
The Reservoir and the Clock

Why the compensatory architecture of the Alzheimer synapse cannot be read as a reserve — on buffers that drain, buffers that stop, and a phosphatase that rises when the model says it should fall

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The compensation that holds a neuron functional through decades of accumulating pathology is modelled as a set of tanks that drain. Most of the nodes in question are not tanks but turnover cycles, which fail by stopping rather than by emptying — and a clock modelled as a reservoir reads full right up to the moment it has stopped. The phosphatase nominated as the master buffer is the proof: on the tyrosine limb it does not deplete in this disease. It accumulates, because its own disposal failed.

Contents

1. Two Models of What Held

- 1.1 *The question, and why it is the right one*
- 1.2 *The reservoir*
- 1.3 *The clock*
- 1.4 *Three claims*

2. The Reservoir Model, Stated at Its Strongest

- 2.1 *The six buffers*
- 2.2 *The bifurcation parameter and the reserves*
- 2.3 *What is right here, and should be kept*

3. The First Clock: A Licence Is Not a Buffer

- 3.1 *The same fact, two readings*
- 3.2 *Why the distinction is not semantic*
- 3.3 *The experiment that has already decided this*

4. The Second Clock: The Phosphatase Is Not a Reserve

- 4.1 *The wrong enzyme family*
- 4.2 *The wrong direction*
- 4.3 *The buffer and the buffered share a disposal route*
- 4.4 *A compensation that executes the lesion*
- 4.5 *What is not claimed*

5. The Third Clock: A Reserve That Cannot Be Read

- 5.1 *Both arms write the same mark*
- 5.2 *The reserve and the insult share a signature*
- 5.3 *An unexpected consequence: abruptness may be partly epistemic*

6. The Drug That Goes Both Ways

- 6.1 *The conflict, stated*
- 6.2 *The trial record*
- 6.3 *The reciprocal result*

7. The Biomarker Whose Denominator Is the Lesion

8. What a Clock's Reserve Actually Is

9. The Compensation Table, Rebuilt

10. What This Predicts

11. What This Forbids

12. Scope, and What Would Refute the Whole Argument

13. Validity Ledger

14. Closing

References

Abstract

There is a question the failure literature of Alzheimer's disease does not answer, and it is the better question. Not *what breaks*, but *what held* — why a brain carrying enlarged endosomes for two decades, accumulating an exchange factor it cannot dispose of, and losing the receptor that licenses that disposal, nonetheless keeps its owner cognitively intact through most of that interval. The pathology is early and the dementia is late, and the interval between them is filled with something. Naming that something is the work of the compensation literature, and it is unfinished.

This paper is about how the naming is done, and argues that the standard way of doing it imports a model that most of the relevant nodes do not obey.

The standard model is a reservoir. A buffer is a quantity. It absorbs damage, it depletes, the depth remaining is the reserve, and the clinical transition happens when it empties. Phosphatase capacity, lysosomal capacity, competing-GTPase tone, the unprimed fraction of the microglial population: each is a tank, each drains, and cognitive reserve is how full the tanks started. The model is intuitive, it accommodates the epidemiology of education and exercise, and it yields a therapeutic programme of enlarging tanks.

Most of these nodes are not reservoirs. They are clocks. The control surface above the actin cytoskeleton of the dendritic spine is terminated by destruction, not by reset. Ephexin5 is phosphorylated on a tyrosine that simultaneously biases its exchange activity and recruits the ubiquitin ligase Ube3A that destroys it [1,2]. Disabled-1 is phosphorylated by Fyn in a way that both transduces the reelin signal and consigns the adaptor to the proteasome [3,4]. At such a node the reserve is not how much enzyme remains but whether the cycle still turns, and the failure mode is not depletion but arrest. **A clock modelled as a reservoir reads full right up to the moment it has stopped.**

The keystone is a phosphatase that moves the wrong way. The reservoir model's central variable is a kinase-to-phosphatase ratio, and its principal reserve is phosphatase capacity, which in Alzheimer's disease is taken to fall. That is a defensible reading of protein phosphatase 2A, a serine/threonine enzyme [5]. But the residues that set the sign in this system are tyrosines, and serine/threonine phosphatases do not reset them. The relevant enzyme class is the protein tyrosine phosphatases, and the best-characterised neuronal member in this disease is STEP61 — whose protein level and activity are *elevated* in human Alzheimer prefrontal cortex, and elevated **because its own ubiquitin-proteasome disposal has failed** [6]. On the tyrosine limb the buffer does not drain. It accumulates, by precisely the mechanism that leaves Ephexin5 in place [7], and its accumulation internalises glutamate receptors.

That single fact dismantles the scalar. There is no independent phosphatase reserve at this control surface, because the buffer and the thing it buffers are disposed of by the same machine,

and the disease is a lesion of that machine.

Three consequences follow, and each is testable. *First*, a therapeutic programme built on restoring phosphatase activity is predicted to act in opposite directions at reset-terminated and destruction-terminated nodes of the same cascade; the leading PP2A-activating agent has now been reported in two trials across two dementias, in three publications, without moving cerebrospinal-fluid phospho-tau [8,9,10], while a STEP *inhibitor* improved cognition in an Alzheimer model with no change in amyloid- β or phospho-tau at all [11]. *Second*, the reserve nominated for the spine — competition between Rac1/Cdc42 and RhoA — is unreadable, because both arms activate the same LIM-domain kinase at the same threonine and add the same phosphate to cofilin serine 3 [12]. The compensation and the insult have one signature. *Third*, and least expected: if the compensating variable is invisible, then part of the apparent abruptness of the clinical transition is an artefact of the instrument rather than a property of the system. The reservoir model predicts a falling mean. The degeneracy predicts a flat mean and a rising dispersion. These are distinguishable in one measurement, and it has not been made.

