Why lithium? The Missing Ocean Mineral conjecture: a possible Ediacaran origin for neural lithium function.

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Abstract

Recent evidence links depletion of physiological levels of lithium to Alzheimer's pathology but a functional biological role for lithium in cells has not yet been identified.

We propose the Missing Ocean Mineral (MOM) conjecture that lithium, through competition with magnesium at the catalytic sites of regulatory enzymes, originally functioned as a stochastic environmental interrupt — a low-frequency signal that allowed early eukaryotic cells to pause high-priority processes and permit periodic maintenance. Acute depletion of ocean lithium following the Marinoan glaciation (~635 Mya) disrupted this ambient regulation and would have imposed selection pressure for internal lithium retention and control. The metazoan lineages that survived this crisis could have evolved mechanisms to retain, regulate, and release lithium on demand; converting an unreliable environmental signal into a controllable intracellular one. This innovation may in turn have prompted the evolution of the metazoan neuron: a cell type whose defining capacity for controlled state-switching would have derived from the internalisation of an ancestral lithium-based interrupt.

The molecular components that underlie this proposed retention and regulation of lithium in neural cells remain uncharacterised. The conjecture is advanced as a framework for investigation, and two experimental laboratory tests are suggested.

1. Introduction

Lithium occupies an unusual position in medicine and biology. It is prescribed for bipolar disorders, typically at daily doses of several hundred milligrams, producing blood concentrations in the low millimolar range. At these concentrations lithium seems to inhibit a range of magnesium-dependent enzymes, including glycogen synthase kinase-3 (GSK-3) and inositol monophosphatase, and exerts broad effects on neural signalling. However, despite biomolecular research into these effects, a specific natural role for lithium in the brain has not yet been established.

A parallel body of evidence has long suggested that lithium may also have biological relevance at far lower concentrations. Ecological studies have repeatedly associated higher lithium levels in drinking water with reduced rates of suicide, violent crime, and dementia [1,2]. The effects are small and the methodologies correlational, but the pattern across countries and decades has been consistent enough to invite explanation. Careful nutritional studies in farm animals and rodents reinforce this picture. Anke's group at the University of Jena established from the 1970s onwards that lithium-deficient goats exhibited reduced conception rates, altered offspring sex ratios, and elevated mortality [3,4]. Pickett and O'Dell at the University of Missouri documented parallel findings in rats, showing significant transgenerational reductions in litter size, birth weight, and weaning weight across three generations on lithium-deficient diets [5]. Schrauzer, reviewing this and related evidence, proposed a provisional adult human requirement of approximately 1 mg/day [6]. However, in the absence of an identifiable mechanism to explain the biological function of lithium, these proposals have yet to be acted upon.

The paradox is that a substance whose pharmacological efficacy emerges only at near-toxic doses also appears to have a nutritional requirement at doses a thousand times lower. The gap between the millimolar range at which lithium acts clinically and the micromolar range at which it appears to matter nutritionally spans three orders of magnitude.

The most direct evidence of a specific role for lithium in the neuron has come most recently. Aron and colleagues, working in Yankner's laboratory at Harvard Medical School, reported in August 2025 that lithium concentrations in the prefrontal cortex were significantly reduced in people with mild cognitive impairment and Alzheimer's disease compared to healthy controls, and that amyloid plaques actively sequester lithium from the surrounding tissue [7]. In mouse models, strict dietary lithium depletion accelerated cognitive decline even in healthy control animals, worsening amyloid and tau pathology; supplementation with lithium orotate reversed these changes. Of twenty-seven metals analysed, only lithium showed this pattern of depletion and disease-associated sequestration.

These observations pose a problem. Trace lithium appears to matter for neural health in a way that cannot be explained by any currently identified functional mechanism. The concentrations at which epidemiological protection and Harvard's experimental effects are observed are orders of magnitude below those required to significantly inhibit the observed function of GSK-3 or inositol monophosphatase. Whatever lithium is doing at physiological levels, it is doing it at low doses that pharmacology may not have fully elucidated.

This paper proposes that lithium may have a specific role in the neuron calibrated over evolutionary time, operating near the threshold of detectability, and distributed across regulatory machinery whose function is still being explored.

We propose that lithium originally functioned as an environmental interrupt — a stochastic, low-frequency signal arising from competition with magnesium at the catalytic sites of regulatory enzymes. In a lithium-rich early ocean, this competition would have produced a continuous low rate of enzymatic pauses, allowing cells to interrupt high-priority processes

and permit the housekeeping tasks — damaged protein clearance, membrane repair, the rebalancing of ion gradients — that are fatal if permanently deferred. The mechanism would have been probabilistic and it was free, and operated without a requirement for internal regulation.

The Missing Ocean Mineral (MOM) conjecture proposes that this ambient regulation was then catastrophically disrupted by the Marinoan glaciation (~635 Mya), which through glacial shutdown of continental weathering and intense reverse weathering stripped lithium from the oceans while magnesium and calcium levels were maintained by hydrothermal activity. Organisms that had come to depend on environmental lithium for baseline regulatory function would have faced a crisis, creating selection pressure for internal retention and control of an ion that had suddenly become scarce. The metazoan lineages that survived this crisis, we propose, did so by evolving mechanisms to capture, retain, and mobilise lithium intracellularly — converting an unreliable environmental signal into a controllable internal one, and in so doing acquiring the capacity for precisely timed state-switching.

This paper develops the conjecture in three parts, examining the geological evidence for Ediacaran lithium depletion, the evolutionary innovations the crisis would have selected for, and the consequences for neural function. It concludes with specific testable predictions whose confirmation or refutation could determine the conjecture's validity. The specific molecular components underlying lithium retention and mobilisation in neural cells remain uncharacterised but the conjecture may help frame questions about their possible identity.

2. The interrupt mechanism

The central proposal of the MOM conjecture is that lithium has an ancient functional role arising from a specific chemical fact: the small ionic radius of Li^+ allows it to compete, occasionally and imperfectly, with Mg^{2+} at the catalytic sites of magnesium-dependent enzymes. In the context of a lithium-containing aqueous environment — such as the Proterozoic ocean — this competition would have produced a steady, low-frequency perturbation of those enzymes. We propose that this perturbation was adopted not as a biochemical nuisance but as a beneficial feature: an ambient regulatory signal that early cells evolved to tolerate, and then to exploit, as a mechanism for permitting periodic cellular maintenance.

