

Recursive Compensation and Threshold Crossing in Degenerative Disease

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Abstract

Biological systems maintain functional stability through recursive compensation: when substrate is lost, surviving components absorb redistributed load, preserving apparent function while underlying capacity degrades. This compensation is not passive. It is an active, iterative process that cycles against accumulating damage, buying time at the cost of reserve.

We propose that across biologically distinct degenerative diseases, this recursive compensation follows a consistent structural shape. Substrate loss accumulates below the threshold of clinical detection. Compensation mechanisms hold functional stability while their own reserve depletes. When substrate loss exceeds the redundancy capacity of the system, compensation fails and the system crosses rapidly into a qualitatively different state: clinically manifest disease. This crossing, termed phenoconversion in the neurological literature, is not the beginning of disease. It is the failure of the system's ability to contain it.

We examine four diseases in support of this pattern: amyotrophic lateral sclerosis, in which surviving motor neurons absorb the load of dying neighbors through axonal sprouting until the quality of neuromuscular transmission degrades and compensation fails; Alzheimer's disease, in which the brain actively recruits compensatory processing strategies and alternative neural pathways to maintain cognitive function against accumulating pathology until compensatory reserve is exhausted; Duchenne muscular dystrophy, in which satellite cells cycle repeatedly to repair fragile muscle membrane until the repair mechanism's own output quality degrades and fibrosis replaces regeneration; and Parkinson's disease, in which dopaminergic compensation amplifies gain to maintain signal until denervation exceeds the coherence limit and compensation produces noise rather than signal.

In neural systems where the threshold has been quantified, it appears to occur within a range of 60-80% substrate loss. We propose this range is not a universal constant but a function of system architecture: the redundancy built into each biological system determines where in the loss curve compensation exhausts its reserve. More redundant systems cross later. Less redundant systems cross earlier. This redundancy hypothesis accounts for the observed range in neural systems but has not been independently

tested, and quantitative threshold data in muscular disease is not comparable to the neural figures.

We further propose that the mechanism connecting substrate loss to decompensation is a degradation in the quality of each compensatory cycle as load increases and reserve depletes. Across all four diseases, the compensation mechanism appears to work harder while producing less faithful output per cycle, though the form this quality degradation takes differs by substrate. We do not claim the quality degradation follows the same mechanism across substrates; we claim the structural pattern of degradation is the same. This framing extends existing work within each disease field, including the cognitive reserve paradox in Alzheimer's research and the compensation-failure model in ALS, into a unified cross-disease structural framework.

1. Amyotrophic Lateral Sclerosis: Rate, Compensation, and Transmission Quality

Amyotrophic lateral sclerosis is conventionally described as a disease of motor neuron death. That description is accurate but incomplete. The mechanism that produces clinical disease is not motor neuron death alone: it is the rate of motor neuron loss exceeding the capacity of surviving neurons to compensate for what has been lost.

The distinction matters. In normal aging, motor neuron loss occurs continuously. Estimates suggest approximately 5% loss per decade before age 60, accelerating to 8-21% per decade thereafter (Kawamura et al., 1977; Tomlinson and Irving, 1977). The system compensates: surviving motor neurons sprout collateral branches to reinnervate muscle fibers whose original motor neuron has died, forming enlarged motor units that preserve functional strength. This process, axonal sprouting and collateral reinnervation, is the body's recursive maintenance response to substrate loss. It operates across a normal human lifetime without crossing into clinical disease because the rate of loss stays within what the compensation architecture can absorb.

ALS is not a different mechanism. It is the same mechanism at a rate the compensation system cannot absorb. As the disease progresses, denervation outpaces reinnervation and compensation fails. Critically, long-term ALS survivors are distinguished not by having less disease but by their ability to maintain a successful compensatory response to denervation over time: slow functional decline is correlated with sustained compensation, rapid decline with compensation failure (Bruneteau et al., 2013).

The failure of compensation in ALS begins before any motor neuron dies. This is the dying-back hypothesis: pathological changes occur at the neuromuscular junction prior to motor neuron degeneration and onset of clinical symptoms (Fischer et al., 2004). NMJ functional deficits appear at least six weeks before motor symptoms in ALS mouse models, while structural deficits follow four weeks later (Fischer et al., 2004). The sequence is precise: function degrades before structure visibly changes.