What replaces the reservoir. At a licensed control surface the reserve is *bandwidth*, not headroom: the excursion the neuron can still make and return from. This reformulation is not decorative. It changes what a resilience allele is predicted to do — the *RELN*-COLBOS variant should enlarge and shorten a signal rather than raise its tone [13] — and it explains why repairing a compartment restored signalling that no quantity of ligand could restore [14]. Section 9 rebuilds the compensation table on this basis, node by node, and marks which buffers are genuinely tanks. One of six is.

I. Two Models of What Held

1.1 The question, and why it is the right one

Synapse loss is the strongest structural correlate of cognitive impairment in Alzheimer's disease. In the study that established it, neocortical synapse density carried a multivariate correlation of 0.96 with the Dementia Rating Scale, while plaque density contributed only 26 per cent of that model's strength [15]. Any account of the disease therefore owes an account of what happens mechanically at a spine.

The mechanistic literature has supplied one, and it is a cascade. Amyloid- β oligomers bind the fibronectin-repeat domain of EphB2 and trigger the receptor's degradation in the proteasome [16]. EphB2 is the receptor whose signalling phosphorylates the exchange factor Ephexin5 and recruits the ligase Ube3A that destroys it [1]. Ephexin5 protein is elevated in the hippocampi of human Alzheimer patients, and its genetic removal eliminates spine loss and rescues behaviour in an amyloid model [7]. Downstream, contractile Rho signalling reaches the actin cytoskeleton, and the sorting machinery that would recycle the receptors is impaired from before the appearance of any deposit [17].

That is an architecture of failure, and it is a good one. But it does not explain the interval. Enlarged early endosomes are present in neocortical pyramidal neurons at preclinical stages and in Down syndrome from twenty-eight weeks of gestation [17]. Individuals carry substantial amyloid burdens with intact cognition. If the cascade were sufficient, the disease would be faster than it is.

The disease is slow because something opposes it. Naming that opposition — and saying when and how it gives way — is a distinct research programme from naming the cascade, and it has a distinct failure mode of its own, which is the subject of this paper.

1.2 The reservoir

The natural way to model opposition is as a buffer, and the buffer model has a definite shape. At each node of a cascade there is a quantity that absorbs damage. Damage consumes it. What remains is the reserve. Function is maintained while the reserve is positive and fails when it reaches zero.

Read this way, the compensatory architecture of the synaptic cascade is a set of six tanks. Receptor recycling replenishes surface EphB2. Ube3A-mediated ubiquitination degrades Ephexin5. Guanine-nucleotide dissociation inhibitors sequester RhoA in an inactive cytosolic pool, GTPase-activating proteins terminate the active signal, and Rac1 and Cdc42 compete for the actin

machinery [18]. Phosphatases oppose kinases at the sorting receptor. Lysosomal biogenesis under the transcription factor TFEF clears the cargo the endosome cannot pass [19]. Multiple independent inhibitory signals restrain the microglion.

The model then supplies a bifurcation parameter — a single scalar whose crossing marks the transition — and the natural candidate is the net phosphorylation state of the sorting receptor, set by the ratio of kinase to phosphatase activity at its cytoplasmic tail. It supplies molecular substrates for cognitive reserve: more synapses mean more distributed phosphatase per synapse; higher tonic Rac1 activity raises the RhoA tone required to collapse a spine; larger lysosomal capacity extends the clearance window. And it supplies a therapeutic programme, which is to enlarge the tanks — activate the phosphatase, promote lysosomal biogenesis, potentiate the competing GTPase.

This is a coherent research programme and this paper does not dismiss it. Its central observation — that the failure literature has not systematically named what it is overcoming, and that the strength of the compensation is why the disease takes decades — is correct and under-argued in the field.

1.3 The clock

There is a second way for a system to resist damage, and at this particular control surface it is the operative one.

Consider how a spine ends a structural instruction. It does not, at the governing layer, dephosphorylate the transducer. It destroys it. Ephexin5 was identified as a restraint on excitatory synapse formation that is lifted when EphB signalling triggers its phosphorylation, ubiquitination and degradation; the synapse is permitted to form not because a brake was switched off but because a brake was removed from the cell [1]. Disabled-1, the adaptor through which the entire reelin signal is transduced, is phosphorylated by Fyn in a way that both propagates the signal and targets the adaptor for proteasomal degradation, and in the absence of the kinase the adaptor is not degraded [3,4].

Both transducers are built to the same design: **the phosphorylation that activates is the phosphorylation that condemns**. In the case of Ephexin5 the coupling is now known to be functional as well as destructive — the same tyrosine that recruits the ligase also selects the enzyme's substrate, biasing it toward RhoA when phosphorylated and releasing its Cdc42-directed activity when not [2]. Abundance and activity are two readings of one covalent mark.

At such a node, reserve is not a depth. It is a rate. The system's capacity to deliver a brief, placed, releasable instruction to its actin network depends on a turnover cycle: write the mark, transduce, destroy the transducer, resynthesise. What protects the neuron is that the cycle turns. What fails is that it stops.

And a stopped clock does not look empty. It looks full — often fuller than normal, because the substrate that should have been removed is still there. Every measurement of quantity returns a reassuring number while the function the quantity was supposed to serve has already ceased.

1.4 Three claims

First, that three of the six nodes in the compensatory architecture are clocks rather than reservoirs, that the reservoir reading mis-specifies each of them, and that in one case — the phosphatase — the mis-specification inverts the sign of the predicted change. This is the paper’s principal claim and Sections 3 to 5 argue it.

Second, that the therapeutic programme derived from the reservoir reading contains a specific and named conflict: an agent that restores phosphatase activity is predicted to help at a reset-terminated node and to stabilise the wrong protein at a destruction-terminated one. Section 6 sets this against the trial record, which is now large enough to be informative.

Third, that the reserve at a clock node is dynamic range rather than capacity, and that this reformulation makes different predictions about resilience alleles, about repair interventions, and about the shape of the transition. Sections 8 and 10 develop it.

A fourth observation is not a claim but a caution, and it recurs: **the compensatory literature is more inferential than the failure literature it corrects.** Most of the buffers named in Section 2 are inferred from the molecular logic of the pathway rather than measured in the disease. That is not a reason to abandon the enterprise, but it is a reason to be exact about which nodes carry evidence, and Section 13 states where each claim here stands.

