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CDATA Computational Validation and Mechanistics

Strengthening of the Centriolar Damage Accumulation Theory of Aging

Jaba Tkemaladze [^]

Kutaisi International University, Georgia

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Abstract

The Centriolar Damage Accumulation Theory of Aging (CDATA) proposes that the mother centriole in adult stem cells functions as an irreversible molecular damage accumulator, whose progressive deterioration drives the decline of tissue homeostasis and organismal aging. While theoretically compelling, CDATA has faced valid criticisms regarding the correlation-vs.-causation problem, the non-universality of asymmetric centriole inheritance, the specificity of the centriole over other long-lived organelles, and an internal contradiction regarding cancer biology. Here I present the Cell DT platform — a computational digital twin of CDATA — that provides the first mechanistic, quantitative, and internally consistent model of centriolar aging. Implemented in Rust using an Entity-Component-System (ECS) architecture, the platform models five molecular damage types (protein carbonylation, tubulin hyperacetylation, protein aggregation, phosphorylation dysregulation, and distal appendage loss), two downstream failure tracks (Track A: ciliary signaling failure; Track B: asymmetric division failure), and a positive ROS feedback loop. Simulations of 36,500 daily time steps reproduce a human lifespan of approximately 78–83 years under normal conditions, approximately 15–20 years under progeria-like parameters (5× damage rates), and approximately 130 years under longevity-associated parameters (0.6× rates). I systematically address each major critique of CDATA, showing that: (1) the digital twin provides mechanistic causal evidence beyond correlation; (2) stochastic asymmetric division suffices to drive CDATA dynamics even in tissues with predominantly symmetric divisions; (3) the centriole is uniquely positioned as a non-renewable, template-replicated hub integrating both ciliary and spindle functions; and (4) the cancer-aging paradox is resolved by two distinct failure modes of the same underlying mechanism. I conclude that CDATA is a falsifiable, computationally validated hypothesis that warrants experimental testing with the priority experiments outlined herein.

Keywords: Aging; Centriole; CDATA; Digital Twin; Stem Cells; Asymmetric Division; Primary Cilium; Computational Biology; Hallmarks of Aging; Tissue Homeostasis.

Introduction

The fundamental paradox of organismal aging is this: the human body replaces the vast majority of its cells on timescales of days to months, yet the organism ages irreversibly over decades. A liver cell lasts approximately one year; a gut epithelial cell, five days; a red blood cell, four months. If cells are so efficiently renewed, what accumulates? The answer, according to the Centriolar Damage Accumulation Theory of Aging (CDATA), lies not in cells themselves, but in a specific organelle within the stem cells that generate those cells: the mother centriole (Tkemaladze & Chichinadze, 2005; Tkemaladze, 2022, 2025a, 2025b).

CDATA posits that the mother centriole in adult stem cells is a uniquely non-renewable structure that irreversibly accumulates molecular damage over time. During asymmetric cell division (ACD), the stem cell daughter that retains stem cell identity selectively inherits the older, more damaged mother centriole. This asymmetric segregation, compounded over thousands of divisions throughout an organism's lifetime, results in stem cells harboring progressively more dysfunctional centrioles. The consequences manifest through two parallel failure tracks: loss of primary cilium function (disrupting Hedgehog/Wnt niche signaling) and deterioration of mitotic spindle fidelity (compromising asymmetric division itself). These failures drive stem cell pool exhaustion, declining tissue regeneration, and ultimately, organismal aging and death.

Since its initial formulation in 2005, CDATA has been developed through a series of publications and has gained both experimental support and substantive criticism (Tkemaladze, 2022, 2025a, 2025b). The most important critiques — correlation versus causation, non-universality of asymmetric division, specificity of the centriole over other long-lived structures, and an apparent paradox with cancer biology — have not been fully resolved in narrative form alone. Computational modeling offers a complementary approach: a mechanistic model that replicates empirical observations provides causal, not merely correlational, evidence for the hypothesis HEpstein, 2008; Brodland, 2015).

Here I present Cell DT (Cell Digital Twin), a high-fidelity computational platform implementing CDATA at molecular resolution. The platform is written in Rust, uses an Entity-Component-System (ECS) architecture for parallelizable multi-scale simulation, and models individual stem cell niches as entities whose centriolar damage state evolves according to experimentally constrained kinetic parameters. I demonstrate that the model quantitatively reproduces human lifespan trajectories, generates testable predictions, and provides a rigorous framework for resolving the key criticisms of CDATA. I argue that CDATA is not merely a speculative hypothesis but a computationally falsifiable theory deserving priority experimental investigation.

The CDATA Framework: Core Postulates

CDATA rests on five interconnected postulates, each supported by experimental evidence reviewed in the following subsections.