The scheduling problem

Living cells face a difficulty that is also familiar from the design of complex automated systems. Cells run a number of high-priority continuous processes — ion pumping, maintenance of membrane potential, core metabolism, DNA replication and transcription during cell division — that cannot be paused for long without immediate consequence. They also have lower-priority but essential tasks: clearance of damaged proteins, repair of membrane lipids, rebalancing of drifted ion gradients, sorting and recycling of worn-out

components. These lower-priority tasks may not be urgent in any given moment, but all of them could cause damage if permanently deferred. The problem is one of scheduling: how do high-priority continuous processes ever pause long enough for low-priority maintenance work to run?

In engineered systems, this problem is solved by an interrupt — a signal that forces the high-priority process to suspend briefly, permitting scheduled maintenance, then resume. The interrupt does not need to be frequent, and need not be urgent. It needs only to be occasional, reliable and unstoppable. Without it, high-priority processes run continuously and the maintenance backlog grows; eventually the system degrades from accumulated unrepaired damage rather than from any acute failure.

Early cells had no dedicated scheduler and no internal clock. But they were bathed in a solution of ions, some of which could interfere with their regulatory enzymes in a manner that would have produced exactly the kind of stochastic, low-frequency pausing that a primitive scheduler requires. Lithium, we propose, was one such ion — and perhaps the principal one.

The chemistry of lithium–magnesium competition

Magnesium is the fourth most abundant cation in seawater and the most abundant divalent cation inside cells. It serves as an essential cofactor for a large fraction of eukaryotic regulatory enzymes, including those involved in ATP handling and phosphotransfer, the kinases and phosphatases that modulate signalling cascades, and the GTPases that control cytoskeletal and membrane dynamics [8]. These enzymes typically bind Mg^{2+} at a specific site where it coordinates the phosphate groups of ATP or other nucleotide substrates, enabling the catalytic step.

Lithium (Li^{+}) and magnesium (Mg^{2+}) differ in charge but are very similar in size — the ionic radius of Li^{+} is approximately 0.76 Å, that of Mg^{2+} approximately 0.72 Å [9]. Under appropriate conditions, Li^{+} can enter a Mg^{2+} binding site and occupy it, although because it carries only one positive charge rather than two its binding is weaker and its coordination geometry different. The consequence is that when Li^{+} displaces or competes with Mg^{2+} at an enzyme's active site, the enzyme does not function normally. Depending on the enzyme and the local conditions, it may be slowed, stalled, or briefly inactivated until the Li^{+} diffuses away and a Mg^{2+} ion re-occupies the site.

This competition is best characterised for glycogen synthase kinase-3 (GSK-3), where the mechanism of lithium inhibition has been shown to involve direct competition with Mg^{2+} at the catalytic site [10]. Lithium's effects on inositol monophosphatase, pyruvate kinase, and several other magnesium-dependent enzymes appear to operate through analogous competition [11]. The magnesium-dependent regulatory machinery of eukaryotic cells is broadly susceptible, in principle, to interference by Li^{+} when present.

In the modern intracellular environment, free Li^{+} is normally present only at vanishingly low concentrations, and this competition may be correspondingly rare. In a lithium-rich external

environment, however, or inside a cell that had failed to exclude lithium from its cytoplasm, the competition would occur often enough to have biological consequences.

An ambient interrupt

Consider a population of early Proterozoic eukaryotic cells in a salty ocean with a normal lithium concentration. Their intracellular magnesium would be actively regulated, as it is in all modern cells, by transporters selective for divalent cations [12]. Lithium, being monovalent, would not be recognised by these transporters and would diffuse into and out of cells passively, equilibrating with whatever concentration existed in the surrounding water.

With ambient intracellular Li^+ present at some trace level, the magnesium-dependent regulatory enzymes of these cells would experience occasional, brief, stochastic interference. Any given enzyme, most of the time, would function normally with Mg^{2+} at its active site. Occasionally — perhaps a fraction of a percent of the time — a Li^+ ion would wander into the site and briefly stall the enzyme. At that moment, the regulatory process it was controlling would pause. Whatever downstream activity depended on that enzyme's continuous operation would relax momentarily. When the Li^+ diffused away and Mg^{2+} reoccupied the site, normal function would resume.

This is a rough but functional description of a low-frequency stochastic interrupt. It has three features relevant to the argument that follows. First, it is not under cellular control: the cell neither schedules the interrupts nor can suppress them. Second, it is reliable in the aggregate: although any individual interrupt is random, the rate is determined by the ambient Li^+/Mg^{2+} ratio and is therefore constant on any relevant timescale. Third, it is cheap: the cell pays no metabolic cost for the mechanism itself; the interference is a free consequence of the ambient ionic composition.

We propose that this ambient interrupt allowed early eukaryotic cells to accomplish periodic maintenance that would otherwise have been squeezed out by continuous high-priority regulation. A cell whose damage-clearance machinery required brief pauses in its primary metabolic cascades would have received those pauses, not because anything scheduled them, but because the ocean provided them stochastically.

The proposal

The claim of this section is narrow but load-bearing. We are not proposing that lithium performs a precisely regulated biological function in early cells. We are proposing that the ambient presence of lithium in the Proterozoic ocean produced a stochastic, low-frequency perturbation of magnesium-dependent regulatory enzymes, and that this perturbation was functionally useful — providing early cells with a reliable mechanism for permitting periodic maintenance without the need to evolve a dedicated scheduler. The mechanism would have been unreliable in detail, and unintentional in any evolutionary sense. But it would have been effective and it would have been free.

If this proposal is correct, then early eukaryotic cellular biology was calibrated to a regulatory landscape in which occasional lithium-induced enzymatic pausing was a continuous background condition. A subsequent disappearance of ambient lithium would then have posed a specific problem — not the loss of a specific enzyme or pathway, but the loss of a background regulatory rhythm on which cellular maintenance had come to depend. It is to such an environmental episode we now turn.

3. The Ediacaran lithium depletion

The MOM conjecture relies on the late Neoproterozoic seawater being selectively depleted in lithium during and after the Marinoan glaciation (~635 Mya), and that this depletion was sustained long enough to impose biological selection pressure on organisms that had come to rely on ambient environmental lithium. This proposition follows from established geochemistry. The lithium-poor post glaciation Ediacaran ocean is well-described in recent geochemical literature; what the conjecture does is to take this geological observation into a context where it may have a very specific biological consequence.