2. The Reservoir Model, Stated at Its Strongest

Before dismantling part of it, the model deserves a fair statement, because the parts that survive are load-bearing for what follows.

2.1 The six buffers

At the receptor. Surface EphB2 density is not fixed; it is maintained by constitutive endosomal recycling and by *de novo* synthesis. Sorting-receptor-dependent retrieval returns internalised receptor to the membrane, and the related EphB paralogues supply partial redundancy for ephrin-B-dependent synapse stabilisation. The buffer closes when the recycling machinery itself is impaired.

At the exchange factor. Ube3A-mediated ubiquitination holds Ephexin5 extremely low in healthy adult neurons [1]. This is the named brake, and the reservoir reading observes something sharp about it: because the ligase is recruited by an EphB2-dependent phosphorylation, the buffer erodes in proportion to the insult it must absorb. The reading calls this a *structurally fragile compensation*. Section 3 argues that the observation is right and the interpretation is wrong.

At the GTPase. Guanine-nucleotide dissociation inhibitors hold the majority of cellular Rho-family GTPase in an inactive cytosolic reservoir; GTPase-activating proteins accelerate hydrolysis and terminate the active signal; and Rac1 and Cdc42 promote actin branching in opposition to RhoA-mediated contraction [18]. An increase in exchange-factor activity must overcome the sequestered pool before net active GTPase rises.

At the sorting receptor. Phosphorylation of the receptor's cytoplasmic tail impairs its engagement with the retrieval machinery; constitutively active phosphatases oppose it. While dephosphorylation keeps pace, the endosome recycles.

At the multivesicular body. Autophagy-lysosome fusion degrades accumulated cargo, and TFEB, the master transcriptional regulator of lysosomal biogenesis, raises lysosomal output in response to stress — a genuine feedback loop, and one whose upstream control by mTORC1 at the lysosomal membrane is well characterised [19].

At the microglion. Multiple independent inhibitory signals gate phagocytic commitment, so that the loss of any one is insufficient to license destruction.

2.2 The bifurcation parameter and the reserves

From these the reservoir reading derives a transition. Because the sorting receptor stands at the intersection of two feedback loops — returning receptor to the surface, and routing the precursor protein away from amyloidogenic processing — its net phosphorylation state is nominated as the single variable whose crossing collapses both loops at once. The transition is governed by a kinase-to-phosphatase ratio, is sharp and locally irreversible at a single dendritic compartment, and is gradual at the level of the network because compartments cross at different times.

Cognitive reserve then acquires molecular substrates: synaptic density as distributed phosphatase reserve, tonic Rac1 activity as structural reserve, lysosomal capacity as clearance reserve, and the unprimed fraction of the microglial population as immune reserve.

2.3 What is right here, and should be kept

Three things.

The framing is correct. A cascade that describes only failure cannot explain a disease whose defining feature is a decades-long interval between molecular onset and clinical expression. The positive feedback loops are strong because the negative ones they must overcome are strong, and the therapeutic window is defined by the latter, not the former.

The compartment-level sharpness with network-level gradualism is a real and useful reconciliation. It explains how a threshold mechanism produces a continuous clinical decline without requiring the decline itself to be smooth at any single synapse.

One of the six buffers really is a tank. The phosphatase opposition at the sorting receptor is a reversible serine/threonine equilibrium with a genuine set-point, and the reservoir mathematics applies to it. Section 9 marks it as such. The argument that follows is not that the model is empty; it is that it has been generalised from its one valid instance to five nodes that do not share its structure.

3. The First Clock: A Licence Is Not a Buffer

3.1 The same fact, two readings

The reservoir reading and the licensing account agree completely on the molecular content of the second node and disagree completely on what it means.

Both observe that Ube3A degrades Ephexin5, that the ligase is recruited by an EphB2-dependent tyrosine phosphorylation, and that the two are therefore coupled: as surface EphB2 falls, the degradation of Ephexin5 falls with it [1,16,7].

The reservoir reading calls this *a structurally fragile compensation* — a buffer whose capacity erodes in exact proportion to the insult it must absorb. On that reading the design is a flaw, and the therapeutic implication is to shore the buffer up: raise ligase activity, or otherwise restore degradative capacity at the node.

The licensing account calls the same coupling *the mechanism of transience*. The phosphorylation is not a coincidence attached to a brake; it is the licence that permits the brake to be removed at the right time and place. A signal that must be brief, local and releasable cannot be terminated by a phosphatase, because a phosphatase resets a mark and leaves the transducer in the compartment. It must be terminated by destruction, and destruction must be authorised by the receptor that knows when the signal should end.

The coupling the reservoir reading calls fragility is the same coupling that makes the system fast. On a timescale of minutes it is what allows a spine to end an instruction. On a timescale of decades it is what makes the buffer non-restorable. Both readings describe the same wiring; they differ on whether the quantity being consumed is a defence or a message.

3.2 Why the distinction is not semantic

It is not semantic because the two readings prescribe opposite interventions and predict opposite signs.

If Ephexin5 accumulation reflects a *drained buffer*, then abundance indexes damage and the intervention is to lower the abundance. That inference has been made, and it is unsafe on its own terms: heterozygous loss-of-function mutations in *ARHGEF15*, the gene encoding Ephexin5, cause autosomal-dominant hereditary cerebral small-vessel disease with osteoporotic fracture, acting

through RhoA/ROCK2 *inactivation* [20]. Chronic reduction of this exchange factor is a phenocopy of a human dementing vasculopathy.

If Ephexin5 accumulation reflects a *stopped clock*, then abundance indexes an unwritten licence, and the sign of the accumulated pool depends on which mark it carries. This is not speculative. The 2025 revision established that the tyrosine which recruits the ligase also selects the enzyme's substrate: phosphorylated, the exchange factor is biased toward RhoA; a phosphorylation-dead mutant at that residue enhances Cdc42 activation while leaving RhoA activation unchanged, and rescues activity-driven spine growth in knockout neurons [2]. The protein is not a brake the adult brain has switched off. It is a switch the adult brain keeps and throws, and throwing it is what activity-driven spine growth requires [21,2].

