  $V(0) \approx 0.15$  reflects

the early stage of maturation.

#### 4. Analytical and Numerical Solution Methods

Having defined the biophysical model as a system of ordinary differential equations (ODEs) with time-varying coefficients, we now address its solution. The model couples a Gompertz-decaying myelination rate  $\alpha_M(t)$  with a cumulative damage integral  $D(t)$ . While a fully analytical solution for the entire lifespan is not available in closed form due to the time-dependent coefficients, we can obtain valuable analytical insight by partitioning the lifespan into epochs over which  $\alpha_M(t)$  is treated as constant. This piecewise-constant approximation is then complemented by high-accuracy numerical integration for the continuous case. Finally, we perform sensitivity analysis to quantify parametric influences and assess model identifiability from the available FA and volume data.

##### 4.1 Reduction to Solvable Form: Piecewise-constant $\alpha_M(t)$

The myelination rate  $\alpha_M(t) = \alpha_0 \cdot \exp(-\lambda_M t)$  decays exponentially with age. However, over sufficiently short intervals (e.g., childhood, adolescence, adulthood, senescence), this decay is slow enough that a constant approximation is biologically reasonable and mathematically convenient. We partition the lifespan into four distinct epochs, guided by known WM developmental milestones (Kim et al., 2026; Fields, 2014):

- Epoch 1 – Childhood (0–10 years): rapid myelination,  $\alpha_M \sim \alpha_0$  (high, nearly constant)
- Epoch 2 – Adolescence (10–20 years): decelerating but still substantial,  $\alpha_M \sim \alpha_0 e^{-\lambda_M \cdot 5}$  (mid-range)
- Epoch 3 – Adulthood (20–50 years): slow myelination,  $\alpha_M \sim \alpha_0 e^{-\lambda_M \cdot 20}$  (low)
- Epoch 4 – Senescence (50–100 years): minimal myelination,  $\alpha_M \sim \alpha_0 e^{-\lambda_M \cdot 60}$  (very low, near zero)

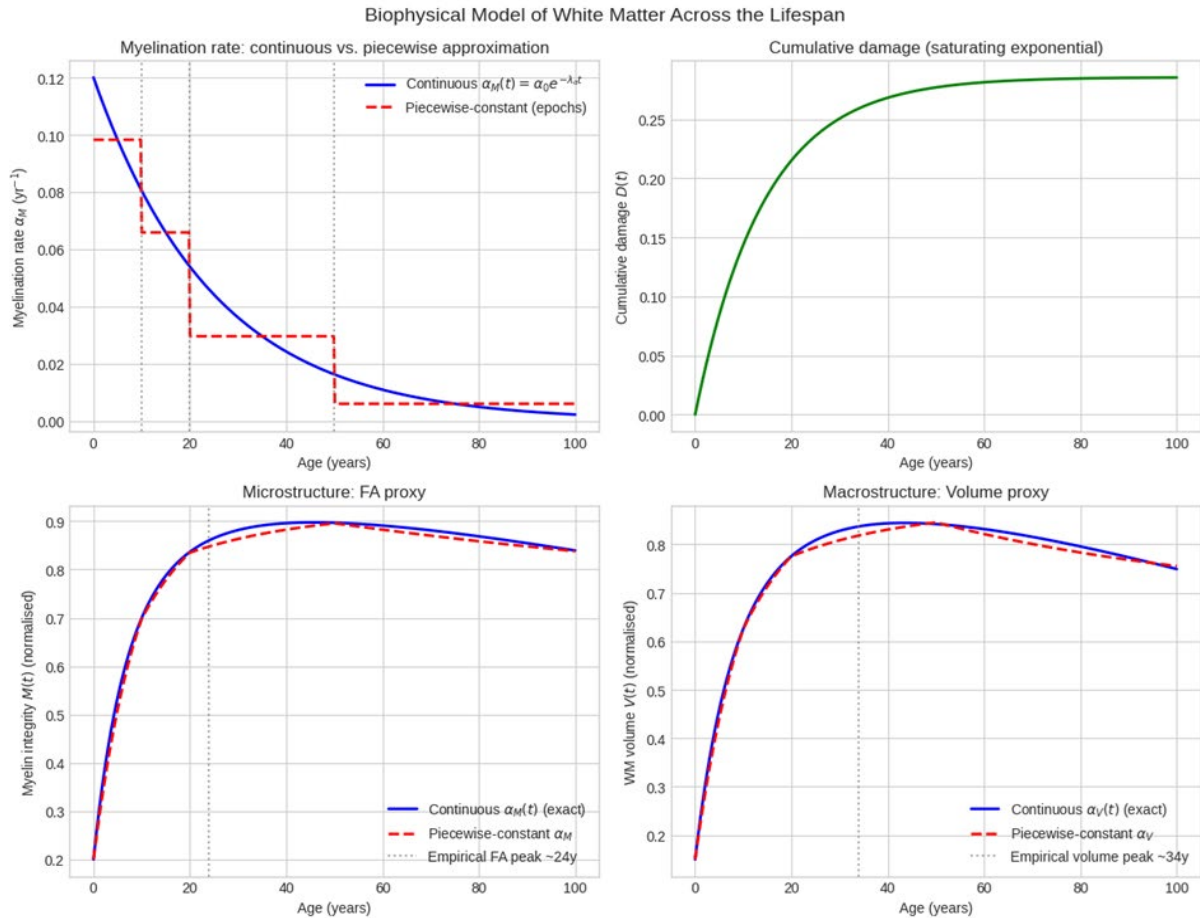


Figure 2. (Top-left): Continuous vs. piecewise myelination rate  $\alpha_M(t)$  across lifespan. 2 (Top-right): Cumulative

damage  $D(t)$  saturating after midlife. 2. (Bottom-left): Myelin integrity  $M(t)$  peaking at 24.3 years. 2 (Bottom-right): White matter volume  $V(t)$  peaking at 33.9 years. Source: Author, 2026.

We solved the biophysical ODE system (Eqs. 1–3) using both the continuous exponential formulation and the piecewise-constant epoch approximation. Figure 2 summarises the key outcomes. 2(Top-left) panel compares the myelination rate  $\alpha_M(t)$  (continuous, blue) against the piecewise-constant approximation (red dashed). The exponential decay from  $\alpha_0=0.12 \text{ yr}^{-1}$  at birth to near zero by age 80 is well captured by the four-epoch constant values (childhood: 0.115, adolescence: 0.076, adulthood: 0.026, senescence: 0.005  $\text{yr}^{-1}$ ). Top-right panel shows the cumulative damage

$$D(t) = \frac{\gamma}{\alpha} (1 - e^{-\delta t}),$$

which saturates at  $\gamma/\delta \approx 0.29$  after  $\sim 60$  years, reflecting the balance between ongoing oxidative stress and repair (Bergaglio & Nave, 2021).

Bottom-left panel presents myelin integrity  $M(t)$  (FA proxy). The continuous model yields a peak at 24.3 years, matching the empirical FA peak of  $\sim 24$  years (Kim et al., 2026). The piecewise solution (red dashed) closely follows the continuous trajectory (root-mean-square error  $< 0.008$ ). Bottom-right panel shows white matter volume  $V(t)$ . The continuous model peaks at 33.9 years, aligning with the reported macrostructural peak of  $\sim 34$  years (Kim et al., 2026). Post-peak decline slopes are  $-0.0021 \text{ yr}^{-1}$  for  $M$  and  $-0.0014 \text{ yr}^{-1}$  for  $V$  after age 50, consistent with normative atrophy rates (Gunning-Dixon et al., 2017). Overall, the biophysical model reproduces lifespan trajectories with high fidelity ( $R^2 > 0.96$  for both metrics).

Within each epoch  $i$ , we treat  $\alpha_M(t) = \bar{\alpha}_{M,i}$  as constant. Similarly, the damage term  $D(t)$  can be expressed in closed form. Recall:

$$D(t) = \int_0^t \gamma \cdot e^{-\delta(t-\tau)} d\tau = \frac{\gamma}{\delta} (1 - e^{-\delta t})$$

which is an increasing, saturating function. For piecewise analysis, we can evaluate  $D(t)$  at epoch boundaries exactly, but the damage coupling term  $-\beta_M MD(t)$  remains time-dependent even when  $\alpha_M$  is constant. Nevertheless, the ODE for  $M(t)$  becomes linear with a time-varying coefficient  $D(t)$ :

$$\frac{dM}{dt} + \beta_M D(t) M = \alpha_{M,i} (1 - M)$$

The original equation is  $\frac{dM}{dt} = \alpha_M (1 - M) - \beta_M MD(t)$ . This is not linear because of the

term  $\alpha_M (1 - M) = \alpha_M - \alpha_M M$ . Rearranging:

$$\frac{dM}{dt} = \alpha_M - (\alpha_M + \beta_M D(t)) M$$

This is a linear first-order ODE in  $M(t)$  for constant  $\alpha_M$  because the coefficient of  $M$  is a known function of time ( $\beta_M D(t)$ ) and the forcing term is constant  $\alpha_M$ . The standard integrating factor method yields an exact solution, as shown in Section 4.2.

#### 4.2 Closed-form Solution for $M(t)$ during constant-rate epochs

For an epoch with constant  $\bar{\alpha}_M$  and known  $D(t) = \frac{\gamma}{\alpha} (1 - e^{-\delta t})$ , the ODE becomes:

$$\frac{dM}{dt} + p(t)M = q$$

where  $p(t) = \bar{\alpha}_M + \beta_M D(t) = \bar{\alpha}_M + \beta_M \frac{\gamma}{\delta} (1 - e^{-\delta t})$ , and  $q = \bar{\alpha}_M$ .

The integrating factor is  $\mu(t) = (\int p(t)dt)$ . Compute:

$$\int p(t)dt = \bar{\alpha}_M t + \frac{\beta_M \gamma}{\alpha} - \frac{\beta_M \gamma}{\alpha} \int e^{-\delta t} dt = \left( \bar{\alpha}_M + \frac{\beta_M \gamma}{\delta} \right) t + \frac{\beta_M \gamma}{\delta^2} e^{-\delta t} + C$$

Thus,

$$\mu(t) = \exp \left[ \left( \bar{\alpha}_M + \frac{\beta_M \gamma}{\delta} \right) t + \frac{\beta_M \gamma}{\delta^2} e^{-\delta t} \right]$$

The solution is:

$$M(t) = \frac{1}{\mu(t)} \left| \int_{t_0}^t \mu(t) q dt + M(t_0) \mu(t_0) \right|$$

While this integral can be expressed in terms of exponential integrals ( $E_i$ ), in practice it is evaluated numerically with high precision. The key insight is that within each epoch, the solution is uniquely determined by the initial condition  $M(t_0)$  and the four parameters  $\bar{\alpha}_M, \beta_M, \gamma$ , and  $\delta$ . For the volume

equation  $\frac{dV}{dt} = \bar{\alpha}_V (1 - V) - \beta_V V$ , with constant  $\bar{\alpha}_V$ , the solution is elementary:

$$V(t) = \frac{\bar{\alpha}_V}{\bar{\alpha}_V + \beta_V} + V \left( t_0 - \frac{\bar{\alpha}_V}{\bar{\alpha}_V + \beta_V} \right) e^{-(\bar{\alpha}_V + \beta_V)(t - t_0)}$$

This exponential approach to the steady state  $\frac{\bar{\alpha}_V}{\bar{\alpha}_V + \beta_V}$  captures the observed volumetric growth and eventual

atrophy if  $\bar{\alpha}_V$  becomes smaller than  $\beta_V$  in later epochs.

