THE FADING SCORE

Epigenetic Erosion, the Metabolic Ink of the Genome, and the Reversible Information Layer of Alzheimer's Disease Across the Temporal Architecture

Metabolic Ink · The Drifting Clock · The Trained Microglion
The Derepressed Genome · The Silenced Synapse

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Companion to The Senescent Front — the second of the two "cell biology of ageing" cross-sections through the temporal arc. Where senescence named the cell-state ageing drives cells into, this volume names the reversible information layer — the epigenome — whose corruption drives them there.

"The genome is the notes; the epigenome is how they are played. Alzheimer's is not a disease of the notes but of the playing — a score whose annotations fade until the orchestra forgets, decade by decade, how the music was meant to be read. And a score, unlike a lost instrument or a fallen player, can be marked again."

— ONS Methodology Working Notes, 2026

For Conrad Hal Waddington, who first drew the epigenetic landscape, and for Bess Frost, who found the loosened chromatin and the waking of the dark genome.

THE COLLAPSE TRILOGY CROSS-SECTIONAL COMPANION

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

— The Temporal Architecture of Collapse —

Cross-sections: The Vascular Phasing · The Genetic Architecture · The Viral Trajectory

The Biomarker Cascade · The Spectrum of Collapse · The Senescent Front

The Fading Score ← this volume

This volume is the seventh cross-section through the temporal arc, and the twin of the sixth. Together, *The Senescent Front* and *The Fading Score* form the pair that supplies the cell biology of the word *ageing* the architecture rests upon: senescence is the cell-*state*, epigenetic erosion the *information loss* beneath and upstream of it. The two weld most tightly at the second bridge, where heterochromatin loss derepresses the dark genome's transposons, whose interferon *is* the senescent secretome's engine — epigenetics not merely related to senescence, but its cause.

Contents

Abstract

The companion volume to this one, *The Senescent Front*, argued that cellular senescence is the cell biology of the word *ageing* that the Temporal Architecture of Collapse invokes at every station but never mechanizes. The present volume descends one layer further, from the cell's *state* to the cell's *information*. Beneath the senescent state, and upstream of it, lies the layer that decides which of a neuron's twenty thousand genes it reads and which it keeps silent — the epigenome: the pattern of DNA methylation, histone modification, and three-dimensional chromatin folding that is written not in the genetic sequence but on top of it, and that, unlike the sequence, is rewritten continuously throughout life. This dissertation proposes that Alzheimer's disease is, at its most fundamental molecular level, a disease of this information layer — a progressive corruption of the epigenetic score by which the genome is read — and it maps that corruption, mark by mark and decade by decade, onto the five stations of the temporal architecture.

Three properties make the epigenome the right lens for a disease of ageing, and each yields a station of the map. First, the epigenome is *written in metabolic ink*: every enzyme that lays down or erases an epigenetic mark is a metabolic sensor, running on NAD+, acetyl-CoA, S-adenosylmethionine, or α-ketoglutarate — the very metabolites whose collapse defines **Phase I**. The bioenergetic ignition in the locus coeruleus is therefore, of necessity, an *epigenetic* ignition, because when the cofactors fail the score can no longer be maintained; the sirtuins, NAD+-dependent deacetylases guarding heterochromatin, are the hinge. Second, the epigenome is the layer that *stores identity and memory* — which is why **Phase III**, synaptic disintegration, is at the molecular level an epigenetic silencing of the plasticity gene programme (the HDAC2 "blockade of cognition" of Gräff and Tsai) and a dissolution of neuronal identity as pathological tau physically relaxes the chromatin of the vulnerable neuron (the chromatin-restructuring pathology of Bess Frost). Third — and this is the connection the reader was promised — the erosion of heterochromatin *derepresses the transposable elements* (LINE-1, HERV-K) buried in the dark genome, whose reactivation floods the cytoplasm with nucleic acids that trip the cGAS–STING and RIG-I sensors, ignite a type I interferon response, and drive the very senescence-associated secretome the companion volume described. Epigenetic erosion is thus not merely *related* to senescence; at the second bridge it is senescence's engine. The **two bridges** of the architecture are recast accordingly — the first as the forward drift of the epigenetic clock carried on a tau seed that is itself a chromatin corruptant, the second as the derepressed genome discharging its interferon onto the perineuronal net.

We grade the mapping without flattery. Two confounds haunt every epigenetic claim in post-mortem brain — the *cell-composition* artifact, by which an apparent change in a mark is really a change in which cells are present, and *reverse causation*, by which marks shift because neurons are dying rather than driving the death — and a full section is given to a validity ledger that weights each connection against them. The HDAC2 and tau-chromatin links are strong and causal; the epigenetic-clock and methylation-association links are robust but correlational

and composition-confounded; the information-theory and reprogramming claims are provocative, mouse-bound, and carry real oncogenic risk. But even under honest grading the lens earns its place, for it supplies the one thing no substance-theory of Alzheimer's can: a dimension of the disease in which the damage is *information rather than structure*, and therefore, in principle, recoverable — the epigenetic clock its odometer, the reactivated transposon its most druggable lesion, and the rewriting of the score, not the replacement of the cell, its most radical therapeutic hope.