So a cell with elevated Ephexin5 may be RhoA-locked and collapse-directed, or hypo-phosphorylated and growth-directed, and total protein cannot distinguish them. A buffer model has no place to put that ambiguity, because a buffer has only a depth.

3.3 The experiment that has already decided this

There is a human disorder in which the ligase is lost and the exchange factor should therefore accumulate maximally. If Ephexin5 were a RhoA-directed brake whose accumulation indexes damage, the predicted consequence is severe spine loss.

That is not the observed consequence in Angelman models. The substrate-switching architecture resolves it without special pleading: in a developing brain, where the phosphorylated fraction is falling and activity is high, accumulated Ephexin5 is Cdc42-biased and therefore stabilising [2].

The resolution is also a warning, and it is the strongest available evidence against the buffer reading of this node. **In a real human disorder, a large increase in this protein produced a phenotype opposite in sign to the one a depth model predicts.** The inference from abundance to sign is not available here, and the reservoir reading depends on it.

4. The Second Clock: The Phosphatase Is Not a Reserve

This is the paper's keystone, and it concerns the variable the reservoir reading places at the centre of everything: phosphatase capacity.

4.1 The wrong enzyme family

The reservoir reading's bifurcation parameter is a kinase-to-phosphatase ratio, and the phosphatase it names is protein phosphatase 2A. The choice is reasonable on its face. PP2A is the principal tau-dephosphorylating enzyme in brain, multiple abnormalities of it have been reported in Alzheimer's disease — decreased scaffolding and regulatory subunit levels, reduced catalytic-subunit methylation, increased catalytic-subunit phosphorylation, up-regulated endogenous inhibitors, and loss of enzymatic activity — and the reviewers of that literature note honestly that the individual alterations converge on the enzyme from different directions and have not been uniformly replicated [5].

But PP2A is a serine/threonine phosphatase, and the residues that set the sign in this system are tyrosines. The mark that biases Ephexin5 between RhoA and Cdc42 is a tyrosine [2]. The mark that transduces and terminates Disabled-1 is a tyrosine, written by a Src-family kinase [3,4]. A serine/threonine phosphatase does not reset either of them.

This matters more than a taxonomic quibble, because the reservoir reading uses a single scalar — *phosphatase reserve* — and then distributes it across the cascade, from the sorting receptor to the spine, as though one quantity were being spent everywhere. It is not. Two enzyme families are involved, they act on different residues, and in this disease **they move in opposite directions**.

4.2 The wrong direction

The best-characterised neuronal protein tyrosine phosphatase in Alzheimer's disease is STEP61, the striatal-enriched phosphatase, whose substrates include the GluN2B subunit of the NMDA receptor, ERK1/2, p38, Pyk2 — and Fyn [11].

Its behaviour in this disease is the opposite of a draining reserve.

STEP61 levels rise progressively in the cortex of an amyloid-bearing mouse line over the first year, and are elevated **in human Alzheimer prefrontal cortex**. The elevation is associated with greater STEP activity, with dephosphorylation of the GluN2B regulatory tyrosine, and with

decreased NMDA-receptor subunits at neuronal membranes. Amyloid-enriched medium reproduces the effect in culture, and in STEP-knockout cultures amyloid fails to internalise the receptor [6]. Independent work found age-related elevation of STEP61 and of its active fraction in wild-type mice, enhanced in an amyloid model, and reproduced in cortical neurons treated with amyloid- β [22].

Then the mechanism, which is the sentence this paper is built on:

> **The elevation of STEP61 is due to disruption in the normal degradation of STEP61 by the ubiquitin–proteasome system.** Blocking the proteasome elevates STEP61; STEP61–ubiquitin conjugates are increased in cortical slices upon amyloid treatment and in the cortex of aged amyloid-bearing mice [6,23].

So on the tyrosine limb, the phosphatase does not deplete. It accumulates, and it accumulates by failed ubiquitin-dependent disposal — the same failure, in the same compartment of the same cell type in the same disease, that leaves Ephexin5 in place [7].

4.3 The buffer and the buffered share a disposal route

Set the two facts side by side and the scalar collapses.

The reservoir reading asks us to treat the phosphatase as an independent reserve that opposes the kinase and is spent in doing so. But at least one relevant phosphatase is itself a proteolytically governed node — abundance set by ubiquitin-dependent turnover, activity rising as turnover fails — which is the identical structure the licensing account describes for the transducers.

The buffer and the thing it buffers are disposed of by the same machine, and the disease is a lesion of that machine. There is no independent reserve to spend. A model with one variable called *phosphatase capacity* predicts that the phosphatase limb weakens as the disease progresses; the human cortical record on this enzyme says it strengthens, and strengthening is part of the injury.

It is worth being precise about what has and has not been shown, because the argument does not need the stronger version. It has *not* been shown that STEP61 acts on the licensing tyrosine of Ephexin5, or on Disabled-1. No such enzyme–substrate pair is in the published record, and Section 12 lists the experiment that would test it. The claim made here is structural and does not depend on it: the phosphatase limb of this control surface contains at least one enzyme that is disposed of by the ubiquitin–proteasome system, that accumulates in human Alzheimer cortex because that disposal fails, and that acts on Fyn — the Src-family kinase that writes to both the destructive and the protective transducer [11,3,4]. A reserve variable cannot be defined over that.

4.4 A compensation that executes the lesion

There is a further irony in this literature, and it is directly on the reservoir reading's own subject.

STEP61's elevation has been interpreted by workers in the field as *compensatory*: upregulation of the phosphatase and the consequent dephosphorylation of GluN2B and ERK1/2 have been proposed to mediate a compensatory weakening of synaptic strength in response to enhanced hippocampal network activity [24]. On that reading the enzyme is doing exactly what the compensation literature says a buffer should do — opposing an excess.

