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Perspective

Epigenetic Clocks in the Cosmic Silence of a Deep Underground Laboratory: Implications for Aging and Space Exploration

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ABSTRACT: DNA methylation aging clocks are among the most accurate biomarkers of chronological and biological age, yet why the methylome encodes time with reproducible precision remains unclear. Current models emphasize developmental patterning, imperfect epigenetic maintenance, chromatin drift, and remodeling associated with DNA repair. However, they do not consider whether the persistent physical noise from Earth's radiation environment contributes to clock variance or coherence. Here, we propose DEEP-CLOCK, an experimental framework that uses the deep underground laboratory (LSC-DUL) at Canfranc (Spain) as a natural protector from a primary external stochastic input, namely surface-level cosmic-ray muons. DULs suppress the muon component of cosmic-ray background radiation by several orders of magnitude without eliminating endogenous biochemical noise and other radiation sources. This enables DNA methylation clocks to be interrogated as noise-limited biosensors by measuring mean epigenetic-age trajectories, clock-CpG variance, and methylation entropy under matched underground and above-ground conditions. Two outcomes are envisioned. Muon depletion may narrow clock variance while preserving the mean trajectory, which is consistent with improved timekeeping precision. Alternatively, muon depletion could reveal structured drift, altered slopes, or metastable offsets, suggesting that extreme radiobiological quietness could destabilize clock coherence. Neither outcome would by itself imply slowed aging, rejuvenation, or improved function alone. However, DEEP-CLOCK will test whether epigenetic clock behavior is fully intrinsic or partly calibrated by chronic low-dose radiobiological background. This reductionist framework could clarify the physical constraints on epigenetic timekeeping and inform how aging clocks function in shielded terrestrial, lunar, and Martian habitats during aging, disease, and future space habitation.

Keywords: Epigenetic clocks, epigenetic drift, DNA methylation, DNA repair, muons, galactic cosmic rays, deep-underground laboratories, space exploration

1. Introduction

Epigenetic aging can be viewed as the interplay of two apparently distinct mechanisms resulting from changes in the ground state of the DNA methylome [1–4]. The first mechanism involves the programmatic and lawful features of epigenetic clocks. At specific CpG dinucleotides, the methylation of cytosines follows highly deterministic trajectories originating in developmental patterning and are maintained by a homeostatic system.

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These evolutionarily conserved, built-in patterns generate cumulative DNA methylation signatures that accurately reflect chronological age [5–8]. The second mechanism is an epigenetic drift, which appears to operate in an unregulated manner. Here, random methylation lesions build up relentlessly as molecular wear and tear accumulates and stress response networks progressively fail. This process provides a record of biological age [9–11].

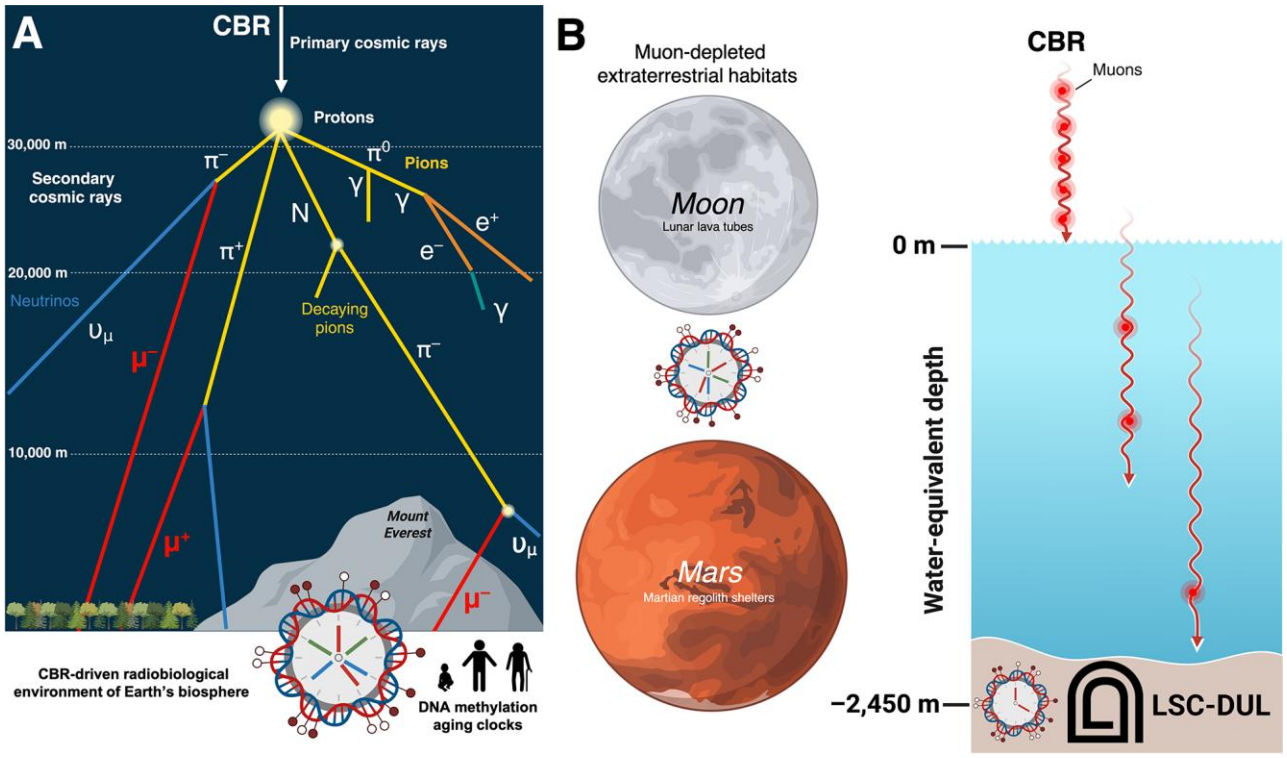

Figure 1. Muon deprivation could reveal the radiobiological logic of epigenetic aging clocks. (A) *The atmospheric origin of the terrestrial muon field.* Primary cosmic rays, which are mainly composed of protons and heavier nuclei, collide with other nuclei in the upper atmosphere. This initiates hadronic air showers. These interactions generate secondary mesons, particularly charged pions and, at higher energies, kaons. These mesons decay into muons and muon neutrinos/antineutrinos. Muons, like electrons, have a negative electric charge, but their mass is more than 200 times greater. Muons have an average lifespan of 2.2 millionths of a second. Like electrons, tau particles, and neutrinos, muons are classified as leptons. Leptons are a class of elementary particles with spin ½ that interact with three of the four known forces: gravity, electromagnetism, and the weak nuclear force. However, leptons do not interact with the strong nuclear force. When highly relativistic, leptons have an extended effective lifetime in the laboratory frame. Consequently, many survive transport through the atmosphere and reach the Earth's surface and subsurface. They constitute the dominant energetic charged component of secondary cosmic radiation. Every minute, ~10,000 muons, which are created by cosmic rays, hit each square meter of the Earth's surface. This persistent, near-surface muon flux is a testable environmental variable that can be used to examine whether chronic, low-dose radiobiological noise contributes to detectable in DNA methylation aging clock behavior in the near-surface terrestrial biosphere. This remains a hypothetical possibility, and the DEEP-CLOCK study is designed to determine whether muon suppression alters clock variance or coherence relative to other established sources of epigenetic variability (CBR: cosmic-ray background radiation). **(B)** *Epigenetic aging in ultra-low CBR, muon-depleted environments.* Studying DNA methylation aging clocks under deep-underground, ultra-low CBR conditions (~2,450 meters of water-equivalent depth) at the Laboratorio Subterráneo de Canfranc (LSC) in Spain could reveal whether epigenetic timekeeping is an intrinsic biological program limited by noise, or if it is partly calibrated by chronic exposure to the Earth's natural muon field. Lunar subsurface settings lack an Earth-like atmospheric muon shower. Martian muon environments, on the other hand, are substantially reshaped by the thin atmosphere and would be further attenuated in regolith-covered or lava-tube shelters. Therefore, muon-depleted biology could offer a means of investigating the radiobiological constraints on the behavior of DNA methylation aging clocks and, at least in part, their performance in future off-world habitats.