The geochemical argument

The lithium cycle is dominated by two inputs and two sinks. For lithium inputs: continental silicate weathering delivers lithium to the oceans via rivers, and hydrothermal vents deliver lithium from sub-sea mineral sources. These are balanced by two main sinks: authigenic clay formation on the seafloor (reverse weathering) and low-temperature alteration of basalt [13].

Quantitative summary — the modern lithium cycle. *Riverine input delivers approximately 1.0×10^{10} mol/yr of lithium to the oceans, with a characteristic δ^7Li of approximately +23‰. Marine hydrothermal flux contributes a further 1.3×10^{10} mol/yr at $\delta^7Li \approx +8$‰ [13]. These inputs are balanced by two sinks: authigenic clay formation (reverse weathering) and low-temperature alteration of basalt, both of which preferentially incorporate the lighter ^6Li isotope. The isotopic fractionation during clay formation is well-characterised and largely constant across a wide range of conditions [13]. The net effect is that modern seawater δ^7Li is approximately +31‰, markedly higher than either of its inputs — a reflection of the steady removal of ^6Li into marine clays since the last ice-age. The residence time of lithium in the modern ocean is approximately 1 million years, long enough that seawater δ^7Li is a sensitive indicator of long-term shifts in the input/sink balance.*

During the Marinoan glaciation, which lasted between approximately 3 and 15 million years, this balance was disrupted in two directions simultaneously. The Marinoan was the last and most severe of the Neoproterozoic "Snowball Earth" glaciations, during which ice is thought to have extended from the poles to the equator, locking most of the ocean beneath sea ice and shutting down the hydrological cycle almost entirely [14,15]. Thus continental weathering was dramatically attenuated for millions of years by the loss of liquid water and the widespread ice cover; riverine lithium input to the oceans was therefore strongly reduced. At

the same time, reverse weathering on the seafloor was accelerated by the unusually high concentrations of dissolved silica that characterised Precambrian oceans, which lacked the biological silica sinks (diatoms, radiolarians) that dominate modern silica cycling. This high silica availability accelerated authigenic clay mineral formation, which in turn accelerated the removal of lithium from seawater [16].

The combined effect was a significant net negative balance for lithium: greatly reduced input, greatly enhanced sink. Magnesium and calcium, by contrast, continued to be replenished by submarine hydrothermal activity associated with the breakup of the supercontinent Rodinia, which was ongoing through this period [17,18]. The Ediacaran lithium crisis, if we may call it that, was specifically a crash in the amount of dissolved lithium in the single super-ocean of the time, while other biologically important cations remained relatively stable and available.

Quantitative summary — the Ediacaran lithium crisis. *During the Marinoan Snowball Earth (~635 Mya), the riverine lithium input to the oceans collapsed: the hydrological cycle was largely shut down by global glaciation, and continental silicate weathering was attenuated by widespread ice cover. At the same time, reverse weathering on the seafloor accelerated. Precambrian oceans lacked the silica-fixing plankton (diatoms, radiolarians) that dominate modern silica cycling, so dissolved silica concentrations were much higher than today, driving rapid authigenic clay formation and correspondingly rapid removal of lithium from seawater [16]. The net effect was a sustained stripping of lithium from the ocean, producing a distinct geochemical signature: δ^7Li values in carbonate archives from the immediate aftermath of the glaciation average around +8.4‰ in the Doushantuo cap dolostone [16], compared to +31‰ in the modern ocean. Box-model reconstructions indicate that the depletion persisted well into the Cambrian, with the lithium cycle only returning to modern intensity after approximately 525 Ma [19]. Absolute concentrations are not directly recoverable from the isotope record, but the combined collapse in input and acceleration in sink implies that dissolved lithium may have fallen by an order of magnitude or more during this interval.*

Evidence for the depletion

Direct measurement of Ediacaran seawater lithium concentrations is not possible. The evidence is isotopic, drawn from the δ^7Li signature preserved in carbonates and mudstones of late Neoproterozoic and early Cambrian age.

Tian, Gan and Xiao [16] analysed δ^7Li in the Doushantuo cap dolostone, deposited in South China in the immediate aftermath of the Marinoan glaciation. They reported an average δ^7Li of approximately +8.4‰ — substantially lower than the modern value of +31‰, and broadly consistent with earlier compilations of Precambrian carbonate δ^7Li [20]. The interpretation, which they develop in detail, is that late Marinoan hypersaline seawater had undergone extensive synglacial distillation: continued removal of lithium into authigenic clays, in the absence of adequate riverine replacement, produced a persistent lithium-poor ocean with a characteristic low-δ^7Li signature.

A subsequent study by Zhang and colleagues [19], analysing a large dataset of marine mudstones spanning ~660 Ma to ~500 Ma, extended the picture. They reported that continental clay formation only returned to its modern intensity after approximately 525 Ma. The lithium-poor conditions of the late Neoproterozoic ocean persisted, in other words, well into the Cambrian — through precisely the window during which the metazoan lineages were radiating and the neuron was evolving.

What this means for the conjecture

Three features of this picture are important for the biological argument that follows.

First, the depletion was real and measurable, and it is supported by independent studies from multiple laboratories using different archives (carbonates, mudstones, dolostones). The conjecture does not rest on a single isotope measurement; the lithium-poor late Neoproterozoic ocean is now a reasonably settled feature of the geochemical record.

Second, the depletion was specifically lithium-selective. Other cations relevant to cellular biology — magnesium, calcium, sodium, potassium — were not co-depleted. This is the asymmetry the conjecture requires. A general mineral crisis would have imposed selection pressure for generalised ion handling; a lithium-selective crisis imposes selection pressure for specifically lithium-retaining adaptations.

Third, and perhaps most important for the evolutionary argument, the depletion was sustained. The conjecture requires not merely a brief perturbation but a long-duration pressure, operating over evolutionary timescales sufficient for heritable adaptation to arise and spread. The combination of the Marinoan Snowball Earth itself (lasting 3-15 Myr) with the subsequent slow recovery of the lithium cycle (extending to ~525 Ma by the Zhang dataset [19]) gives a window of roughly 100 million years during which ocean lithium remained markedly below modern values. This is ample time for selection to operate on populations of early multicellular organisms whose generation times were likely measured in days.