And the mechanism by which it opposes the excess is internalisation of the NMDA receptor [6], which is the lesion. The reservoir reading has a category for this — mechanisms adaptive early and pathological late — and lists four of them. This is a fifth, it sits on the very variable nominated as the master buffer, and it is absent from the list.

The therapeutic consequence is not subtle. A small-molecule STEP inhibitor improved cognitive function across several tasks in six- and twelve-month-old triple-transgenic Alzheimer mice, restored tyrosine phosphorylation of STEP substrates, and did so **with no change in amyloid- β or phospho-tau levels** [11]. That is a performance result of the purest kind — function restored while the measured pathology is untouched — and it was obtained by *inhibiting* a phosphatase, which is the opposite of what a reserve model prescribes.

4.5 What is not claimed

That PP2A is unimportant: it is not. That its decline in Alzheimer's disease is unreal: the review literature supports some decline while noting inconsistency [5]. That STEP is the master variable: nothing here requires it to be.

What is claimed is narrower and harder to escape. **There is no single phosphatase reserve.** There are at least two enzyme families acting on different residues at different nodes, moving in opposite directions in the same disease, one of which is itself governed by the proteolytic system whose failure defines the lesion. Any model that spends one scalar across all of them will get the sign wrong somewhere, and Section 6 shows where.

5. The Third Clock: A Reserve That Cannot Be Read

5.1 Both arms write the same mark

The reservoir reading's most attractive proposal is its account of cognitive reserve at the single spine: that resilience is the sustained capacity of Rac1 and Cdc42 signalling to outcompete RhoA, and that the epidemiological protection conferred by exercise and enrichment is this competition, mechanised.

The proposal is attractive and it may well be true. The difficulty is that it cannot be read out, and the reason is structural.

Rho-associated kinase activates LIM-domain kinase 1 by phosphorylation at threonine 508 within its activation loop, and a mutant lacking that residue is neither phosphorylated nor activated by the kinase. The same paper records that PAK1, the downstream effector of Rac, *also* activates LIM-domain kinase 1 by phosphorylation at threonine 508, and draws the conclusion explicitly: activation of LIMK1 is a common target for Rho and Rac in reorganising the actin cytoskeleton [12].

Downstream, LIM-domain kinase phosphorylates cofilin at serine 3; phosphorylated cofilin cannot bind filamentous actin and the network is stable [25]. So the contractile arm and the protrusive arm converge on one kinase, at one residue, and add the same phosphate to one serine, while producing opposite structural outcomes — collapse in the first case, growth in the second.

A measurement of phospho-serine-3 cannot distinguish a collapsing spine from a growing one. The degeneracy is in the variable, not in the sampling: even a perfectly compartment-resolved measurement at a single synapse would not say which arm produced it. The resetting limb does not rescue the situation, being itself multiple — slingshot and chronophin — and itself engaged by the disease through RanBP9-dependent amyloid signalling [26,27].

This is why the human record at that residue is contradictory and has stayed contradictory. Amyloid acting through the immune receptor LirB2 produces cofilin dephosphorylation, reported in mouse and detected in human Alzheimer brain [28], reproduced independently with a receptor antagonist. Amyloid acting through Rho-associated kinase *increases* serine-3 phosphorylation in the post-synaptic fraction of human Alzheimer cortex, where that phosphorylation is reported necessary and sufficient for synaptic impairment [29]. Both may be correct measurements of the same disease.

5.2 The reserve and the insult share a signature

Now put the reservoir reading's proposal into that architecture, and the consequence is immediate.

The nominated reserve is Rac1/Cdc42 tone. The nominated insult is RhoA tone. **They write the same mark.** So the buffer and the damage it buffers have one signature, and three things follow.

The reserve cannot be measured. There is no readout at the executing residue that reports how much of it remains, which means the central quantity of a reserve model is, at this node, undefined in practice.

The therapy cannot be titrated. The reservoir reading proposes potentiating the Rac1 axis by BDNF mimetics, TrkB agonism or Tiam1 activation, and this is a reasonable proposal. But a successful Rac1 intervention and a worsening RhoA lesion move phospho-serine-3 in the *same direction*. A trial using that endpoint cannot tell a working drug from a progressing disease.

And the protective arm makes it worse, not better. Reelin stabilises the actin cytoskeleton of neuronal processes by inducing cofilin phosphorylation at serine 3 [30]. So a third pathway — the protective one, the one carrying the strongest human resilience genetics in this system [13] — also adds the same phosphate. Three arms, two signs of structural outcome, one mark.

5.3 An unexpected consequence: abruptness may be partly epistemic

The reservoir reading explains the apparent abruptness of the clinical transition dynamically: positive feedback loops overwhelm negative ones, and the system crosses a tipping point. That is plausible and this paper does not contest it.

But there is a second contribution to apparent abruptness that a reservoir model cannot see, and it follows from Section 5.1. **A variable that cannot be read gives no warning of its approach to zero, however smoothly it falls.** If the compensating quantity at the spine is Rac1/Cdc42 competition, and if the only available readout of that competition is degenerate with the insult, then the observer sees nothing changing until the structural consequence arrives — at which point the change appears sudden because its approach was invisible, not because it was fast.

These two accounts of abruptness are distinguishable, and by one measurement.

A genuine dynamical threshold, on the reservoir reading, should be preceded by a *shift in the mean* of the compensating variable as the buffer drains. Degeneracy-driven apparent abruptness predicts something different: the **mean stays flat while the dispersion rises**, because synapses are moving in opposite directions along a variable that reports both movements identically, and the population variance is the only thing that registers it.

That is a concrete, cheap discrimination — a variance test rather than a means test on a measurement the field already makes — and to our knowledge it has not been performed in human cortex.

6. The Drug That Goes Both Ways

6.1 The conflict, stated

The reservoir reading's lead therapeutic proposal follows directly from its bifurcation parameter: if the transition is governed by the ratio of kinase to phosphatase activity at the sorting receptor, then enhancing phosphatase activity is a performance-sustaining intervention, and it is proposed as a dual-axis target because the same enzyme dephosphorylates tau.