Although epigenetic clocks preserve developmental time codes from conception to death, the underlying cellular identity information of the epigenome landscape gradually deteriorates due to epigenetic drift [1,2,6,11,12]. However, what was once considered random pure noise is now understood to be a quasi-deterministic process, constrained by the declining fidelity of chromatin architecture and repair. Shifts in

chromatin-modifying complexes follow directional, genomic sector-specific patterns that reproducibly erode epigenomic stability [13,14]. Consequently, the seemingly unregulated process of entropy-driven drift can be harmoniously aligned with the regulated progression of epigenetic clocks [15]. However, the evolutionary and mechanistic logic behind the contributions of the deterministic and quasi-stochastic components of a composite DNA methylation clock to epigenetic aging remains largely unknown.

Here, we present the rationale and objectives of the DEEP-CLOCK project. This pioneering initiative examines the chronological and biological time-sensing capabilities of DNA methylation aging clocks in a deep underground laboratory (DUL) facility. DULs are shielded from cosmic-ray background radiation (CBR) and other environmental disturbances, a condition known as "cosmic silence". Rather than being a mechanistic claim, "cosmic silence" refers operationally to the DUL condition in which the surface-level, cosmic-ray muon component of CBR is reduced by several orders of magnitude, while other radiation sources and biological noise can remain present. Research conducted in DULs advances our understanding of particle physics and provides answers to key cosmological questions, including those concerning the nature of dark matter and neutrino oscillations, as well as the origin of the matter-antimatter asymmetry [16–19]. Beyond physics, DULs can also reveal how cellular and molecular mechanisms in living organisms respond to the absence of natural radiation sources. Studies in these ultra-low CBR facilities have revealed that optimal cellular function, DNA repair, and stress responses unexpectedly depend on the presence of a continuous low-dose radiation exposure [20–24]. We hypothesize that when a major source of environmental randomness such as CBR is absent, DNA methylation aging clocks will reveal their ultimate molecular resolution for timekeeping due to the discreteness of their intrinsic, noisy fluctuations. These experiments will provide new insights into the evolutionary role of the constant, sublethal genotoxic pressure exerted by the inevitable CBR flux for millions of years. This flux may have influenced the radiobiological origin of DNA methylation aging clocks in the near-surface Earth biosphere (Fig. 1A).

Importantly, the DEEP-CLOCK framework does not assume that cosmic-ray muons at surface levels dominate the determination of DNA methylation aging clocks. Instead, the framework treats muons as a controlled environmental perturbation in order to test whether a small, persistent, and unavoidable component of natural radiobiological noise contributes measurably to epigenetic timekeeping. Currently, there is no direct experimental evidence demonstrating that removing cosmic-ray muons alters DNA methylation age, clock CpG variance, or epigenetic drift. Therefore, any potential muon-related contribution must be interpreted in the context of larger, established sources of methylome variability. These sources include replication-linked methylation maintenance errors, oxidative metabolism, inflammatory signaling, cell-state heterogeneity, transcriptional bursting, DNA repair activity, and culture-dependent variables, among others. Nevertheless, understanding this process could also help us predict and mitigate biological risks related to the timekeeping fidelity of aging clocks during space exploration in extraterrestrial settings with drastically different CBR conditions such as lunar lava tubes and Martian regolith shelters (Fig. 1B; Table 1).

Table 1. Operational comparison of shielding depth and muon attenuation across terrestrial and planetary environments.

Environment	Approximate overburden/ shielding	Expected muon condition	Interpretation for DEEP-CLOCK
Earth surface/AGL	0 m.w.e. shielding beyond atmosphere; sea-level muon flux ≈10,000 muons m^{-2} min^{-1}	Reference near-surface muon field	Baseline condition for matched controls
DUL/LSC	~2,450 m.w.e. rock overburden	Muon flux suppressed by several orders of magnitude	Experimental muon-depleted condition
Lunar shallow regolith	~6–7 m regolith ≈1,000 g cm^{-2} ≈10 m.w.e.	No Earth-like atmospheric muon shower; muons generated inefficiently in upper regolith	Planetary subsurface comparison, not a full spaceflight analogue
Martian regolith shelter	~3 m regolith	Simulations suggest ~90% attenuation of Martian surface muon flux	Partially muon-depleted planetary shelter scenario

Water-equivalent depth is defined as the thickness of water that provides the same areal mass overburden as rock or regolith. Thus, one meter of water equivalent (m.w.e.) corresponds to approximately 100 g cm^{-2}. This metric provides a common scale for comparing the environments of Earth's surface, DUL, lunar regolith, and Martian regolith. However, it does not specify particle composition, LET (Linear-Energy Transfer) spectrum, or biological dose. Therefore, DEEP-CLOCK will use m.w.e. and measured local dosimetry together. m.w.e. will describe the shielding geometry, and the biologically relevant radiation field will be defined by absorbed dose, dose rate, LET composition, radon, neutron flux, and material-associated radioactivity.

2. The epigenetic causes of aging: Programmatic clocks and (quasi)stochastic loss-of-information

Epigenetic clocks are low-dimensional, multivariate biomarkers that quantify an organism's rate of aging by integrating the combinatorial dynamics of changes in cytosine methylation at specific CpG sites over time [25–27]. Studies of mammalian genomes suggest that ~70 to 1,000 CpG sites, primarily in Polycomb-repressed regions, are sufficient to construct universal clocks that measure chronological age across dozens of species [28–32]. These CpGs all follow the same straight-line path in every tissue, and their slopes correlate with the clock's accuracy and the life-history traits unique to each species [32–35]. Mathematical modeling indicates that CpG methylation levels tend to drift toward site-specific, steady-state equilibria at defined rates, collectively settling onto a low-entropy landscape that is established during embryogenesis [36,37]. This stability is maintained by an epigenetic maintenance system (EMS) that proofreads methylation marks with high, stringent fidelity during early developmental phases. According to EMS theory, the "tick" of CpG clocks results from errors arising from imperfect DNA methylation maintenance machinery. While this variation initially provides adaptive flexibility, it can evolve into a pathogenic quasi-program that accelerates age-associated disease processes over time [6].

Epigenetic drift is rather viewed as a stochastic aspect of epigenetic aging [10]. Copying errors that occur progressively in DNA methylation and higher-order chromatin structures decouple the DNA methylome and the chromatin state landscape from their lineage-defining templates. This process undermines cellular identity and is reinforced by the random relocation of chromatin-modifying complexes and shifts in genomic topology [9–12]. Within an information-theoretic framework of aging, each round of double-strand break (DSB) DNA repair can randomly redistribute chromatin-remodeling factors, erasing the positional cues that characterize youthful chromatin [38–44]. This redistribution drives a genome-wide rise in methylome entropy and destabilizes nuclear organization. Experimental evidence from inducible cutting-and-excision (ICE) mice suggests that break-induced relocalization accelerates entropy gain. This diminishes the robustness of the epigenome, erodes Waddington's developmental landscape, and precipitates transcriptional decoherence and senescence [43,45–47]. Unlike the deterministic, locus-specific trajectories that define epigenetic clocks, epigenetic drift is global and non-clock-like, yet reversible. Transcription factor- and chemically induced partial reprogramming accordingly restores the low-entropy ground state, reinstating canonical chromatin topology and DNA methylation landscapes [13, 48–52].