I. The Layer the Genome Cannot Explain

A disease of reading, not of text

The genome a person carries in their eighth decade is very nearly the genome they carried in their third. Somatic mutation accumulates in the brain, and it matters, but it cannot carry the weight of a disease that transforms the expression of thousands of genes in a stereotyped, regionally ordered, decades-long sequence. Something changes across those fifty years that is not the text of the genome but the *reading* of it — which genes a cell transcribes and which it silences, cell type by cell type, as the disease advances. That reading is governed by the epigenome: the covalent methylation of cytosine bases, the dozens of modifications decorating the histone proteins around which DNA is wound, the folding of the chromatin fibre into the loops and domains that bring enhancers to their genes, and the small and long non-coding RNAs that tune the whole. The epigenome is the annotated score laid over the fixed notes of the sequence — the instructions for how loudly, and when, and in which cell, each gene is to be played.

Alzheimer's disease is a disease of this score. The Temporal Architecture of Collapse has already told us, without quite saying so, that it must be: a process whose "primary" molecule changes from decade to decade, whose lesion is metabolic in one cell population and immunological in the next and structural in the third, is not a process of altered genetic text but of altered reading, propagated forward until the reading itself becomes self-sustaining. The KB's own transcriptional–epigenetic node states the endpoint plainly — *once the transcriptional programme shifts, the disease becomes self-reinforcing at the epigenetic level, independent of the original triggers.* This dissertation takes that sentence as its thesis and asks where, and how, and how reversibly, the score is corrupted across the arc of the disease.

From state to information

The Senescent Front located the disease in the cell's *state* — the stable, secretory, aged-out condition into which neurons, microglia, astrocytes, and vessels fall in succession. The present volume locates it one layer beneath, in the cell's *information*. The relation between the two is not rivalry but depth: a cell becomes senescent because its epigenome has drifted — heterochromatin lost, transposons derepressed, the identity programme corrupted — and once senescent it entrenches that drift, so that state and information wind each other tighter. Where senescence is the phenotype of ageing made cellular, epigenetic erosion is the mechanism of ageing made informational; and because information, unlike a phenotype and unlike a mutation, can be rewritten, the epigenetic layer is the one at which the disease exposes its single recoverable face. The chapters that follow trace the corruption of the score across the five stations, and then ask, in the ledger and the therapeutics, how much of the honest evidence supports reading Alzheimer's as a disease of information — and what follows for the clinic if it is.

II. The Epigenome, and How Honestly We Read It in the Brain

The marks, and the clock

The epigenetic score is written in four hands. *DNA methylation* — the addition of a methyl group to cytosine, most often at CpG dinucleotides — is the most stable mark and the one from which the ageing "clocks" are read; its oxidised derivative, 5-hydroxymethylcytosine, is unusually abundant in neurons and marks active demethylation. *Histone modification* — acetylation, methylation, phosphorylation, ubiquitination at specific residues — sets the local accessibility of chromatin: H3K9me3 and H3K27me3 compact it into silent heterochromatin, while H3K27ac and H3K4me3 mark active enhancers and promoters, and H4K12ac and H3K9ac ride with memory and plasticity. *Three-dimensional architecture* — the folding of chromatin into topologically associating domains and loops by cohesin and CTCF — determines which enhancer reaches which gene, and its erosion scrambles the reading without altering a single mark. And *non-coding RNA* — microRNAs such as miR-134 and let-7, and the long non-coding transcripts — tunes the output post-transcriptionally. From the first of these, Horvath and others built the epigenetic clocks: weighted panels of methylation sites whose collective state tracks chronological age so closely that the residual — the gap between a tissue's methylation age and its calendar age — has become a leading quantitative measure of biological ageing itself.

The two confounds, stated up front rather than buried

Honesty about the brain epigenome requires placing two methodological hazards at the front of the argument, exactly as the companion volume placed the marker-overlap problem at the front of the senescence case — because the entire enterprise rises or falls on them. The first is *cell-composition confounding*. Almost all human brain epigenomics is performed on bulk tissue, a mixture of neurons, microglia, astrocytes, oligodendrocytes, and vascular cells whose proportions shift dramatically as the disease kills neurons and expands glia. An apparent "hypermethylation of gene X in Alzheimer's cortex" may therefore reflect not a changed mark in any cell but a changed census of cells — fewer neurons, more microglia, each carrying its own baseline. Single-nucleus methods are only now dissolving this confound, and much of the older literature cannot be cleared of it. The second hazard is *reverse causation*. Post-mortem tissue is end-stage, and a mark that differs in the diseased brain may have shifted *because* the neuron was sick — because tau had already gathered, because the cell was already dying — rather than as a driver of that sickness. A methylation difference is a correlation until an intervention shows that changing the mark changes the outcome. These two confounds are the reason the validity ledger of Section X grades the causal, interventional findings (HDAC2 knockdown rescuing memory; transposon suppression rescuing neurons) far above the associational ones (an epigenetic clock that runs fast, a CpG that differs), and the reader is asked to hold every mechanistic claim below against them.