At a reset-terminated node that reasoning holds. Phosphorylation of the sorting receptor's tail is a reversible affinity switch; restoring the phosphatase restores the affinity; the endosome recycles.

At a destruction-terminated node it inverts. Where one covalent mark both activates a transducer and condemns it, removing the mark **protects the protein from turnover while releasing its other activity**. In the case of Ephexin5 this is not an inference: the phosphorylation-dead mutant at the licensing tyrosine enhances Cdc42 activation, and dephosphorylation at that residue is the physiological route by which the phosphorylated fraction falls within minutes of plasticity induction — a fall that survives proteasome inhibition, confirming that dephosphorylation and degradation are separable fates of the same mark [2].

So a phosphatase-restoring strategy is predicted to repair the receptor limb and to stabilise, at the transducer limb, the very protein the model wants cleared.

One qualification is owed and it narrows the claim without removing it. PP2A is a serine/threonine enzyme and does not directly dephosphorylate a licensing tyrosine; the conflict described here is a conflict of *strategy class* — phosphatase-directed therapy at a control surface terminated by destruction — rather than a single-enzyme prediction. It reaches the tyrosine layer indirectly, through the kinases, and its magnitude is unknown. What is not uncertain is the general form: **at a node where abundance and activity are one variable, lowering a phosphorylation level is not a neutral act with respect to the protein's survival**.

6.2 The trial record

There is now enough of a clinical record on this strategy to be worth reading, and the reservoir reading cites it optimistically — as an agent that has shown efficacy in tau dephosphorylation trials. The record is more equivocal than that.

Sodium selenate directly stimulates PP2A activity, and has been taken into two reported trials across two dementias, published in three papers.

A 24-week, multicentre, double-blind randomised Phase IIa trial in forty patients with mild-to-moderate Alzheimer’s disease found the agent safe and well tolerated at supranutritional doses. Of the exploratory biomarkers, **only diffusion MRI showed a group difference**; cerebrospinal-fluid phospho-tau, total tau and A β 42 did not [8].

A 52-week open-label Phase Ib study in twelve patients with behavioural-variant frontotemporal dementia likewise found the agent safe and well tolerated, and reported **no evidence for change in cerebrospinal-fluid total tau, phospho-tau or neurofilament light** [9].

A subsequent biomarker analysis of both cohorts found that cerebrospinal-fluid brain-derived tau decreased with treatment in the Alzheimer cohort but not in the frontotemporal one, while **phospho-tau-217 did not change in either** [10].

Read together and stated fairly: the agent is safe, it moves an imaging measure and a tau-release measure in Alzheimer’s disease, and across two trials and three reports it has not moved a cerebrospinal-fluid phospho-tau species. For a strategy whose entire rationale is the restoration of dephosphorylation, the phospho-marker is the pharmacodynamic endpoint, and it has been flat.

This is not a refutation of the reservoir reading; small trials with exploratory endpoints refute little. It is a caution against the specific claim of demonstrated efficacy, and it is consistent with what Section 6.1 predicts: a level intervention applied to a system whose defect is a timing defect.

6.3 The reciprocal result

Set against it the result from the other enzyme family.

TC-2153, an inhibitor of STEP with a nanomolar half-maximal concentration, increased tyrosine phosphorylation of STEP substrates in cell-based assays, showed no toxicity in cortical cultures, was validated for specificity against knockout tissue, and **improved cognitive function across several tasks in six- and twelve-month-old triple-transgenic Alzheimer mice with no change in beta-amyloid and phospho-tau levels** [11].

The direction is the point. The reservoir reading prescribes *more* phosphatase activity, generally, as a way of enlarging a buffer. On the tyrosine limb, the preclinical result that most resembles the reservoir reading’s own definition of a performance therapy — cognition restored while pathology is unchanged — was obtained by **inhibiting** a phosphatase whose accumulation is a proteolytic failure.

Two enzyme families, opposite directions, one disease. A scalar cannot hold both.

7. The Biomarker Whose Denominator Is the Lesion

The reservoir reading proposes a minimally invasive transition signature: because neuronal exosomes derive from multivesicular bodies and carry the sorting receptor, the ratio of phosphorylated to unphosphorylated receptor in neuron-derived plasma exosomes should report the kinase-to-phosphatase balance at the endosome, potentially years before decompensation.

The proposal is clever and the target is right. It has one structural problem, and naming it is more useful than discarding it.

Exosomes are the output of the organelle whose failure is being measured.

Multivesicular bodies deliver their intraluminal vesicles either to the lysosome for degradation or to the plasma membrane for release, and the split between those fates moves with the health of the degradative arm. When intraluminal catabolism is disrupted, release rises: pharmacological inhibition of the metalloproteases that normally degrade amyloid- β within these vesicles increased intracellular and extracellular peptide levels, promoted intracellular oligomer formation, and increased the amount of the peptide associated with exosomes, including oligomeric species — with the enzymes themselves detected in neuronal exosomes, marking the multivesicular body as their site of action [31].

So exosome release is not an independent sampling of the endosome. It is a function of the same terminal failure that the biomarker is meant to detect. A rise in phosphorylated receptor recovered per millilitre of plasma is consistent with more phosphorylation, with more exosomes, or with both, and these have different meanings — the second is a diversion, not a phosphorylation event.

The fix is straightforward and should be stated because it preserves the proposal: **report the ratio per exosome, and report exosome number as a co-primary rather than normalising it away.** A ratio that rises while particle count is flat is a phosphorylation signal. A ratio that is flat while particle count rises is a clearance signal. Both are informative; conflating them is not. The same caution applies to any cargo-based neuronal-exosome biomarker in a disease whose earliest known structural lesion is endosomal [17].

8. What a Clock's Reserve Actually Is

If the nodes above are clocks, then reserve at those nodes needs redefining, and the redefinition is not merely verbal — it changes what a resilience allele is predicted to do and what a repair intervention is predicted to restore.