At face value, epigenetic drift appears to be a distinct, purely stochastic loss-of-information process that occurs upstream and is mechanistically different from the deterministic ticking of clock CpGs. However, a quasi-stochastic deterioration of epigenetic landscapes more accurately explains epigenetic aging [13–15]. As the maintenance of CpGs that were vital during development declines with age, stochastic variation accelerates at dispensable sites for tissue survival or homeostasis. Regions with low maintenance efficiency and marginal functional importance therefore have fast-drifting CpGs. This leaves fundamental loci under tighter control. These errors can generate consistent, reproducible patterns of directional disorder, reconciling the seemingly chaotic drift with the regular ticking of epigenetic clocks. Comparative studies further demonstrate that long-lived species exhibit slower rates of disorder, even in CpG-sparse domains. Taken together, these findings support the presence of additional safeguards that mitigate age-related entropy [39,40]. These safeguards include sirtuin-mediated chromatin policing and repair systems, which favor essential loci and extend epigenomic stability in organisms with greater longevity [53,54]. When chromatin modifiers abandon their binding sites to repair DSBs, the unguarded loci progressively acquire disordered methylation states–a phenomenon long recognized as a source of age-related chromatin instability [41]. However, this accumulation follows directional shifts confined to particular genomic sectors, producing reproducible patterns of disorder [39,40,55,56]. Consequently, a genetically programmed limit on global maintenance and repair permits the accumulation of damage over time rather than reflecting random noise alone. This rationally explains how entropy-driven drift aligns aging clocks derived from data with precise measurements of an organism's aging rate [57].

As epigenetic drift is increasingly viewed as being constrained by programmatic rules, can endogenous and exogenous contributions to the timekeeping function of the DNA methylome naturally separate into deterministic, clock-like, versus quasi-stochastic drift? Conversely, if the progression of epigenetic clocks reflects a tightly regulated process that is mixed with random perturbations, can aging clocks improve theur ability to store and process time information improve to an unprecedented degree of precision in the absence of key sources of environmental noise? To answer these questions, we need formal stress-testing paradigms that can manipulate randomness and measure its impact on the coherence time of aging clocks at the molecular level.

3. The DEEP-CLOCK project: Studying aging clocks as noise-limited biosensors in a muon-depleted environment

One way to distinguish the proximate ("how") from the ultimate ("why") aspects of epigenetic aging is to understand the biological and statistical physics that limit the precision with which DNA methylation clocks measure chronological and biological time. How can we achieve this? Mitigating randomness provides an ideal lens through which to study the measurement ability and capacity functions of any sensor, whether physical or biological. In physics, this is achieved by removing or minimizing external noise sources, so that measurement precision is constrained only by intrinsic fluctuations [58]. Similar principles have been established in biological systems. Once extrinsic variability is removed, the internal noise of molecular processes can dominate. These limits define the fundamental capabilities of sensing and information transfer [59–62].

