From Clocks to Coordinates: Controlled Human Perturbations Reveal Hidden Directions in ECG Biological Age

A condensed account of the central result

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Abstract

Neural "ECG age" and organ-age models return a single scalar, collapsing biophysically distinct processes into one number. The finding of this work is narrower and sharper than the slogan that biological age is "a direction": *a phase-resolved ECG-age representation contains mechanism-aligned physiological directions that are hidden by its scalar output.* Four phase-of-heartbeat age clocks compress into a *shared axis* A and an orthogonal *disagreement radius* D, with the geometry frozen on CODE-15 *before any outcome was read.* The unsigned radius D was null on its single prespecified confirmatory mortality test (hazard ratio 1.01 per SD, 95% CI 0.98 to 1.04, $p = 0.48$)—the honest negative that motivates a *signed* analysis. A randomized I_{Kr} blocker (dofetilide) displaced the ST-T repolarization clock (+4.2 SD·h, FDR-adjusted $q = 0.002$), defining a covariance-scaled signed direction $\mathbf{w}_{I_{\mathrm{Kr}}}$—the coordinate the unsigned radius discards. $\mathbf{w}_{I_{\mathrm{Kr}}}$ is *one retrospectively derived, outcome-blind direction, frozen for external testing*; a second I_{Kr} blocker (quinidine, +0.83) gave within-cohort held-mechanism support, and direction-derivation is reported as exploratory (Holm-adjusted permutation $p = 0.069$). Carried unchanged into an independent external cohort (Chapman–Shaoxing/Ningbo, $n = 44\,550$, 386 QT-extension cases), it added *conditional* information about physician-assigned QT-interval extension beyond conventional intervals, A and D (fully adjusted odds ratio 1.23 per SD, $p = 1.9 \times 10^{-4}$; marginally null—conditional and adjustment-dependent). The shared axis A was separately mortality-associated; its underlying whole-ECG clock reconstructed on the geographically distinct cohort at $r = 0.646$ with chronological age. This condensed account presents that result; a 56-page technical manuscript provides the full methods, the supporting multiscale atlas and every frozen artifact.

1 The claim

Biological-age models—whether a neural network reading an electrocardiogram or a volumetric organ clock—almost always return *one number*: an age gap. That scalar discards direction. Two people equally "old for their age" may be old in physiologically opposite ways. The question this work answers is whether that lost direction is real, measurable and *transportable*: can a controlled human perturbation reveal a fixed coordinate in an age–state space, and does that coordinate carry information in a cohort that never saw the perturbation? The answer is a signed, IKr-aligned perturbation direction derived from a randomized ion-channel blockade and tested unchanged, frozen, on an external cohort—not a claim that every age gap hides a useful vector.

2 The coordinates, and why the sign matters

Each patient's four phase-age gaps $\mathbf{z} = (z_P, z_{AV}, z_{QRS}, z_{STT})$ are split into a one-dimensional shared component and a three-dimensional contrast. With the all-ones direction $u = (1, 1, 1, 1)$, the shared axis is the projection $A = u^\top \mathbf{z}/\|u\|$, and the contrast vector is $\mathbf{q} = C\mathbf{z}$, where C maps into the subspace orthogonal to u ($Cu = 0$, $CC^\top = I_3$). The unsigned *disagreement radius* is the covariance-normalized length of that contrast,

$$D = \sqrt{\mathbf{q}^\top \Sigma_q^{-1} \mathbf{q}},$$

with Σ_q estimated on the frozen healthy calibration cohort. D is a non-negative scalar: it keeps the *magnitude* of the disagreement and throws away its *direction*. A signed score restores exactly that discarded direction. Given a unit contrast direction $\mathbf{w}$ in the whitened space, the patient's signed coordinate is the projection