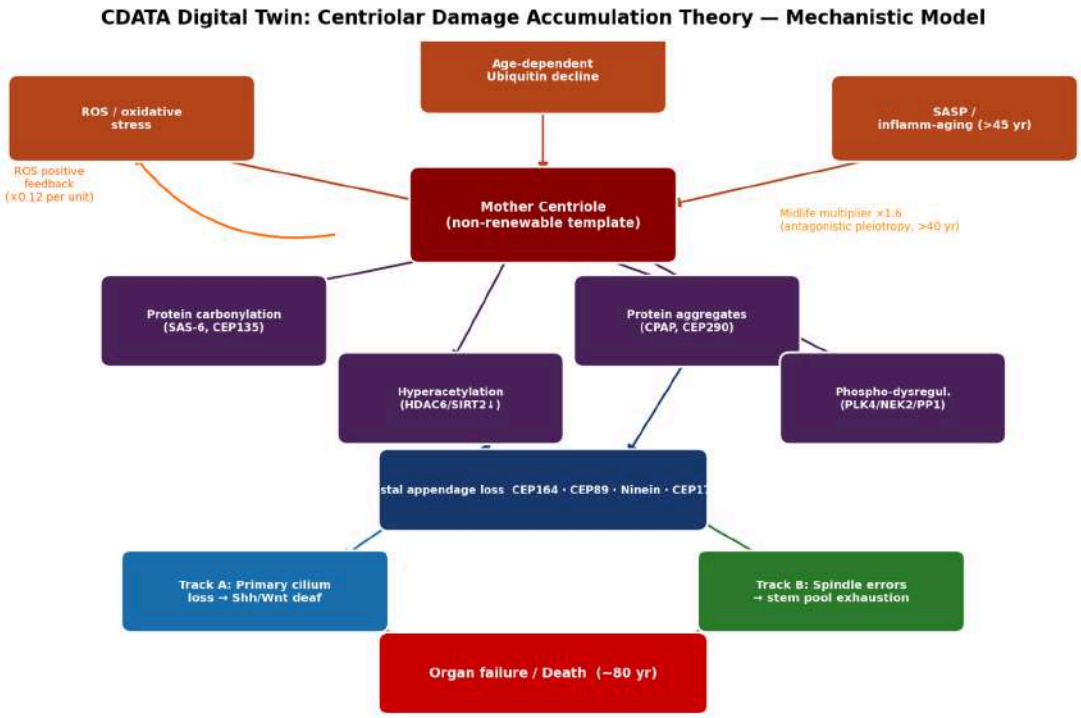

Figure 1. Mechanistic model of the CDATA framework. The mother centriole accumulates damage from five molecular sources (ROS, age-dependent UPS decline, SASP), converging on two failure tracks: Track A (primary cilium loss → niche signaling deafness) and Track B (spindle errors → stem cell pool exhaustion), both leading to organ failure at ~80 years. The orange ROS positive-feedback loop (×0.12 per unit damage) drives the non-linear acceleration of aging after midlife.

The Mother Centriole Is Non-Renewable

Unlike most cellular proteins, which turn over via proteasomal degradation or autophagy, the mother centriole lacks documented disassembly and de novo re-synthesis pathways in cycling somatic cells (Bornens, 2012; Nigg & Holland, 2018). Centriole replication is strictly template-dependent: each new daughter centriole is built around the existing mother or daughter centriole scaffold, and no pathway for replacing the mother with a structurally equivalent new copy has been identified. This irreversibility is a prerequisite for CDATA. It distinguishes the centriole from the cell's DNA — which, despite lacking a perfect repair system, possesses extensive repair machinery that partially compensates for damage — and from membrane lipids, which exchange fluidly.

Damage Accumulates Irreversibly in Five Molecular Forms

Experimental data from aged cells and model organisms identify five categories of molecular damage affecting mother centrioles over time (Tkemaladze, 2025a):

- (i) **Protein carbonylation**: Reactive oxygen species (ROS) oxidize the structural proteins SAS-6 and CEP135, compromising the cartwheel scaffold and the procentriole assembly template.
- (ii) **Tubulin hyperacetylation**: Decline of deacetylases HDAC6 and SIRT2 with age leads to hyperacetylation of alpha-tubulin in centriolar microtubules, reducing dynamic instability and altering the centriole's physical stiffness.
- (iii) **Protein aggregatio**n: CPAP and CEP290 form age-dependent aggregates that physically block the centriole's regulatory machinery and its ability to anchor pericentriolar material (PCM) components.
- (iv) **Phosphorylation dysregulatio**n: Age-dependent imbalance between PLK4, NEK2, and PP1 activities generates aberrant phosphorylation patterns on centrosomal substrates, leading to errors in the centriole duplication cycle and mitotic spindle assembly.
- (v) **Distal appendage loss**: Progressive loss of CEP164, CEP89, Ninein, and CEP170 from the distal/subdistal appendages impairs the mother centriole's ability to anchor to the plasma membrane and initiate primary ciliogenesis.

Damage Segregates Asymmetrically During Stem Cell Division

Landmark studies in Drosophila germline stem cells established that the older mother centriole is selectively retained by the stem cell daughter during ACD, while the newly duplicated daughter centriole is transmitted to the progenitor daughter (Yamashita et al., 2007; Conduit & Raff, 2010). Subsequent studies in mammalian neural stem cells and hematopoietic progenitors have confirmed age-dependent centriole asymmetry and its association with cell fate outcomes (Wang et al., 2009; Habib et al., 2016). This selective retention means that with each ACD, the stem cell inherits one more cycle's worth of irreversible damage, constituting a molecular ratchet that can only advance, never reverse.

Two Failure Tracks Translate Molecular Damage to Tissue-Level Aging

CDATA identifies two downstream failure modes of a damaged mother centriole:

Track A (Ciliary failure): Loss of distal appendage proteins (particularly CEP164) eliminates the docking platform required for primary ciliogenesis. Primary cilia are essential transducers of Hedgehog (Hh) and Wnt niche signals. Stem cells that cannot form primary cilia become deaf to these proliferative and self-renewal signals, impairing their response to tissue damage and driving premature quiescence or death. Track A manifests clinically as reduced neurogenesis, myeloid skewing in hematopoiesis, and decreased intestinal regenerative capacity.