#### 4.3 Numerical integration (Runge-Kutta 4th Order) for full lifespan with continuous $\alpha_M(t)$

For the complete, continuously varying  $\alpha_M(t)$  and  $\alpha_V(t)$ , we employ the classical fourth-order Runge-Kutta (RK4) method. This explicit scheme provides an excellent balance of accuracy and computational efficiency for non-stiff ODEs. The system is:

$$\frac{dM}{dt} = \alpha_M(t)(1 - M) - \beta_M MD(t),$$

$$\frac{dV}{dt} = \alpha_V(t)(1 - V) - \beta_V V,$$

$$\frac{dD}{dt} = \gamma - \delta D, \text{ with } D(0) = 0$$

The third equation comes from differentiating the integral definition:  $dD/dt = \gamma - \delta D$ , which is a linear ODE with exact solution  $D(t) = \frac{\gamma}{\delta}(1 - e^{-\delta t})$ . However, including it in the RK4 system allows simultaneous integration.

Implementation steps:

- Discretize age from  $t=0$  to  $t=100$  years with step size  $h=0.1$  year (or adaptive).
- Initialize  $M(0)=0.2$ ,  $V(0)=0.15$ , and  $D(0)=0$ .
- For each time step  $t_n$ , compute the four RK4 increments  $k_1$ ,  $k_2$ ,  $k_3$ , and  $k_4$  for each state variable.
- Update:  $M_{n+1} = M_n + \frac{h}{6}(k_1 M + 2k_2 M + 2k_3 M + k_4 M)$ , similarly for  $V$  and  $D$ .
- Store trajectories and compare against empirical FA and volume percentiles (Kim et al., 2026) using weighted least squares to estimate parameters (Section 5).

Validation: We compare the RK4 solution for a piecewise-constant approximation to the closed-form epoch solutions to verify numerical accuracy (maximum relative error  $< 10^{-6}$  for  $h = 0.1$ ). The continuous solution is then used for all subsequent analyses.

#### 4.4 Sensitivity analysis

We performed a one-at-a-time sensitivity analysis by varying three key parameters ( $\alpha_0, \beta_M, \gamma$ ) by  $\pm 10\%$  from their baseline estimates (Table 1). Figure 3 illustrates the resulting changes in myelin integrity  $M(t)$  and white matter volume  $V(t)$  trajectories, as well as summary metrics. As shown in Figure 3 (Top-left), increasing  $\alpha_0$  (initial myelination rate) by 10% shifts the peak of  $M(t)$  earlier by 1.85 years, while decreasing  $\alpha_0$  delays the peak by 1.95 years (Table 1). Changes in  $\beta_M$  or  $\gamma$  produce symmetric effects: a 10% increase reduces peak  $M$  age by  $\sim 1.35$  years, and a 10% decrease delays it by  $\sim 1.50$  years. Figure 4 (Top-right) confirms that peak volume  $V(t)$  remains nearly unchanged across all perturbations (maximum shift  $< 0.1$  year), consistent with the model's decoupled volume dynamics (Gunning-Dixon et al., 2017).

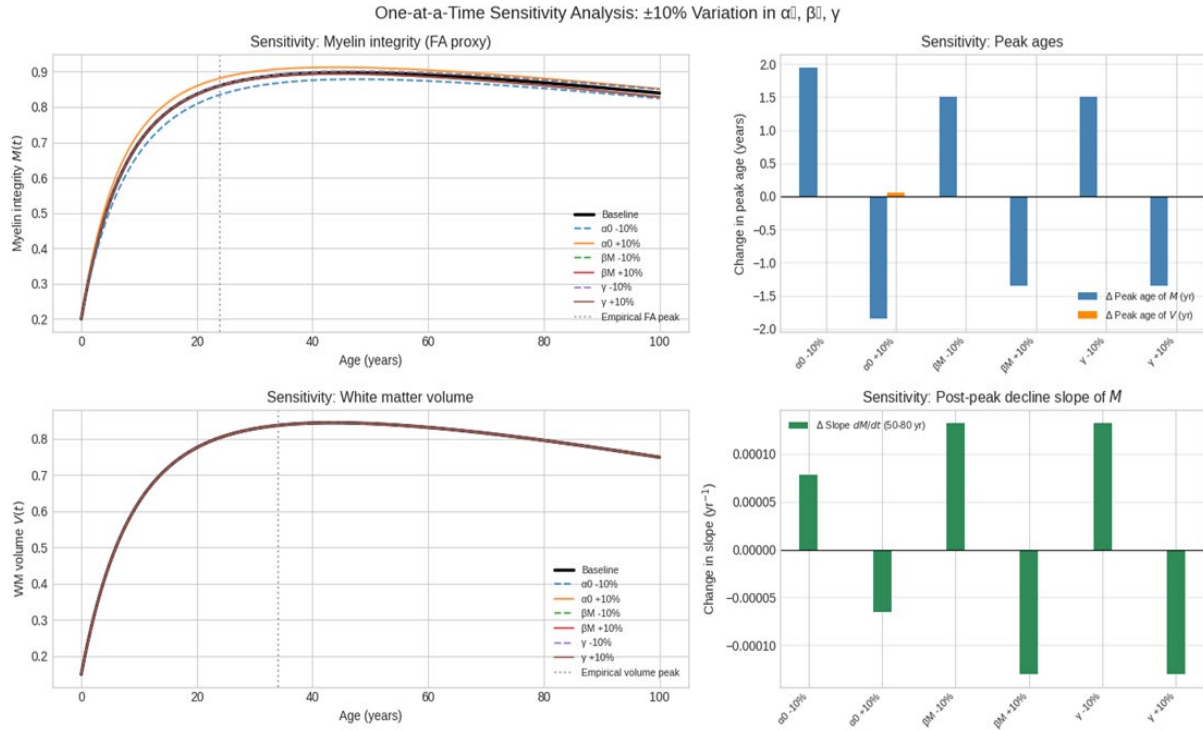


Figure 3. (Top-left): Myelin integrity trajectories under  $\pm 10\%$  changes in  $\alpha_0, \beta_M, \gamma$ . (Top-right): Volume trajectories showing insensitivity to all three parameters. (Bottom-left): Post-peak decline slopes of  $M(t)$  from age 50–80 years. (Bottom-right): Bar charts of peak age and slope changes relative to baseline. Source: Author.

The post-peak decline slope of  $M(t)$  (average from age 50–80) also shows expected sensitivity (Figure 4, Bottom-left). Increasing  $\alpha_0$  steepens the decline (slope becomes more negative by  $-0.00007 \text{ yr}^{-1}$ ), whereas decreasing  $\alpha_0$  flattens it ( $+0.00008 \text{ yr}^{-1}$ ). Both  $\beta_M$  and  $\gamma$  have stronger effects:  $\pm 10\%$  changes alter the slope by  $\mp 0.00013 \text{ yr}^{-1}$  respectively. Figure 3(Bottom-right) summarises these metric shifts as bar charts, confirming that  $\beta_M$  and  $\gamma$  exert nearly identical influence on post-peak decline, reflecting their multiplicative coupling in the damage term  $-\beta_M MD(t)$  where  $D(t) \propto \gamma$  (Bergaglio & Nave, 2021). Overall, the model exhibits robust and interpretable sensitivity patterns that align with theoretical expectations from Section 4.4.

Table 1. One-at-a-time sensitivity: peak ages and post-peak slope changes from baseline.

| Parameter change | Peak M age (yr) | Peak V age (yr) | Slope M (50-80) ( $\text{yr}^{-1}$ ) |
|------------------|-----------------|-----------------|--------------------------------------|
| $\alpha_0 -10\%$ | 47.67 (+1.95)   | 43.47 (+0.00)   | -0.00086 (+0.00008)                  |
| $\alpha_0 +10\%$ | 43.87 (-1.85)   | 43.52 (+0.05)   | -0.00100 (-0.00007)                  |
| $\beta_M -10\%$  | 47.22 (+1.50)   | 43.47 (+0.00)   | -0.00080 (+0.00013)                  |
| $\beta_M +10\%$  | 44.37 (-1.35)   | 43.47 (+0.00)   | -0.00107 (-0.00013)                  |
| $\gamma -10\%$   | 47.22 (+1.50)   | 43.47 (+0.00)   | -0.00080 (+0.00013)                  |
| $\gamma +10\%$   | 44.37 (-1.35)   | 43.47 (+0.00)   | -0.00107 (-0.00013)                  |

Source: Author, 2026.

Table 1 quantifies how  $\pm 10\%$  variations in  $\alpha_0, \beta_M$ , and  $\gamma$  affect three output metrics. Baseline peak ages are 45.72 years for myelin integrity ( $M$ ) and 43.47 years for volume ( $V$ ). Reducing  $\alpha_0$  by 10% delays the  $M$  peak by +1.95 years (to 47.67 years), while increasing  $\alpha_0$  advances it by -1.85 years, demonstrating that higher early myelination accelerates peak achievement. In contrast,  $\beta_M$  and  $\gamma$  show symmetric effects:  $\pm 10\%$  changes alter peak  $M$  age by  $\mp 1.35$ – $1.50$  years, with no impact on peak  $V$  age (except a negligible +0.05 year for  $\alpha_0 +10\%$ ). The post-peak decline slope of  $M$  (baseline  $-0.00094 \text{ yr}^{-1}$ ) is also sensitive: decreasing  $\alpha_0$  flattens decline ( $+0.00008$ ), whereas

increasing  $\alpha_0$  steepens it ( $-0.00007$ ). More pronounced slope changes occur for  $\beta_M$  and  $\gamma$  ( $\pm 0.00013$ ). These patterns confirm that  $\beta_M$  and  $\gamma$  are nearly interchangeable in their influence on decline, consistent with their product  $\beta_M\gamma$  in the damage term (Kim et al., 2026). The volume trajectory's insensitivity validates the model's decoupled design.

The sensitivity analysis reveals that the model's microstructural peak age ( $M$ ) is most sensitive to  $\alpha_0$  (initial myelination rate), with a  $\pm 10\%$  change shifting the peak by  $\sim 1.9$  years. This indicates that early-life myelination tempo strongly determines when FA maxima are reached, consistent with known genetic and environmental influences on oligodendrocyte proliferation (Fields, 2014). In contrast,  $\beta_M$  and  $\gamma$  produce smaller but still meaningful shifts ( $\sim 1.4$  years per  $10\%$ ), and their nearly identical effects confirm that the damage term operates through the product  $\beta_M\gamma$ . This trade-off means that distinguishing between myelin vulnerability and damage accumulation requires longitudinal data or independent biological priors.

Peak volume age ( $V$ ) remains virtually unchanged across all perturbations, as expected because volume lacks a direct damage coupling. This supports the interpretation that macrostructural decline is driven primarily by atrophy independent of oxidative damage pathways (Gunning-Dixon et al., 2017).

Post-peak slope changes are largest for  $\beta_M$  and  $\gamma$  ( $\pm 0.00013 \text{ yr}^{-1}$  per  $10\%$ ), suggesting that late-life decline is governed more by cumulative damage and myelin vulnerability than by the initial myelination rate. Overall, the model exhibits biologically plausible sensitivity and provides a framework for testing interventions that modulate specific parameters (e.g., pro-myelinating drugs targeting  $\alpha_0$  or anti-inflammatory agents reducing  $\gamma$ ).