$$S = \mathbf{w}^\top \mathbf{q}, \qquad |S| \le D,$$

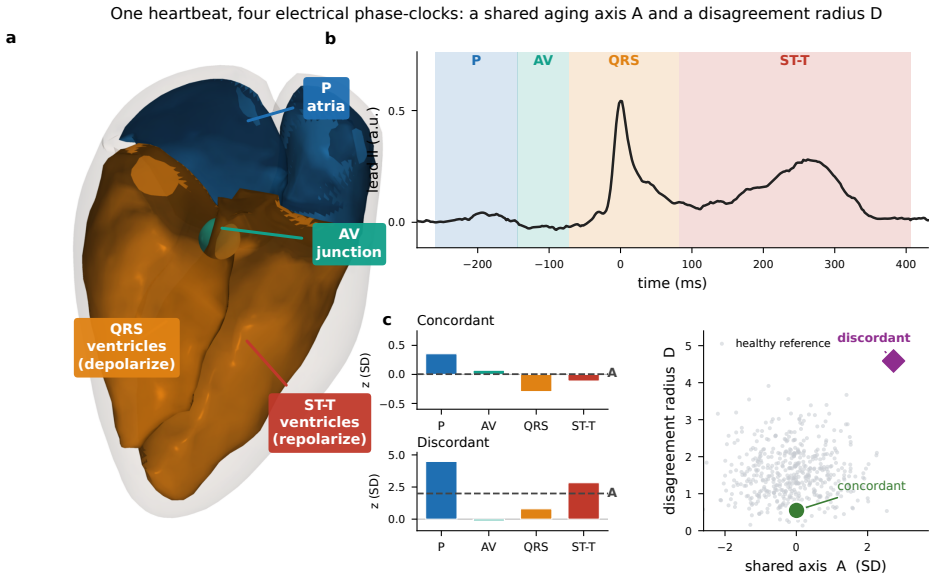

Figure 1: Biological age as a vector, not a scalar. Four phase-of-heartbeat age clocks (P, AV, QRS, ST-T) are standardized against a frozen healthy calibration cohort and read as a point in a four-dimensional gap space. Its coordinates are a *shared axis* A (the common displacement—how uniformly old the heartbeat looks) and an orthogonal *disagreement radius* D (how much the four clocks disagree). The geometry was frozen on CODE-15 (233 770 patients) before any outcome was read.

so every signed score is bounded by the radius that discarded it. The rest of this account is about finding a physiologically meaningful $\mathbf{w}$—not from the data's own variance, but from a controlled human perturbation—and showing that the resulting S carries information the unsigned D cannot.

The shared axis A behaves the way a biological-age summary should. In frozen CODE-15 development it was associated with mortality (hazard ratio 1.22 per SD); it generalized to whole-body organ-system aging in NHANES (+1.21 per SD, 95% CI 1.13 to 1.29). On a geographically distinct Chinese cohort (Chapman–Ningbo) the construction reconstructed without refitting: the underlying whole-ECG age clock that anchors it transferred at correlation $r = 0.646$ with chronological age. (A itself, a residual over age-adapted gaps, correlates with age only weakly there, $r = 0.26$; the transfer evidence is that the frozen clocks and construction reconstruct on an untrained cohort, not that A is a strong age predictor in it.) The shared axis is the part of the decomposition that behaves like a conventional biological-age summary—and, as the next sections show, the part that hides a mechanism once its sign is restored.

3 A controlled human perturbation reveals a hidden direction

The decisive experiment is a randomized-controlled human ion-channel perturbation. In the ECG-RDVQ crossover study, a specific I_{Kr} (rapid delayed-rectifier potassium current) blocker, dofetilide, was administered against placebo. I_{Kr} blockade has a textbook electrophysiological signature: it prolongs repolarization, that is, the ST-T segment. If the age–state space is physically meaningful, this perturbation should displace the ST-T phase clock along a *reproducible direction*.

It does. Dofetilide displaced the ST-T repolarization clock by +4.2 SD·h (FDR-adjusted $q = 0.002$), while a negative-control QRS contrast was null. From the mean placebo-corrected displacement $\mathbf{m}$, a covariance-scaled signed direction was defined,

$$\mathbf{w}_{I_{\mathrm{Kr}}} = \Sigma_q^{-1}\mathbf{m} \Big/ \sqrt{\mathbf{m}^\top \Sigma_q^{-1}\mathbf{m}},$$

precisely the coordinate the unsigned radius D discards. The supporting evidence is layered, and its strength is stated plainly. A *second*, chemically distinct I_{Kr} blocker (quinidine) projected positively on the frozen axis (+0.83, 95% CI 0.52 to 1.20). This is *within-cohort, held-mechanism* support—quinidine and dofetilide are arms of the same 22-person crossover, so it shows the axis reproduces across two I_{Kr} blockers, not that it generalizes to a new sample. The multichannel comparators ranolazine and verapamil are *active drugs*, not clean negative controls; their projections are weaker with confidence intervals spanning zero (Fig. 2b). We therefore make *no formal specificity claim*: distinguishing I_{Kr} from non-I_{Kr} drugs would require a prespecified between-drug contrast, which this study does not perform. Because two perturbation directions (I_{Kr} and acute ischemia) were screened,

the honest multiplicity-corrected permutation test on the direction's magnitude is only nominal (Holm-adjusted $p = 0.069$); the direction-*derivation* is therefore reported as exploratory, and its conditional phenotype support comes from the external cohort in the next section.