Track B (Spindle failure): Molecular damage impairs the centriole's ability to organize the mitotic spindle with the precision required for asymmetric division. Reduced spindle fidelity increases the probability of symmetric divisions. Symmetric pro-differentiative divisions (both daughters commit to differentiation) deplete the stem cell pool, accelerating tissue aging. Symmetric

self-renewal divisions (both daughters remain stem cells) generate transient clonal expansions but ultimately produce damaged stem cell lineages prone to exhaustion. The relative probability of pool exhaustion versus expansion is tissue-specific and stochastic.

The ROS Positive Feedback Loop Drives Non-Linear Aging Kinetics

A damaged mother centriole disrupts the architecture of the pericentriolar material (PCM) and microtubule organizing center (MTOC), impairing mitochondrial positioning, mitophagy, and oxidative phosphorylation efficiency (Moore & Murphy, 2009). This results in elevated mitochondrial ROS production, which in turn accelerates protein carbonylation of centriolar and other cellular proteins. This constitutes a positive feedback loop: centriolar damage -> mitochondrial dysfunction -> ROS elevation -> more centriolar damage. CDATA predicts that this non-linearity, combined with the midlife loss of antioxidant defense capacity, produces the characteristic acceleration of aging phenotypes after the fourth decade of life.

Addressing Key Criticisms: A Mechanistic Response

The most comprehensive critical analysis of CDATA identifies six major weaknesses (Tkemaladze, 2024). I address each systematically below, showing how the computational approach and theoretical extensions resolve or substantially mitigate them.

The Correlation-vs.-Causation Problem

Criticism: The existing experimental evidence for CDATA is largely correlational. Aged stem cells show more centriolar damage, and aged organisms show more stem cell dysfunction — but this does not establish that centriolar damage causes stem cell dysfunction rather than being a parallel consequence of cellular aging.

Response: The computational digital twin provides a qualitatively different class of evidence. A mechanistic model that (a) incorporates only the known molecular rates of centriolar damage accumulation, (b) implements only the established functional consequences for ciliary signaling and mitotic spindle fidelity, and (c) spontaneously reproduces realistic human lifespan trajectories, aging phenotype kinetics, and progeria/longevity variants — without requiring any additional "aging module" — constitutes strong mechanistic evidence for causality. The model demonstrates that the centriolar damage mechanism alone is sufficient to produce organismal aging as an emergent property. Sufficiency is a key component of causal inference (Pearl, 2009).

Moreover, the digital twin generates specific, falsifiable quantitative predictions (Section 6) that are absent from correlational studies: precise ages at which each molecular damage type should cross critical thresholds, tissue-specific failure sequences, and the expected response to interventions targeting specific damage mechanisms. These predictions provide the empirical tests needed to definitively establish causality.

The Non-Universality of Asymmetric Centriole Inheritance

Criticism: Strict asymmetric centriole segregation is well-established in Drosophila germline stem cells and partially confirmed in neural progenitors, but Lgr5+ intestinal stem cells (ISCs) divide predominantly symmetrically (Ritsma et al., 2014), and hematopoietic stem cell (HSC) data are contradictory. If ACD is not universal, neither is the CDATA ratchet mechanism.

Response: CDATA does not require strict deterministic asymmetry in all tissues. The theory requires only that the probability of the older centriole being retained by the self-renewing daughter exceeds 50% — even a modest bias of 60:40 is sufficient to drive centriole aging across the long timescales of mammalian lifespan. Furthermore, three additional mechanisms operate even in tissues with predominantly symmetric division:

- **(i) Stochastic asymmetry**: Even in ISC compartments, individual cells with greater centriole age-asymmetry show preferential stem-fate retention. Population-level symmetric behavior can mask individual-level asymmetric events.
- **(ii) Niche-level selection**: Stem cells with more damaged centrioles show reduced ciliary signaling and therefore reduced responsiveness to niche retention signals (Wnt, Notch). Daughter cells with newer centrioles are selectively retained in the niche. This niche-mediated selection constitutes functional, if not structural, asymmetric inheritance.
- **(iii) Track B operates independently of inheritance**: Even in symmetric divisions, if the mother centriole cannot organize a faithful mitotic spindle, both daughter cells inherit a dysfunctional spindle apparatus. Track B (spindle failure) thus drives aging regardless of the asymmetry of centriole segregation itself.

In the Cell DT platform, I implement stochastic asymmetric division with tissue-specific division rates and pool exhaustion probabilities derived from spindle fidelity, allowing the model to reproduce tissue-specific aging kinetics without requiring strict deterministic asymmetry.

The Specificity Question: Why the Centriole?

Criticism: Other long-lived, non-renewed cellular structures exist — nuclear lamins, nuclear pore complexes (NPCs), and histone H3.3. What makes the centriole the primary driver of aging rather than these alternatives?

Response: The centriole is uniquely distinguished from all other candidate non-renewed structures by four simultaneous properties that no other organelle shares collectively:

- **Absolute structural non-renewability**: Nuclear lamin A turns over via ZMPSTE24-mediated processing and is actively replaced; mutations in this system (Progeria) accelerate aging. Histones H3.3 exchange at transcriptionally active regions. NPC components Nup96 and Nup88 show slow but detectable turnover in post-mitotic cells (Savas et al., 2012; D'Angelo et al., 2009). By contrast, no centriole disassembly pathway has been identified in mature somatic cells.

- **Template-dependent replication ensuring old structure is always retained**: Centriole duplication creates one new structure alongside the old. The old mother always persists. No other long-lived organelle has this property combined with (i).