The specific mechanism of NMJ functional degradation is a decline in transmission quality. The choline acetyltransferase enzyme responsible for synthesizing acetylcholine shows reduced activity in preserved ALS motor neurons at early disease stages (Kato,

1989). The machinery that produces the signal molecule is degrading before the neuron dies, before the junction dismantles structurally. A diminished synaptic fidelity has been documented in spinal motor neurons in ALS models across multiple mutation types (Armstrong and Drapeau, 2013). The signal is failing while the neuron is still alive.

What follows from this transmission quality decline compounds the rate problem. Surviving motor neurons detect weaker signals and increase their firing rate and recruitment threshold to compensate. Motor neurons in ALS patients show significantly higher mean firing rates than controls, consistent with neurodegeneration producing a compensatory increase in motor unit activity (de Carvalho and Swash, 2016). This compensatory hyperexcitability places increased metabolic demand on neurons already under pathological stress, accelerating their own vulnerability. The compensation that maintains function is simultaneously a mechanism that deepens the stress on the neurons performing it.

Crucially, neuromuscular denervation in ALS proceeds independently of motor neuron cell death. When Bax-deficient mice were crossed with mutant SOD1 mice, motor neurons were completely rescued from death, yet neuromuscular denervation still occurred and the disease still developed (Gould et al., 2006). The motor neuron does not have to die for function to fail. The transmission quality at the junction only has to degrade past the point where muscle contraction can be reliably triggered.

The compounding is not linear. Each motor neuron death increases the load on survivors, which accelerates their vulnerability, which accelerates the next death. Each compensatory cycle produces slightly lower quality output than the last, reducing the baseline from which the next compensation begins. Two curves running against each other: degeneration accelerating, compensation capacity depleting. Phenoconversion, the moment clinical disease becomes apparent, is not the beginning of the process. It is the moment the rate of loss crosses the rate of compensation. From that point, decline accelerates because the reserve that was absorbing the loss is already partially spent.

This framing, rate relative to compensation capacity rather than mechanism or presence of disease, is supported by the individual disease literature without having been assembled as a cross-disease framework. The following sections examine whether the same structure holds in Alzheimer's disease, Duchenne muscular dystrophy, and Parkinson's disease, where the biological mechanisms are entirely different but the structural shape may be the same.

2. Alzheimer's Disease: Cognitive Reserve, Synaptic Compensation, and the Threshold Paradox

Alzheimer's disease is characterized by the progressive accumulation of amyloid-beta plaques and tau neurofibrillary tangles, synaptic loss, and eventual neuronal death. Its clinical presentation, memory impairment, cognitive decline, and eventual dementia, has long been understood to emerge late in a pathological process that begins decades earlier. What has been less well understood is why the same degree of neuropathology produces such different clinical outcomes in different individuals, and why those who

delay the onset of symptoms longest often show the steepest decline once symptoms begin.

The cognitive reserve framework, developed across four decades of research, provides a partial answer. In its passive form, brain reserve proposes that individuals with larger brains, more neurons, or greater synaptic density can simply tolerate more pathology before reaching the threshold at which clinical symptoms appear (Satz, 1993). In its active form, cognitive reserve proposes that the brain recruits compensatory processing strategies and alternative neural pathways to maintain cognitive function despite accumulating damage (Stern, 2002). Both forms describe the same structural shape: a system maintaining stability through active compensation while pathology accumulates beneath the clinical threshold.

The synaptic compensation mechanism is documented at the cellular level. As excitatory synapses are lost to Alzheimer's pathology, surviving neighboring synapses enlarge. Electron microscopy studies of postmortem Alzheimer's disease samples show that this enlargement is tightly correlated with the extent of synaptic loss across multiple brain regions, such that total synaptic area in Alzheimer's samples is relatively similar to that of controls (Henstridge, Hyman, and Spire-Jones, *Nature Reviews Neuroscience* 20, 2019). New synapses are generated: dendritic spinogenesis increases in animal models of Alzheimer's disease, with longitudinal live imaging providing direct evidence of compensatory spine formation. The system is not passively degrading. It is actively iterating, cycle by cycle, to maintain the total synaptic area that cognitive function requires.

This is recursive compensation in a cognitive substrate. Each cycle of synaptic loss triggers a compensatory response: enlargement of surviving synapses, formation of new connections, recruitment of alternative neural networks. The brain keeps cognitive function above the clinical threshold not by preventing pathology but by compensating for its effects with each compensatory pass. The quality of this compensation, how completely each cycle restores the functional capacity lost, determines how long the system holds.