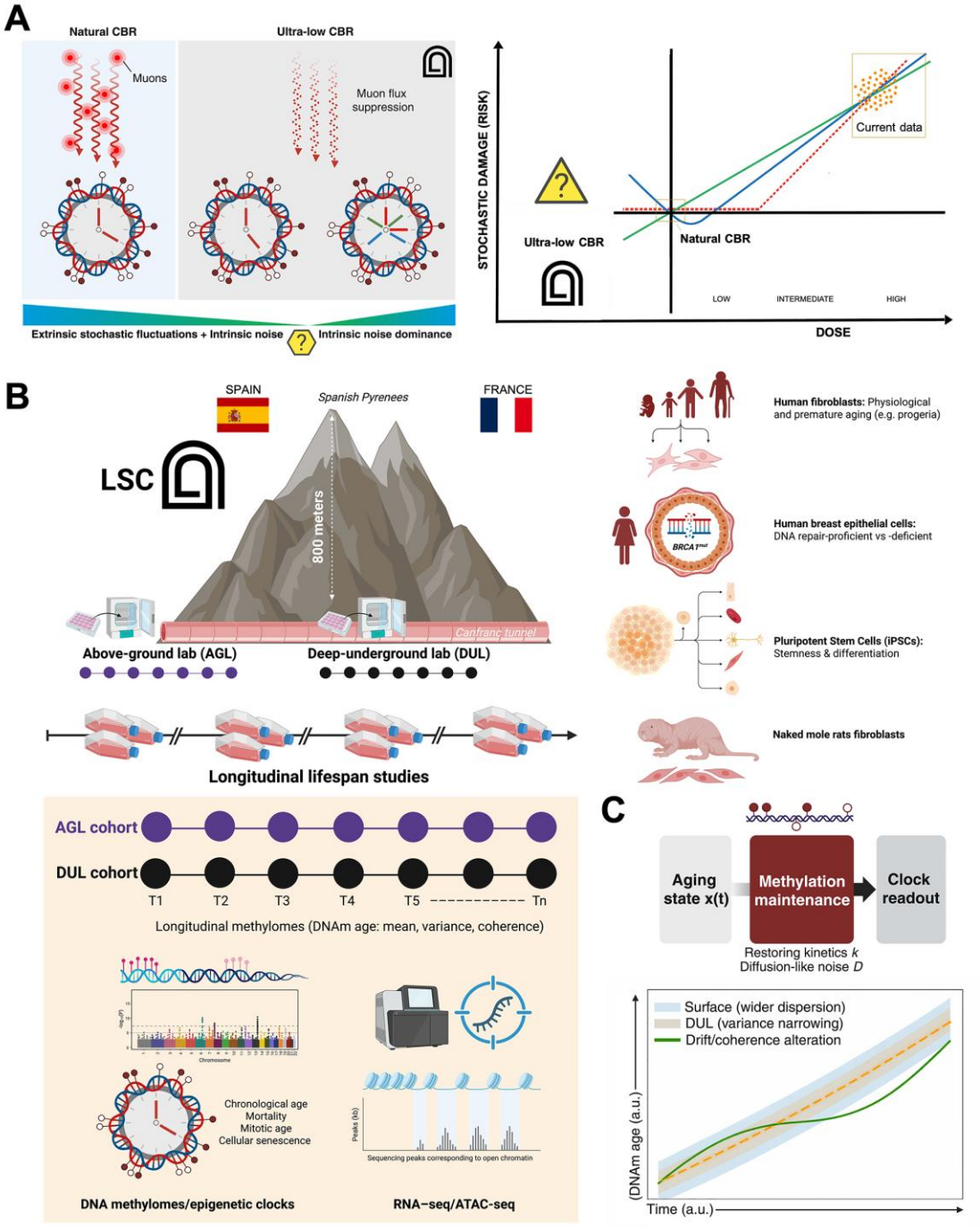

Figure 2. The DEEP-CLOCK project: conceptual rational, experimental platform and dynamical framework for testing epigenetic aging in cosmic silence. (A) *Conceptual rationale for probing aging clocks below natural background radiation.* The left schematic illustrates the transition from an environment with natural cosmic-ray background radiation (CBR), where muons contribute to persistent extrinsic stochastic radiobiological noise, to an environment with ultra-low-CBR: a muon-suppressed deep-underground laboratory (DUL). In this environment, clock behavior is expected to approach an intrinsic-noise-dominated regime. The right schematic illustrates the unresolved dose–response range below natural background radiation. In this context, we use the linear non-threshold (LNT) model as an operational reference to determine whether DNA methylation clock readouts change monotonically with reductions in the measured dose rate, especially the muon component. This approach is preferred over using the model for radiation protection claims. DEEP-CLOCK will test whether the mean DNAm-age trajectory, clock-CpG variance, methylation entropy, and clock coherence scale linearly, nonlinearly, or not at all with quantified changes in the radiological environment across DUL and AGL conditions. Threshold-like, hormetic, supralinear, or null responses remain possible and cannot be assumed a priori. Thus, the ultra-low-CBR, muon-suppressed DUL setting provides an opportunity to determine whether aging-clock outputs are radiobiologically indifferent, more precise, or structurally altered when one external radiation component is selectively suppressed. (**B)** *Parallel above-ground versus deep-underground experimental designs at the Laboratorio Subterráneo de Canfranc (LSC).* The DEEP-CLOCK initiative will conduct longitudinal studies on the lifespans of matched cell populations. Some of these populations will be maintained in an unshielded above-ground laboratory (AGL), while others will be maintained in the LSC DUL. The DUL is located 800 meters beneath the granite rock under the Tobazo Mountain on the Spanish side of the Pyrenees. Access to the DUL is horizontal through the international Somport road tunnel, which connects Spain and France. This allows for side-by-side experiments in the shielded, deep-underground Biology Platform and an unshielded AGL at an identical altitude [124]. The cosmic-muon flux decreases from $1.5\pm0.1\times10^{4}$ m^{-2} s^{-1} to $5.26\pm0.1\times10^{-3}$ m^{-2} s^{-1} by 2,400 meters of water-equivalent rock overburden, wrapped in polyethylene, cadmium and lead. This overburden also attenuates neutrons and γ-rays from primary cosmic rays hitting the Earth's atmosphere by $>10^{5}$. The environmental concentration of radon, the main source of natural radiation in underground facilities, falls to 70 ± 10 Bq/m^3 (approximately one-third of surface levels). Forced ventilation further reduces the radon concentration to ≈1 mBq/m^3 in the LSC DUL atmosphere. AGL and DUL cohorts will be sampled at various time points to quantify DNA methylation (DNAm) age trajectories. The integrated readout combines genome-scale DNA methylomes and epigenetic clock outputs with transcriptomic and chromatin-accessibility profiling. The cellular systems will include human fibroblasts representing physiological and premature aging states such as progeroid conditions; human mammary epithelial cells with and without (*BRCA1*-associated) DNA repair proficiency; induced pluripotent stem cells (iPSCs), which will be assayed for stemness and differentiation dynamics; and naked mole-rat fibroblasts, which will serve as a negligible-senescence comparator. This will enable a direct comparison of epigenetic timekeeping under natural versus muon-depleted conditions. Mathematical methods will be used to decipher the regulated versus noisy fluctuations of the slope, variance, and steady-state set points of DNA methylation maps caused by a muon-free field. **(C)** *Minimal dynamical model of clock behavior in cosmic silence.* DNA methylation aging clocks are represented as readouts of methylation maintenance dynamics acting on an underlying aging state, $x(t)$. In this formulation, a deterministic restoring component (k) captures programmed maintenance kinetics, and a diffusion-like term (D) captures the stochastic broadening of clock trajectories. The lower schematic summarizes the key predicted outcomes. Under surface conditions, clock trajectories exhibit broader dispersion. Under DUL conditions, muon suppression may narrow variance if external stochastic noise is reduced. Alternatively, cosmic silence may alter drift and coherence if background radiobiological noise contributes to long-term clock stabilization or calibration. From an operational standpoint, variance collapse will be evaluated based on reduced dispersion of clock-CpG and epigenetic age without significant deviation from the mean trajectory. Conversely, metastable drift will be evaluated based on persistent structured deviations, altered slopes, subpopulation offsets, or increased temporal autocorrelation across longitudinal samples.

To reduce randomness in our experiments and reveal some of the intrinsic operational principles of DNA methylation aging clocks, we have recently launched the DEEP-CLOCK initiative. Our goal is to test the maximum resolution ability and effective capacity of DNA methylation clocks to sense and measure aging events at their fundamental shot-noise limit (Fig. 2A, left panel). To accomplish this, we will exploit the selective suppression of a specific external component of the natural background radiation – surface-level cosmic-ray muons– attainable in DULs. Muons are high-energy relativistic leptons that constitute the primary source of low-level radiation at ground level. DULs facilities are buried beneath the equivalent of thousands of meters of water (m.w.e.), i.e., the depth of rock required to achieve the same level of shielding against high-energy particles from space as underwater [19,29,63–65]. These facilities reduce the muon component of external stochastic radiation levels by several orders of magnitude, drastically reducing background radiation signals to nearly zero [65–69]. DULs enable astrophysical sensor devices to detect and measure rare, minuscule particle physics phenomena such as proton decay, dark matter searches, and neutrino interactions [16–18]. Interestingly, DULs are emerging as groundbreaking settings for biological research. By providing an environment with ultra-low CBR, DULs offer a unique opportunity to study the impact of natural background radiation –the dominant source of public exposure worldwide– on life. A growing body of research confirms that cells and organisms respond measurably to stochastic radiobiological noise when natural background radiation is removed or

suppressed [20–24; 64–77]. However, this intervention does not entirely eliminate environmental radiation, nor does it eliminate endogenous stochastic biological damage arising from internal radioactivity, metabolic ROS, spontaneous hydrolysis, replication errors, repair infidelity, or enzymatic noise.

The DEEP-CLOCK project will utilize the Laboratorio Subterráneo de Canfranc (LSC) in Spain. The LSC is an innovative experimental platform combining ultra-low-background physics and aging research [72]. The LSC is the second largest DUL facility in Europe and one of the 14 operational DULs worldwide. Instead of using the linear non-threshold (LNT) model as a radiation protection framework, the DEEP-CLOCK project will apply the LNT concept in a limited operational sense. The project will determine whether DNA methylation clock readouts consistently change with measured reductions in background radiation dose rates, especially the muon component, under DUL and AGL conditions. Thus, the question is not whether epigenetic clocks validate or refute the LNT policy, but rather, whether the mean clock trajectory, CpG-level variance, methylation entropy, and clock coherence scale linearly, nonlinearly, or not at all with under ultra-low CBR conditions [65,73,76,78] (Fig. 2A, right panels; Fig. 2C). When cells are chronically protected from DNA damage by muons, the need for continuous DNA repair is substantially attenuated [79]. Since DNA methylation clocks indicate the innate processes accompanying aging, the DEEP-CLOCK approach would reveal how fundamental particle physics influences the origins and function of the signals detected by DNA methylation aging clocks. We acknowledge that the DUL intervention does not entirely eliminate DNA damage or epigenetic noise because other sources of variability remain active. However, the intervention selectively reduces the contribution of surface-level cosmic-ray muons. This enables us to test whether this chronic external input measurably contributes to DNA methylation clock behavior.