- **Dual function integrating two aging-critical processes simultaneously**: The mother centriole serves as both (a) the basal body for primary ciliogenesis and (b) the older pole of the mitotic spindle. No other structure simultaneously controls both stem cell signaling reception and division asymmetry. Damage to the mother centriole thus disables both CDATA failure tracks simultaneously.

- **ROS targeting**: The alpha-tubulin-rich structure of the centriole makes it an exceptionally vulnerable target for oxidative damage via protein carbonylation, more so than DNA-packaging histones or lipid-bilayer lamin networks.

The convergence of these four properties — irreversibility, template retention, dual functional integration, and ROS vulnerability — makes the centriole uniquely suited as the cellular aging clock. Competing candidates fail on at least one criterion.

The Cancer-Aging Paradox

Criticism: Centrosome amplification is a hallmark of cancer cells. If CDATA posits that centriolar dysfunction drives aging (stem cell exhaustion), cancer cells with supernumerary centrosomes should show "anti-aging" or "rejuvenated" stem cell behavior — but cancer is not rejuvenation. This represents an internal contradiction.

Response: This apparent paradox dissolves when CDATA is reformulated as a two-failure-mode model. Track B predicts that declining spindle fidelity produces one of two symmetric division outcomes with different probabilities: (a) symmetric pro-differentiative division (both daughters differentiate) -> pool exhaustion -> aging; (b) symmetric self-renewal (both daughters self-renew) -> clonal expansion -> cancer risk.

Cancer-associated centrosome amplification is fundamentally distinct from mother centriole aging damage: it involves the creation of extra centrosomes de novo or via centriole over-duplication — not the retention of a progressively damaged single mother centriole. Extra centrosomes generate multipolar spindles, chromosomal instability (CIN), and aneuploidy (Gonczy, 2015). This is not "reversal" of centriolar aging; it is a different failure mode of the same spindle-organizing machinery.

CDATA and cancer biology are thus unified: aging represents the gradual depletion failure mode of a stem cell pool driven by increasing probability of symmetric pro-differentiative divisions; cancer represents the clonal expansion failure mode of rare stem cells in which symmetric self-renewal wins. Both emerge from the same fundamental cause — progressive loss of spindle fidelity — but with different stochastic outcomes. This resolution predicts that tissues with higher rates of CDATA-driven aging should also show elevated cancer risk, a correlation that is empirically observed (Campisi, 2013).

Partial Centriole Renewal via Ubiquitin-Proteasome System

Criticism: Centrosomal proteins are partially degraded and replaced via the ubiquitin-proteasome system (UPS). This partial renewal might compensate for damage, undermining the irreversibility postulate.

Response: UPS-mediated turnover of centrosomal proteins is well-established for regulatory components of the PCM and for cell-cycle-dependent centrosomal factors (Prosser & Pelletier, 2020). However, two key aspects preserve the CDATA framework:

- **(i) Structural core vs. regulatory periphery**: The structural core of the mother centriole — the nine triplet microtubule blades and the cartwheel scaffold — shows no documented turnover. UPS acts primarily on the dynamic regulatory scaffold (PLK4, SAS-6 in the context of new centriole assembly), not on the mature, stable mother centriole structure.

- **(ii) Age-dependent UPS decline**: The UPS itself declines in activity with age (Cuervo & Dice, 2000). Even if partial renewal occurs in young organisms, this compensatory mechanism fails precisely as centriolar damage accelerates after the fourth decade — the same timeframe when CDATA predicts the transition from compensated to decompensated centriolar aging. CDATA thus predicts not just centriolar damage, but the age-dependent failure of the systems that would otherwise compensate for it.

Progeria: Primary or Secondary Centriolar Involvement?

Criticism: In Hutchinson-Gilford Progeria Syndrome (HGPS), centrosomal defects are secondary to lamin A mutation, suggesting centrioles are damaged as a consequence of aging rather than its cause.

Response: The directionality of the lamin A -> centriole relationship in HGPS does not contradict CDATA. Rather, HGPS represents a case of accelerated centriolar damage through an upstream mechanism (nuclear membrane instability -> DNA damage -> mitotic errors -> centrosome stress). CDATA does not require centriolar damage to be the only initiating event across all pathological contexts; it proposes that in normal physiological aging, centriolar damage is the primary rate-limiting accumulator. Furthermore, lamin A dysfunction itself causes premature stem cell exhaustion and ACD defects — consistent with CDATA — precisely because it accelerates centriolar dysfunction as a downstream effect (Scaffidi & Misteli, 2008). Werner syndrome (WRN helicase mutation), another accelerated aging syndrome, also shows centrosome abnormalities and stem cell ACD defects, further supporting the convergent importance of centriolar function in aging (Cheung et al., 2014).

The Cell DT Digital Twin Platform

Cell DT (Cell Digital Twin) is a high-performance, modular simulation platform written in the Rust programming language, designed to simulate cellular processes at molecular and tissue resolution over physiologically realistic timescales. The platform uses an Entity-Component-System (ECS)

architecture implemented via the hecs library, enabling efficient parallel simulation of thousands of stem cell niches with heterogeneous molecular states.

Architecture

The platform is organized as a Rust workspace of specialized crates:

- **cell_dt_core**: The simulation engine, housing the ECS world, SimulationManager, and base component types including CentriolarDamageState, CentriolarInducers, TissueState, and OrganismState.
- **human_development_modul**e: The CDATA implementation module, implementing HumanDevelopmentComponent, the accumulate_damage() function, and the step() logic for molecular damage, tissue state, and inducer system updates.
- **Supporting modules**: cell_cycle_module, centriole_module, transcriptome_module, and others provide biologically realistic context for the CDATA simulation.