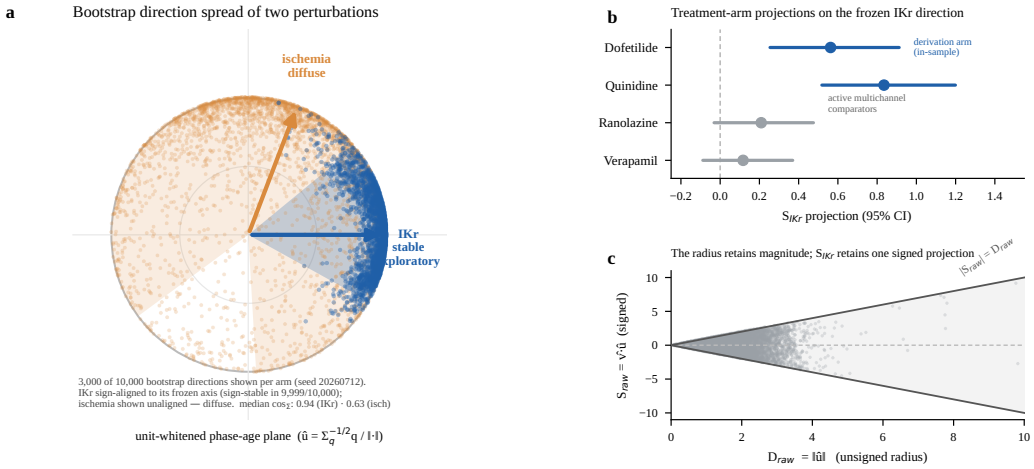

Figure 2: An outcome-blind, signed perturbation direction captures an IKr-aligned perturbation direction the unsigned radius discards, and is frozen for external transport. (a) Bootstrap spread of the recovered direction in a two-dimensional slice of the three-dimensional whitened contrast space: the I_{Kr} axis is a stable exploratory direction (bootstrap median $\cos_\Sigma = 0.94$; 9999 of 10 000 bootstraps reproduce its sign), whereas the acute-ischemia axis is diffuse because ischemia moves the vector along the shared axis A rather than within the contrast subspace. **(b)** The two I_{Kr} blockers separate from zero; the active multichannel comparators do not (no formal specificity contrast is claimed). **(c)** In raw whitened coordinates the signed score is bounded by the unsigned radius, $|S_{\mathrm{raw}}| \le D_{\mathrm{raw}}$: the radius keeps the magnitude but discards the angular (directional) information of the contrast, while the signed score S retains one signed projection of it onto the frozen axis.

4 The direction transports to an external cohort

A direction is only useful if it carries information where it was never trained. The frozen $\mathbf{w}_{I_{\mathrm{Kr}}}$ was carried, unchanged, into an independent external cohort (Chapman–Shaoxing and Ningbo, $n = 44\,550$; 386 patients with a physician-assigned diagnosis of QT-interval extension, SNOMED 111975006). Added to a model already containing age, sex, heart rate, the conventional intervals (QTc, QRS), the shared axis A and the disagreement radius D, the signed I_{Kr} score carried *conditional* information about that diagnosis. The association emerged only after covariate adjustment and is therefore conditional and potentially model-dependent—an adjustment ladder that is itself the evidence (Fig. 3a):

Model	Odds ratio per SD (95% CI)	p
Marginal (unadjusted)	1.00	0.996
+ age, sex	1.09	0.090
+ conventional intervals	1.15	0.0073
Fully adjusted ($+A, +D$)	1.23 (1.10 to 1.36)	1.9×10^{-4}

The marginal association is null (odds ratio 1.00); the estimate increased only after conditioning on conventional intervals, A and D—a model-dependent pattern consistent with statistical suppression. This adjustment dependence is not implied by geometric orthogonality. The two sites agree in direction (Ningbo odds ratio 1.20, $p = 0.0019$, 329 cases, a positive larger-site estimate; Chapman–Shaoxing odds ratio 1.44, $p = 0.018$, 57 cases, underpowered; Fig. 3b).

Limitation — rhythm-context dependence. The QT-extension phenotype is not independent of coarse rhythm categories, and the signed-score association depends on which are included (Fig. 3c). Excluding atrial flutter/fibrillation, the effect holds (odds ratio 1.18, $p = 0.014$, 227 cases); excluding sinus bradycardia alone it attenuates to borderline (odds ratio 1.13, $p = 0.096$, 245 cases); and *excluding both* it is null (odds ratio 0.93, $p = 0.48$, 86 cases). Because the transported association is not prespecified as rhythm-stratified, the AV-flutter and bradycardia subgroups are reported here as *post-hoc*: they show the transported direction is entangled with

rhythm context and is best read as a conditional, hypothesis-generating signal rather than a rhythm-independent one. This dependence is disclosed as a limitation, not framed as a mechanistic result.