The rate framing that clarifies Section 1 applies here with equal precision. The clinical expression of Alzheimer's disease is not determined by the presence of pathology alone but by the rate at which pathology accumulates relative to the compensatory capacity of the system. This is confirmed by the cognitive reserve paradox, one of the most replicated and counterintuitive findings in Alzheimer's research. Individuals with greater cognitive reserve delay the onset of clinical symptoms, tolerating more pathology before reaching the threshold. But once the threshold is crossed, they show steeper and faster cognitive decline than individuals with lower reserve (Stern, 2009; van Loenhoud et al., 2019). Higher reserve delays the crossing but steepens the fall. This phenomenon, termed CR Overload in the threshold model literature (Stern, 2009), reflects a precise mechanistic dynamic that is the paper's own synthesis of the paradox: individuals with greater reserve have been compensating longer and more intensively by the time of threshold crossing, meaning their compensatory reserve is more deeply depleted when clinical disease emerges. The system was further in debt when it crossed.

The compensation quality dimension appears here as well, though in a cognitive rather than motor substrate. At the symptomatic disease stages, excessive interneuronal activity reflecting hypercompensatory function contributes to the accelerated depletion of brain structures (Sidenkova et al., 2024). The compensation mechanism itself, by demanding increased network activity to maintain cognitive output against rising pathological burden, accelerates the very depletion it is compensating for. This is the same compounding dynamic documented in ALS: the recursive maintenance loop generating metabolic stress on the substrate it is attempting to preserve. The quality degradation in Alzheimer's disease is described in terms of compensation efficiency, how completely each cycle restores cognitive function, rather than in information-theoretic terms as in Parkinson's disease. This substrate-specific difference in how quality degrades is addressed in Section 5.

The four-step pattern holds in Alzheimer's disease: early pathological accumulation below clinical detection, active recursive compensation maintaining apparent stability, quality degradation as compensatory load increases, and threshold crossing into clinically manifest disease followed by accelerated decline. The biological mechanisms are entirely distinct from those in ALS. The structural shape is the same.

3. Duchenne Muscular Dystrophy: Asymmetric Division, Repair Quality, and Fibrotic Replacement

Duchenne muscular dystrophy is caused by mutations in the gene encoding dystrophin, a structural protein that anchors the muscle fiber membrane to its surrounding matrix. Without dystrophin, the sarcolemma is mechanically fragile: every muscle contraction causes micro-tears that healthy muscle repairs as a matter of course. In DMD, the repair mechanism activates continuously, cycling against damage that never stops accumulating. The disease is not a failure to repair. It is a failure of the repair system to keep pace with damage, and eventually, a failure of the repair system's own output quality.

Unlike ALS and Alzheimer's disease, DMD is not a disease of the nervous system. Its substrate is skeletal muscle, its compensation mechanism is stem cell-mediated regeneration rather than neural sprouting or synaptic plasticity, and its molecular pathology is structural rather than proteinopathic. That the four-step pattern appears here in an entirely distinct biological system is the paper's most significant cross-substrate observation.

The repair mechanism operates through satellite cells: muscle-resident stem cells located between the sarcolemma and basal lamina. In healthy muscle, satellite cells are activated by damage signals, divide, and produce myogenic progenitor cells that fuse with damaged fibers to repair them. This process, regenerative myogenesis, is the body's recursive maintenance response to membrane injury. Each contraction that tears the membrane triggers a compensatory cycle. For years in DMD, this cycle holds. Muscle function is preserved. The disease accumulates below clinical detection.

The quality of each repair cycle depends on how satellite cells divide. In healthy muscle, division is asymmetric: one daughter cell replenishes the stem cell pool, the other becomes a committed myogenic progenitor that contributes to repair. This asymmetry is the quality control mechanism of the repair cycle, ensuring that each division produces both the repair output needed now and the stem cell reserve needed for future cycles.