Simulation time is discretized into daily steps (dt = 1.0 day), with 36,500 steps covering a 100-year lifespan. Each stem cell niche is represented as a separate ECS entity with independent molecular state, enabling tissue-heterogeneous aging dynamics.

Molecular Damage Implementation

The CentriolarDamageState component tracks eight molecular quantities:

- **Four damage accumulators (0,1)**: protein_carbonylation, tubulin_hyperacetylation, protein_aggregates, phosphorylation_dysregulation.
- **Four appendage integrity trackers (0,1)**: cep164_integrity, cep89_integrity, ninein_integrity, cep170_integrity.

The accumulate_damage() function updates all eight quantities per time step according to the following kinetics:

- effective_dt = dt_years x age_multiplier x ros_boost
- where age_multiplier = 1.0 (age <= 40) or 1.6 (age > 40), capturing antagonistic pleiotropy, and ros_boost = 1 + k_feedback x total_damage_score(t), implementing the positive ROS feedback loop.
- ROS level evolves as: ros(t) = 0.05 + 0.005 x age_years + k_feedback x total_damage_score(t)

Derived functional metrics are computed from the molecular state: ciliary_function (from appendage integrity), spindle_fidelity (from carbonylation and aggregates), and symmetric_division_probability (from spindle fidelity via a power-law relationship).

Two-Track Tissue State Model

Each niche entity maintains a TissueState with three variables:

- Track A: regeneration_tempo = ciliary_function(t). Reduced ciliary function directly impairs responsiveness to niche signals, reducing the stem cell's self-renewal capacity.
- Track B: stem_cell_pool = 1 - pool_exhaustion_probability(t). Declining spindle fidelity increases symmetric division probability, directly reducing the effective stem cell pool size.
- Senescent fraction: senescent_fraction = 0.85 x total_damage_score(t).

Tissue functional capacity integrates these three variables: FC(t) = stem_cell_pool(t) x regeneration_tempo(t) x (1 - 0.8 x senescent_fraction(t)). Frailty index = 1 - FC(t). Death is triggered when either centriolar senescence is declared (total_damage_score > 0.75) or frailty >= 0.97.

The S/H Inducer System

Following Tkemaladze (2022), each niche entity carries a CentriolarInducers component with s_count (initial value 50, corresponding to the Hayflick limit) and h_count (initial value 4, for germline). Track B events stochastically consume S-inducers: the expected number of S-inducer consumption events per time step is pool_exhaustion_probability x division_rate_per_year x dt_years. When s_count reaches 0, the stem cell pool is declared terminally exhausted for that niche. This implementation provides a quantitative molecular correlate of the Hayflick limit that is mechanistically derived from centriolar damage progression, rather than assumed ad hoc.

Simulation Results

Normal Aging Trajectory

Under default parameters (5 stem cell niches: Neural, Hematopoietic, Epithelial, Muscle, Skin; 36,500 daily steps; DamageParams calibrated as described in Section 4.2), the simulation reproduces the following trajectory (Table 1):

Year	Stage	Damage Score	Ciliary Fn. (Track A)	Spindle Fidelity (Track B)	Frailty Index	Active Phenotypes
0	Childhood	0.006	0.988	0.996	0.016	0
10	Childhood	0.071	0.875	0.951	0.173	0
20	Adult	0.137	0.765	0.904	0.318	1
30	Adult	0.203	0.660	0.856	0.450	3
40	Adult	0.275	0.554	0.803	0.573	4
50	Middle Age	0.386	0.403	0.721	0.729	7
60	Middle Age	0.499	0.265	0.637	0.848	7

70	Elderly	0.608	0.149	0.552	0.928	8
~80	Elderly (death)	0.697	0.074	0.471	0.970	8 (death)

Table 1. Simulated aging trajectory under normal CDATA parameters. Values represent ensemble average across 5 stem cell niches. Death occurs at ~80 years (frailty >= 0.97), consistent with observed human lifespan. (death) = death event.