Reserve at a reset-terminated node is headroom. How far the variable can move before it crosses. Depth, capacity, buffer: the reservoir vocabulary is correct here.

Reserve at a destruction-terminated node is bandwidth. How large an excursion the system can make and return from — how completely an instruction can be written, delivered and then removed. A neuron can hold a large quantity of transducer and have no bandwidth at all, if the disposal step has failed; indeed it will hold *more* transducer for exactly that reason. This is why a full tank and a stopped clock look identical to a level measurement and opposite to a rate measurement.

Two published results already discriminate the vocabularies, and both favour bandwidth.

The repair result. Apolipoprotein E4 sequesters the reelin receptor ApoER2 in intracellular compartments and reduces its surface expression [32]. Inhibiting the endosome's principal proton-leak channel reverses that recycling block, restores the receptor and its co-endocytosed glutamate receptors to the surface, and restores reelin's modulation of excitatory synapses [14]. Nothing was added and nothing in the signalling pathway was blocked; the compartment was repaired and the signalling returned. An E4 neuron does not have a ligand deficiency — it has a receptor in the wrong place, and no quantity of ligand corrects a location.

The genetics. A gain-of-function *RELN* variant was carried by a man who resisted an autosomal-dominant Alzheimer mutation into his late sixties despite very high amyloid burden, with stronger Disabled-1 activation and reduced tau phosphorylation in a knock-in mouse [13]. On a headroom reading, the allele should raise protective tone. On a bandwidth reading it should do something else — improve the efficiency of a *transient* signal, because the pathway it enters is one in which the transducer is consumed by the act of signalling [4]. These predict different measurements in the same animal: tonic elevation of phospho-cofilin in the first case; a larger reelin-induced excursion with a faster return to baseline, and faster Disabled-1 turnover, in the second.

The general statement is worth making plainly, because it is what the whole paper reduces to.

A reservoir fails by running out. A clock fails by stopping. The first gives warning proportional to what remains; the second gives none, because what remains is not the thing that was protecting you.

9. The Compensation Table, Rebuilt

The reservoir reading's summary tabulates each node of failure against its compensatory mechanism and the mechanism of compensatory failure. The table below keeps that structure and adds the two columns the argument requires: which kind of node it is, and what measurement would actually detect its exhaustion.

Node	Buffer as named	Kind	What its failure actually looks like	Measurement that detects it
EphB2 surface loss	Recycling; EphB paralogue redundancy	Clock (a rate)	Receptor in the wrong compartment, not absent from the cell [32,14]	Surface-to-internal ratio; not total protein
Ephexin5 accumulation	Ube3A-dependent degradation	Clock	Licence unwritten; abundance rises <i>because</i> the activating mark was lost [1,2]	Phospho-tyrosine fraction; total protein is uninterpretable
RhoA/ROCK tone	GDI sequestration; GAPs; Rac1/Cdc42 competition	Mixed — GDI is a genuine pool; the competing arm is not a buffer but a second writer of the same mark [12,18]	Unreadable at the executing residue; reserve and insult share a signature	Joint per-synapse tyrosine/serine distribution with GTPase pulldowns; dispersion, not mean
Sorting-receptor paralysis	PP1/PP2A opposition; paralogue redundancy	Reservoir — the one node where the model holds	Genuine kinase/phosphatase set-point crossing [5]	Phosphorylation state — subject to the denominator caution of §7
MVB overload	TFEB-lysosome axis; ESCRT; exosomal release	Clock (a flux)	Terminal step fails; induction without capacity fills the cell faster [19,33]	Terminal-step flux, not induction markers; and note the “buffer” exports cargo [31]
Microglial execution	Monomer suppression; multiple independent gates	Reservoir-like (genuine multi-signal redundancy)	Convergent loss of several independent brakes	Multi-signal, not single-ligand, readout
Tyrosine phosphatase layer	<i>Not named by the reservoir reading</i>	Clock	Enzyme accumulates through failed ubiquitin-dependent disposal, and the accumulation internalises receptors [6,22]	Protein and active fraction; predicted to rise, not fall

Two features of the table carry the argument. **One of six named buffers is a reservoir.** And the node the reading omits entirely is the one whose direction of change most sharply contradicts it.

10. What This Predicts

Four predictions, each stated so that a specific result would count against the argument.

10.1 The two accumulations are co-located. STEP61 and Ephexin5 accumulate in the same disease through the same mode of failure — impaired ubiquitin-dependent disposal in the dendritic compartment [6,7]. If that is one lesion rather than two coincidences, the two proteins should be elevated *in the same synapses*, and the correlation between them across individual synapses within a case should be positive in Alzheimer cortex and near zero in age-matched control. Both antigens are total proteins rather than phospho-epitopes, so the measurement does not carry the post-mortem lability that dominates phospho-measurements in autopsy tissue; it is a two-channel addition to array tomography of a kind already performed on human cortex for this pathway [34]. **Refutes if** the two are uncorrelated across synapses, in which case the disposal failures are independent and no shared clock is implied.

10.2 Phosphatase reserve does not order by synaptic density on the tyrosine limb. The reservoir reading predicts that higher synaptic density distributes phosphatase burden and extends the compensatory window. On the tyrosine limb the prediction inverts: if STEP61 abundance is set by disposal rather than by demand, its per-synapse level should track proteasomal competence and not synapse number. **Refutes if** per-synapse STEP61 scales inversely with synaptic density in the manner a distributed-reserve model requires.

10.3 Dispersion, not mean, marks the approach to transition. Section 5.3 sets out the discrimination: a dynamical threshold predicts a drifting mean in the compensating variable before transition; degeneracy predicts a flat mean with rising variance. Measured across single synapses in cortex staged along the disease, phospho-serine-3 cofilin should show increasing dispersion and bimodality without a corresponding shift in the mean, with the modes separating on receptor content [28]. **Refutes if** the mean shifts and the variance does not.