4. Uncovering the intrinsic limits of epigenetic timekeeping by DNA methylation aging clocks

The DEEP-CLOCK initiative frames DNA methylation clocks as noise-limited biosensors, highlighting their dual nature as they are simultaneously constrained by deterministic and probabilistic factors that limit precision. To better understand this analogy to physical systems, in which performance reflects a trade-off between a stable signal and unavoidable fluctuations [14,80,81], we can view DNA methylation clocks as a combination of a deterministic component that pulls methylation states along a programmed age trajectory and a stochastic, diffusion-like component that broadens clock readouts over time. In this minimal dynamical decomposition, the former component captures the deterministic relaxation toward age-associated trajectories and lineage-specific attractor states. Conceptually, this reflects developmental and maintenance setpoints that constrain CpG methylation landscapes. Mechanistically, it represents the overall kinetics (k) of methylation addition and removal by DNA methyltransferases and TET demethylases, as well as chromatin remodeling activities that stabilize methylation patterns. These activities establish the baseline "carrier" trajectory of the clock and largely determine the mean path of epigenetic aging. Superimposed on this deterministic backbone is a second-order term that captures diffusion-like variance (D) growth around the mean trajectory. This reflects the cumulative effects of stochastic perturbations that cause trajectories to diversify across cells and over time. These perturbations include replication and repair infidelity, transcriptional bursting, chromatin state switching, enzymatic noise, methylation miss-setting, and damage-associated lesions. Together, these perturbations increase the variance of epigenetic age readouts, thereby degrading the precision with which biological or functional age can be inferred (Fig. 2C). However, this framework should not be interpreted to mean that DNA methylation clocks are merely DNA damage counters. Many clock CpGs are developmentally patterned, sensitive to cell type, and embedded in specific chromatin contexts. Therefore, any reduction in clock noise following muon depletion should be considered an experimentally testable outcome rather than an assumed consequence of reduced DNA damage.

5. Working assumption and experimental boundaries

The central working assumption of DEEP-CLOCK is not that muons dominate epigenetic aging. Rather, the assumption is that removing muons provides a rare opportunity to alter a specific source of chronic environmental stochasticity while monitoring clock behavior over time. If muons have an effect, it is expected to be small and must be disentangled from other sources of variance at the CpG and sample levels. Therefore, DEEP-CLOCK readouts should be interpreted alongside parallel measurements of proliferation history, replication-associated methylation maintenance errors, oxidative stress and mitochondrial metabolism, DNA damage and repair signaling, inflammatory or senescence-associated states, transcriptional variability, cell-state composition, passage number, oxygen tension, medium composition batch effects, and other culture conditions. Nevertheless, this framework enables us to quantitatively test the muon-depletion hypothesis instead of presuming its mechanism.

6. Operational DEEP-CLOCK experimental framework

To make the DEEP-CLOCK hypothesis experimentally testable, the initial implementation will utilizes two core conditions for mammalian cell systems: (i) a DUL condition, in which the surface-level cosmic-ray muon component is reduced by several orders of magnitude; and (ii) an AGL-matched control condition. DUL and AGL cultures will be maintained in identical or functionally matched incubators. Common experimental variables, such as temperature, humidity, CO_2/O_2 tension, and medium composition, as well as environmental variables associated with underground placement, such as residual gamma radiation, radon, vibration, the electromagnetic environment, handling frequency, personnel access, and reciprocal transfer, will be continuously logged. The primary DEEP-CLOCK experimental substrate will be longitudinally cultured human cell systems because DNA methylation clocks are well-established in these systems. Primary human fibroblasts will serve as the anchor model, and complementary non-transformed human cell types will be used for validation. These models also allow for repeated sampling over time without the confounding factors present in whole-organism studies (Fig. 2B). More complex systems, including organoids, gastruloids, and model organisms, are proposed as exploratory extensions for future research on multicellular organization and developmental timing.

Because DUL and AGL environments may differ in non-radiation parameters, the DEEP-CLOCK design will explicitly control for location-specific experimental confounders. Sampling, feeding, passaging, and harvesting will be synchronized across sites using predefined standard operating procedures. Sample processing, methylation profiling, and downstream bioinformatic analyses will be performed blinded to the experimental condition whenever possible. To further distinguish radiation-related effects from site-specific handling or environmental effects, reciprocal transfer experiments will be incorporated. In these experiments, matched cultures will be moved from DUL to AGL and from AGL to DUL after defined exposure intervals. Only changes that are reproducible across matched incubator conditions, synchronized passage, and reciprocal transfer designs will be considered candidate effects associated with muon-depletion.

Since muon depletion does not eliminate the entire radiation background, DEEP-CLOCK will characterize the complete radiological environment under experimental condition. We will monitor the total absorbed dose and dose rate, the relative contributions of low- and high-linear energy transfer (LET) components, residual gamma radiation, neutron flux, radon and radon progeny, and laboratory- and material-associated radioactivity in parallel DUL and AGL settings. When possible, will we will match and evaluate culture media, plastics, incubator materials, and biological samples for relevant internal radionuclide contributions, including potassium-40 (40K) and carbon-14 (14C). These measurements will enable us to analyze any methylation-clock effect in relation to the measured radiation field as a covariate, rather than attributing it generically to "cosmic silence" or to muon suppression alone.

Since any muon-dependent contribution to clock behavior is expected to be more subtle than the noise and variability associated with the intrinsic methylome, sampling will be conducted over the course of several weeks or months, extending across multiple passages, DNA methylation will be measured using genome-scale platforms that profile methylation and are compatible with established human epigenetic clocks. These platforms will be used to analyze the variance of clock-CpG levels, including chronological age clocks and second-generation biological age clocks when applicable. To distinguish genuine methylation-clock effects from indirect consequences of altered cell physiology, all DEEP-CLOCK comparisons will be conditioned on matched growth and cell-state parameters. Cultures will be seeded, passaged, and harvested according to identical schedules and they will be matched for population doublings, passage number, culture density, oxygen tension, nutrient availability, and batch handling. In parallel, we will include orthogonal cellular and molecular endpoints to determine whether the changes in the methylation clock reflect radiobiological effects or secondary changes in cell state. These endpoints will include DNA damage and repair pathway activity, proliferation rate, cell-cycle distribution, mitochondrial/oxidative state, apoptosis or stress-resistance markers, senescence fraction, and cell-state composition. These measurements will enable us to contextualize any apparent clock effect in relation to recognized sources of epigenetic variation rather than attributing it directly to muon depletion. Apparent underground-associated clock changes will be considered DEEP-CLOCK effects only if they persist after adjusting for these variables. Conversely, clock changes that covary with these parameters will be treated as indirect effects of cell or culture state rather than as primary consequences of muon depletion.

Since there is currently no direct estimate of the effect size of muon removal on DNA methylation clocks, the first phase of the DEEP-CLOCK study is a longitudinal experimental trial designed to estimate the effect size rather than a definitive, endpoint-driven trial. Sample size will therefore be based on repeated biological replicates, independent culture batches, and longitudinal within-line

comparisons. Primary endpoints will include changes in the mean epigenetic age trajectory, changes in clock CpG-level variance, the dispersion of epigenetic age among replicates, the stability of longitudinal slope, the autocorrelation of deviations from the expected trajectory, the drift of epigenetic age at non-clock CpGs, and the relationship between clock behavior and DNA damage, oxidative stress, inflammation, senescence, and the transcriptional state. Thus, the statistical analysis will focus on estimation, variance decomposition, and longitudinal modeling rather than on a single confirmatory endpoint. The effects associated with DUL will be assessed using matched longitudinal models, treating condition (DUL versus AGL), time/passage, and their interaction as fixed effects, and donor, cell line, culture batch, and biological replicate modeled as random effects when applicable. The mean clock trajectory will be evaluated through changes in epigenetic-age slope and condition-by-time interactions. Clock dispersion will be assessed using variance-component analysis and by comparing residual CpG-level or sample-level variance across conditions. All primary results will be reported as effect sizes with confidence intervals, rather than being interpreted solely through nominal significance testing. Other aforementioned covariates will be incorporated to distinguish muon-associated clock effects from indirect culture- or cell-state effects. Thus, the first DEEP-CLOCK phase will provide the effect-size and variance-component estimates necessary for designing a future, adequately powered confirmatory campaign.