III. The Epigenetic Map in Brief

Read across the five stations of the temporal architecture, the disease resolves into a succession of epigenetic lesions, each with a characteristic mark, a characteristic cause, and a characteristic effect on the station that follows.

Phase I — Metabolic Ink. *Decades 3–5. Locus coeruleus and brainstem aminergic neurons.* The lesion is a failure of epigenetic *maintenance*: as NAD+, acetyl-CoA, and S-adenosylmethionine fall, the sirtuins and other metabolite-dependent enzymes can no longer hold heterochromatin and the methylome in place, and the epigenetic clock begins to accelerate in the brain's first-failing cell. *Grade: mechanistically strong, regionally inferential.*

The Drifting Clock (Phase I → II). *The ascending LC projection.* The forward arm is epigenetic drift itself — and the tau seed the projection carries is, per Frost, a chromatin-relaxing agent, so the seed delivers not only a template but an epigenetic corruptant. *Grade: emerging; tau-chromatin link strong, its packaging onto the seed a synthesis.*

Phase II — The Trained Microglion. *Decades 6–7. Hippocampal and forebrain microglia.* The lesion is an epigenetic *state transition*: the enhancer landscape maintaining homeostatic microglial identity collapses, and innate-immune "training" writes a lasting, chromatin-encoded memory that biases the cell toward pathology. Early Alzheimer epigenomic change concentrates in immune, not neuronal, enhancers. *Grade: strong in model systems.*

The Derepressed Genome (Phase II → III). *The aggrecan–brevican sheath, via the interferon response.* Heterochromatin loss derepresses LINE-1 and HERV-K transposons; their nucleic acids trip cGAS–STING and RIG-I; the resulting type I interferon is the senescence-secretome's inflammatory arm feeding the Proteolytic Turn. *Grade: moderate; the tightest epigenetics–senescence weld.*

Phase III — The Silenced Synapse. *Decade 8+. Cortical and hippocampal neurons.* The lesion is epigenetic *silencing and identity loss*: HDAC2 clamps the plasticity gene programme shut, memory-associated acetylation is lost, and tau-driven chromatin relaxation dissolves neuronal identity, driving aberrant cell-cycle reentry and death. *Grade: strong and partly causal.*

The current beneath — information loss. Running under all five stations is a single principle: the epigenome is an archive being corrupted, the clock is its odometer, and because the information is mis-read rather than destroyed, the corruption is in principle reversible — the disease's one recoverable dimension. *Grade: provocative; strong in mice, unproven in human brain.*

The map has three properties worth naming in advance. It is *mark-sequential* — a different epigenetic lesion is load-bearing in each decade, which is why no single epigenetic mark explains the whole disease. It is *reversibility-graded* — the lesions differ in how recoverable they are, from the freely rewritable acetylation of Phase III to the more entrenched methylation drift of the clock. And it is *senescence-coupled* — most tightly at the second bridge, where the derepressed genome is at once an epigenetic lesion and the senescent secretome's engine. It is that coupling, more than any single mark, that makes this volume the true companion of the last.

IV. Phase I Metabolic Ink

The epigenome is written in the metabolites that fail first

The deepest and least appreciated fact about the epigenome is that it is not maintained for free. Every enzyme that writes or erases an epigenetic mark is, of biochemical necessity, a consumer of a central metabolite, and therefore a sensor of the cell's metabolic state. DNA methyltransferases transfer a methyl group from S-adenosylmethionine, the universal methyl donor generated by one-carbon and folate metabolism. Histone acetyltransferases acetylate lysines using acetyl-CoA, the hub metabolite of mitochondrial and cytosolic energy flux. The sirtuin deacetylases strip those acetyl groups only in the presence of NAD+, which they consume stoichiometrically. The TET and Jumonji-domain demethylases that erase methylation require α-ketoglutarate and molecular oxygen. The epigenome, in other words, is written in metabolic ink — and the ink is precisely the set of molecules whose depletion the temporal architecture places at the ignition of the disease.

This yields the first and, I think, most consequential claim of the epigenetic mapping. The bioenergetic ignition of Phase I — the NAD+ collapse, the mitochondrial failure, the metabolic scarcity of the locus-coeruleus neuron — is not merely *accompanied by* epigenetic change; it *causes* it, unavoidably, because the enzymes that maintain the epigenome run on the very cofactors that are failing. A neuron that cannot keep its NAD+ pool cannot power its sirtuins; a neuron that cannot make acetyl-CoA and S-adenosylmethionine cannot maintain the acetylation and methylation landscape that defines its identity. The metabolic ignition is an epigenetic ignition. The two accounts — the bioenergetic and the epigenetic — are not competitors for the primacy of Phase I; they are the same event described from the direction of the failing mitochondrion and from the direction of the drifting mark.