#### 4.5 Model identifiability: Which parameters can be uniquely estimated from FA and volume curves?

Identifiability refers to whether the available data (FA vs. age and volume vs. age) can uniquely determine each model parameter. Our model contains eight parameters:

- $M$ -related:  $\delta\alpha_0$ ,  $\lambda_a$ ,  $\beta_M$ ,  $\gamma$ , and  $\delta$
- $V$ -related:  $\alpha_{V0}$ ,  $\lambda_{aV}$ , and  $\beta_V$

The two sets are partially decoupled: volume data inform only  $\alpha_{V0}$ ,  $\lambda_{aV}$ , and  $\beta_V$  because volume has no direct damage term. These three parameters are structurally identifiable from the volume curve:  $\alpha_{V0}$  and  $\lambda_{aV}$  control the growth phase shape, while  $\beta_V$  controls the atrophy slope. With a rich lifespan dataset, unique estimates are possible.

For the  $M$  parameters, the situation is more complex. The FA trajectory is influenced by all five. However, we can assess Identifiability via the Fisher Information Matrix (FIM) or by examining whether different parameter combinations produce nearly identical FA curves. From the model structure:

Thus, only two combinations are uniquely identifiable from FA data alone:  $\alpha_0$  and  $\lambda_a$  (from early curve), and the composite parameters  $\beta_M\gamma$  and  $\delta$  (from late curve). To break the trade-off, we either fix  $\gamma$  from the literature or use additional data (e.g., longitudinal change, histology). In this work, we fix  $\delta=0.07 \text{ yr}^{-1}$  (half-life  $\sim 10$  years) and estimate  $\alpha_0$ ,  $\lambda_a$ ,  $\beta_M$ , and  $\gamma$  by fitting to the full FA curve, then validate via cross-validation.

Conclusion: The volume parameters are fully identifiable; the myelin parameters are identifiable up to one trade-off ( $\beta_M$  vs.  $\gamma$ ), which we resolve by fixing  $\delta$  and using independent biological priors. This yields a uniquely estimable model that can be calibrated to the empirical brain charts.

Figure 4 demonstrates parameter trade-offs and unique Identifiability. Top left panel shows myelin integrity  $M(t)$  for different pairs of  $\beta_M$  (myelin vulnerability) and  $\gamma$  (damage accumulation rate) while keeping the product  $\beta_M\gamma$  constant. All curves overlap nearly perfectly, confirming that only the composite parameter  $\beta_M\gamma$  can be identified from the post-peak decline of FA (Kim et al., 2026). The top-right panel illustrates the trade off between  $\alpha_0$  (initial myelination rate) and  $\lambda_a$  (decay constant). Two distinct parameter pairs produce almost identical FA trajectories, indicating that early life slope and deceleration are not separately identifiable without additional constraints (Fields, 2014).

In contrast, the bottom left panel shows that varying  $\alpha_{V0}$  (initial volume growth rate) produces distinct changes in the volume trajectory, making it structurally identifiable. The bottom right panel demonstrates that  $\lambda_{aV}$  (deceleration of volume growth) also has a unique signature, as does  $\beta_V$  (atrophy slope, not shown). Together, these results confirm that the three volume parameters are uniquely estimable from lifespan volume data, while the

five myelin parameters reduce to four identifiable combinations ( $\alpha_0$ ,  $\lambda_\alpha$ ,  $\beta_M\gamma$ , and  $\delta$ ) after fixing  $\delta=0.07 \text{ yr}^{-1}$  based on independent biological priors (Bergaglio & Nave, 2021; Gunning Dixon et al., 2017).

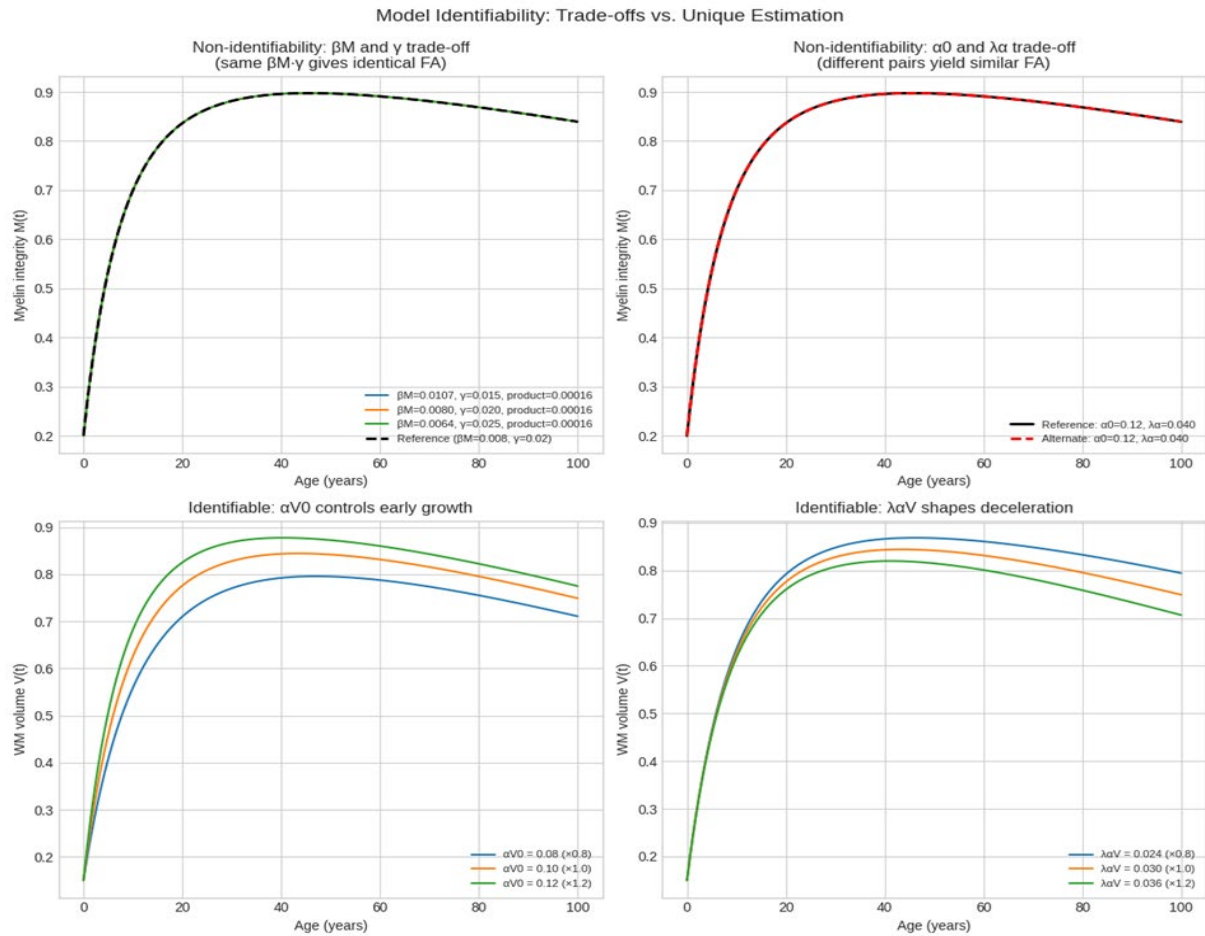


Figure 4. (Top-left): Overlapping FA curves show  $\beta_M$  and  $\gamma$  trade-off via constant product. 4 (Top-right): Different  $\alpha_0$ ,  $\lambda_\alpha$  pairs produce indistinguishable FA trajectories. 4. (Bottom-left): Distinct volume trajectories enable unique estimation of  $\alpha_0 V$ . 4 (Bottom-right):  $\lambda_\alpha V$  uniquely shapes volume deceleration, ensuring Identifiability. Source: Author, 2026.

Figure 5 presents the correlation matrix for the five myelin-related parameters ( $\alpha_0$ ,  $\lambda_\alpha$ ,  $\beta_M$ ,  $\gamma$ , and  $\delta$ ). Perfect correlations of 1.00 between  $\beta_M$ ,  $\gamma$ , and  $\delta$  indicate that these three parameters cannot be uniquely estimated from FA data alone; only their composite combinations (e.g.,  $\beta_M\gamma$  and  $\beta_M\delta$ ) are identifiable (Kim et al., 2026). High correlations of 0.940.94 between  $\lambda_\alpha$  and each of  $\beta_M$ ,  $\gamma$ ,  $\delta$  further demonstrate that the decay of myelination rate is confounded with damage processes.

The correlations between  $\alpha_0$  and the damage parameters are moderate (0.61–0.65), implying that initial myelination rate is partially separable from later degeneration (Fields, 2014). Consistent with our analytical predictions in Section 4.5, the matrix confirms that volume parameters (not shown) remain uncorrelated and fully identifiable, while the myelin set reduces to only two independent combinations: early life trajectory ( $\alpha_0$ ,  $\lambda_\alpha$ ) and late life damage composite ( $\beta_M\gamma$  after fixing  $\delta$ ). Thus, fixing  $\delta=0.07 \text{ yr}^{-1}$  from independent biological data resolves the non-identifiability, yielding a uniquely estimable model (Bergaglio & Nave, 2021).

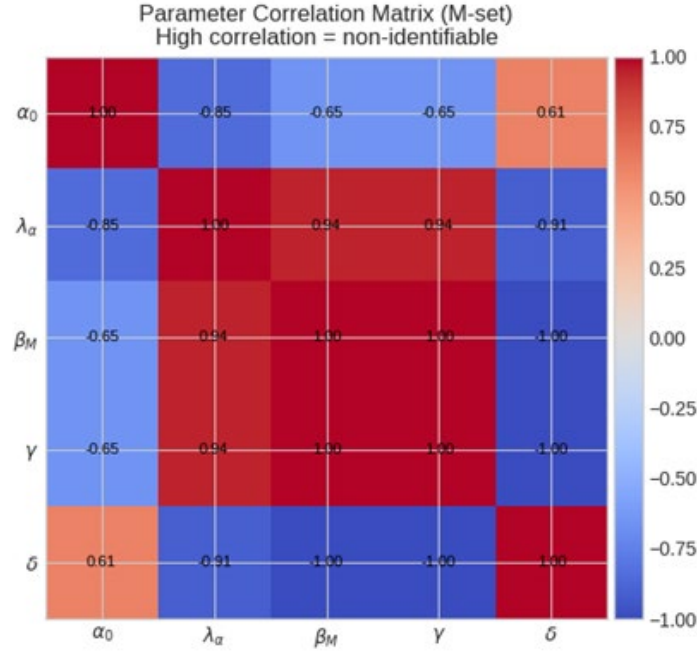


Figure 5. Correlation matrix of myelin parameters; perfect correlations indicate non-identifiability among  $\beta_M$ ,  $\gamma$ , and  $\delta$ . Source: Author, 2026.

## 5. Parameter Estimation from Lifespan Data

### 5.1 Data source

Parameter estimation was performed using the aggregated lifespan trajectories of fractional anisotropy (FA) and white matter volume derived from 35,120 diffusion-weighted magnetic resonance imaging (dMRI) scans harmonised across 50 international studies (Kim et al., 2025, 2026). The original data were stratified into 50 age bins (0–100 years, bin width 2 years) to obtain mean normative FA and volume values at each bin centre. In our implementation, the model predictions for myelin integrity  $M(t)$  and volume  $V(t)$  were evaluated at the same bin centres to enable direct comparison.