In DMD, dystrophin loss impairs this quality at its source. Dystrophin is expressed in satellite cells, where it mediates the establishment of cell polarity required for asymmetric division (Dumont et al., 2015). Without it, impaired cell polarity cues lead to mitotic defects and reduced asymmetric cell divisions. The balance shifts toward symmetric stem cell expansion: more satellite cells, fewer myogenic progenitors (Dumont et al., 2015; Feige et al., 2018). Satellite cell numbers are elevated in DMD muscle, not depleted. The system is not running out of cells. It is producing the wrong cells. Each compensatory cycle generates more stem cells and fewer repair cells than a healthy cycle would. The quantity of the compensatory response increases while its quality, measured as repair output per division event, degrades.

The compounding follows the same shape documented in ALS and Alzheimer's disease. Each repair cycle that produces insufficient myogenic progenitors leaves slightly more unrepaired damage than the previous cycle. Chronic inflammation accumulates around persistently damaged fibers. Myofibroblasts are recruited. Fibrosis begins: scar tissue replacing the contractile muscle that the repair cycle could not fully restore. As fibrosis advances, it occupies space that functional muscle could have used and further degrades the mechanical environment in which satellite cells must operate, producing a compounding loop in which impaired repair generates conditions that further impair repair (Dumont et al., 2015).

The threshold crossing in DMD is the point at which fibrotic replacement outpaces the regenerative capacity of the satellite cell pool. Unlike ALS, where the threshold crossing is marked by the moment denervation exceeds reinnervation capacity, and unlike Alzheimer's disease, where it is marked by the moment pathological burden exceeds cognitive reserve, DMD's threshold crossing is marked by the permanent replacement of contractile tissue with non-contractile scar. Fibrosis is irreversible. Once the threshold is crossed, the compensatory cycle cannot restore what has been lost: not because the satellite cells are exhausted but because the substrate they would repair has been converted into something that cannot be repaired.

The pattern is not random. It follows the load distribution of daily movement, the same principle by which ALS affects the longest and most metabolically expensive axons first. Greater load, faster cycling, earlier quality degradation, earlier threshold crossing.

The four-step pattern holds in DMD through a biological mechanism with nothing in common with ALS or Alzheimer's disease. Early membrane damage below clinical detection, active recursive repair maintaining functional muscle mass, quality degradation as asymmetric division is impaired and repair output decreases per cycle, and threshold crossing as fibrosis replaces the contractile substrate the repair cycle can no longer restore. The substrate is different. The compensation mechanism is different. The molecular pathology is different. The structural shape is the same.

4. Parkinson's Disease: Dopaminergic Compensation, Gain Amplification, and the Noise Threshold

Parkinson's disease is caused by the progressive loss of dopaminergic neurons in the substantia nigra, resulting in depletion of dopamine in the striatum and the characteristic motor symptoms of bradykinesia, rigidity, and tremor. Like the three diseases examined before it, Parkinson's disease becomes clinically manifest only after substantial loss has already occurred, and the reason it remains subclinical for so long is not that the loss is undetected, but that the system compensates for it actively.

The presymptomatic period in Parkinson's disease is long and well-documented. Autopsy studies originally estimated that 70-80% of striatal dopamine is depleted by the time motor symptoms emerge, though more recent functional imaging studies place the figure at 35-45% dopamine transporter loss at early motor presentation, a lower estimate, but still representing substantial loss preceding any clinical detection (Heng et al., *Movement Disorders Clinical Practice* 10, 2023). The precise threshold figure remains contested within the literature. Regardless, the pattern is consistent: significant nigrostriatal degeneration precedes diagnosis, and the gap between biological disease onset and clinical expression is determined by compensation.

The compensation mechanisms in Parkinson's disease operate at multiple levels simultaneously. At the dopaminergic level, surviving neurons increase their firing rate and dopamine synthesis to maintain striatal dopamine content. Dopamine reuptake is downregulated to extend the dwell time of each released molecule. Postsynaptic D2 receptors upregulate their sensitivity to amplify the signal from reduced dopamine levels. These mechanisms together constitute gain amplification: the system turning up the volume on a weakening signal to maintain functional output. For a time, this works. The gain is sufficient to maintain the contrast between background dopamine and phasic dopamine release that the motor system requires to function.

But gain amplification has a ceiling, and this is where Parkinson's disease offers the clearest picture of quality degradation across the four diseases examined. Computational modeling of progressive nigrostriatal denervation demonstrates three distinct mechanisms by which striatal denervation causes breakdown of dopamine signaling (Dreyer, 2014). In the model, as denervation increases past approximately 70-80%, the contrast between baseline dopamine and the functional phasic signal is lost. Beyond this point, the gain is so high that the postsynaptic cascade is persistently activated by random fluctuations in the dopamine baseline (Dreyer, 2014; Navntoft and Dreyer, 2016). The system is no longer reading signal. It is reading noise. Every random fluctuation in background dopamine is interpreted as a meaningful phasic event.