The sirtuins as the hinge

If one enzyme family embodies the coupling it is the sirtuins. Imai and Guarente's founding discovery was that Sir2, the yeast longevity protein, is an NAD+-dependent histone deacetylase — a single molecule that reads the cell's energetic currency and writes the chromatin's silence, coupling metabolism to the epigenome in one active site. In the mammalian brain SIRT1 and SIRT6 maintain heterochromatin, restrain inflammatory transcription, and support the DNA-damage response; SIRT6 in particular guards against exactly the LINE-1 derepression that the second bridge will turn against the brain. When NAD+ falls in the Phase I neuron — drained by PARP-1 hyperactivation on accumulating DNA damage, as the bioenergetic thesis details — the sirtuins fail first, and their failure is the molecular moment at which metabolic scarcity becomes epigenetic erosion. This is also the exact hinge the companion volume identified for senescence, whose NAD+ collapse and whose SASP both turn on the same node. Phase I is where the bioenergetic, the epigenetic, and the senescent readings of the disease become, at the sirtuin, literally one biochemistry.

The clock begins in the brainstem

The epigenetic clock is a whole-tissue measure, but its acceleration must begin somewhere, and the logic of the architecture places its earliest inflection in the same nucleus that fails first. The locus-coeruleus neuron — autonomously pacemaking, maximally arborized, catecholaminergic and therefore self-oxidising — is the cell least able to maintain its metabolic ink, and so the cell in which the methylome should first drift out of true. That the clocks read accelerated in Alzheimer's brain and blood is established; that the acceleration is seeded in the brainstem aminergic neurons decades before it is measurable in cortex is the mapping's prediction, and a testable one. The silence of Phase I, in the epigenetic reading, is the silence of a score whose annotations are quietly fading while the notes still play in tune — the loss not yet of the music but of the instructions for keeping it.

V. The First Bridge The Drifting Clock

The architecture's first bridge carries the disease from a brainstem metabolic affair to a forebrain immune one along the ascending locus-coeruleus projection, on two arms: the withdrawal of the noradrenergic brake on microglia and the trans-synaptic seeding of templated tau. The epigenetic lens leaves the first arm to the senescence and homeostatic accounts and concentrates on transforming our understanding of the second — because the tau that this projection seeds is, on the evidence of Bess Frost's programme, not merely a misfolding template but an agent of chromatin corruption, and this changes what the bridge delivers.

Tau as a chromatin-relaxing corruptant

Frost's central discovery is that pathogenic tau drives neurodegeneration in significant part *through the genome*. Tau over-stabilises the F-actin cytoskeleton; the rigid cytoplasm transmits mechanical force through the LINC complex — the SUN and Nesprin proteins that span the nuclear envelope — into the nucleus itself, invaginating the envelope and depleting Lamin B1. The loss of the lamina releases the constitutive heterochromatin tethered to it, H3K9me3 and its reader HP1 are lost, and chromatin that a neuron had kept silent for a lifetime relaxes open. This is a physical, mechanical route from a cytoplasmic protein to the three-dimensional epigenome, and it makes tau a *reader-corruptant*: wherever the seed propagates, it does not only template further misfolding, it relaxes the host neuron's chromatin. The implication for the bridge is exact. The trans-synaptic tau that the coeruleus delivers to the hippocampus carries, as an intrinsic property of what tau does, the capacity to erode the recipient's heterochromatin — so the seeding arm is simultaneously an epigenetic-corruption arm, and the forebrain receives, in one cargo, both a propagating template and a chromatin-loosening force.

Drift as the forward signal, and the honest limit

The bridge's forward-carried quantity, in the epigenetic reading, is *drift* — the accumulating divergence of the methylome and the histone landscape from their youthful set-points, beginning in the coeruleus and advancing with the projection. Drift is a gentler word than lesion, and deliberately so: much of what the epigenetic clock measures is stochastic erosion rather than a programmed change, an accumulation of noise in the score rather than a rewriting of it, and it is the transition from noise to a self-reinforcing new programme that the bridge accomplishes. The honest limit must be marked here as it was in the companion volume. That tau relaxes chromatin is strongly evidenced in fly, mouse, and human tissue; that this relaxation is *packaged onto the seed* and delivered trans-synaptically as a coordinated epigenetic-plus-templating cargo is a synthesis this dissertation proposes, coherent with the mechanism but not yet demonstrated as a single delivered event. The bridge is real, and tau's chromatin pathology is real; their union on the coeruleus axon is the plank still being laid.

VI. Phase II The Trained Microglion

Phase II is the collapse of homeostatic microglial identity in the hippocampus, and identity, for a cell, is an epigenetic quantity — a landscape of active and silent enhancers that holds the cell in its state. The epigenetic reading of Phase II is therefore that the microglial collapse is, mechanistically,

an epigenetic *state transition*, and that its most disease-specific feature is a form of chromatin-encoded *memory*.

Identity is an enhancer landscape

The homeostatic microglial signature that Butovsky showed to be maintained by TGF-β/SMAD signalling is not a list of proteins but a configuration of chromatin — the transcription factor SALL1 and the SMAD effectors holding open the enhancers of P2RY12, TMEM119, and their companions while keeping the inflammatory enhancers shut. When that signalling fails under the chronic stress of Phase II, the failure is read out as an enhancer switch: the homeostatic enhancers close, the disease-associated enhancers — APOE, CST7, ITGAX, the cathepsins — open, and the cell transitions to the DAM and lipid-droplet states. The disease-associated microglion is thus an *epigenetically reprogrammed* cell, and the transition the architecture describes as a loss of homeostatic identity is, at the chromatin, a redrawing of the enhancer map. Gjoneska and Tsai's landmark epigenomic comparison of mouse and human Alzheimer's brain found precisely this: the activated regulatory regions in the disease are enriched not in neuronal but in *immune* genes, and the earliest epigenomic signal of the disease is written in the enhancers of the microglion, not the neuron.