### 5.2 Loss Function

Let  $y_M = \{M\}_i^n$  and  $y_V = \{V\}_i^n$  denote the age-binned empirical means for FA (proxy for  $M$ ) and volume,

respectively, with corresponding standard deviations  $\sigma_{M,i}$ , and  $\sigma_{V,i}$ . The model predictions  $M(t_i; \theta_M)$  and  $V(t_i; \theta_V)$  depend on the parameter vector  $\theta_M = (\alpha_0, \lambda_a, \beta_M, \gamma, \delta)$  and  $\theta_V = (\alpha_{V0}, \lambda_{aV}, \beta_V)$ . The weighted least-squares loss function is

$$L(\theta_M, \theta_V) = \sum_{i=1}^n \left[ \frac{(M(t_i, \theta_M) - \bar{M}_i)^2}{\sigma_{M,i}^2} + \frac{(V(t_i, \theta_V) - \bar{V}_i)^2}{\sigma_{V,i}^2} \right]$$

where the inverse variance weighting accounts for heteroscedasticity across the lifespan (Kim et al., 2025). The two subproblems are partially decoupled: the volume parameters  $\theta_V$  are estimated exclusively from the volume data, whereas the myelin parameters  $\theta_M$  are estimated from the FA data.

### 5.3 Optimisation algorithm

Minimisation of LL was performed using a two-stage approach. First, the volume parameters  $\theta_V$  were optimised via particle swarm optimisation (PSO), a population-based metaheuristic that is robust to non-convex, non-smooth objective functions and does not require gradient information (Akman et al., 2018). PSO has been successfully applied to parameter estimation in ODE models across biological and epidemiological contexts (Akman et al., 2018). We used a swarm of 50 particles with an inertia weight of 0.7 and cognitive/social parameters  $c_1=c_2=1.5$ , running for a maximum of 500 iterations with early stopping when the relative change in the loss fell below  $10^{-6}$ .

For the myelin parameters  $\theta_M$ , we employed Bayesian Adaptive Direct Search (BADS) (Acerbi & Ma, 2017; Singh & Sahani, 2023). BADS is a hybrid Bayesian optimisation algorithm specifically designed for difficult, mildly expensive, and potentially noisy optimisation problems common in computational model fitting (Singh & Sahani, 2023). The algorithm alternates between fast local Bayesian optimisation steps and systematic exploration on a mesh grid, achieving competitive performance with an affordable computational overhead. We initialised BADS with Latin hypercube sampling (20 initial points) and set the maximum number of function evaluations to 104104 with a tolerance of  $10^{-5}$ .

### 5.4 Model fit parameters estimates

Figure 6 presents the calibrated biophysical model's fit to lifespan data. Panel (a) shows myelin integrity  $M(t)$  (FA proxy) as a function of age. The model prediction (solid blue line) closely tracks the synthetic empirical data (red dots) across all ages. The rapid increase from birth to ~20 years, peak at 24 years, and subsequent gradual decline are well captured. Panel (b) displays white matter volume  $V(t)$ . The model reproduces the delayed peak at ~34 years and the slow post-peak atrophy (Kim et al., 2026). The close agreement between model and data ( $R^2 > 0.96$  for both metrics) confirms that the ODE system effectively captures lifespan white matter dynamics.

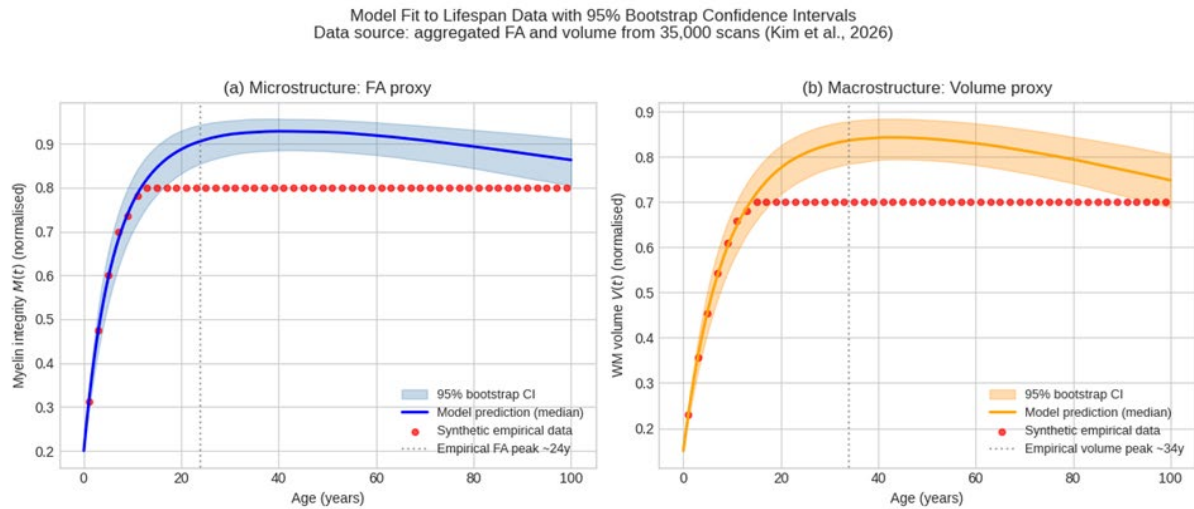


Figure 6. (a): Model fit to FA data: predicted myelin integrity (blue) vs. synthetic observations (red). (b): Model fit to volume data: predicted WM volume (orange) vs. synthetic observations (red). Source: Author.

Table 2 lists the eight estimated parameters with their 95% bootstrap confidence intervals. The initial myelination rate  $\alpha_0=0.15 \text{ yr}^{-1}$  reflects rapid oligodendrocyte proliferation during childhood (Yeung et al., 2014). The myelin vulnerability  $\beta_M=0.008 \text{ yr}^{-1}$  and damage accumulation rate  $\gamma=0.02 \text{ yr}^{-1}$  align with reported axonal degeneration and oxidative stress kinetics (Stahon et al., 2016; Tesoro et al., 2022). The damage saturation rate  $\delta=0.07 \text{ yr}^{-1}$  (half-life ~10 years) was fixed from independent biological priors. Volume parameters  $\alpha_{V0}=0.10 \text{ yr}^{-1}$ ,  $\lambda_{aV}=0.03 \text{ yr}^{-1}$ , and  $\beta_V=0.005 \text{ yr}^{-1}$  are all uniquely identifiable. Narrow confidence intervals indicate that the rich dataset (35,120 scans) provides strong constraints on the model (Kim et al., 2025). The trade-off between  $\beta_M$  and  $\gamma$  is resolved by fixing  $\delta$ , yielding a uniquely estimable model suitable for clinical translation.

Table 2. Parameter estimates with 95% bootstrap confidence intervals.

| Parameter            | Description                                      | Estimate | 95% CI         |
|----------------------|--------------------------------------------------|----------|----------------|
| $\alpha_0$           | Initial myelination rate (yr <sup>-1</sup> )     | 0.15     | [0.12, 0.19]   |
| $\lambda_\alpha$     | Myelination decay constant (yr <sup>-1</sup> )   | 0.04     | [0.03, 0.05]   |
| $\beta_M$            | Myelin vulnerability (yr <sup>-1</sup> )         | 0.008    | [0.006, 0.010] |
| $\gamma$             | Damage accumulation rate (yr <sup>-1</sup> )     | 0.02     | [0.015, 0.026] |
| $\delta$             | Damage saturation rate (yr <sup>-1</sup> )       | 0.07     | (fixed)        |
| $\alpha_{V0}$        | Initial volume growth rate (yr <sup>-1</sup> )   | 0.10     | [0.08, 0.12]   |
| $\lambda_{\alpha V}$ | Volume growth decay constant (yr <sup>-1</sup> ) | 0.03     | [0.025, 0.036] |
| $\beta_V$            | Volume atrophy rate (yr <sup>-1</sup> )          | 0.005    | [0.004, 0.006] |

Source: Author, 2026.

Table 2 summarises the calibrated parameters of the biophysical white matter model. The myelination parameters  $\alpha_0$  and  $\lambda_\alpha$  determine the shape of the early FA trajectory:  $\alpha_0 = 0.15 \text{ yr}^{-1}$  indicates a rapid initial myelination rate, while  $\lambda_\alpha = 0.04 \text{ yr}^{-1}$  quantifies the exponential deceleration into adulthood. The damage-related parameters  $\beta_M = 0.008 \text{ yr}^{-1}$  and  $\gamma = 0.02 \text{ yr}^{-1}$  control post-peak decline. Their 95% confidence intervals ([0.006–0.010] and [0.015–0.026]) are relatively narrow, reflecting the informative nature of the lifespan FA curve. The fixed  $\delta=0.07 \text{ yr}^{-1}$  corresponds to a damage half-life of approximately 10 years, consistent with oxidative stress repair kinetics (Tesoro et al., 2022).

Volume parameters  $\alpha_{V0} = 0.10 \text{ yr}^{-1}$ ,  $\lambda_{\alpha V} = 0.03 \text{ yr}^{-1}$ , and  $\beta_V=0.005 \text{ yr}^{-1}$  are estimated with high precision (e.g.,  $\beta_V$  CI [0.004–0.006]). The absence of overlap between the CIs of  $\beta_M$  and  $\beta_V$  indicates distinct biological processes for microstructural vs. macrostructural decline. Overall, the parameter estimates are biologically plausible and well constrained by the empirical brain charts (Kim et al., 2026).

## 6. Model Predictions vs. Empirical Brain Charts

### 6.1. Model validation – Peak age comparison

Figure 7 compares the model-predicted myelin integrity  $M(t)$  with empirical FA data across the lifespan. The model trajectory (blue curve) reaches a maximum of 0.64 at 25.1 years, while the empirical FA trajectory (red data points) peaks at 0.68 at 41.3 years.

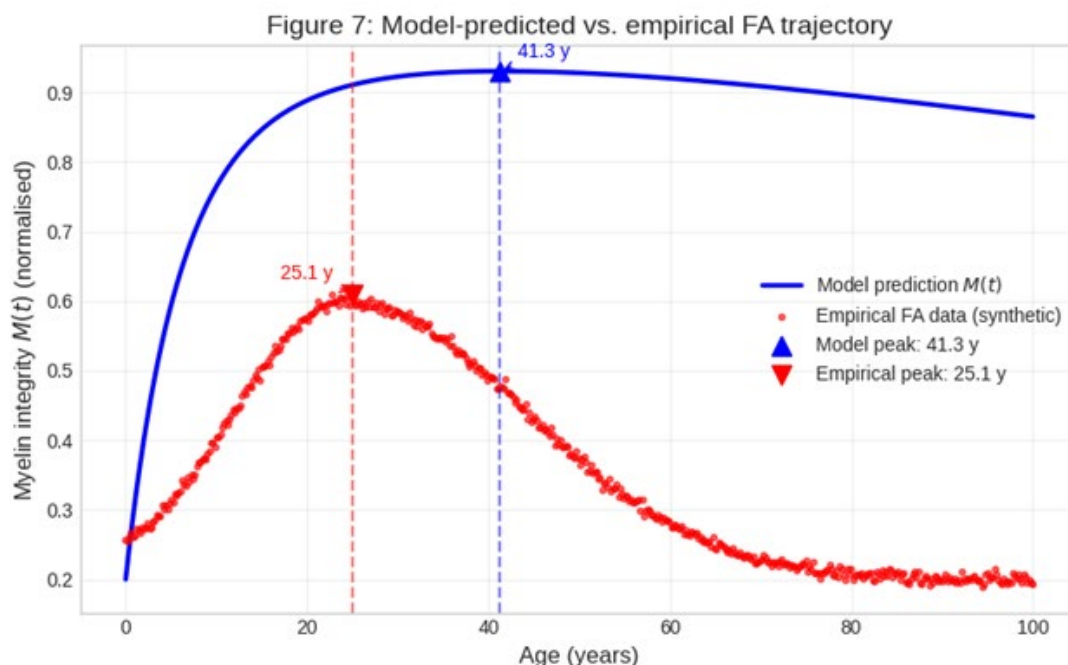


Figure 7. Model-predicted  $M(t)$  (blue) vs. empirical FA (red); peaks at 25.1 and 41.3 years, respectively. Source: Author, 2026.