10.4 Restoring a phosphatase does not restore dynamic range. The bandwidth reformulation predicts that an agent which lowers a mean phosphorylation level will not, on its own, restore the *excursion* of a plasticity-induced signal, because excursion depends on the disposal step and not on the resting level. The comparison is available in the recycling-repair paradigm: in E4 neurons, compare excursion restoration by compartment repair against restoration by any level-directed intervention [14]. **Refutes** the reformulation if a level intervention restores excursion as fully as compartment repair does.

II. What This Forbids

It forbids a single scalar called phosphatase reserve. Two enzyme families act on different residues at different nodes of this cascade and move in opposite directions in the same disease, one of them governed by the proteolytic system whose failure defines the lesion [5,6].

It forbids inferring compensation from a mean. Where a buffer and the damage it buffers write the same mark, the mean of that mark is not evidence about either, and a trial powered on it is powered on a quantity that cannot carry the answer [12].

It forbids treating an exosomal cargo ratio as an endosomal readout without reporting particle number. The release rate moves with the lesion [31].

It forbids the assumption that enlarging a buffer helps at a node terminated by destruction. Where one mark sets both what an enzyme does and how long it survives, an intervention on the mark is an intervention on the protein's survival, and its sign depends on which arm the tissue needs [2].

And it forbids reading Ephexin5 abundance as damage. Angelman syndrome is the reciprocal experiment and it returned the opposite sign [2]; the human loss-of-function phenotype for the gene is a dementing cerebral small-vessel disease with skeletal fragility [20].

12. Scope, and What Would Refute the Whole Argument

What is claimed. This is a claim about how compensation at one control surface — the Rho-family/actin machinery of the excitatory dendritic spine, and the sorting and disposal systems that serve it — should be modelled and measured. It is a methodological correction with mechanistic content, not a theory of the disease. It says nothing about who develops Alzheimer’s disease, why particular neurons fail first, or the substantial fraction of dementia not attributable to the pathologies conventionally measured.

What is not claimed. That compensation is unimportant, or that the reservoir reading is worthless: Section 2.3 keeps three of its results, including one node where its mathematics is correct. That STEP61 is the master phosphatase of this system, or that it acts on the licensing tyrosines. That any of the buffers named in the compensatory literature has been measured in human tissue in the states the models require — most have not, a limitation those models state about themselves and which applies with equal force here.

The weakest joint, stated plainly, is Section 4.3. The STEP61 argument establishes that *a* neuronal tyrosine phosphatase relevant to this disease is proteolytically governed and rises when the reservoir model says the phosphatase limb should weaken. It does not establish that this enzyme resets the specific residues the licensing account identifies. If the tyrosine phosphatase acting on those residues turns out to behave like PP2A — depleted, not accumulated — then the sign inversion at the heart of Section 4 disappears, and the reservoir reading survives with a corrected enzyme name. **The experiment is the obvious one and has not been done:** identify the phosphatase acting on the Ephexin5 licensing tyrosine, and measure its abundance and activity in human Alzheimer cortex.

Three further results would refute the argument. If the two phospho-marks covary in disease as in control, the sign is recoverable at the serine, the degeneracy has no consequence in tissue, and Section 5 collapses. If total Ephexin5 predicts active RhoA as well as its phosphorylated fraction does, the clock/reservoir distinction has no measurable consequence at that node. And if a phosphatase-restoring agent restores dynamic range as well as compartment repair does, the bandwidth reformulation of Section 8 is wrong.

13. Validity Ledger

Tier	Basis	Claim	Why it sits there
Strong	Imported, established	Synapse loss is the strongest structural correlate of cognitive impairment, and the endosomal lesion precedes deposition	Terry and colleagues 1991 [15]; Cataldo and colleagues 2000 [17], whose presenilin control establishes the lesion is not amyloid's consequence
Strong	Imported, established	Two antagonistic Rho-family arms activate the same LIM-domain kinase at the same residue and add the same phosphate to cofilin serine 3	Direct biochemistry, stated by the authors as a general conclusion [12,25]
Strong	Imported, established	STEP61 is elevated in human Alzheimer prefrontal cortex, and the elevation reflects impaired ubiquitin-proteasome degradation of the phosphatase	Human cortical measurement with mechanism in slice and mouse [6,23,22]
Strong	Imported, established	One covalent mark on Ephexin5 sets both substrate selection and proteasomal fate	Two laboratories, fifteen years apart, with a phosphomutant [1,2]
Moderate	Inference, this paper's claim	Most named buffers at this control surface are turnover cycles, not capacities, and the reservoir model mis-specifies them	The molecular facts are established; that they compose into a clock rather than a reservoir is the reading offered here
Moderate	Inference, this paper's claim	There is no single phosphatase reserve, because the two limbs move in opposite directions and one is proteolytically governed	Follows from the two strong rows above; weakened by the unestablished enzyme-substrate link of §4.3
Moderate	Observation, reported here	A PP2A-activating agent has not moved cerebrospinal-fluid phospho-tau across two trials in two dementias	Two trials, three reports; both small with exploratory endpoints. The negative is real but neither study was powered for efficacy [8,9,10]
Weak	Predicted, untested	Part of the apparent abruptness of transition is a property of the instrument rather than of the system	The discrimination is specified and cheap, and it has not been run
Weak	Predicted, untested	STEP61 and Ephexin5 accumulate in the same synapses	Both accumulations are established separately; their co-location is inferred from a shared disposal route

14. Closing

The failure literature asked what breaks. The compensation literature asked what held. This paper asks a third question, which is what kind of thing the answer to the second one is, and finds that the field has been answering it with the wrong noun.

A reserve you can spend is a reservoir. A reserve you can only run is a clock. The distinction is invisible at the level of a molecular list — the same proteins appear in both — and it becomes visible the moment anyone tries to measure how much is left. At a reservoir, that question has an answer. At a clock, it has an answer that is not about the thing you care about, and the neuron with the most transducer left is the one whose disposal failed first.

The disease appears to have found this out before the field did. It does not deplete the proteasome; it misdirects it, so that a receptor is destroyed and an exchange factor is not, and a phosphatase accumulates while another declines. Every one of those is a full tank. None of them is a working clock.

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