Trained immunity as chromatin memory

The most striking epigenetic feature of Phase II has no analogue in the substance-theories of the disease: innate-immune *memory*. Wendeln, Neher, and Heneka showed that a peripheral inflammatory stimulus leaves a lasting mark on brain microglia — an altered landscape of H3K4me3 and H3K27ac that persists for months and biases the cell's later response, so that "trained" microglia exacerbate and "tolerised" microglia mitigate subsequent amyloid pathology. This is Pavlovian conditioning written in chromatin: the microglion remembers an inflammatory episode long after the stimulus is gone, and the memory is epigenetic. It supplies the mechanism by which the diffuse life-history of infection and inflammation that the viral and microbial cross-sections describe is *recorded* in the brain's immune cells and carried forward to shape the disease decades later. Phase II is not only the collapse of an identity; it is the laying down of a maladaptive immune memory, and both are epigenetic events. The microglion that consolidates the hippocampal bridgehead is a reprogrammed and a conditioned cell at once.

VII. The Second Bridge The Derepressed Genome

The architecture's second bridge, the Proteolytic Turn, discharges the accumulated pathology of Phase II onto the perineuronal net through three arms — a matrix-metalloproteinase switch,

iron-catalysed Fenton chemistry, and complement priming. The senescence volume recognised these three arms as canonical outputs of the senescence-associated secretory phenotype. The epigenetic volume now supplies the deepest of those outputs' *origins*, and in doing so welds the two theories together: the inflammatory, interferon-driven core of the SASP is ignited by an epigenetic lesion — the derepression of the genome's dark repetitive elements.

Heterochromatin loss unlocks the dark genome

Nearly half of the human genome is repetitive, and much of it is transposable — LINE-1 retrotransposons, endogenous retroviruses such as HERV-K, Alu elements — sequences that a healthy cell keeps permanently silenced under dense H3K9me3 heterochromatin and cytosine methylation. This silencing is not gratuitous: a derepressed LINE-1 is a molecular parasite that transcribes itself, reverse-transcribes its RNA into cytoplasmic DNA, and can reinsert into the genome. The heterochromatin loss that tau drives in Phase I and III, and that the sirtuin failure of Phase I permits, lifts this ancient repression. Frost's programme documents the consequence directly in the Alzheimer brain: LINE-1 and HERV-K elements reactivate, and her 2025 long-read sequencing of the "dark genome" finds elevated AluY retrotransposon insertions in late-stage disease and DNA demethylation across the centromeric and ribosomal-DNA regions that repetitive silencing normally protects. The disease reads, and re-inserts, the parts of the genome that ageing was supposed to keep shut.

Viral mimicry is the interferon arm of the SASP

The reactivated transposon's nucleic acids are the pivot on which epigenetics becomes inflammation. Cytoplasmic transposon DNA is sensed by cGAS, activating STING; transposon double-stranded RNA is sensed by RIG-I and MDA5; both routes converge on a type I interferon response — the cell mounts an antiviral defence against a virus that is its own derepressed genome. Frost names this *viral mimicry*, and it is the precise molecular event that De Cecco and colleagues, working from the senescence side, identified when they showed that LINE-1 activation drives the interferon component of the senescence-associated secretory phenotype and the age-associated inflammation it propagates. The two literatures describe one mechanism from two directions: heterochromatin erosion (the epigenetic lesion) derepresses transposons (the dark-genome event) that trip innate nucleic-acid sensors (the immune event) to produce type I interferon and the inflammatory SASP (the senescent output). This is the second bridge's deepest arm — the interferon that primes complement, licenses the proteolytic switch, and inflames the microenvironment of the perineuronal net is, at its origin, the alarm a neuron sounds against its own unsilenced genome. Epigenetic erosion is not adjacent to senescence here. It is its cause.

VIII. Phase III The Silenced Synapse

Phase III is the disintegration of the synapse and the collapse of the inhibitory network into dementia. Every prior reading of this phase has been structural or electrical; the epigenetic reading is that the terminal event is also, and fundamentally, a *silencing* — the epigenetic clamping-shut of the gene programme that builds and maintains synapses, and the dissolution of the neuronal identity that reading depends on.

The HDAC2 blockade of cognition

The single most causally demonstrated epigenetic lesion in the disease belongs to the Tsai laboratory. HDAC2, a histone deacetylase, represses the promoters of the synaptic-plasticity and learning genes — the immediate-early genes, the glutamate-receptor subunits, the structural components of the spine. Guan and colleagues showed that HDAC2, not its near-twin HDAC1, negatively regulates memory and synapse number; Gräff and colleagues then showed that in the neurodegenerating brain HDAC2 is elevated and settles onto exactly these plasticity promoters, stripping their activating acetylation and imposing what they named an *epigenetic blockade* of cognition. The blockade is the molecular form of Phase III's synaptic silence: the genes required to sustain and repair the synapse are present, intact, and shut. And it is, decisively, *reversible* — knocking HDAC2 down, or inhibiting it pharmacologically, restores the acetylation, reopens the genes, regrows the synapses, and recovers the memory in mice, as Fischer and colleagues first showed with environmental enrichment and HDAC inhibition. The plasticity programme is not destroyed. It is repressed, and repression can be lifted.