In this framework, "variance collapse" is defined as a reproducible reduction in CpG- or sample-level dispersion under certain conditions (e.g, muon-less DUL environment), provided that there is no significant change in the mean epigenetic age trajectory (Fig. 3). This outcome suggests that removing a chronic external stochastic input improves clock precision while leaving the deterministic carrier trajectory largely intact. It is important to note that a reduction in clock-CpG or epigenetic-age variance should be interpreted as a change in timekeeping precision or coherence rather than as evidence of slowed biological aging, rejuvenation, or improved cellular function. Thus, we will analyze the mean clock trajectory, clock variance, biological-age estimates, methylation entropy, and functional cellular-aging phenotypes as distinct, non-interchangeable endpoints. Conversely, "metastable drift" is defined as the emergence of persistent, structured deviations from the expected trajectory. These deviations may include altered clock slopes, stable subpopulation offsets, increased temporal autocorrelation, and new methylation-state attractors that are not averaged over serial passages (Fig. 3). This outcome suggests that extreme radiobiological quietness not only reduces uncorrelated noise, allowing residual internal biases or long-lived epigenetic states to dominate clock behavior. Thus, the DEEP-CLOCK design could convert the conceptual alternatives of variance collapse versus metastable drift into measurable statistical and biological endpoints.

7. Null hypothesis: Improved sensor-like aging resolution

Relocating DNA methylation aging clocks to a DUL is expected to more easily disrupt the diffusion-like component than the programmed component. However, this assumes that maintaining DNA methylation biology does not depend on other intrinsic and environmental sources of randomness. The null hypothesis states that shielding from cosmogenic muons will stabilize aging clocks by reducing the contribution of exogenous factors to the diffusion component while leaving the deterministic component relatively unchanged (Fig. 3A). The latter component is dominated by intrinsic cellular programs, core enzymatic processes, and chromatin kinetics, making it comparatively insensitive to environmental shielding from cosmic-ray background radiation. However, the former contains an exogenous component arising from rare high-energy events and their downstream mis-setting "hot spots", which should be reduced when such events are suppressed. Even under extreme shielding, though, the diffusion component is not expected to vanish. Instead, it should approach a floor set by intrinsic biochemical and physiological noise sources. These sources include, among others, reactive oxygen species (ROS), which are linked to baseline nutrient sensing metabolism and mitochondrial activity –two aging hallmarks that significantly influence epigenetic aging [35]–, finite replication and repair fidelity, stochastic chromatin remodeling, transcriptional bursts, and residual internal radioactivity. Under this stabilization scenario, the most notable underground signature would be the preservation of the mean epigenetic aging trajectory alongside a measurable reduction in variance. Epigenetic age means would track similarly at a given chronological age. However, intercellular and intersample dispersion would narrow. Other expected outcomes include faster convergence back toward the programmed trajectory following perturbation and reduced short-lag wandering in longitudinal measurements over weeks to months, with no systematic shift in the mean trajectory. Together, these outcomes would collectively suggest improved sensor-like resolution of aging clocks rather than a wholesale deceleration of aging (Fig. 3A).

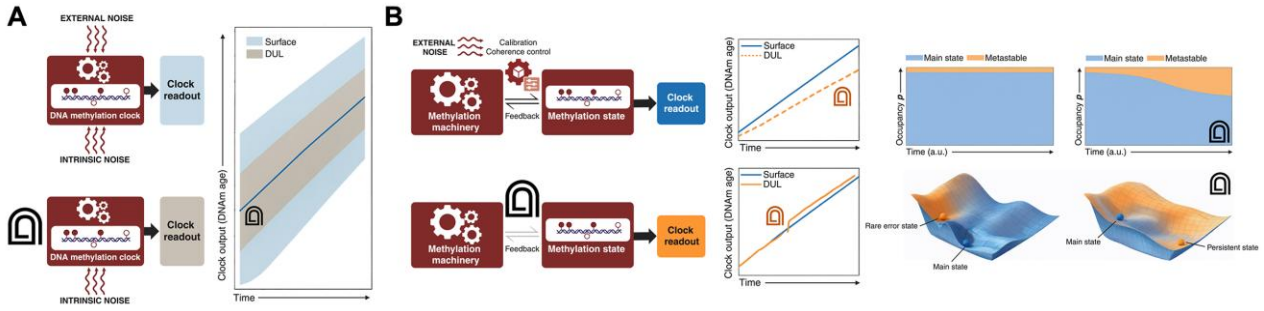

Figure 3. Competing predictions for epigenetic aging in cosmic silence: improved precision versus altered coherence. DUL experiments leverage cosmic silence, a rare experimental tool that suppresses a prevalent class of exogenous ionizing inputs while preserving core biological processes. DUL shielding reduces a primary source of stochastic noise, enabling the molecular noise fluctuations intrinsic to the epigenetic maintenance machinery to dominate the clock readout. A key question is whether reduced noise merely improves estimation accuracy (less dispersion) or if the system degenerates into self-monitoring. **(A)** *External-noise suppression reveals the intrinsic noise floor of epigenetic timekeeping.* According to the null hypothesis, DUL conditions suppress exogenous stochastic noise while preserving the programmed trajectory of DNA methylation aging clocks. In this scenario, the mean DNAm-age trajectory remains essentially unchanged, but the variance around that trajectory narrows relative to surface conditions, approaching the intrinsic noise limit. Thus, muon suppression is predicted to improve the precision of epigenetic age estimation by reducing dispersion driven by the radiobiological environment without producing a systematic shift in clock behavior. **(B)** *Cosmic silence as a falsifiable test of CBR as a radiobiological calibrator of epigenetic timekeeping.* The alternative hypothesis states that low-level environmental radiobiological noise contributes to the calibration and control of coherence in the methylation-maintenance machinery. In that case, DUL conditions would reduce scatter and reveal structured deviations in clock behavior. These deviations could include altered apparent ticking rates, step-like offsets, correlated drift, or the emergence of metastable methylation states. The schematic line plots illustrate representative outcomes in which underground trajectories diverge from surface trajectories. The occupancy plots and attractor landscape diagrams depict the stabilization of persistent altered states resulting from rare errors, i.e., "freeze-in" prevented by noise versus noise-related correlation. On the left, external "kicks" can return the system to the main basis. On the right, reduced perturbations may allow errors to persist. Therefore, longitudinal comparisons of matched surface and underground samples can therefore distinguish between two outcomes. The first outcome is variance collapse around an unchanged mean trajectory, which is consistent with improved sensor-like resolution. The second outcome is altered mean behavior and reduced coherence, which is consistent with the idea of epigenetic timekeeping in response to chronic environmental radiobiological perturbations.