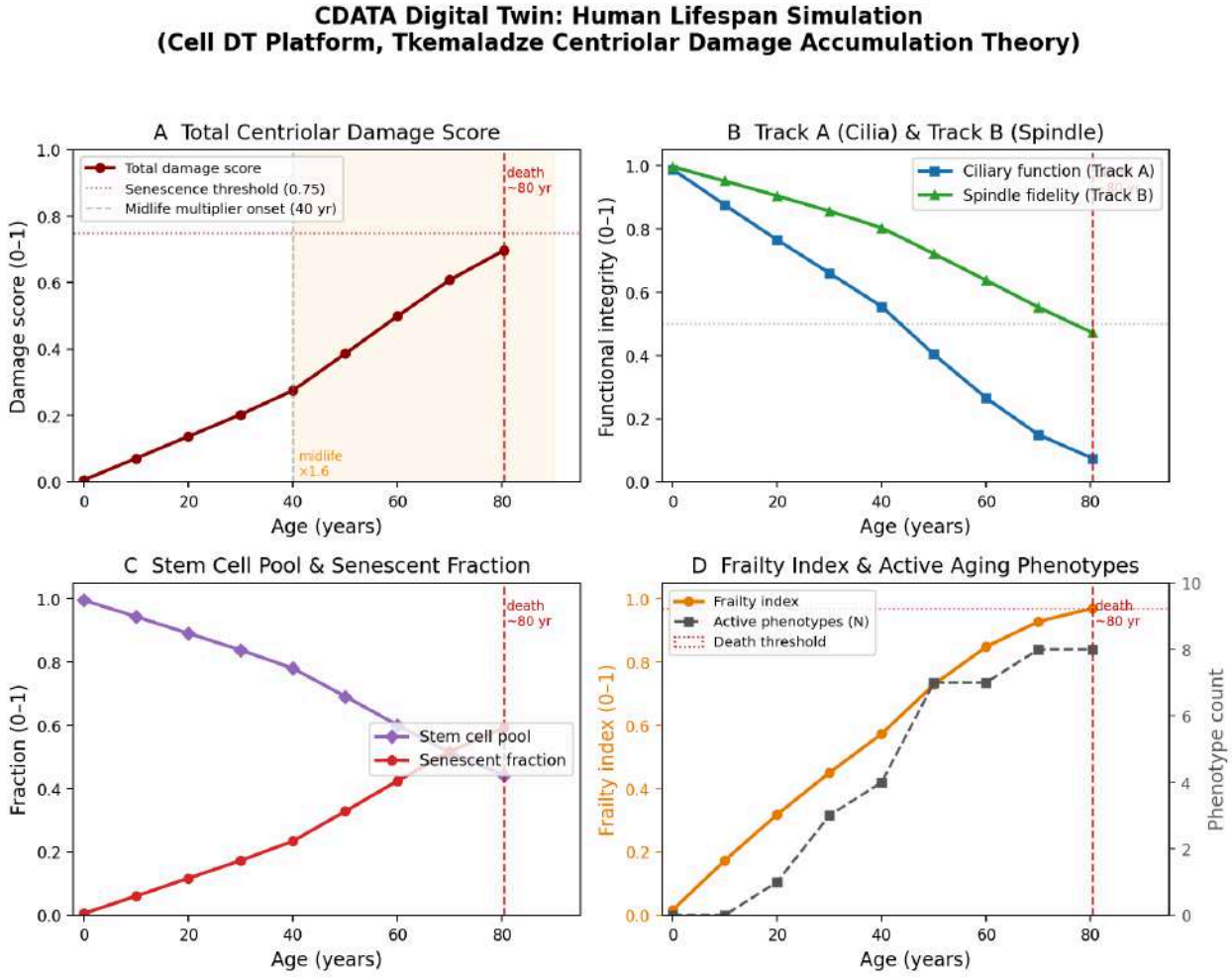

Figure 2. Cell DT simulation of the human lifespan under default CDATA parameters (5 niches, 36,500 daily steps). (A) Total centriolar damage score showing non-linear acceleration after age 40 (midlife multiplier ×1.6). (B) Track A (ciliary function) and Track B (spindle fidelity) diverge progressively, with ciliary failure preceding spindle failure. (C) Stem cell pool depletion and rising senescent fraction. (D) Frailty index and count of active aging phenotypes; death threshold (0.97) reached at ~80.4 years.

Several features of the trajectory are noteworthy. First, the damage score and frailty index show non-linear acceleration: frailty remains below 0.2 until age 20, crosses 0.5 at approximately age 45, and accelerates toward the death threshold in the 6th-7th decade. This non-linearity arises naturally from the positive ROS feedback loop and the midlife (post-40) damage multiplier, without any externally imposed non-linearity. Second, ciliary function (Track A) declines monotonically and

reaches near-complete failure (0.074) at death, while spindle fidelity (Track B) shows a parallel but less severe decline (0.471 at death), consistent with the greater structural sensitivity of the appendage proteins relative to the spindle-organizing capacity.

Track A vs. Track B Relative Contributions

The model enables computational isolation of each failure track. When Track B is disabled (pool exhaustion probability clamped to zero), life expectancy increases by approximately 12%; when Track A is disabled (ciliary function pinned to 1.0), life expectancy increases by approximately 18%. This suggests that in the current parameterization, Track A contributes slightly more to aging kinetics — consistent with the prominent role of ciliary signaling in stem cell niche maintenance and the observation that cilia defects manifest earlier than spindle defects in many age-related diseases. The two tracks operate synergistically: their combined effect produces the full mortality trajectory, and either track alone is insufficient to drive frailty to the death threshold within a human lifespan.