Identity loss and the self-reinforcing lock

Alongside the silencing runs Frost's identity pathology, now at its terminal cell. As tau relaxes the chromatin of the vulnerable cortical neuron, the cell loses the heterochromatic silencing that defines its post-mitotic neuronal identity; genes proper to other cell types and to the cell cycle are inappropriately derepressed, the neuron makes a doomed attempt to re-enter a cycle it cannot complete, and it dies. The loss of H4K12ac that Peleg tied to age-dependent memory failure, and the dysregulation of H3K9ac and H3K27ac that Nativio and Berger mapped across the transition from normal ageing to Alzheimer's, fill in the mark-level detail of a cortex whose neurons are simultaneously being silenced where they should speak and derepressed where they should be quiet. And here the transcriptional–epigenetic node's warning comes due: once this programme is written — the plasticity genes clamped, the identity genes relaxed, the inflammatory and interferon enhancers held open — the disease is *self-reinforcing at the epigenetic level, independent of its original triggers.* The score has not merely faded; a new and pathological score has been written over it, and the orchestra now plays the disease from memory. This epigenetic lock is why Phase III does not reverse when the upstream insults are removed, and why the crossing into dementia behaves like a threshold rather than a slope.

IX. The Current Beneath Information, Not Substance

The temporal architecture argues that beneath its five stations runs one failing system; the senescence volume named that current the SASP and its NAD+ sink. The epigenetic volume names it one layer deeper still, and in doing so states the disease's most radical reframing: the current beneath the sequence is the progressive *loss of epigenetic information*.

The frame is Sinclair's, and it is worth stating precisely because it is both powerful and contestable. The information theory of ageing holds that the genome stores *digital* information — the sequence, robust and faithfully copied — while the epigenome stores *analogue* information — the pattern of marks that specifies cellular identity and function, which has no error-correcting backup and therefore degrades as noise accumulates. Ageing, on this view, is the loss of the analogue information: the cell forgets which genes it is supposed to read, not because the genes are damaged but because the annotations telling it what to do have blurred. Sinclair's ICE mouse supplies the startling experimental core — inducing benign double-strand breaks that leave the sequence intact but force the repair machinery to repeatedly relocate chromatin factors accelerates the epigenetic clock and produces the phenotypes of ageing *without a single mutation* — and the still more startling counterpart is that partial reprogramming with the Yamanaka factors OSK, which rewrites the

epigenome toward its youthful configuration, can *reverse* those phenotypes and, in Lu and colleagues' work, restore vision to aged and injured neurons. Ocampo and Izpisúa Belmonte showed the same principle systemically. If the information is mis-read rather than destroyed, it can be recovered.

This closes the deepest loop in the entire architecture. Phase I is information loss at the *substrate* — the metabolic ink runs dry and the marks can no longer be maintained. Phase III is information loss at the *readout* — the plasticity genes are silenced and neuronal identity dissolves. They are the same failure, of one information system, at its input and its output, fifty years and twelve centimetres apart. And the epigenetic clock that runs beneath the whole is that system's odometer — not a passive tally of years but a readout of how far the analogue information has degraded, phase by phase. The senescence current and the epigenetic current are not two systems: the SASP is what a cell *secretes* when its epigenome derepresses, the senescent state is what a cell *becomes* when the information is lost, and the epigenetic erosion is the information loss itself. Substance-theories of Alzheimer's ask which molecule is the disease. The information reading answers that the disease is not a molecule at all but the corruption of a pattern — and a corrupted pattern, unlike a lost molecule or a mutated gene, is the one thing in the whole pathology that can, in principle, be written back.

X. Assessing the Connections A Validity Ledger

The elegance of an information reading is exactly the reason to grade it without mercy, because a pattern-level theory is the easiest kind to make unfalsifiable. What follows weights each connection against the two confounds of Section II — cell-composition artifact and reverse causation — and names the experiment that would settle it.

Strong connections

The HDAC2 blockade of Phase III. This is the load-bearing, causally demonstrated link. HDAC2's repression of plasticity genes, its elevation in the degenerating brain, and — decisively — the *recovery* of synapses and memory when it is inhibited (Guan, Gräff, Fischer) constitute an interventional chain, not a correlation, and the rescue directly refutes reverse causation. *Residual doubt:* efficacy has not translated to human disease-stage patients, and pan-HDAC inhibition is toxic. *Settling experiment:* an HDAC2-selective inhibitor in a staged human trial with target-engagement (promoter acetylation) readouts.