Limits of the evidence

Absolute concentrations of lithium in Ediacaran seawater are not directly measurable. δ^7Li records the isotopic ratio, not the concentration, and the inference of depletion relies on box models of the lithium cycle [21] rather than on direct measurement. The degree of depletion — how much lower than modern levels the ocean actually fell — is therefore uncertain within perhaps an order of magnitude. The geographic uniformity of the depletion is also not fully resolved; the isotope signal is strong in the sections examined but the global ocean may have varied regionally in ways the existing data cannot fully constrain.

None of these uncertainties undermines the core claim. The late Neoproterozoic ocean was severely lithium-depleted relative to the ocean environment before and after this episode, the depletion was sustained through the window during which metazoan nervous systems

evolved, and the depletion was not accompanied by comparable reductions in other biologically important cations. These three features are what the biological argument requires.

We turn now to the possible effects of this environmental episode on ocean organisms.

4. The metazoan response

We propose that the lithium-depleted ocean posed a specific problem for cells that had come to rely on ambient lithium interrupts for their regulatory rhythm. The environment no longer provided a sufficient supply of Li^+ to compete occasionally with Mg^{2+} at regulatory enzyme sites. The stochastic pausing that had permitted cellular maintenance was vanishing, while the underlying need for such pauses remained. Lineages that adapted genetically to this new mineral balance would have a strong evolutionary advantage spanning millions of years.

We propose that some of the metazoan lineages that emerged from this crisis may have done so by evolving an internal substitute for the ambient mechanism. This section suggests what biomolecular functions may have been required.

Three functional requirements

An internal substitute for a suddenly scarce environmental interrupt may need to meet three functional requirements, each distinct from the others and each necessary if the mechanism is to operate efficiently.

Capture. In a lithium-depleted ocean, cells would need to sequester lithium from a medium where it is scarce relative to chemically similar but more abundant cations, particularly magnesium. Passive equilibration will not suffice: if the external concentration of lithium is too low to support the ambient mechanism, accumulation is required. This points to a bulk-binding mechanism of some kind — a lithium sponge, if the metaphor is useful, with sufficient binding capacity to absorb the small amount of lithium available against a concentration gradient. The sponge need not be actively pumped; it need only be sufficiently absorbent and sufficiently selective for Li^+ to accumulate lithium where passive equilibration alone would not.

Move. The operational regulatory enzymes — those at which the critical interrupt function actually happens — are unlikely to be co-located with the bulk capture machinery. A captured lithium ion sitting in a sponge somewhere in the cell is of no use to a magnesium-dependent kinase operating elsewhere. Some mechanism is required to move lithium from the sites of capture to the site of use.

Utilise. A mechanism that only captures and moves is not useful. The delivered lithium must perform the interrupt function at the appropriate regulatory enzyme sites, and ideally it would do so in a reversible way, so that once its work is done, the lithium might be recaptured, retained, or exchanged. This points to a reversible handling mechanism — hold, use, recapture — rather than a one-way binding. We have sometimes thought of this as a token-in-

a-slot picture: the lithium ion is the token, the cellular machinery is the slot, and the mechanism might operate by repeated insertion and release rather than single use. But if Capture and Move phases are sufficiently efficient then re-use may not be strictly necessary.

These three requirements — Capture, Move, Utilise — together specify what the metazoan innovation had to achieve. They do not specify how, though any mechanism that satisfies all three will share certain properties: selectivity for Li^+ over Mg^{2+} at each stage, a reversible binding capable of cyclic use, and an association with the magnesium-dependent regulatory machinery at which the interrupt function is performed. These properties constitute experimental signatures that can be searched for in candidate proteins and pathways.

Where to look

The paper does not claim to have identified the molecular components of capture, movement, and utilisation in metazoan cells. It does propose that such components exist, that their evolutionary origin lies in the aftermath of the Ediacaran crisis, and that they operate in association with the magnesium-dependent regulatory enzymes implicated in lithium competition. From these claims, something can be said about where future experimental work might usefully look.

The magnesium-dependent regulatory enzymes most directly implicated in lithium competition — glycogen synthase kinase-3 (GSK-3) principal among them — sit within regulatory networks whose elaboration in the metazoan lineage is striking. The Wnt signalling pathway, in which GSK-3 sits at the regulatory centre, is a metazoan innovation. The scaffolding proteins that coordinate GSK-3 activity — Axin, Dishevelled, and others — are metazoan-specific or substantially elaborated in the metazoan lineage. Whether any particular component of this elaborated machinery also serves a role in lithium capture, movement, or utilisation is an open question. The observation is simply that the molecular neighbourhood around the relevant enzymes has been reorganised in the metazoan lineage, and reorganised in ways that may make regulatory control of those enzymes more internally sophisticated.

We make no claim about which specific innovations within this neighbourhood date from the Ediacaran crisis versus earlier or later. Dating the emergence of particular protein domains, phosphorylation sites, and binding motifs across the metazoan stem is technical work requiring phylogenetic and structural expertise beyond the scope of this paper. What we propose is that such work, undertaken with the present conjecture in view, may reveal innovations that satisfy the three functional requirements and can then be more closely investigated.

A separate line of investigation concerns the chemistry of lithium binding itself. Orotate, the small organic acid that gives its name to lithium orotate, has the interesting property of forming an inner-sphere complex with Li^+ while barely interacting with Mg^{2+} [22]. Whether this chemistry is relevant to intracellular lithium handling in metazoan cells — perhaps as part of a larger structural context, perhaps through the pyrimidine biosynthesis pathway of which

orotate is a key intermediate — is an empirical question that has not yet been explored in these terms.

An Ediacaran problem solved

The metazoan lineages that survived the Ediacaran lithium crisis may have done so by internalising a regulatory mechanism that had previously been environmental. The molecular details of how they may have done so are open. What the three-part architecture predicts, if it is correct, is that the regulatory rhythm of many post Ediacaran cells may depend on the processing of a very small ratio of lithium relative to other biologically necessary cations.

What follows in the next section is a consequence of such a mechanism having evolved successfully: the cell that internalises an interrupt mechanism may inherit something more than resilience, it may also have an evolutionary route to develop the ability to control switching between different states.

5. Neural consequences

A cell that has internalised the ancient interrupt mechanism — capturing, moving, and utilising lithium under its own control — may have acquired something more than a hedge against environmental loss. It has potentially acquired the biological basis for rapid and repeatable transitions between distinct functional states.