8. Alternative hypothesis: Destabilization of sensor-like aging resolution

Extreme environmental quietness could cause the sensor-like behavior of DNA methylation clocks to become unstable [82–87]. This would occur if cosmic silence eliminated a weak yet functionally significant source of stochastic driving [88–90]. According to this alternative hypothesis, the near-complete absence of natural external randomness in terms of muonic damage could render the aging clock system overly sensitive to residual coherent drifts and long-lived internal states. This would increase effective wandering rather than reduce it. In other words, the epigenetic maintenance biology, including the machinery that writes and erases methylation and the chromatin remodelers, may require some degree of background stochasticity or dissipation to prevent rare but persistent deviations from dominating the trajectory. Underground placement would be expected to reduce uncorrelated scatter and produce structured, correlated deviations that do not average out overtime (Fig. 3B). These deviations could manifest as drift-like, persistent subpopulation offsets that are not subjected to state fluctuations due to internal noise or as metastable states that lock lineages into altered methylation trajectories. This could be considered an epigenetic version of "freezing the wrong time in place", referring to persistent methylation-state offsets, altered clock slopes, or metastable subpopulation trajectories that do not average over serial passages [42,91–94]. In this destabilization scenario, despite reduced exogenous noise, precision would not improve. Rather, the clock would become more fragile, with readouts increasingly governed by residual internal biases and long-lived states rather than by a simple narrowing of diffusion around an unchanged programmed drift (Fig. 3B).

Table 2 summarizes the expected changes across in the main areas of methylation, DNA damage/repair, transcription, and reversibility after returning to surface radiation. This clarifies how the null and alternative scenarios will be distinguished experimentally.

9. DULs cosmic silence: an environmental lens through which to view the radiobiological origins of epigenetic aging

DNA methylation aging clocks compress vast epigenomic heterogeneity into a nearly linear temporal coordinate that

is surprisingly reproducible across tissues and, in some cases, across mammals. However, descriptive performance is not the same as mechanism. Why should a methylome –continuously perturbed by replication, repair, chromatin motion, and enzymatic turnover– drift along such constrained trajectories? For over 3.5 billion years, life on Earth has evolved amid varying levels of CBR, raising intriguing questions about its role in the development and evolution of living organisms as an abiotic factor [95–97]. From an evolutionary perspective, the emergence of methylation-based timekeeping could be interpreted, at least in part, as a prolonged transition in how life has responded to Earth's fluctuating radiation environment over geologic time.

Table 2. Operational predictions of the DEEP-CLOCK null and alternative scenarios.

Readout	Null hypothesis: improved clock precision	Alternative hypothesis: metastable drift/loss of coherence
Mean methylation age trajectory	Largely preserved, with no major shift in slope or mean epigenetic age	Altered slope, shifted trajectory, or persistent deviation from the expected age path
Clock CpG/ epigenetic-age variance	Reduced intercellular or inter-replicate dispersion	Structured variance persists or increases despite reduced uncorrelated noise
Methylation entropy	Stable or modestly reduced if stochastic dispersion decreases	Increased or redistributed entropy in specific CpG/chromatin sectors
DSB markers	Reduced or unchanged, depending on whether muon-associated lesions contribute significantly	Unchanged or altered secondarily if clock drift reflects internal stress states
DNA repair signatures	Reduced activation of damage/repair pathways, or no detectable change	Persistent or remodeled repair/chromatin signatures despite shielding
Transcriptional noise	Reduced short-lag fluctuation if extrinsic stochasticity contributes	Increased autocorrelation and state locking or structured transcriptional deviations
Reversibility after returning to surface radiation	Variance returns toward the above-ground baseline if the effect reflects reversible noise suppression	Persistent offsets or slow relaxation if underground exposure induces metastable states

Throughout most of the history of the near-surface biosphere, "radiobiological quiet" has been rare. From this perspective, DNA methylation clocks can be viewed as phenotypes that manage and reflect information about the long-term balance between a first-order, Markovian, replication-linked deterministic channel that restores regulatory identity and tissue-specific programs. One example is the DNMT1-UHRFF1-TET maintenance copying and proofreading axis, which repeatedly revisits CpG states and pulls them toward locus-specific setpoints in regulatory or Polycomb-associated chromatin contexts that are frequently "checked and corrected" [98–104]. The second channel is a second-order, quasi-stochastic channel involving damage-responsive chromatin mobility. This channel creates cumulative, yet constrained, perturbations in chromatin organization. These perturbations introduce a diffusion-like component into methylome space without completely randomizing regulatory topology. The near-linearity of many aging clocks is then an emergent signature of the constrained maintenance of stable epigenetic information in a constantly changing radiobiological environment –an echo of the selection, over deep time, for epigenetic error correction rather than an "aging program" per se. While it may be tempting to suggest that aging clocks could bear the imprint of radiobiological genesis and operate as sensitive indicators of disturbances that impact genome and chromatin integrity, this notion should be considered a speculative evolutionary scenario and working hypothesis rather than an inherent characteristic of DNA methylation clock architecture. If DNA methylation clocks are both relic and instrument, DUL conditions are then positioned as an ideal way to distinguish between the two experimentally. In this regard, DEEP-CLOCK is designed to test for measurable coupling between chronic radiobiological background and clock variance, trajectory, or coherence, rather than assuming it.

DUL experiments can help transform the long-standing descriptive success of epigenetic clocks into mechanistic and evolutionary tests. Does methylation-based timekeeping merely survive radiation as a robust readout, or is it the clock-like structure of epigenetic aging partially a product of radiation –an adaptation for managing information shaped by Earth's fluctuating yet persistent low-dose genotoxic landscape– that evolved into the chronometers observed in modern multicellular life? Eliminating the muonic component of environmental variability could reveal, at least in part, some of the intrinsic fluctuations that determine the ultimate precision of any measurement, including aging [59,105]. DUL cosmic silence could help us to identify the component (k and/or D) most significantly impacted by near-surface radiobiology. This would provide a lens through which to study the radiobiological origins of DNA methylation clocks and epigenetic aging. This is a testable evolutionary scenario in which chronic, low-dose radiobiological background may have contributed to shaping epigenetic maintenance constraints rather than being an established property of the methylation clock itself. If DUL cosmic silence reduces dispersion without altering the mean trajectory, then DNA methylation clocks are then high-resolution, intrinsic chronometers that are limited by intrinsic molecular noise when external shocks are suppressed (Fig. 3A). This would demonstrate

that the near-surface CBR can function as an extrinsic decorrelator, obscuring an intrinsic, programmed trajectory. However, if the CBR participates in long-term calibration by continuously nudging repair/maintenance attractors or preventing rare copying errors from becoming persistent, then extreme radiobiological quiet could reshape mean behavior. This could manifest as altered ticking rates, new drift modes, or metastable states that become enriched when perturbations vanish (Fig. 3B). Thus, if the DUL cosmic silence reshapes the trajectories of DNA methylation clocks, a more provocative possibility emerges: that the clocks may remain partly coupled, evolutionarily and mechanistically, to the radiobiological texture of the environment in which epigenetic stability first became possible. This scenario suggests that operability itself is evolutionarily intertwined with the environmental stochasticity caused by constant, unavoidable CBR. This is consistent with the idea that epigenetic maintenance systems evolved in response to background radiobiological forces and continue to exploit them to prevent rare, yet persistent errors. The DEEP-CLOCK findings could transform epigenetic clocks from descriptive biomarkers into experimentally interrogable dynamic systems. This would enable us to study whether DNA methylation clocks encode an evolved compromise –epigenetic memory that is stable enough to preserve identity, yet repairable under persistent physical insult— and whether the modern clock is partly a legacy of such radiobiological constraint.