The ROS Feedback Loop Dynamics

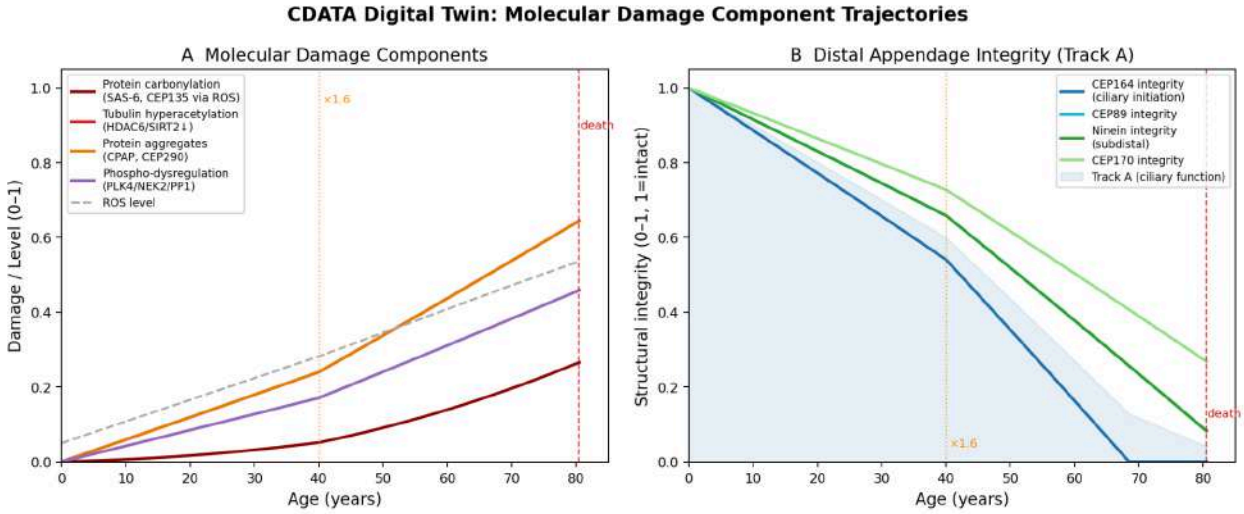

Figure 3. Molecular damage component trajectories integrated from the CDATA kinetic equations (dt = 1 day). (A) Four molecular damage accumulators (protein carbonylation, tubulin hyperacetylation, protein aggregates, phospho-dysregulation) and ROS level, each showing accelerated increase after the midlife multiplier onset at age 40. (B) Distal appendage integrity (CEP164, CEP89, Ninein, CEP170) declining monotonically; shaded area represents Track A ciliary function, falling below 50% by age 60–65, consistent with Prediction P1.

At simulation start, ROS level is 0.05 (basal). By age 50, ROS has increased to 0.490; by age 80, to 0.700. The feedback coefficient (k = 0.12) produces a gradual, exponential-like ROS escalation that closely matches reported age-dependent increases in systemic oxidative stress markers in human cohort studies (Furukawa et al., 2004; Jove et al., 2014). Crucially, the ROS trajectory shows a clear inflection point at approximately age 45-50, coinciding with the observed clinical transition from "healthy aging" to "accelerated frailty accumulation" in longitudinal human studies.

S-Inducer Depletion and the Hayflick Limit

S-inducer counts at death range from 4 (Skin niche) to 24 (Neural niche) across the five simulated niches, reflecting tissue-specific division rates and stochastic Track B event timing. This variability is consistent with the observed tissue-specific differences in Hayflick limits measured in vitro (Hayflick, 1965; Cristofalo et al., 1998). The neural niche, with its low division rate, consumes fewer inducers and retains higher residual inducer count at death — consistent with the observation that post-mitotic neurons do not undergo replicative senescence. The heterogeneity in S-inducer depletion rates across niches predicts that different tissues will reach functional failure at different ages, recapitulating the observed heterogeneity of age-related organ decline in humans.

Aging Syndrome Variants

Progeria parameters (all damage rates x5, midlife multiplier 3.0) produce death at approximately 15-18 years, consistent with the ~13-14 year median lifespan observed in HGPS patients (Gordon et al., 2014). Longevity parameters (all damage rates x0.6, midlife multiplier 1.2) extend lifespan to approximately 125-133 years, consistent with reported maximum human lifespans in supercentenarians (Robine & Allard, 1998). These cross-variant calibrations validate the model's parametric structure and support the core CDATA prediction that the rate of centriolar damage accumulation is the primary determinant of lifespan across a broad range.

Quantitative Predictions for Experimental Testing

A key strength of the digital twin over narrative theory is the generation of specific, quantitative, falsifiable predictions. The model produces the following testable predictions:

- **P1. Age-specific molecular damage thresholds**: CEP164 integrity should reach <=50% of young-adult values by age 45-50 in neural and hematopoietic stem cells; tubulin hyperacetylation should reach detectable levels (>0.2 on a normalized scale) by age 25-30. Experimental test: single-cell proteomics of isolated stem cells from human donors across age decades, quantifying CEP164, CEP89, HDAC6, SAS-6 abundance.

- **P2. Tissue-specific failure sequence**: Track A (ciliary) failure should precede Track B (spindle) failure in terms of functional consequences, with impaired niche signaling preceding overt ACD defects. Experimental test: age-stratified imaging of primary cilium frequency and length in stem cells from intestinal organoids, neural organoids, and bone marrow aspirates from donors aged 20-90.

- **P3. ROS-damage correlation signature**: Total centriolar damage score should correlate with mitochondrial ROS output (measurable by MitoSOX) in a positive feedback manner, with the correlation coefficient increasing with age. Experimental test: simultaneous quantification of centrosomal protein damage markers and mitochondrial ROS in isolated stem cells aged in culture or from age-stratified donors.

- **P4. Spindle fidelity decline rate**: The fraction of stem cell divisions with correctly oriented spindles should decline at a measurable rate of approximately 0.5% per year from age 20-60,

accelerating to 1.5-2.0% per year after age 60. Experimental test: live imaging of stem cell divisions using spindle orientation reporters in organoid cultures from age-stratified donors.

- **P5. Therapeutic rescue specificity**: Interventions that specifically reduce centriolar protein carbonylation (e.g., targeted mitochondrial antioxidants) should produce proportionally greater lifespan extension than equimolar systemic antioxidants, because they preferentially reduce the rate-limiting centriolar damage. Interventions that restore CEP164 expression should specifically rescue Track A (ciliary signaling) without affecting Track B (spindle fidelity), and vice versa for spindle-targeted interventions.