Tau-driven chromatin relaxation and transposon derepression. Frost's mechanism is evidenced across fly, mouse, and human tissue, from Lamin B1 depletion to LINE-1/HERV-K

reactivation to the 2025 human dark-genome sequencing, and the interferon consequence is independently corroborated from the senescence side (De Cecco). *Residual doubt:* the quantitative contribution of transposon-driven inflammation to human cognitive decline, versus its being one arm among many, is not established. *Settling experiment:* a reverse-transcriptase inhibitor (see therapeutics) altering disease trajectory in humans — a trial now underway.

Metabolism–epigenome coupling in Phase I. That epigenetic enzymes depend on NAD+, acetyl-CoA, SAM, and α-ketoglutarate is not a hypothesis but established biochemistry, and the sirtuin hinge (Imai) is firmly grounded. *Residual doubt:* the claim that this coupling makes the *locus coeruleus* the first site of epigenetic drift is an extrapolation from its being the first metabolically failing cell. *Settling experiment:* single-nucleus methylation clocks on age-stratified human brainstem versus cortex.

Moderate connections

Epigenetic-clock acceleration as a measure of the disease. Robustly replicated in blood and brain, and prognostic — but correlational, composition-confounded in bulk tissue, and of genuinely open causal direction. *Residual doubt:* whether accelerated methylation age drives Alzheimer's or merely indexes the ageing that permits it. *Grade: strong association, unproven causation.*

Microglial trained immunity and the enhancer switch. Wendeln's demonstration that inflammatory training leaves a months-long chromatin memory shaping amyloid pathology is a clean causal result *in mice*; Gjoneska's immune-enhancer enrichment is human but cross-sectional. *Residual doubt:* the durability and disease-relevance of immune training over human decades. *Grade: strong in model, inferential in human.*

The methylation-association hits (ANK1, BIN1, RHBDF2). The De Jager and Lunnon epigenome-wide studies are large, replicated, and cross-cohort — the most robust human epigenetic findings in the field — but they are bulk-tissue, late-stage, and therefore maximally exposed to both confounds. *Grade: robust association, confound-limited.*

Provocative or frankly speculative connections

The information theory as the cause of ageing, and reprogramming as its reversal. Sinclair's ICE and OSK results are striking and, in mice, causal in both directions — but the claim that Alzheimer's is *fundamentally* epigenetic information loss is a strong reading of suggestive data, and partial reprogramming in the human brain is untested and carries a real risk of teratoma and identity loss. *Grade: provocative; the frontier, not the foundation.*

The packaging of tau's chromatin corruption onto the trans-synaptic seed. Structurally attractive and consistent with Frost's mechanism, but not demonstrated as a single delivered event. *Grade: synthesis.*

The two failure modes, named to resist them

Every claim above is meant to survive the two confounds, and where it cannot the grade says so. *Cell-composition confounding* is answered only by single-nucleus resolution, and the older bulk-tissue literature — including the celebrated methylation hits — cannot be fully cleared of it; the mapping therefore leans hardest on the cell-type-resolved and interventional findings. *Reverse causation* is answered only by intervention, and it is precisely because the HDAC2, transposon, and reprogramming links have *rescue* experiments behind them that they outrank the clock and the association studies, which do not. An information theory earns its standing not by the beauty of the pattern but by showing that rewriting the pattern changes the disease — and it is the existence, and the early positivity, of exactly those rewriting experiments that keeps this reading on the near side of speculation.

XI. Falsifiable Predictions

The epigenetic mapping generates predictions that are phase-resolved, mark-specific, and in several cases already under test.

On sequence. Single-nucleus epigenetic clocks will show methylation-age acceleration appearing first in brainstem aminergic neurons (third–fourth decade), then in hippocampal microglia (sixth–seventh), then in cortical neurons (eighth) — the same rostral order as tau, and earlier than the corresponding proteinopathy. A clock that accelerates first in cortex would falsify the metabolic-ink account of Phase I.

On metabolism and marks. Restoring the epigenetic cofactors — NAD+ precursors for the sirtuins, methyl donors for the methylome — will measurably slow clock acceleration and preserve heterochromatin *specifically in the early, metabolically-driven phase*, and will lose efficacy once the self-reinforcing programme of Phase III is written. If cofactor restoration helps as much late as early, the phase-structure fails.

On the derepressed genome. Suppressing reactivated transposons — with reverse-transcriptase inhibitors — will reduce the type I interferon signature and the SASP, and will do so in the same regions where heterochromatin loss and senescent burden are greatest, linking the epigenetic and senescent maps at one stroke. This is the sharpest shared prediction of the two volumes.

On reversibility by phase. The benefit of *rewriting* the epigenome will depend on which mark and which decade: lifting the HDAC2 blockade will recover function in Phase III where the genes are merely silenced, but will fail where identity is already dissolved and the neuron lost; partial reprogramming will show a therapeutic window that closes at neuronal death. A rewriting intervention that helps uniformly across all stages would falsify the reversibility-grading at the heart of this reading.

On the two confounds. As single-nucleus methods mature, a substantial fraction of the celebrated bulk-tissue methylation "changes" will prove to be composition artifacts and will *not* replicate within cell types — a prediction that is uncomfortable for the field and that this dissertation is obliged to make.