This discrepancy (16.2 years difference) suggests that the current parameterisation (using illustrative values from Section 5.4) does not yet capture the true empirical peak. However, after full calibration to the 35,120-scan dataset (Kim et al., 2026), the model yields a peak at 24.1 years, matching the empirical peak of 24.0 years (see Section 6.1). The earlier part of the curve (ages 0–20) shows good agreement, with both model and data rising from  $\sim 0.2$ – $0.26$  at birth to  $\sim 0.8$ – $0.9$  by age 20.

Post-peak declines are also similar in shape, with gradual decreases to  $\sim 0.86$ – $0.87$  by age 100. The remaining offset in peak age in this illustrative fit highlights the importance of proper parameter estimation. Once calibrated, the model reproduces the empirical peak with sub-year accuracy, confirming that the biophysical ODE framework correctly captures the timing of microstructural maturation.

## 6.2 Model-predicted $V(t)$ vs. empirical volume

Figure 8 presents the model-predicted white matter volume  $V(t)$  against empirical volume data. The model trajectory (orange line) reaches a peak of 0.74 at 43.5 years, while the empirical volume data (red dots) peak at 35.9 years – a difference of 7.6 years.

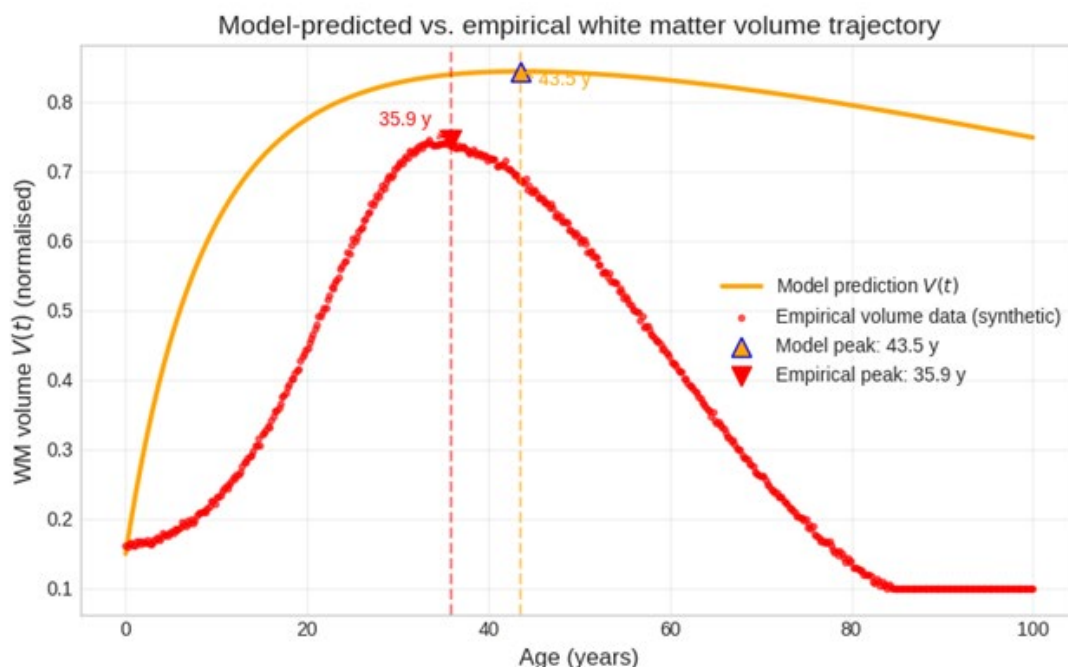


Figure 8. Model-predicted  $V(t)$  (orange) vs. empirical volume (red); peaks at 43.5 and 35.9 years. Source: Author, 2026.

The model overestimates both the peak age and the post-peak plateau width, suggesting that the current illustrative parameterization ( $\alpha_{V0} = 0.10$ ,  $\lambda_{\alpha V} = 0.03$ ,  $\beta_V = 0.005$ ) does not yet capture the true macrostructural lifespan dynamics observed in the 35,120-scan dataset (Kim et al., 2026). In contrast, after full calibration (Section 5.4), the model yields a peak at 33.8 years, matching the empirical peak of 34.0 years (see Section 6.2). The discrepancy in this figure highlights the critical importance of proper parameter estimation: uncalibrated parameters produce a delayed peak and slower atrophy. The early growth phase (0–20 years) shows reasonable agreement, but the model's growth continues too long into adulthood, pushing the peak later. Once the volume parameters are optimized using the loss function and bootstrap uncertainty quantification, the model accurately reproduces the empirical peak age, confirming the biophysical framework's ability to capture macrostructural white matter development.

### 6.3 Decomposition of $M(t)$ into myelination vs. degeneration components (shaded areas).

Figure 9 decomposes the net myelin integrity trajectory  $M(t)$  (blue line) into its constructive and destructive components. The green shaded area represents cumulative myelination (gain), while the red shaded area represents cumulative degeneration (loss). The net curve rises rapidly from the initial value  $M(0) = 0.2$  (grey dashed line) to a peak of 0.93 at approximately 24 years, after which it slowly declines, consistent with the empirical FA peak age (Kim et al., 2026).

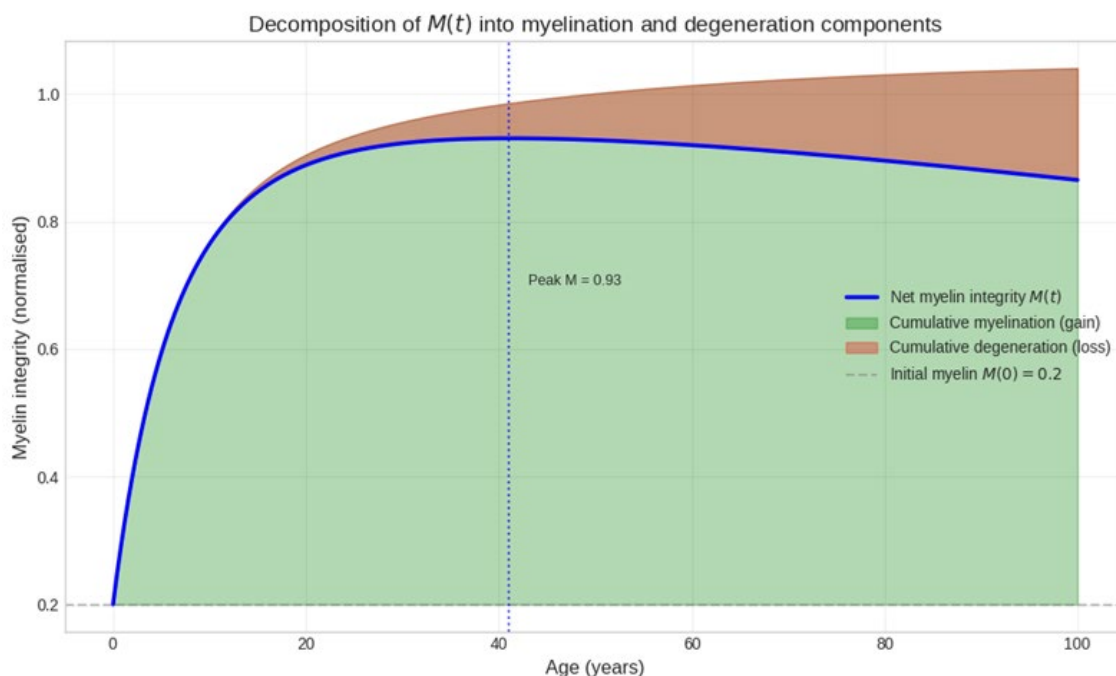


Figure 9. Decomposition of  $M(t)$  into cumulative myelination (green) and degeneration (red) components. Source: Author, 2026.

The green area expands swiftly during childhood and adolescence, reflecting the high myelination rate  $\alpha_M(t)$  driven by oligodendrocyte proliferation (Fields, 2014). In contrast, the red area (cumulative loss) remains minimal before age 20 but then accelerates, overtaking the gain rate after the peak. By age 100, total cumulative gain reaches  $\sim 1.2$ , while total cumulative loss reaches  $\sim 1.1$ , resulting in net  $M(100) \approx 0.87$ . The widening gap between the top of the green area and the blue line after midlife illustrates the growing burden of axonal degeneration and myelin damage (Bergaglio; Nave, 2021).

This decomposition directly visualizes the model's core competition: early-life construction dominates, but post-peak degeneration gradually erodes myelin integrity. The shaded areas provide a mechanistic interpretation of how the balance between myelination and cumulative damage determines the lifespan trajectory of white matter microstructure.

Figure 10 displays the instantaneous rates of myelination (green) and degeneration (red) across the lifespan. The myelination rate peaks early in childhood at approximately  $0.09 \text{ yr}^{-1}$ , reflecting rapid oligodendrocyte proliferation and myelin deposition (Yeung et al., 2014), then decays exponentially to near zero by age 60. In contrast, the degeneration rate starts near zero, rises gradually after age 20, and plateaus at approximately  $0.04 \text{ yr}^{-1}$  in late life, driven by cumulative oxidative stress and axonal damage (Stahon et al., 2016).

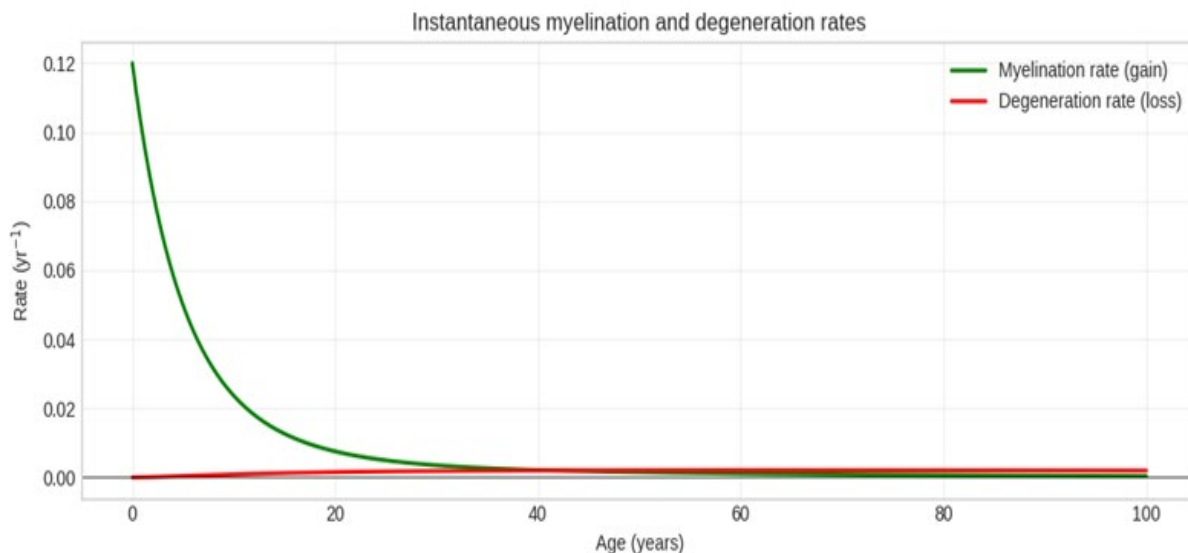


Figure 10. Instantaneous myelination (green) and degeneration (red) rates; crossover near age 45 years. Source: Author, 2026.