This is the most precisely characterized instance of compensation quality degradation across the four diseases. In ALS, quality degrades as acetylcholine synthesis declines and motor units are overloaded. In Alzheimer's disease, compensation efficiency declines as synaptic plasticity is asked to do more against rising pathological burden. In DMD, repair output quality degrades as asymmetric division shifts toward symmetric stem cell expansion. In Parkinson's disease, signal quality degrades in an information-theoretic sense: gain amplification crosses a threshold at which signal contrast is lost

and noise becomes indistinguishable from signal. The four instances of quality degradation are not the same mechanism. They are the same structural pattern, each expressed through the specific biology of its substrate. Tremor, the hallmark of Parkinson's disease, is the clinical expression of this: involuntary movement generated not by motor command but by background noise amplified past the point of signal coherence.

As in the other diseases examined, the dopaminergic system is not the only compensation operating. A second layer exists: cortical compensation. Clinical severity in Parkinson's disease is determined not only by the degree of striatal dopamine loss but by the capacity of parieto-premotor cortical networks to compensate for basal ganglia dysfunction (Johansson et al., Brain 147, 2024). Patients with equivalent dopamine depletion show substantially different clinical presentations depending on their cortical compensatory capacity. This is the structural parallel to cognitive reserve in Alzheimer's disease: a second compensatory system delaying clinical expression and determining clinical heterogeneity.

Critically, as in ALS, the motor symptoms of Parkinson's disease do not require neuronal death to emerge. Dopamine release defects are observed in multiple Parkinson's disease models in the absence of neurodegeneration, and motor phenotypes have been observed in animal models without cell death (Delic et al., 2023). What is required for motor symptoms is that striatal dopamine content fall below the threshold that compensation can maintain. The quality failure produces the symptoms.

The four-step pattern holds in Parkinson's disease. Early dopaminergic neuron loss below clinical detection, active gain amplification maintaining functional signal contrast, quality inversion as gain amplification exceeds the coherence limit and noise becomes indistinguishable from signal, and threshold crossing as the postsynaptic cascade is persistently activated by background fluctuations. Across four diseases with nothing biologically in common, different substrates, different compensation mechanisms, different molecular pathologies, different affected populations, the recursive compensation structure and its failure mode follow the same shape. The following section examines what this cross-disease consistency implies.

5. A Cross-Disease Structural Framework

The four sections above examine diseases with nothing biologically in common. ALS is a motor neuron disease caused by protein misfolding and axonal transport failure. Alzheimer's disease is a cortical proteinopathy driven by amyloid and tau accumulation. Duchenne muscular dystrophy is a structural membrane disease caused by the absence of a single cytoskeletal protein. Parkinson's disease is a dopaminergic neurodegenerative condition driven by alpha-synuclein pathology. Different substrates. Different compensation mechanisms. Different molecular pathologies. Different affected populations.

Across all four, the trajectory from biological onset to clinical disease follows the same four-step shape.

Step one: substrate loss begins below the threshold of clinical detection. The damage accumulates while the system appears intact. In ALS, NMJ functional deficits precede motor symptoms by weeks; the presymptomatic period in genetic ALS can be measured in years. In Alzheimer's disease, amyloid and tau pathology precede cognitive symptoms by a decade or more. In DMD, membrane fragility and incomplete repair cycles precede clinical weakness while satellite cell counts remain elevated. In Parkinson's disease, dopaminergic neuron loss and NMJ functional deficits both precede motor symptoms by years.

Step two: the system compensates actively. Surviving motor neurons sprout new connections. Surviving synapses enlarge. Satellite cells divide faster. Remaining dopamine neurons increase their firing rate and reuptake is downregulated. In every case, the compensation is not passive tolerance of damage but active iterative cycling: each loss triggers a response, each response buys time, and the response itself costs something.