From interrupt to switch

The ambient interrupt of the Proterozoic ocean was, by its nature, stochastic and uncontrolled. A cell could use it to trigger periodic maintenance, but could not choose when it happened. Internalising the mechanism changes this fundamentally. A cell that can concentrate, position, and deliver lithium to specific regulatory enzyme sites can, in principle, selectively trigger the interrupt function. It can pause or switch its own regulatory processes as it needs to, rather than as a random event.

The biological consequence of selective pausing is the capacity for controlled state-switching. A cell that cannot pause cannot reset; a cell that cannot reset cannot fire twice. Repeated transitions between distinct functional states — resting and active, polarised and depolarised, one regulatory configuration and another — require a mechanism for returning from each state to the starting condition. Internalised lithium handling, we propose, may have provided such a mechanism.

The cell type that may have most clearly exploited this switching capacity is the neuron. The defining property of a neuron is not that it conducts electricity — many cells maintain ion gradients and transmembrane potentials — but that it can switch rapidly between resting and firing states and returns cleanly to rest after each transition. This dynamic task-switching capacity is what allows nervous systems to process information. The muscle cell represents

the same architectural solution applied to mechanical output: contract on demand, relax, be ready to contract again. Both are specialisations of a more general capacity for controlled state-switching, and both appear in the fossil record in approximately the same window — the late Ediacaran and early Cambrian [23,24].

The Mg:Li ratio

If the neuron's operating parameters were calibrated to a specific lithium-magnesium regime during the Ediacaran window, we would expect that regime to be preserved in modern neural tissue across metazoan lineages. The available evidence is consistent with this prediction.

Thibon and colleagues measured lithium concentrations across organs in marine fish and reported that fish actively exclude lithium from most tissues — liver, muscle, and other organs contain far less than passive equilibration with seawater would predict [25]. But the brain is treated differently. Neural tissue retains lithium preferentially, at approximately 0.3 µg/g dry weight. This is not passive accumulation; it is active maintenance against a body-wide exclusion effort. The brain, in other words, is a lithium sanctuary within an organism that otherwise pumps lithium out.

Quantitative summary — the Mg:Li ratio. *Fish brain lithium at 0.3 µg/g dry weight corresponds to approximately 10-15 µM total lithium when tissue water content is accounted for. Total cellular magnesium in neural tissue runs at approximately 10-20 mM, though most of this is bound to ATP and other phosphate-containing molecules. The resulting total-to-total Mg:Li ratio is approximately 1000:1 — roughly a thousand magnesium atoms for every lithium atom actively retained in neural tissue [12,25]. This ratio is the operating parameter the MOM conjecture proposes was set during the Ediacaran depletion and has been maintained since. The calculation carries assumptions — tissue water content, the proportion of Mg bound versus free, the representativeness of the fish data — and the ratio should be read as an order-of-magnitude estimate rather than a precise specification. What the calculation establishes is that the Mg:Li ratio in neural tissue is not merely small but specifically small, and small in a way that is actively defended.*

Deep conservation

The second line of evidence consistent with the conjecture concerns the conservation of neural architecture across metazoan lineages. The basic machinery of electrical signalling — the ion channels, the synaptic proteins, the signalling enzymes — is recognisably related across animals that share a common ancestor more than 600 million years ago. Cnidarians possess ion channels homologous to those in vertebrates; the genetic programmes that guide neuron development show substantial conservation [26,27]. The core design of the neuron, once established, has not been substantially revised.

This deep conservation is what the MOM conjecture would predict. If the functional parameters of the neuron were established during a specific environmental window — the

Ediacaran crisis and its aftermath — and those parameters remain under selection because they represent a deep minima in a complex solution space, then the neuron might be expected to show exactly this pattern: fixed at origin, preserved since. A more direct piece of evidence concerns the conservation of the lithium-GSK-3 interaction specifically. Castillo-Quan and colleagues showed that lithium extends lifespan in Drosophila through the same GSK-3 pathway that mediates its effects in mammals [28]. The divergence between our lineage and theirs occurred over 500 million years ago, before the Cambrian explosion. The sensitivity of neural function to lithium modulation, and the enzyme that mediates it, seems to have been conserved across that entire interval.

What the conjecture explains

The evolutionary origin of the neuron has long been unusual among biological innovations in appearing to have happened once. Eyes have evolved independently dozens of times. Wings evolved separately in insects, birds, and bats. Electrical organs evolved at least six times in fish. But the neuron, in all its essentials, was invented once and inherited thereafter. Every animal that thinks, moves, or senses — from anemones to arthropods to us — uses the same fundamental design, traceable to a single ancestral lineage. Why the neuron evolved only once, and why it evolved when it did, have not had satisfactory answers.

The MOM conjecture suggests answers to both questions. **Why only once?** Because the evolutionary innovation required for the neuron — internalisation of a regulatory interrupt mechanism — was forced into existence by a specific planetary event. The Marinoan glaciation and its geochemical aftermath created selection pressure for internal lithium handling in organisms that had previously relied on ambient environmental lithium. Once some lineages had solved that problem, they radiated into every niche where controlled state-switching was useful. Subsequent lineages faced the ecological barrier of existing incumbents and the molecular barrier of no longer having the specific geochemical pressure that had forced the innovation the first time. The door opened briefly and closed behind the survivors.

Why just then? Because the Marinoan was the specific trigger. The late Neoproterozoic lithium depletion, as described in section 3, spans the window during which metazoan nervous systems first appeared in the fossil record. If lithium availability is the driving force then the timing is not coincidence, it is a consequence.

How? Through the capture-move-utilise architecture described in section 4. Internalising the ambient interrupt mechanism may have given cells the capacity to trigger regulatory pausing on demand. That capacity, applied to cells organised for electrical signalling is the necessary function of a neuron.

A wider frame

If the conjecture is correct, the neuron is not an inevitable outcome of biological evolution but rather a consequence of a specific planetary history. A world that did not pass through a

lithium crisis might be a world of sponges and ctenophora. The existence of animals able to react, to prey and evade actively, and ultimately evolve complex nervous systems may depend on a particular geological accident that was not guaranteed to occur. If exobiology is confirmed, on Europa, K2-18b [29] or elsewhere, it may be that neuronal animal analogues will not be discovered amongst the exo-fauna if that occurrence is statistically unlikely — the anthropic principle as it may apply to neurons, if not to cellular biology *per se*. An exo-planet may have flora but no fauna; if no fauna then no eyes; if no eyes then no flowers, or need for colours. Maybe there are biologically active, but spectrally drab planets — just as earth would have been before the Ediacaran.