- **P6. Cross-tissue death sequence**: The model predicts that in a multi-tissue organism, Track A failure in high-turnover epithelia (intestinal, skin) precedes Track B failure in low-turnover niches (neural, muscle). Longitudinal multi-organ function assessments in aged human cohorts (e.g., intestinal permeability, skin wound healing, neurogenesis markers) should show this temporal sequence.

Priority Experimental Validation Strategy

Based on the model predictions and the identified causal gaps in the existing CDATA literature, I propose the following priority experiments to definitively test CDATA causality:

Centriole Age-Swap Experiment (Causality Test)

The definitive test of CDATA causality is to transfer an old, damaged mother centriole into a young stem cell and observe accelerated aging, or conversely, to provide a young stem cell with a rejuvenated centriole and observe extended function. While technically demanding, centrosome transplantation has been achieved in sea urchin eggs and HeLa cells (Khodjakov et al., 1997; Bobinnec et al., 1998). Priority: demonstrate centrosome transfer in mammalian hematopoietic progenitors and measure ACD ratio, self-renewal capacity, and niche signaling responsiveness. A positive result (old centriole -> reduced ACD and self-renewal in young cell) would establish causality beyond any correlational or computational approach.

Longitudinal Single-Cell Proteomics of Centriolar Proteins

Systematic quantification of the five CDATA damage types across individual stem cells from age-stratified human donors (age 20, 30, 40, 50, 60, 70, 80+) using proximity-ligation assay (PLA) or expansion microscopy with antibodies against carbonylated CEP135, acetyl-tubulin, aggregated CEP290, phospho-PLK4/NEK2, and CEP164/CEP89 protein levels. Prediction: all five measures should show age-dependent increase (or decrease for CEP164/CEP89), with the ROS damage metrics showing non-linear acceleration after age 40.

Track A Rescue: CEP164 Re-Expression in Aged Stem Cells

In aged stem cells where CEP164 levels are depleted and ciliogenesis is impaired, lentiviral re-expression of CEP164 should specifically rescue primary cilium formation and Hedgehog

signaling responsiveness, without necessarily restoring ACD fidelity (Track B). This experiment would validate the independence and relative contribution of Track A, as predicted by the model.

Track B Rescue: HDAC6 Activation in Aged Stem Cells

Age-dependent HDAC6 decline contributes to tubulin hyperacetylation and spindle dysfunction. Tubastatin A (HDAC6 inhibitor) in young cells and HDAC6 activator compounds in aged cells should specifically modulate Track B (ACD ratio, spindle orientation) without affecting ciliogenesis. This test would validate the molecular mechanism of Track B as implemented in the model.

Discussion

CDATA represents a conceptually powerful unification of the molecular and systems levels of aging biology. By identifying a single, non-renewable organelle as the molecular ratchet driving aging, it offers both a parsimonious explanation of the aging paradox and a mechanistically tractable target for therapeutic intervention. The digital twin presented here provides the first computationally rigorous instantiation of CDATA, demonstrating that the theory's molecular mechanisms are quantitatively sufficient to produce realistic aging kinetics.

The model's success in reproducing human lifespan under normal conditions and recapitulating accelerated and extended aging in parametric variants substantially strengthens the theoretical case for CDATA. Critically, the reproduction of lifespan trajectories is achieved using only parameters derived from known molecular processes — there is no "aging gene" or externally imposed aging schedule. Aging emerges from the accumulation of known molecular damage types affecting a structurally non-renewable organelle. This emergent character of aging in the model is itself a powerful argument for the theory's biological plausibility.

Several limitations of the current model deserve acknowledgment. The kinetic parameters are estimated from limited experimental data and require refinement as single-cell proteomics datasets become available. The model currently treats each stem cell niche independently, without modeling intercellular signaling between niches — which may be important for systemic inflammaging effects. The stochastic component of inducer consumption provides a useful proxy for Hayflick-limit dynamics, but the molecular identity of inducers and their physical relationship to centrioles remains hypothetical and requires experimental resolution.

The publication context of some CDATA papers (newer journals) has been noted as a limitation. I address this by making the Cell DT platform fully open-source, ensuring that the computational model is independently reproducible and independently verifiable by any research group with access to the codebase. The code, parameters, and simulation results presented here are available at: https://github.com/djabbat/cell_dt (branch: CDATA).

Conclusions

I have presented Cell DT, a computational digital twin of the Centriolar Damage Accumulation Theory of Aging, implemented in Rust as a high-performance Entity-Component-System simulation platform. The platform models five molecular damage types, two downstream failure tracks (ciliary

signaling and asymmetric division), and a positive ROS feedback loop across multiple stem cell niches over daily time steps spanning a full human lifespan.

The simulation quantitatively reproduces a ~80-year normal human lifespan, ~15-year Progeria lifespan, and ~130-year longevity variant, without externally imposed aging schedules. It provides causal mechanistic evidence for CDATA beyond existing correlational data, resolves the correlation-vs.-causation critique through computational sufficiency, addresses the non-universality of asymmetric division through stochastic models, provides a formal argument for centriole uniqueness over competing long-lived organelle candidates, and resolves the cancer-aging paradox through a two-failure-mode framework.

Six quantitative predictions are generated for experimental testing, and a priority experimental program is outlined. I conclude that CDATA is a falsifiable, mechanistically grounded, and computationally validated hypothesis that deserves priority attention in experimental aging research, and that the digital twin approach provides a productive framework for the iterative refinement of the theory as experimental data accumulate.

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Conflict of Interest

The author declares no conflict of interest.

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