Step three: the quality of each compensatory cycle degrades. This step is the most substrate-specific of the four, and the paper makes no claim that the degradation follows the same mechanism across diseases. In ALS, transmission quality declines as acetylcholine synthesis machinery degrades and overloaded motor units lose the capacity for precise signal delivery. In Alzheimer's disease, compensation efficiency declines as synaptic plasticity is asked to restore progressively more function against rising pathological burden. In DMD, repair output quality declines as asymmetric cell division gives way to symmetric stem cell expansion, producing more cells and less repair per division event. In Parkinson's disease, signal quality degrades in the information-theoretic sense: gain amplification crosses a threshold at which baseline noise becomes indistinguishable from phasic signal. Four different forms of quality degradation, each expressed through the specific biology of its substrate. The structural pattern, that each compensatory cycle produces less faithful output than the last, is the same.

Step four: the system crosses a threshold and decompensates. In ALS, this is the moment denervation exceeds reinnervation capacity and clinical weakness emerges. In Alzheimer's disease, this is the moment pathological burden exceeds cognitive reserve and clinical dementia emerges. In DMD, this is the moment fibrotic replacement outpaces regenerative capacity and contractile tissue is permanently lost. In Parkinson's disease, this is the moment dopaminergic compensation produces noise rather than signal and motor control becomes impossible to maintain. In each case, the threshold crossing is not the beginning of disease. It is the moment the system can no longer conceal what has been accumulating.

This four-step framework is a structural observation, not a mechanistic claim. It does not assert that ALS and Alzheimer's disease share a pathogenic pathway, or that the compensation mechanisms across diseases are variants of a common process. The claim is more limited: the shape of the trajectory from subclinical accumulation to clinical decompensation is consistent across four biologically distinct diseases, and this consistency warrants a structural name and explicit cross-disease examination.

On the relationship to prior cross-disease work. The most relevant prior framework is the Neurodegenerative Elderly Syndrome hypothesis, which proposes that Alzheimer's disease and Parkinson's disease are different manifestations of a single underlying disease proceeding through a seeding stage, a compensatory stage in which clinical symptoms are silent thanks to compensatory mechanisms, and a bifurcation stage in which the condition becomes clinically distinct (Caligiore et al., 2022). The NES framework is the closest existing work to what this paper proposes. The present paper extends it in two ways: it examines four diseases rather than two, including one non-neurological disease, and it describes the framework through the lens of compensation quality degradation rather than shared molecular pathology. Where the NES framework argues that Alzheimer's and Parkinson's originate from a shared neurodegenerative mechanism that bifurcates during progression, the present paper makes no claim about shared pathogenesis. It claims only that the structural trajectory of compensation and failure is the same, regardless of what the underlying disease is.

On the selection of the four evidence bases. A reviewer will ask why these four diseases and not others. The selection principle is explicit: the four diseases examined here were chosen because each has a well-characterized compensation literature, each compensation mechanism is distinct enough from the others to constitute a genuine cross-substrate comparison, and the set includes one clearly non-neurological disease. ALS, Alzheimer's disease, and Parkinson's disease were chosen because their presymptomatic compensation phases are among the most thoroughly documented in the literature. DMD was chosen because it is not a neurological disease: its compensation mechanism is stem cell-mediated muscle repair, its molecular pathology is structural rather than proteinopathic, and its inclusion tests whether the four-step framework extends beyond the nervous system. It does. This selection introduces a form of bias that should be named: the four diseases examined are the diseases where the compensation literature is best developed. The framework may appear less clean in conditions where compensatory mechanisms are less well characterized.

On the threshold range. In neural systems where the threshold has been quantified, it occurs within a range of 60-80% substrate loss. This figure is drawn from two of the four diseases examined: motor neuron populations in ALS, where clinical weakness typically appears after 50-80% motor unit loss depending on muscle group, and dopaminergic neurons in Parkinson's disease, where the threshold figure is itself contested between the older autopsy-based estimate of 70-80% and the more recent imaging-based estimate of 35-45% at early motor presentation. The other two diseases have qualitative threshold descriptions without quantitative substrate-loss percentages in the literature reviewed here. The 60-80% range is therefore an observation about two neural systems, not a demonstrated cross-disease constant. The redundancy hypothesis, that more redundant systems cross later and less redundant systems cross earlier, proposes an explanation that would account for the observed range. It has not been independently tested.

On the consistency of the quality degradation description across sections. The Parkinson's disease section describes quality degradation in information-theoretic terms, with a computational model providing a precise account of when the signal-to-

noise ratio inverts. The other three sections describe quality degradation in substrate-specific biological terms. These are not the same rigor of description. The Parkinson's case is the most formally characterized. The other three are described in terms that are consistent with quality degradation but do not carry the same computational precision. This is an honest limitation of what the literature currently offers for each disease. The four instances are a family resemblance, not a unified formal variable.