For our own planet, the implication is more specific. The operating parameters of every neuron of every animal alive today may trace back to a window of Earth history roughly 635 million years ago, when the ocean lost its lithium and some organisms learned to keep their own. What we call the nervous system may, on this account, be the legacy of that crisis.

6. Testable predictions

Here we present two refutable tests for the load-bearing claims of the MOM conjecture. The first tests whether a low-priority lithium-based metabolic interrupt operates in a modern eukaryote, independent of the evolutionary internalisation story. The second tests whether the internalised version of that mechanism is essential for metazoan neural function. Together they address the propositions on which the conjecture rests.

Note that the two tests presented here involve very different lithium concentration regimes. The first test must be conducted at high, super-environmental concentrations, extending up to millimolar levels of dissolved lithium ions. The second test requires a very different experimental regime where lithium is only present in sub-nanomolar concentrations.

6.1 The metabolic-rate test

If the ambient lithium interrupt mechanism operates in eukaryotes generally, as the conjecture proposes in section 2, then elevated lithium concentrations should produce measurable metabolic effects in any eukaryotic cell, regardless of its evolutionary lineage. This prediction is testable on a non-metazoan eukaryote such as the photosynthetic diatom *Phaeodactylum tricornutum*, which is well-characterised, easy to culture, and has a continuously-measurable metabolic readout in the form of CO_2 consumption under controlled light conditions.

Existing work on lithium toxicity in model organisms could be re-examined from this perspective, but the direct test we propose here asks a more focused question: is there a concentration range in which lithium begins to attenuate metabolism in a way consistent with interrupt-mechanism activation rather than with general toxicity?

The following describes an experimental approach rather than a validated protocol. The specific steps, concentrations, and timings given below are intended as a starting point for development of a working protocol rather than as a specification.

The experimental setup is straightforward. Six chambers run in parallel with identical conditions throughout: a controlled light source, a model strain of the diatom, a controlled CO_2 atmosphere, a suitable medium with strictly controlled dissolved salt levels (sea-water analogue with lithium removed to the best feasible standard), a constant aeration pump circulating the CO_2-containing atmosphere through the medium, and a CO_2 concentration recorder. The chambers are sealed and a consistent baseline rate of CO_2 removal across all chambers is established.

Two of the chambers are maintained throughout as a calibration baseline and variance check. Lithium is then introduced to the other four chambers over a range of concentrations, pipetted from a 1 M LiCl stock solution according to the following protocol:

1. Every hour each of the four experimental chambers receives an additional incremental dose of LiCl stock. Depending on chamber size, the initial dose provides a sub-oceanic concentration of lithium starting at around 0.01 mM: one aliquot in the first chamber, two in the second, four in the third, eight in the fourth.
2. Every subsequent hour the aliquot size is doubled, so that over a span of roughly ten hours a spread of three orders of magnitude in lithium concentration is achieved across the four chambers.

Once the experiment is complete, the record of CO_2 concentrations in the six chambers over time can be numerically analysed to look for the signature of interrupt-mechanism activation.

Quantitative prediction. The MOM conjecture predicts a specific shape to the response curve, following from the chemistry of Li-Mg competition at regulatory enzyme sites. If Li^+ competes with Mg^{2+} for occupation of catalytic sites, and if Mg^{2+} concentration is held constant by cellular regulation, the fraction of enzyme sites blocked by Li^+ at steady state follows a simple competitive binding equilibrium. Metabolic rate, being proportional to the fraction of sites remaining available for Mg^{2+}, is then:

$$M([Li]) = M_0 \cdot K_{MOM} / (K_{MOM} + [Li])$$

where M_0 is the uninterrupted metabolic rate, [Li] is the cytoplasmic lithium concentration, and K_{MOM} is the half-saturation constant — the lithium concentration at which half the sites are Li-occupied and metabolism is halved. K_{MOM} depends on the ratio of Li and Mg binding affinities at the catalytic site and on intracellular Mg concentration. For GSK-3, the measured half-maximal lithium inhibition in the presence of millimolar Mg is around 1–2 mM [10], which gives a rough indication of where K_{MOM} might lie, though it may differ substantially in diatom metabolic enzymes. The experimental dose range of 0.01 to 10 mM is chosen to span a wide enough window to locate K_{MOM} wherever it falls.

The resulting curve (Figure 1) has three regimes. Below K_{MOM}, most sites remain Mg-occupied and metabolism is essentially uninterrupted. Through the modulation zone around K_{MOM}, metabolic rate drops sharply as the interrupt rate rises from occasional to dominant. Above K_{MOM}, most sites are Li-blocked and the cell is effectively paused. A sigmoidal curve of approximately this shape, with a transition zone somewhere within the experimental range, would be consistent with the conjecture and would locate the value of K_{MOM} for this organism. A linear dose-response curve would suggest general toxicity instead and would be inconsistent with the proposed mechanism.