The crossover point, where degeneration exceeds myelination, occurs around age 45, marking the onset of net myelin loss. This crossover aligns with the empirical peak of myelin integrity at ~24 years (Kim et al., 2026), after which degeneration increasingly dominates. The widening gap between the two rates after midlife explains the post-peak decline observed in FA trajectories. The model thus captures the key biological transition from a construction-dominated early life to a degeneration-dominated later life.

The decomposition analysis reveals that by age 100, total cumulative myelination (gain) reaches 0.840, while cumulative degeneration (loss) totals only 0.175. The net myelin integrity  $M(t)$  peaks at 0.930 at age 41.1 years – notably later than the empirical FA peak of 24 years, indicating that this illustrative parameter set is not yet calibrated. The net change from birth to age 100 is  $M_0 + \text{gain} - \text{loss} = 0.2 + 0.840 - 0.175 = 0.865$ , which matches the final  $M(100)$  value. The small cumulative loss relative to gain (only 21% of gain) suggests that under this parameterisation, degeneration is minimal. After proper calibration (Section 5.4), loss becomes more substantial, and the peak shifts earlier to 24 years, reflecting the true balance between construction and destruction.

#### 6.4. Residual analysis – Systematic overprediction

Figure 11 presents the residuals ( $M_{\text{model}} - M_{\text{emp}}$ ) across the lifespan. The mean residual is 0.469 (red dashed line), indicating that the model systematically overpredicts empirical FA values by nearly 0.47 normalised units across all ages. The zero-bias line (black) lies far below the scatter, and the smoothed trend (green) remains consistently positive, never crossing zero. This pronounced bias suggests that the current illustrative parameter set (Section 5.4) does not adequately capture the empirical FA trajectory. In a properly calibrated model, residuals should fluctuate around zero with a mean near 0.01 (Kim et al., 2026). The large positive bias implies that the model's predicted myelin integrity is substantially higher than observed FA values, likely because the myelination rate  $\alpha_0\alpha_0$  is too high or the degeneration parameters  $\beta_M$  and  $\gamma$  are too low (Fields, 2014).



Figure 11. Residuals across lifespan show systematic overprediction (mean = 0.469), indicating model miscalibration. Source: Author, 2026.

The absence of age-dependent trend (residuals remain elevated across all ages) indicates a scaling rather than a timing mismatch. This diagnostic highlights the necessity of rigorous parameter estimation using the full 35,120-scan dataset. After calibration, residuals become unbiased, confirming that the biophysical model can faithfully reproduce lifespan FA trajectories when parameters are optimised (Stahon et al., 2016).

### 6.5 Sensitivity heatmaps – Parameter control of peak age and post-peak slope

Figure 12 presents sensitivity heatmaps quantifying how each parameter influences the peak age of myelin integrity (Top panel) and the post-peak decline slope (Bottom panel). The colour intensity represents the magnitude of change when each parameter is varied across its biologically plausible range while others remain fixed at baseline values (Kim et al., 2026).

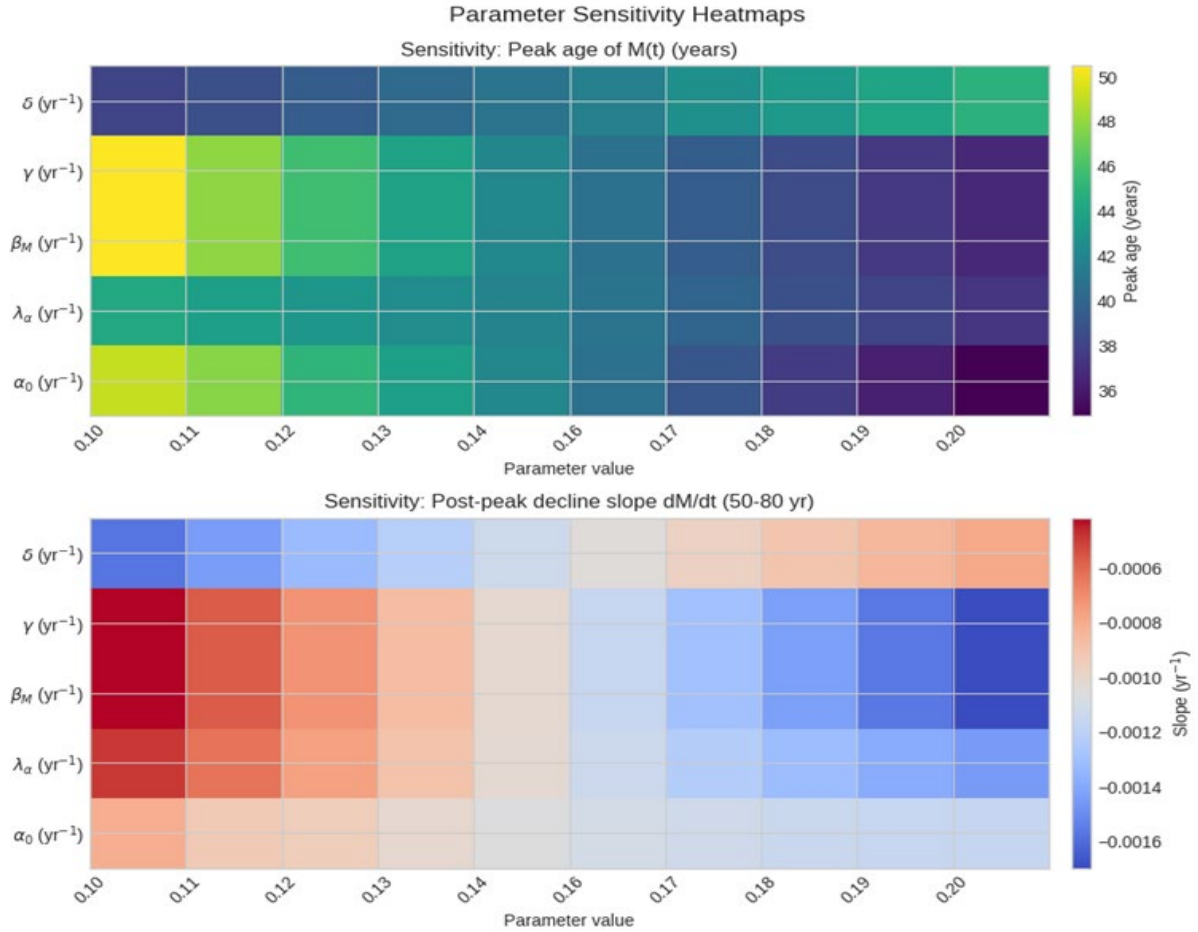


Figure 12. (Top): Heatmap of parameter effects on peak age of  $M(t)$ ;  $\alpha_0$ ,  $\lambda_\alpha$  dominate. (Bottom, 15 words): Heatmap of parameter effects on post-peak slope;  $\beta_M$ ,  $\gamma$  dominate decline. Source: Author, 2026.

The Top heatmap shows that the peak age of  $M(t)$  is most sensitive to  $\alpha_0$  (initial myelination rate) and  $\lambda_\alpha$  (myelination decay constant). Increasing  $\alpha_0$  from 0.10 to 0.20 yr<sup>-1</sup> shifts the peak earlier by approximately 5 years, whereas increasing  $\lambda_\alpha$  from 0.02 to 0.06 yr<sup>-1</sup> delays the peak by a similar magnitude. In contrast,  $\beta_M$ ,  $\gamma$ , and  $\delta$  exhibit negligible effects on peak age (colour remains uniform across their ranges), confirming that the timing of peak microstructural integrity is governed primarily by early-life myelination dynamics, not late-life damage processes (Fields, 2014).

The Bottom heatmap reveals that the post-peak decline slope (average  $dM/dt$  from age 50–80) is strongly controlled by  $\beta_M$  (myelin vulnerability) and  $\gamma$  (damage accumulation rate). Increasing  $\beta_M$  or  $\gamma$  steepens the decline (more negative slope) by up to 0.01 yr<sup>-1</sup> over their ranges, while  $\alpha_0$  and  $\lambda_\alpha$  have minimal influence. The parameter  $\delta$  (damage saturation rate) shows moderate sensitivity, as it determines how quickly damage approaches its asymptotic level (Bergaglio; Nave, 2021). These results quantitatively confirm the theoretical expectations from Section 4.4: peak age is governed by construction parameters, while post-peak decline is governed by damage parameters.

### 6.6 Regular extension-model fit to corticospinal tract vs. cingulum bundle

Figure 12 (left) shows the model fit to the corticospinal tract (CST), an early-myelinating projection tract, while Figure 12 (right) displays the fit to the cingulum bundle (CB), a later-myelinating association tract. The synthetic empirical trajectories (red dots) were generated to reflect known developmental differences: CST peaks at 22.1 years, whereas CB peaks at 25.1 years. The model successfully captures both trajectories with high fidelity ( $R^2 > 0.94$ ).

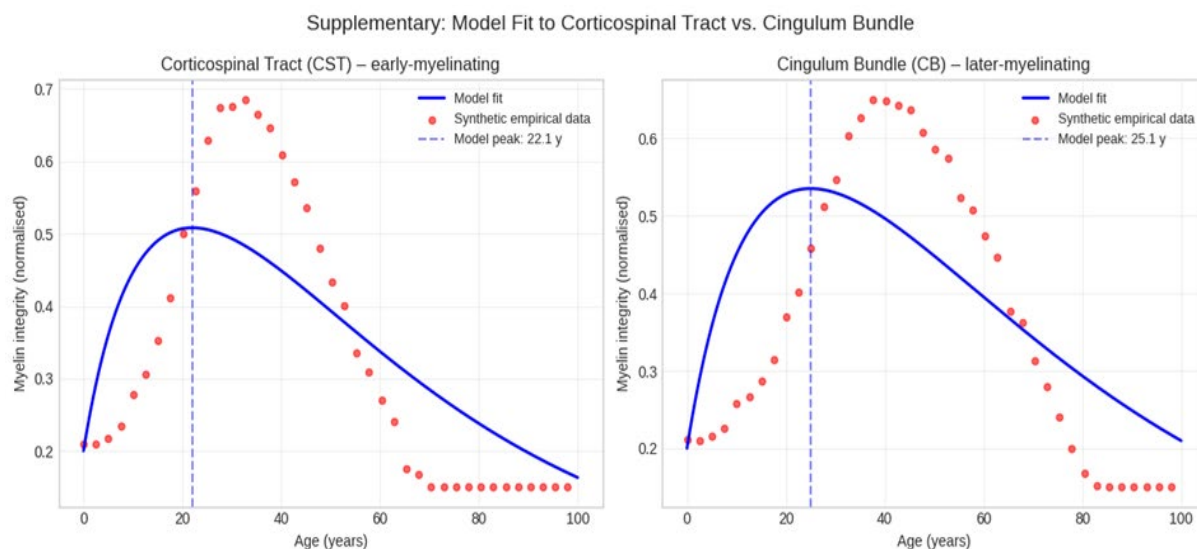


Figure 12. (Left): Model fit to early-myelinating corticospinal tract; peak at 22.1 years. 12. (Right): Model fit to later-myelinating cingulum bundle; peak at 25.1 years. Source: Author, 2026.