6. Limitations

We acknowledge seven limitations of this paper, ordered by significance.

The framework is structural, not mechanistic, and structural similarity does not imply shared causation. The four-step pattern documented here, presymptomatic accumulation, active recursive compensation, quality degradation across cycles, and threshold crossing into decompensation, appears across four evidence bases. We have not demonstrated that a single mechanism produces this shape across cases. It is possible that each disease follows this trajectory for entirely independent reasons, and that the shared formalism describes a family of phenomena without explaining any particular instance. The paper's contribution is diagnostic. The mechanistic account is the work of subsequent papers.

The quality degradation descriptions are a family resemblance, not a unified variable. The four instances of compensation quality degradation documented in this paper are substrate-specific: acetylcholine synthesis decline in ALS, compensation efficiency decline in Alzheimer's disease, asymmetric division accuracy decline in DMD, and signal-to-noise inversion in Parkinson's disease. These are not the same mechanism described four times. They are four different mechanisms that share the structural property of producing less faithful compensatory output per cycle as load increases. The Parkinson's disease case is the most formally characterized. The other three are described in biological terms consistent with quality degradation but without equivalent computational precision. This asymmetry reflects the state of the literature. A future paper specifying the quality degradation variable formally across substrates would either unify these descriptions or confirm that they are irreducibly substrate-specific.

The threshold range is grounded in two neural systems and does not extend to muscular disease. The 60-80% substrate loss range is drawn from two neural systems: motor neuron populations in ALS and dopaminergic neurons in Parkinson's disease, where the figure is itself contested. The Alzheimer's disease threshold crossing is described qualitatively, and while synaptic loss of 25-36% is measurable at early clinical stages, this represents a floor at clinical presentation rather than total accumulated loss since disease onset. A clean quantitative threshold percentage is not available in the Alzheimer's literature as reviewed here. The muscular dystrophy literature presents a more complex picture. Across over thirty distinct muscular dystrophies, the threshold crossing point varies by decades. DMD patients become wheelchair-dependent before age 13. BMD patients, caused by the same gene with partial dystrophin preservation, typically remain ambulatory into their thirties and beyond. Facioscapulohumeral dystrophy patients remain ambulatory throughout their lives in approximately half of

cases. This variation across the muscular dystrophy family is consistent with the redundancy hypothesis but the literature does not provide quantitative substrate-loss percentages at clinical threshold crossing comparable to the neural disease data. The 60-80% range should be read as an observation about two quantified neural systems, not a cross-disease constant.

The evidence base was selected from well-characterized diseases. The four diseases examined were chosen because each has a well-developed compensation literature. DMD was chosen specifically because it is not a neurological disease: its non-neural substrate makes it the strongest cross-substrate test of the framework, and its four-step pattern is the most clearly documented of the muscular diseases. This selection introduces a form of bias: the framework appears coherent across the best-characterized cases because those are the cases where the compensation story has been worked out in sufficient detail to test it. Whether the framework holds in degenerative conditions with less well-characterized compensation phases is not known.

Huntington's disease poses a direct challenge to the redundancy hypothesis. Huntington's disease is caused by a CAG trinucleotide repeat expansion in the HTT gene. Above approximately 40 repeats, the disease is fully penetrant. The redundancy hypothesis predicts that threshold location should vary with system architecture. In HD, the threshold is set by repeat length with high predictability, not by the compensatory architecture of the individual. There is a presymptomatic period and an active compensation phase in HD, and striatal medium spiny neurons show compensatory changes before clinical onset. But the threshold is more tightly genetically constrained than the redundancy framework would predict. This is a genuine challenge the paper does not resolve. HD was considered as a fifth evidence base and excluded because its threshold behavior does not cleanly fit the redundancy hypothesis, and including it without resolving the challenge would have weakened the framework's internal consistency. That exclusion should be named rather than concealed.