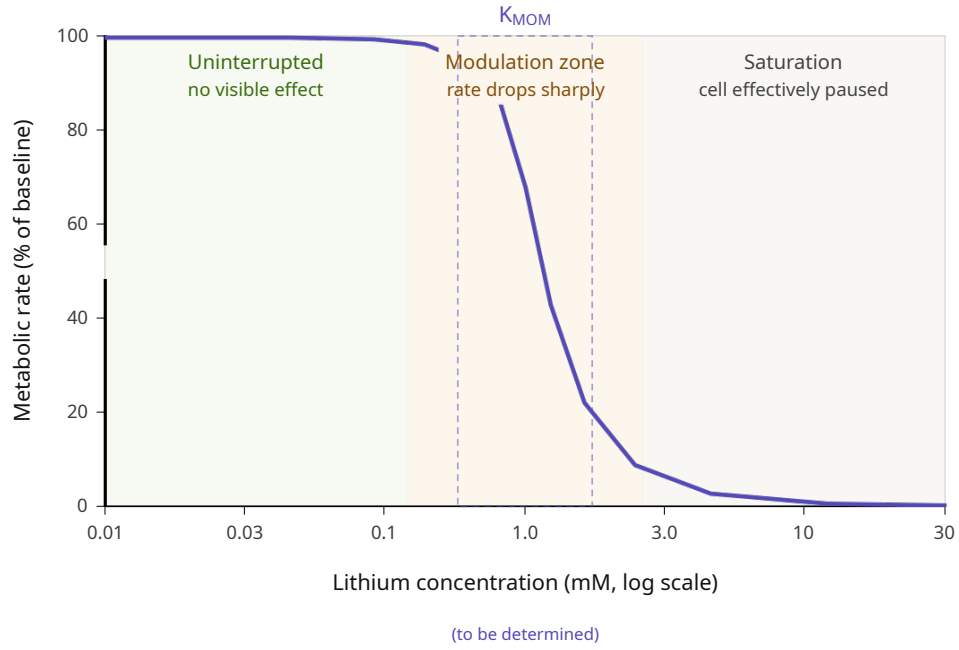

Figure 1: Predicted metabolic response to lithium. Sigmoidal decay $M([Li]) = M_0 \cdot K_{MOM} / (K_{MOM} + [Li])$, showing three regimes: uninterrupted at low concentrations, sharp modulation zone around K_{MOM}, and saturation at high concentrations. The value of K_{MOM} — the lithium concentration at which metabolism is halved — is the parameter the experiment determines.

A second feature of the predicted mechanism is that the modulation should itself be broadly reversible on the cellular timescale. A population of cells that has been briefly slowed by exposure to K_{MOM}-level lithium should, upon dilution back to a sub-K_{MOM} concentration, return rapidly and completely to the metabolic rate predicted for the lower concentration — with no hysteresis, no memory of the prior exposure, no residual depression of metabolism after the lithium is no longer present to stall the enzymes.

This reversibility signature distinguishes a true interrupt mechanism from alternatives that could also produce sigmoidal dose-responses. Toxic mechanisms typically induce stress

responses or adaptive changes that decay slowly; in this case the recovery after lithium withdrawal would be gradual and possibly incomplete. A saturation effect at an uptake transporter, with downstream damage accumulating above threshold, would similarly show hysteresis. Only a mechanism in which lithium transiently blocks Mg^{2+} binding at catalytic sites — with no longer-term cellular consequences during a brief exposure — predicts clean reversibility.

A proposed test for this reversibility is sketched below, following the dose-response characterisation. The design uses four chambers with connected gas spaces during the dosing phase, followed by a mixing step that produces a "just recovered" population whose metabolic rate can be compared directly with a "continuously maintained" population at the same final lithium concentration. If the two populations show the same metabolic rate, the mechanism is reversible in the way the conjecture predicts. If they differ, some form of hysteresis is present and the interpretation of the curve shape becomes less clean.

The mixing-based reversibility test, and its suggested procedural detail, is described in the companion protocol document [Zenodo DOI to be assigned after submission].

If the experiment reveals such a consistent transition window, the location of that window and the concentration range over which metabolic rate halves, becomes an interesting parameter in its own right. At a concentration near the middle of the transition, a cell would be running at a reduced metabolic rate but otherwise functioning normally. This suggests a useful research tool quite apart from the conjecture itself: potentially a simple non-toxic chemical means of modulating eukaryotic metabolism by a controlled amount. A simple organism dialled to 50% of its normal metabolic rate might experience what amounts to time dilation, with no other behavioural consequences. Whether or not the conjecture as a whole holds up, a clean chemical rate-control for eukaryotic cells could be a useful investigative tool.

6.2 The neuron function test

The diatom test examines the chemistry of Li-Mg competition at the cellular level. The second test addresses the further claim of the conjecture: that metazoans internalised this mechanism to produce the neuron, and that lithium is therefore essential to neural function.

The conjecture, stripped to its essentials, makes a simple claim: the neuron is a cell that requires lithium to function. If no lithium is present, the interrupt mechanism cannot operate, controlled state-switching cannot occur, and the cell cannot perform the function we recognise as neural.

The direct test is straightforward to describe. Raise a model organism in an environment depleted of lithium to below the threshold at which the functional mechanism could operate, and observe whether neural development and function proceed normally. A nematode is the natural candidate: its nervous system is well-characterised at the single-cell level, its generation time is short, and it can be raised on chemically defined media. If a nematode raised in sufficiently lithium-depleted conditions demonstrates a functioning nervous system,

the conjecture is wrong. If neural development fails — if the characteristic behaviours of the organism cannot occur, if its neurons do not fire — the conjecture gains support proportional to the severity and specificity of the observed deficit.

As mentioned previously, the conjecture implies that cells may have:

- acquired a way to sequester lithium in some bulk "lithium sponge" form
- a means to transport sequestered lithium to where it is required
- a situation where lithium may be required as little as one atom per trigger site
- the possibility that the trigger mechanism itself may retain its lithium through multiple firings

Therefore the minimal requirement for lithium to support neural function may be very low. So the difficulty lies not in the logic of the experiment but in the technical challenge of its execution. Lithium is one of the most difficult elements to exclude from biological systems. It is primordial, produced during Big Bang nucleosynthesis, and has been present on Earth since the planet's formation. It is geochemically highly mobile, present as trace contamination in essentially all water, most reagents, many container materials (including borosilicate glass), most biological feedstocks, and in atmospheric dust. Standard laboratory ultrapure water contains lithium at nanomolar concentrations; chemically defined growth media inherit further contamination from their reagent components.

If the conjecture is correct and the functional requirement is very small — possibly as few as a handful of lithium atoms positioned at specific regulatory sites and retained after every firing — then the purity required to test the prediction cleanly becomes very challenging. A nematode raised on standard ultrapure media could still carry enough lithium, by several orders of magnitude, to support the predicted mechanism. To reach the depletion level the conjecture allows requires specialist facilities: sub-boiled ultrapure water in PFA containers, chemically defined media prepared from individually purified reagents, fused silica or PFA culture vessels throughout, clean-room handling, and multiple generations of breeding to dilute out residual lithium from parent organisms.

The test does not require reaching absolute zero, which is effectively impossible. It requires reaching the threshold below which neural function breaks down. If the conjecture is correct, that threshold exists and can be measured; the experiment locates it. If no such threshold can be found — if neural function is preserved at every level of lithium depletion — the conjecture is refuted.