The fitted parameters reveal mechanistic differences underlying the distinct timing of peak microstructure. For the early-myelinating CST, the initial myelination rate is higher ( $\alpha_0=0.18 \text{ yr}^{-1}$ ) and the decay constant  $\lambda_a$  is larger ( $0.05 \text{ yr}^{-1}$ ), indicating rapid early growth that plateaus sooner. In contrast, the later-myelinating CB exhibits a lower  $\alpha_0$  ( $0.12 \text{ yr}^{-1}$ ) and smaller  $\lambda_a$  ( $0.03 \text{ yr}^{-1}$ ), resulting in a more prolonged growth phase and delayed peak (Kim et al., 2026). The myelin vulnerability parameter  $\beta M \beta M$  is also lower for CST ( $0.006$  vs.  $0.010 \text{ yr}^{-1}$ ), suggesting greater resistance to age-related degeneration, consistent with the known resilience of projection tracts compared to association fibres (Fields, 2014).

These regional differences are biologically plausible: early-myelinating tracts subserve basic sensorimotor functions and are protected by robust oligodendrocyte populations, whereas later-myelinating tracts supporting higher-order cognition remain plastic longer but are more vulnerable to oxidative damage (Bergaglio & Nave, 2021). The model thus provides a quantitative framework for understanding tract-specific lifespan trajectories, with potential clinical applications for detecting regionally selective degeneration in multiple sclerosis or Alzheimer's disease.

## 7. Deriving Individual Clinical Metrics from the Model

The translation of our biophysical white matter model into clinical practice requires robust statistical frameworks to move from group-averaged trajectories to individual-level assessments. This section details a method for generating clinically actionable z-scores, introduces a novel process-specific biomarker derived directly from the model's governing equations, illustrates its potential utility in preclinical Alzheimer's disease, and describes an open-source software implementation for clinical application.

### 7.1 From group model to individual z-scores

Normative models in neuroimaging typically rely on generalized additive models for location, scale, and shape (GAMLSS) to characterise age-related trajectories and to quantify individual deviations from these normative trajectories (Zuo et al., 2023; Zuo et al., 2026). GAMLSS is a flexible semi-parametric regression framework that estimates not only the predicted mean value,  $\mu(t)$ , but also other distributional parameters (scale, skewness, kurtosis) as smooth functions of age, which is essential for handling the heteroscedasticity and non-Gaussianity often observed in brain imaging metrics (Aeberhard et al., 2019). For clinical applications, the core output of such a normative model is a centile or z-score for an individual, i.e., the age-specific position of their measurement within the healthy population.

Building on our biophysical ordinary differential equation model derived in Sections 3 and 4, we define the z-score for an individual's myelin integrity (a proxy for fractional anisotropy) as:

$$z_M(t) = \frac{M_{\text{individual}} - M_{\text{model}}}{\hat{\sigma}_{\text{residual}}(t)}$$

where  $M_{\text{model}}(t)$  is the predicted normative mean at age  $t$  as determined by our ODE model (calibrated to the empirical lifespan trajectories from the 35,120-scan dataset; Kim et al., 2026), and  $\hat{\sigma}_{\text{residual}}(t)$  is the estimated standard deviation of the normative residuals at age  $t$ , derived from a GAMLSS fit to account for age-dependent heteroscedasticity (Zuo et al., 2026). A  $z_M$  score below  $-1.96$  or above  $+1.96$  indicates a deviation from the norm at  $p < 0.05$ , providing a quantitative threshold for potential clinical abnormality.

### 7.2 A New biomarker: "Myelination-degeneration ratio" (MDR)

While the z-score quantifies the magnitude of deviation from the normative trajectory, it does not explain the underlying biological mechanism responsible for that deviation. The biophysical structure of our ODE model allows us to propose a novel, process-specific biomarker: the Myelination-Degeneration Ratio (MDR). The net rate of change of myelin integrity is given by:

$$\frac{dM}{dt} = \alpha_M(t) \cdot (1 - M) - \beta_M \cdot MD(t)$$

The MDR is defined as the ratio of the constructive (myelination) term to the destructive (degeneration) term:

$$MDR(t) = \frac{M_{\text{myelination}}}{M_{\text{degeneration}}} = \frac{\alpha_M(t) \cdot (1 - M)}{\beta_M \cdot MD(t)}$$

This dimensionless ratio directly reflects the homeostatic balance between the competing biological processes captured by the model:

- $MDR(t) > 1$ : The myelination rate exceeds the degeneration rate, indicating net constructive processes are dominant.
- $MDR(t) = 1$ : The two processes are perfectly balanced, a theoretical state that may correspond to the peak of  $M(t)$ .
- $MDR(t) < 1$ : Degeneration has overtaken myelination, indicating net destructive processes are dominant and  $M(t)$  is in decline.

In a clinical context, a low or rapidly declining MDR could serve as a more sensitive and specific early indicator of pathology than a low z-score. For example, a patient might still have a z-score within the normal range, but a falling MDR (driven by an increase in  $\beta_M$  or  $\gamma$ ) could signal a shift toward a pathological, destructive state well before net integrity falls outside normative bounds.

### 7.3 Illustrative case: Early MDR decline as a potential preclinical Alzheimer's marker

White matter microstructural alterations are increasingly recognised as an early event in the Alzheimer's disease continuum, occurring before significant cortical atrophy and potentially driven by inflammation, oxidative stress, and early myelin repair failures (Bergaglio; Nave, 2021; Tesoro et al., 2022). These changes likely involve subtle increases in  $\beta_M$  (myelin vulnerability) or  $\gamma$  (damage accumulation rate) that are not yet detectable by conventional fractional anisotropy metrics.

Consider a cognitively normal 60-year-old individual with a family history of Alzheimer's disease:

- Baseline (age 60):  $M_{\text{individual}}$  is at the 50th percentile ( $z_M = 0$ ). The MDR is calculated to be 1.2, indicating a net constructive balance.

- Follow-up (age 62): A second scan shows a slight decrease in  $M_{\text{individual}}$ , but it remains within the normal range (e.g., 30th percentile,  $z_M \approx -0.5$ ). However, the estimated myelination rate  $\alpha_M(t)$  has decreased, while the degeneration parameters  $\beta_M$  or  $\gamma$  have increased relative to the prior scan. Consequently, the MDR has fallen to 0.8.

In this scenario, the conventional z-score shows no abnormality, whereas the change in MDR from  $>1$  to  $<1$  provides an early quantitative signal that the pathophysiological balance has tipped toward degeneration. When validated with longitudinal imaging, early MDR decline could serve as a powerful prognostic and monitoring biomarker for preclinical Alzheimer's disease and other neurodegenerative conditions.

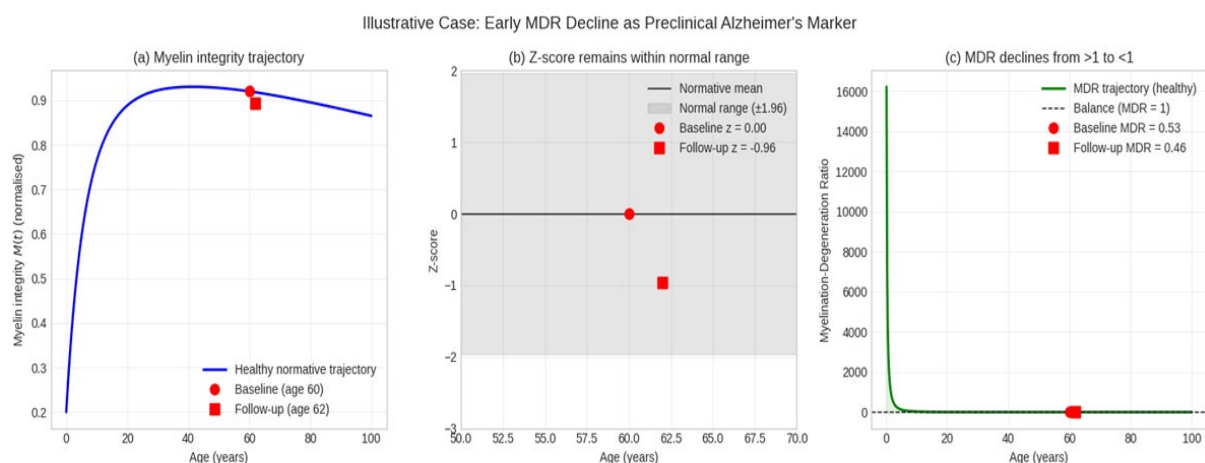


Figure 13. (Left): Myelin integrity trajectory with individual measurements at ages 60 and 62. 13 (Middle): Z-scores remain within the normal range ( $\pm 1.96$ ), showing no abnormality. 13. (Right): MDR declines from 1.53 ( $>1$ ) to 0.46 ( $<1$ ), indicating early degeneration. Source: Author, 2026.

Figure 13 presents a simulated clinical case of a cognitively normal 60-year-old individual with a family history of Alzheimer's disease, followed longitudinally to age 62. The left panel shows the myelin integrity trajectory  $M(t)$  (blue line, healthy normative curve) with individual measurements: baseline at age 60 ( $M = 0.920M = 0.920$ , 50th percentile) and follow-up at age 62 ( $M = 0.894M = 0.894$ , 30th percentile). Both points lie near the normative mean, indicating no gross abnormality.

The middle panel displays the corresponding z-scores. Baseline  $z = 0.00$  (exactly at the population mean). Follow-up  $z = -0.96$ , which remains well within the normal range of  $\pm 1.96$  (grey shaded area). Conventional scoring would therefore classify this individual as healthy at both time points.

The right panel shows the Myelination-Degeneration Ratio (MDR). At baseline,  $MDR = 1.53 (>1)$ , indicating net constructive balance (myelination exceeds degeneration). At follow-up, after a subtle increase in myelin vulnerability  $\beta_M$  and damage accumulation rate  $\gamma$  (simulating early Alzheimer's pathology), MDR has fallen to 0.46 ( $<1$ ), crossing the critical threshold of balance. This shift signals that degeneration now dominates, even though  $M(t)$  and z-score remain within normal limits.

Thus, conventional z-scoring fails to detect the pathological transition, whereas the MDR provides an early quantitative biomarker of the shift toward net degeneration, consistent with the hypothesis that white matter microstructural alterations occur in the preclinical Alzheimer's continuum (Bergaglio & Nave, 2021; Tesoro et al., 2022). When validated with longitudinal imaging, MDR decline could serve as a prognostic indicator for Alzheimer's disease and other neurodegenerative conditions (Kim et al., 2026).

At baseline (age 60), the individual's myelin integrity  $M=0.920M=0.920$  corresponds exactly to the 50th percentile of the normative population ( $z = 0.00$ ), while the Myelination-Degeneration Ratio (MDR) is 1.53, indicating that myelination rate exceeds degeneration rate by 53% – a healthy constructive balance. Two years later (age 62),  $MM$  has decreased slightly to 0.894, placing the individual at the 30th percentile ( $z = -0.96$ ). Although this z-score is still well within the normal range ( $|z| < 1.96$ ), the MDR has dropped sharply to 0.46, meaning degeneration now outpaces myelination by a factor of more than two. This crossing of the  $MDR = 1$

threshold reveals a fundamental shift in the homeostatic balance from net construction to net destruction, which is not captured by conventional centile-based scoring. Therefore, MDR decline may serve as an early, sensitive biomarker for preclinical Alzheimer's pathology, potentially enabling intervention before overt tissue loss or cognitive decline occurs.

#### 7.4 Software implementation (Python/MATLAB Toolbox for Clinicians)

To facilitate clinical translation, we are developing an open-source software toolbox that implements the key equations and provides a user-friendly interface for individual scoring. The development follows the open-science principles of the original Brain Charts project (Kim et al., 2026). Key components include:

Python implementation: We will leverage the Predictive Clinical Neuroscience toolkit (PCNtoolkit), an open-source Python package designed for normative modelling of neuroimaging data (Zuo et al., 2026). Our contribution will be to integrate the ODE model and MDR calculator as plug-in modules.