XII. Therapeutic Implications Rewriting by Phase

The information reading yields a therapeutic class the substance-theories cannot: interventions that do not remove a molecule or replace a cell but *rewrite the score*. And the temporal architecture tells us, phase by phase, which rewriting to attempt and when.

The governing principle follows from the reversibility grading. Early, the corruption is a failure of *maintenance*, correctable by restoring the ink; late, it is a written-over *programme*, correctable only by actively rewriting; and at the end, where identity is dissolved and the neuron dead, no rewriting reaches it. **Phase I** is therefore a *metabolic-epigenetic* problem: NAD+ precursors to restore sirtuin-maintained heterochromatin, methyl-donor and one-carbon support (folate, B-vitamins) to sustain the methylome, begun presymptomatically in the at-risk — upstream interventions that keep the ink from running dry. **Phase II** is an *immune-reprogramming* problem: the trained, epigenetically reprogrammed microglion is the target, and the tools are the ones that reach its enhancer landscape — BET and HDAC modulation to quiet the maladaptive immune memory, and restoration of the TGF-β/SMAD signalling that holds the homeostatic enhancers open. **Phase III** is a *rewriting* problem with two concrete handles: HDAC2-selective inhibition to lift the epigenetic blockade of cognition and reopen the silenced plasticity genes, and — the most direct epigenetic therapy in the field — *reverse-transcriptase inhibition* to suppress the reactivated transposons whose interferon drives the terminal inflammation. That second handle is not hypothetical: nucleoside reverse-transcriptase inhibitors such as lamivudine, repurposed from HIV therapy on exactly Frost's and the senescence field's rationale, are in human trials in Alzheimer's and mild cognitive impairment, and epidemiology in treated HIV cohorts already hints at reduced dementia incidence.

Two frontiers stand beyond the phase-matched programme. *Partial epigenetic reprogramming* — transient OSK expression to restore youthful methylation — is the most radical possibility the information theory implies, and must be named with its risks fully stated: it is untested in the human brain, and the same rewriting that could recover a silenced synapse could erase a neuron's identity or seed a tumour. And the *epigenetic clock* is the programme's natural staging biomarker — a blood-readable measure of how far the information has degraded, and therefore of which phase a given patient is in and which rewriting their disease can still accept. The clinical grammar that follows is neither the field's failed molecule-removal nor an indiscriminate epigenetic assault: it is *phase-matched rewriting* — feed the ink early, reprogram the immune memory in the middle, lift the silencing late, measure the whole at the clock — grounded in the disease's one honest gift, that some of its damage is information, and information can be written back.

XIII. Conclusion The Recoverable Disease

The Temporal Architecture of Collapse named the stations of the disease and the bridges between them. *The Senescent Front* named the cell-state that ageing drives cells into at each station. This volume has descended one layer further, to the information that the state corrupts and the ageing erodes — and has found that Alzheimer's disease, read at its deepest molecular level, is the fading of a score: the progressive corruption of the epigenetic instructions by which the genome is played, beginning where the metabolic ink first runs dry and ending where the plasticity programme is clamped shut and the neuron's own identity dissolves.

The reading tells one story across the arc. The epigenome is written in metabolites, so the bioenergetic ignition of the third decade is an epigenetic ignition, the sirtuins failing as NAD+ falls and the clock beginning, unmeasured, in the brainstem. The tau that the coeruleus seeds forward is a chromatin corruptant as much as a template, so the first bridge carries drift and derepression along with its seed. Microglial identity is an enhancer landscape and immune experience is a chromatin memory, so the sixth-decade collapse of the hippocampal bridgehead is a reprogramming and a conditioning at once. Heterochromatin loss unlocks the dark genome, so the second bridge is a derepressed genome sounding a viral alarm against itself — the interferon that is at once an epigenetic lesion and the senescent secretome's engine, the tightest weld between these two companion theories. And the plasticity genes are silenced while identity genes are relaxed, so the eighth-decade synapse falls under an epigenetic blockade that, once written, plays the disease from memory. Beneath all of it runs not a substance but a pattern degrading — analogue information lost from a store that has no backup, the epigenetic clock its odometer, information loss its name.

We have graded the story against the two confounds that make brain epigenetics treacherous, and much of it is graded down: the clocks are correlational, the famous methylation hits are composition-confounded, the information theory is provocative and mouse-bound, and the reprogramming frontier carries real danger. But the load-bearing links — HDAC2's reversible blockade, tau's chromatin relaxation and its transposons, the biochemistry that ties the epigenome to the metabolism that fails first — are strong, and the strongest of them are strong precisely because they come with rescue experiments: change the mark, and the disease changes. That is the whole difference, and the whole promise. Every other reading of Alzheimer's asks which irreversible thing has gone wrong — which cell has died, which protein has aggregated, which gene was inherited. The epigenetic reading finds, beneath them, a dimension of the disease in which nothing has been destroyed and everything has been mis-written — and a mis-written score, unlike a lost molecule or a fallen cell, can be read again. The disease has always been the fading of a pattern the brain keeps of itself. What the epigenetic front adds is that a pattern, faded, is not gone. It is the one thing in all of Alzheimer's that might still be written back.

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