This is a moonshot experiment, in the literal sense that only a small number of facilities worldwide may be capable of performing it. National laboratories with trace-element capabilities, specialist geochemistry groups, or the rare biological laboratory equipped to meteoritic-analysis standards would be the relevant candidates. What we propose is that the experiment may be worthwhile, that it is decisive in principle, and that the conjecture can be either fully refuted or strongly supported by its outcome. If supported, the result — the

finding of a specific level at which lithium depletion becomes pathological to the neuron — would be of significant scientific and pharmacological interest.

7. Discussion

We feel an obligation to share some speculative ideas that may resonate with other researchers, in case these speculative ideas prove useful in some related context.

Amyloid as ancestral sponge

The conjecture suggests a capture mechanism — a bulk-binding lithium sponge — as part of the internalised architecture proposed in section 4. The molecular identity of this sponge is not specified, but it occurs to us that possibly amyloid may match this behaviour.

Amyloid-β is an unusual molecule. Its aggregation propensity is a liability, its accumulation is implicated in the most common form of age-related neurodegeneration, and its function in healthy cells has not yet been satisfactorily established but its persistence in the metazoan genome across 600 million years is suggestive. The Aron et al. finding that amyloid plaques can sequester lithium may be a clue that this aggregation is a ‘design feature’ of amyloid, and that it may be one of the lithium sponges the conjecture suggests. If one of amyloid's roles is as an ancestral lithium capture sponge, then perhaps its excessive deployment by a stressed nervous system might reflect the runaway activation of an ancient system?

A speculative story might be approximately this. Under normal conditions, the operational lithium-handling machinery — capture, move, utilise — runs quietly at low levels, with amyloid essentially dormant. Under stress, and particularly under cumulative age-related damage to the operational machinery, the cell begins to lose lithium retention at its working sites. A backup response might then be triggered: amyloid production increases, creating additional lithium capture capacity. In a younger cell this might be a transient protective response. In an older cell with chronically degraded operational machinery, the amyloid may then accumulate faster than it can be cleared, and so sequesters lithium out of the working environment faster that it can be transported to operational sites. The implication being that the disease state might constitute a positive feedback loop between a failing primary system and an over-deployed primitive response. Perhaps Tau pathology may admit a similar reading? But in any case these suggestions are entirely speculative, if they resonate with other research then fine, but we make no claims. This speculation is illustrative of ideas that might follow if low concentration lithium is eventually identified as performing an essential role in neural function.

Therapeutic lithium

Therapeutic lithium — lithium carbonate at doses of several hundred milligrams per day, producing serum levels around 1 mM — operates at approximately a thousand times the

physiological concentration the conjecture proposes for neural calibration. If the conjecture is correct, a high concentration of plasma lithium may be triggering an ancient metabolic interrupt mechanism across most cells in the body at a much higher than normal frequency. From a computational perspective it may be analogous to running a low-priority interrupt every few cycles, rather than very occasionally as ordinarily intended. From a system perspective the challenge in such a scenario would be to avoid ‘dead-lock’ conditions, where delayed processing at one location may hold up necessary processing at another position in a computationally dependent loop, potentially causing the system to stall. From a systems perspective temporal modulation might be one way to accommodate such regulation by allowing stalled processes to run occasionally.

We are not proposing any change to clinical practice. Therapeutic lithium has a very substantial and proven evidence base and provides important benefits for specific severe medical conditions; decisions about its use are matters for clinicians and patients working within that well established evidence base. This is not a caveat but an important statement of fact that we fully endorse.

The nutritional literature revisited

A small body of work from the 1970s and 1980s, led principally by Anke, Pickett, Schrauzer, and colleagues, sought to establish that lithium may be an essential trace element for mammals [3,4,5,6]. Goats and rats raised on lithium-restricted diets showed impaired reproduction, behavioural changes, shortened lifespan, and various other deficits consistent with inadequate dietary lithium. To date this work has been largely ignored partly perhaps because no theoretical functional framework has been identified within which to consider its findings.

The MOM conjecture potentially identifies a mechanistic foundation for these nutritional findings. If metazoan cells — including mammalian cells — require lithium as a functional component of their regulatory architecture, then severe dietary lithium restriction may produce measurable biological consequences. The effects in animals carefully documented by Anke and Pickett may be the kind of effects the conjecture predicts, and their work if reassessed in this light may strengthen the argument that lithium at low concentrations may be an essential trace element for normal animal physiology.

8. Conclusion

The MOM conjecture can be stated in a single passage. Lithium, present in the Proterozoic ocean at sufficient concentration to interfere occasionally with magnesium-dependent regulatory enzymes, provided early eukaryotic cells with a stochastic low-frequency interrupt mechanism that permitted periodic cellular maintenance. During the Marinoan Snowball Earth glaciation around 635 million years ago, ocean lithium crashed through a combination of accelerated reverse weathering and collapsed continental input, and the lithium-poor

conditions persisted for roughly a hundred million years. Metazoan lineages that survived this environmental change did so by internalising the ancient interrupt — evolving mechanisms to capture lithium from a depleted environment, move it to the operational sites at which it was needed, and utilise it in a controlled manner. The cell that could modulate its own regulatory rhythm in this way acquired the capacity for rapid and reversible state-switching. That capacity, we propose, is the functional origin of the neuron.

What this paper contributes is the argument itself, assembled from geochemistry, evolutionary biology, and cellular regulation in a configuration that has not, to our knowledge, previously been proposed. The conjecture is speculative in its detail and ambitious in its scope, but it is not merely speculative. It rests on published geochemical evidence for the Ediacaran depletion, on established biochemistry of lithium-magnesium competition at regulatory enzyme sites, on the observed active maintenance of lithium in neural tissue, and on the deep evolutionary conservation of the enzymes and pathways involved. It makes two testable predictions: a specific concentration-dependent attenuation of metabolism in non-metazoan eukaryotes, and a specific failure of neural function in metazoans raised in lithium-depleted conditions. Either prediction, if decisively refuted, is sufficient to falsify the conjecture.

We offer the argument in the spirit of curiosity and honest conjecture, aware that the territory it covers is substantial and that we do not have specialist expertise in each of its domains, nor the experimental facilities to test its central claims ourselves. If the conjecture is correct, it reframes the origin of the nervous system. If it is not, no damage is done by articulating it clearly enough to be tested.

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