10. Aging clocks in cosmic silence: Fromthe origin of biological time to Mars exploration

In developmental terms, biological time only emerges and becomes meaningful when developmental systems act collectively on cells that generate spatial and structural order, i.e., during morphogenesis. Thus, biological time is an emergent property of organized multicellular activity – the coordination of cellular events necessary for forming three-dimensional structures. The existence of universal, mammalian-like epigenetic clocks in invertebrates is still being debated [106–110], but exploring the impact of a muon-less DUL environment on the formation of multicellular structures and embryonic development at the extremes of metazoan evolution would be fascinating [111–116]. First, how would cosmic silence affect the aggregative and/or clonal multicellular stages that played a crucial role in the evolutionary transition from unicellular to multicellular organisms? Second, how would cosmic silence affect the self-organized fate transitions that occur during the early mammalian embryogenesis by using gastruloid cell aggregates derived from pluripotent stem cells [117–121]?

The Moon lacks a substantial atmosphere capable of generating an Earth-like secondary muon shower (Table 3). Primary galactic cosmic rays therefore interact directly with the lunar regolith –the layer of loose, unconsolidated material covering solid bedrock on airless bodies in space– where hadronic cascades develop over much shorter physical distances than they would in an atmosphere. Consequently, muon production and transport in the upper lunar subsurface differ significantly from conditions at Earth's surface [122]. For reference, an overburden of 1,000 g cm^{-2} regolith corresponds to a water equivalent of 10 m, or approximately 6.3 m of regolith with a bulk density of 1.6 g cm-3. This depth lies within the typical 4-5 m thick lunar regolith column in mare regions and the 10-15 m thick column in highland regions. Mars represents a different case (Table 3). Although its surface pressure is less than 1% of Earth's, its lower gravity increases the atmospheric column relative to what would be expected based on pressure alone. Geant4 simulations suggest that this thin atmosphere generates a muon field on the Martian surface that is similar to the muon environment at sea level on Earth [123]. However, Martian regolith provides much denser shielding than the atmosphere. Three meters of regolith at 1.6 g cm-3 corresponds to approximately 480 g cm-2, about 30 times the Martian atmospheric column and nearly half of Earth's. Consistent with this, simulations suggest that a 3-meter-thick layer of Martian regolith overburden could reduce the surface muon flux by approximately 90% [123].

To mitigate or totally avoid the hazards posed by meteorites, radiation, and structural and logistical failures, any future bases on the Moon or Mars should be built underground. In order to balance protection from heavy-ion galactic cosmic-rays (GCR) with the scale of mining activities required to excavate sufficient underground space while avoiding excessive resource consumption, these bases should be between two and ten meters deep [123]. The DEEP-CLOCK project partially mimics the conditions of strong muon attenuation that would be expected when using existing lunar and Martian lava tubes (>20 m deep) as shelters for colonists on the lunar and Martian surfaces. Therefore, the knowledge from the DEEP-CLOCK project –i.e., how chronological and biological age readouts from DNA methylation clocks converge or diverge under cosmic silence– would help us examine the effects of prolonged cosmic silence on epigenetic timekeeping fidelity in future crewed missions to extraplanetary habitats with atmospheres exhibiting cosmic showers lacking Earth's characteristic near-surface muon fluxes. However, it is important to note that DUL exposure should not be viewed as a complete simulator of lunar or Martian underground habitats. These environments combine muon attenuation with other

variables, such as galactic cosmic rays, solar particle events, secondary radiation generated in shielding or regolith, altered gravity, circadian disruption, isolation, closed-atmosphere conditions, and habitat-specific engineering factors. Thus, DEEP-CLOCK is a reductionist, Earth-based analog that solely isolates one experimentally controllable component of the space and planetary subsurface environments: muon depletion. It is not a comprehensive model of spaceflight biology. In this more limited sense, DEEP-CLOCK may help determine whether muon-depleted conditions alone measurably affect the variance, coherence, or trajectory of DNA methylation clocks before these readouts are interpreted within the broader context of extraterrestrial habitats.

Table 3. Approximate shielding and muon-environment parameters relevant to lunar and Martian subsurface habitats.

Environment	Key physical feature	Approximate shielding/column	Relevance to DEEP-CLOCK
Earth surface	Atmospheric secondary muon shower	~1,000 g cm^{-2} atmospheric column	Reference near-surface muon condition
DUL / LSC	Rock overburden suppresses cosmic-ray muons	~2,400–2,450 m.w.e	Experimental muon-depleted condition
Lunar regolith	No Earth-like atmosphere; GCRs interact directly with regolith	1,000 g cm^{-2} ≈ 10 m.w.e. ≈ 6.3 m at 1.6 g cm^{-3}	Strongly non-Earth-like muon-production environment
Mars surface	Thin atmosphere but sufficient target for secondary-particle production	~6–7 mbar; low gravity	Simulated surface muon field may be Earth-like in magnitude
Martian regolith shelter	Dense regolith rapidly attenuates low-energy muons	3 m ≈ 480 g cm^{-2}; ~90% simulated muon reduction	Partially muon-depleted planetary shelter analogue

11. Corollary

The DEEP-CLOCK initiative uniquely reframes DNA methylation clocks as noise-limited biological metrology by shifting epigenetic timekeeping into the cosmic silence of a DUL. There, the dominant stochastic genotoxic input at Earth's surface, cosmogenic muons, is suppressed by several orders of magnitude. This makes them experimentally controllable, which is unachievable in standard biomedicine. The project aims to push aging clock readouts toward their shot-noise floor by reducing exogenous radiation to zero. This could allow for a clearer distinction between the deterministic "carrier" dynamics (programmed methylome relaxation) and diffusion-like variance growth (repair/maintenance infidelity) in longitudinal multi-omics time series. This would transform epigenetic aging from a descriptive biomarker issue into a testable dynamical system in which one specific component of environmental randomness – surface-level cosmic-ray muons– can be reduced experimentally. The goal is not to assume that muons are a major driver of clock behavior but rather determine whether suppressing them produces any reproducible change in mean epigenetic age, clock CpG variance, longitudinal drift, or coherence after accounting for intrinsic and experimental sources of methylome variability.

If the DEEP-CLOCK project determines that muon suppression yields either variance collapse at conserved mean trajectories (enhanced precision) or emergent metastable drift modes (loss of coherence), then it would suggest fundamental limits on the information capacity and stability of epigenetic timekeeping. The expected impact is twofold. First, the project will illuminate actionable strategies to preserve or re-engineer clock fidelity. This will be achieved by targeting the specific processes that determine the intrinsic noise floor. Examples of these processes include maintenance, repair, and chromatin kinetics in physiological aging. Second, the project will establish a preliminary framework for predicting epigenetic aging behavior in muon-deprived extraterrestrial habitats, such as regolith/lava tube shelters, where clock operability may diverge from Earth-calibrated baselines.

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Author Contributions

JAM: Conceptualization, Project administration, Supervision, Resources, Methodology, Formal analysis, Visualization, Writing–original draft, Writing– review & editing. CP-G: Conceptualization, Resources, Supervision, Writing–original draft; TA: Conceptualization, Resources, Supervision, Methodology, Visualization, Writing–original draft, Writing– review & editing. EC: Conceptualization, Project administration, Supervision, Resources, Methodology, Visualization, Writing–original draft, Writing– review & editing.

Competing Interest

All of the authors declare that they have no known competing financial interests or personal relationships that could appear to have influenced the work reported in this paper.

Consent for Publication

All authors agreed to the publication of the article.

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