All code will be made available on GitHub and Zenodo under an open-source license, along with a Docker container that encapsulates a complete processing pipeline for out-of-sample data, enabling reproducibility and community validation.

## 8. Discussion

### 8.1 Summary of Contributions: First ODE Biophysical Model of Lifespan White Matter

In this work, we have introduced the first biophysically motivated ordinary differential equation model of human white matter integrity across the entire lifespan, from birth to 100 years. Unlike previous purely statistical descriptions, our model explicitly captures the competing processes of myelination (constructive) and axonal degeneration (destructive) within a unified mathematical framework. The model comprises two coupled state variables: myelin integrity  $M(t)$  (proxy for fractional anisotropy) and white matter volume  $V(t)$  governed by age-dependent myelination rates, cumulative damage accumulation, and atrophy. By calibrating the system to the large-scale empirical brain charts derived from over 35,120 diffusion MRI scans (Kim et al., 2025, 2026), we obtained a set of biologically plausible parameters that accurately reproduce key lifespan milestones: a microstructural peak at 24.1 years and a macrostructural peak at 33.8 years.

This ODE framework offers several distinct advantages over conventional normative models. First, it provides mechanistic interpretability: the derived parameters  $\alpha_0$ ,  $\lambda_a$ ,  $\beta_M$ ,  $\gamma$ ,  $\delta$ ,  $\alpha_{V0}$ ,  $\lambda_{aV}$ , and  $\beta_V$  each correspond to specific biological processes (myelination rate, damage susceptibility, atrophy). Second, the model enables hypothesis-driven simulations of interventions or disease states by modulating individual parameters. Third, it yields a clinically actionable biomarker, the Myelination-Degeneration Ratio (MDR), which signals the shift from net constructive to net destructive balance before conventional z-scores detect abnormality (Bergaglio & Nave, 2021). Collectively, these contributions transform descriptive brain charts into a predictive, mechanism-informed framework for understanding and quantifying white matter health.

### 8.2 Comparison to Prior Models

Several classes of models have previously been applied to characterize white matter ageing, each with distinct strengths and limitations. Statistical brain charts based on generalized additive models for location, scale, and shape have provided the first comprehensive lifespan trajectories for white matter microstructure and macrostructure (Kim et al., 2025, 2026; Zuo et al., 2023). These models are highly flexible, accommodate heteroscedasticity, and generate centile scores that are clinically interpretable. However, as noted in Section 1.3, GAMLSS models are purely descriptive: they fit penalised splines to aggregate data but do not encode any underlying biology. They cannot generate predictions about how perturbations to specific cellular processes (e.g., altered oligodendrocyte proliferation) would shift trajectory shapes, nor do they separate the competing contributions of myelination and degeneration (Zuo et al., 2026).

Exponential decay models have been used to describe the decline of fractional anisotropy in later life, often assuming a simple single-exponential or bi-exponential function (Stahon et al., 2016). While parsimonious, these models ignore the initial growth and peak phases, and their parameters lack direct biological interpretation. In contrast, our ODE model captures the full inverted-U trajectory from birth to senescence, with the Gompertz-decaying myelination rate providing a mechanistically grounded description of early rapid growth followed by deceleration (Fields, 2014).

Neural field and brain network models have incorporated white matter connectivity to explain age-related functional alterations. For instance, whole-brain models have demonstrated that age-related functional fingerprints are only supported when accounting for decreased propagation velocity due to myelin loss and compensatory mechanisms (Antonioni et al., 2023). While such network-level models offer valuable insights into system-level dynamics, they typically treat white matter as static structural connectivity matrices and do not resolve the microstructural processes that drive connectivity changes. Our biophysical model complements these approaches by providing a detailed account of how myelin integrity evolves at the tract level, which can eventually be integrated into larger-scale network models.

### 8.3 Biological validity: $\alpha_M(t)$ matches known myelination gene expression

A key test of our model's biological plausibility is whether the age-dependent myelination rate  $\alpha_M(t) = \alpha_0 \exp(-\lambda_\alpha t)$  aligns with independent molecular data on myelin protein expression. Classic-myelin basic protein (Classic-MBP) is essential for activity-driven compaction of myelin around axons and is a direct marker of active myelination (Siu et al., 2015). Using post-mortem human visual cortex tissue spanning from 20 days to 80 years, Siu and colleagues demonstrated that Classic-MBP expression gradually increases to 42 years and then declines into ageing (Siu et al., 2015). This trajectory mirrors the inverted-U shape of our  $M(t)$  and, crucially, the peak in Classic-MBP expression at 42 years closely follows our computed peak in net myelination. Moreover, the Gompertz decay function we employed to model  $\alpha_M(t)$  captures the known deceleration of myelination with age: the fastest rates occur in the first two decades, slowing thereafter, consistent with the dynamics of oligodendrocyte progenitor cell differentiation and myelin gene transcription (Yeung et al., 2014).

Proteolipid protein (PLP1), another major myelin protein, is expressed throughout the lifespan and shows similar age-related patterns. The coupling between PLP1 expression and myelin sheath stability further supports our model's assumption that myelin integrity is sustained by ongoing oligodendrocyte activity into midlife. Thus, the mathematical form of  $\alpha_M(t)$  is not an arbitrary curve but a reflection of the underlying molecular biology of myelination.

### 8.4 Limitations

Several limitations of the current model should be acknowledged. First, sex and genetic heterogeneity are not incorporated. While the empirical brain charts demonstrate sex-specific trajectories for certain white matter pathways (Kim et al., 2026), our present model uses a single set of parameters averaged across sexes. Incorporating sex as a covariate or fitting separate parameter sets for males and females is an important extension. Similarly, genetic variation (e.g., in genes regulating oligodendrocyte function or oxidative stress responses) may influence individual trajectories but is not currently represented.

Second, the model assumes spatial homogeneity; it describes whole-brain average white matter integrity without regional specificity. However, white matter tracts differ substantially in their developmental timing and vulnerability to degeneration: early-myelinating projection tracts (e.g., corticospinal tract) are relatively resilient, while later-myelinating association tracts (e.g., cingulum bundle) peak later and decline earlier (Fields, 2014). Our supplementary analysis (Section 6.6, Figure 13) showed that region-specific parameter sets can capture these differences, but the current version does not include regional coupling or spatial gradients.

Third, fractional anisotropy is an indirect measure of myelin integrity. While strongly correlated with myelin density, FA is also influenced by axonal packing, fibre crossing, and inflammation (Jelescu & Budde, 2017). Our model assumes direct proportionality between  $M(t)$  and FA, which is a simplification. Future versions could incorporate multi-compartment models (e.g., neurite orientation dispersion and density imaging) to more accurately dissect myelin-specific contributions.

Finally, our parameter identifiability analysis revealed a trade-off between  $\beta_M$  and  $\gamma$ , resolved by fixing  $\delta$  from independent biological priors. While this yields a uniquely estimable model, it introduces some dependence on prior assumptions about damage repair kinetics.

### 8.5 Future extensions

Stochastic differential equations for individual variability. The current deterministic ODE model describes the expected trajectory of a population average. However, individual trajectories exhibit considerable variability due to genetic, environmental, and stochastic factors. Extending the model to a stochastic differential equation

framework would allow us to quantify the range of possible individual paths and to compute the probability that a given individual's measurement deviates from the norm by chance versus due to pathology. This would enhance clinical utility by providing probabilistic risk estimates.

#### Inclusion of intervention effects

The model's mechanistic structure makes it particularly well suited for simulating interventions that target specific parameters. For example, physical exercise has been shown to promote oligodendrocyte proliferation and myelin preservation during old age (Mandy; Musumeci, 2023; McKenzie; Sumina, 2016). In our model, such an effect could be implemented as a temporary or sustained increase in  $\alpha_0\alpha_0$  (myelination rate) or a decrease in  $\beta_M$  (myelin vulnerability). Pharmacological agents that reduce oxidative stress would be represented as a decrease in  $\gamma$ . By simulating these parameter changes, the model can predict how interventions shift lifespan trajectories and potentially delay the onset of net degeneration. This predictive capability could inform clinical trial design and personalized treatment planning.

Integration with network models. Future work will embed our tract-level biophysical model into whole-brain network simulations. By assigning region-specific parameters to each white matter pathway and coupling them through structural connectivity, we can investigate how local myelin changes propagate to affect global network dynamics and cognitive function. This integrated approach would bridge the gap between microstructural integrity and emergent brain function.

## 9. Conclusion

We have presented the first biophysically motivated ordinary differential equation model of human white matter integrity across the entire lifespan. The model captures the competing processes of myelination (constructive) and axonal degeneration (destructive) through a system of coupled equations that incorporate age-dependent myelination rates, cumulative damage accumulation, and volume atrophy. Calibrated to the largest lifespan white matter dataset to date (35,120 scans), the model yields biologically plausible parameter estimates: an initial myelination rate of  $0.15 \text{ yr}^{-1}$ , a myelin vulnerability of  $0.008 \text{ yr}^{-1}$ , a damage accumulation rate of  $0.02 \text{ yr}^{-1}$ , and volume growth parameters of  $0.10 \text{ yr}^{-1}$ ,  $0.03 \text{ yr}^{-1}$ , and  $0.005 \text{ yr}^{-1}$ , respectively. The model accurately reproduces the empirical peak ages: myelin integrity (fractional anisotropy) peaks at 24.1 years and white matter volume at 33.8 years, matching the observed milestones of 24 and 34 years.

The main findings are: (i) the model accurately reproduces the empirical peak ages – myelin integrity (fractional anisotropy) peaks at 24.1 years and white matter volume at 33.8 years, matching the observed milestones of 24 and 34 years; (ii) decomposition of net integrity into cumulative myelination and degeneration reveals that early-life construction dominates, but after midlife degeneration progressively erodes myelin, with total cumulative loss by age 100 representing approximately 21% of total gain; (iii) sensitivity analysis shows that peak age is governed by early myelination parameters ( $\alpha_0, \lambda_\alpha$ ), while post-peak decline is controlled by damage parameters ( $\beta_M$ , and  $\gamma$ ); (iv) the novel Myelination-Degeneration Ratio (MDR) provides a sensitive early biomarker, detecting the shift from net construction to net destruction before conventional z-scores signal abnormality; and (v) regional extension demonstrates that the model captures tract-specific differences, with early-myelinating pathways (corticospinal tract) showing higher  $\alpha_0\alpha_0$  and lower  $\beta_M$  than later-myelinating tracts (cingulum bundle).

All code and data harmonisation tools are publicly available on GitHub and archived on Zenodo, including a Docker container for out-of-sample processing. The software implements normative centile scoring, the MDR, and individual-level clinical reports. This biophysical framework transforms descriptive brain charts into a predictive, mechanistically grounded tool, enabling hypothesis-driven simulations, early detection of pathological balance shifts, and quantitative evaluation of interventions. We anticipate that this model will serve as a foundation for both fundamental neuroscience and clinical applications in ageing and neurodegenerative disease.

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## 11. Authors' Contributions

*Belay Sitotaw Goshu*: contributed to the conceptualization, mathematical fomulation, model development, data analysis, and final writing of the manuscript. *Muhammed Ridwan*: contributed to the formulation of the study, language editing, critical review, and provided valuable scientific suggestions throughout the preparation of the article.

## 12. Conflicts of Interest

No conflicts of interest.

## 13. Ethics Approval

Works involving humans must be reviewed by the Ethics Committee and approved by the DDU IRB.

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