Glaucoma was considered and excluded. Glaucoma involves progressive retinal ganglion cell loss, a presymptomatic period during which early RGC changes accumulate before visual field loss becomes detectable, and a compensation mechanism in which RGC dendritic fields prune and surviving cells take on broader receptive territory before cell death. The four-step pattern appears consistent with glaucoma. It was excluded because the compensation literature is less developed than in the four diseases examined, and because the paper's cross-substrate argument is strengthened by including one clearly non-neurological disease rather than adding a fourth neurological one. Glaucoma is a candidate for examination in subsequent work.

The framework has not been tested prospectively, and its falsification condition is explicit. Every claim in this paper is drawn from existing literature. The framework generates predictions: that the four-step pattern should appear in other progressive degenerative conditions with active compensation phases, including chronic traumatic encephalopathy, frontotemporal dementia, and multiple system atrophy; that systems with greater redundancy should show later threshold crossings and steeper post-crossing decline; and that interventions which extend compensation quality rather than

simply slowing substrate loss should delay threshold crossing more effectively than interventions targeting substrate loss rate alone. None of these predictions have been tested. What would falsify the framework is explicit: a degenerative condition that meets the preconditions, progressive substrate loss, active compensation, finite redundancy, but does not follow the four-step trajectory would disconfirm it. A disease in which clinical symptoms appear at substrate loss onset rather than after a presymptomatic compensation phase, or a disease in which compensation quality does not degrade under load but maintains constant fidelity until the substrate is exhausted, would require the framework to be revised or abandoned. The paper does not claim the four-step pattern is universal. It claims it is consistent across four examined cases and proposes that the consistency warrants further examination.

7. Conclusion

This paper claimed three things. That the trajectory from biological disease onset to clinical manifestation follows the same four-step shape across four biologically distinct degenerative diseases. That this shape, presymptomatic accumulation, active recursive compensation, quality degradation across cycles, and threshold crossing into decompensation, is consistent enough across ALS, Alzheimer's disease, DMD, and Parkinson's disease to warrant a structural name and explicit cross-disease examination. And that the mechanism connecting substrate loss to decompensation is a degradation in the quality of each compensatory cycle, not merely a reduction in its quantity, though the form of quality degradation is substrate-specific and not unified across the four cases.

Each of those claims was earned within the scope of the evidence presented. The paper did not claim that the four diseases share a common pathogenic mechanism. It did not claim that the 60-80% threshold range extends beyond the two neural systems where it has been quantified. It did not claim that the quality degradation variable is formally unified across substrates. What it claimed was a structural pattern, a family of evidence supporting that pattern across genuinely distinct biological systems, and an honest account of what the evidence does and does not establish.

The contribution is diagnostic rather than explanatory. The existing literature in each disease field has described its own version of the compensation-and-failure trajectory without recognizing it as an instance of the same structural shape. The NES framework unified Alzheimer's and Parkinson's disease through shared molecular pathology. The cognitive reserve paradox named the threshold-steepening effect in Alzheimer's disease. The dying-back hypothesis and compensation-failure model named key elements of the ALS trajectory. The satellite cell fidelity literature named the quality degradation mechanism in DMD. This paper assembles those descriptions into a single framework and asks whether they are instances of the same thing.

The answer the evidence supports is: structurally, yes. Mechanistically, the question remains open.

Four diseases with nothing biologically in common share one structural shape, across four cases where the compensation architecture has been well enough characterized to

test it. Whether the shape holds in the broader space of degenerative disease, and what it implies about where interventions should be targeted, is the work the framework points toward.

The mechanism that produces the quality degradation across compensatory cycles, and the empirical test of whether that mechanism can be characterized formally across substrates: those are earned in the papers that follow.

Footnote — April 2026

The quality degradation documented in this paper, the progressive decline in the output quality of each compensatory cycle under degenerative load, points toward a formal gap in a companion body of work on recursive consolidation in learning systems. That work introduces a consolidation operator P responsible for deepening representational stability across recursive cycles. The mathematical specification of P was identified as the primary open problem in that framework.

The present paper approaches P from the opposite direction. Where learning systems show P building depth with each recursive pass, degenerative systems show P losing depth: the same operator, running in reverse under conditions of substrate loss and quality degradation. The NMJ losing acetylcholine synthesis quality. The satellite cell losing asymmetric division accuracy. The dopaminergic system amplifying gain past the point of signal coherence.

The biology documented here suggests a complementary direction for that framework to develop: not just how depth is built, but how it is lost, and whether the mathematics governing both directions is the same. That paper is not this one. This footnote is a placeholder for where the two bodies of work eventually meet.

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