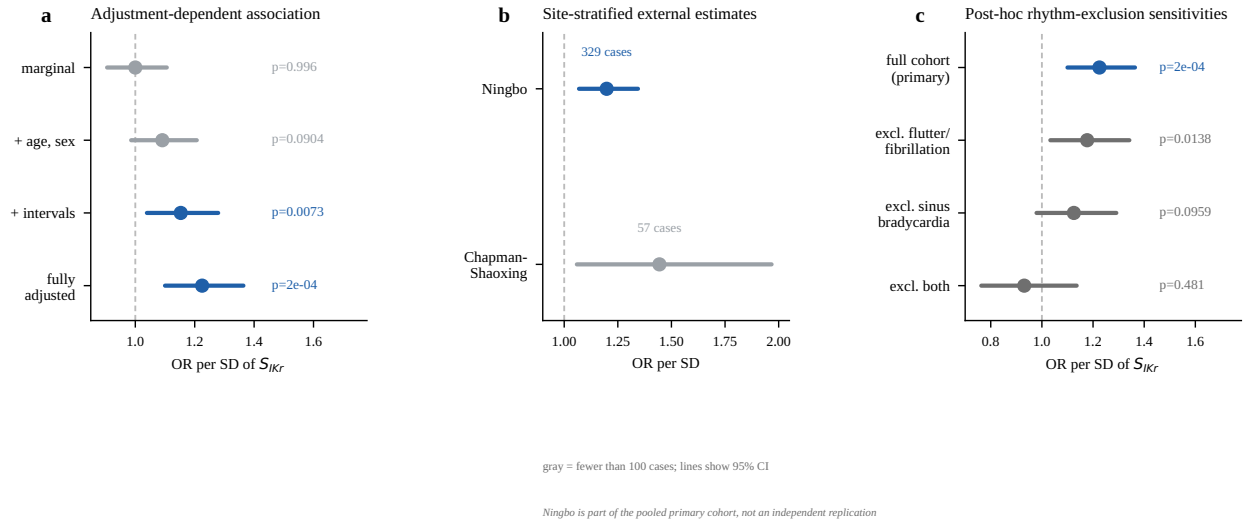

Figure 3: The frozen I_{Kr} direction transports to Chapman–Shaoxing/Ningbo as conditional information, with an honest rhythm-context limitation. (a) Adjustment ladder: the odds ratio for QT-extension per SD of the signed score rises from a null margin to a fully adjusted odds ratio of 1.23 ($p = 1.9 \times 10^{-4}$) as age/sex, conventional intervals and the shared coordinates are added—i.e. conditional on adjustment. **(b)** Site-stratified external estimates: the larger Ningbo site (329 cases), part of the combined primary cohort rather than an independent replication, drives the pooled estimate; Chapman–Shaoxing agrees in direction but is underpowered (57 cases). **(c)** Rhythm-exclusion sensitivity: the association survives excluding atrial flutter/fibrillation, weakens excluding sinus bradycardia, and is null excluding both (86 cases)—a disclosed limitation that keeps the claim conditional.

5 Why the signed direction, and not the unsigned radius

The disagreement radius D was the original hypothesis: that *how* the clocks disagree adds prognostic information beyond the shared level. It does not. On its single prespecified confirmatory test—a model-frozen Cox likelihood-ratio test on the locked CODE-15 final-test partition—D was null (hazard ratio 1.01 per SD, 95% CI 0.98 to 1.04, $p = 0.48$; $n = 74\,715$, 2583 deaths). It showed no detectable association with independent cardiac structure and did not change under acute physiological stress. The null radius motivated a different question: whether physiologically meaningful orientation was being discarded. The randomized perturbation supplied one exploratory signed direction through that space.

The contrast with the perturbation result is the point. The unsigned radius is a variance-defined magnitude, blind to *which way* the clocks disagree; on its own confirmatory test it carries no mortality information. The signed coordinate $\mathbf{w}_{I_{\mathrm{Kr}}}$, defined from a controlled I_{Kr} blockade rather than from variance, recovers a direction inside the very subspace the radius summarizes—and that direction, frozen, is what transports. The second screened perturbation, acute ischemia, fits the same picture in reverse: it moves the vector along the shared axis A (+3.8 years whole-ECG apparent age) rather than along a stable signed contrast, which is why it fails the direction gate and is reported as diffuse rather than as a second recovered coordinate.

6 The supporting multiscale atlas, and the frozen record

The electrical perturbation above is the finding. The full manuscript surrounds it with a deliberately *supporting* multiscale atlas: related coordinate-based questions posed at other biological scales using scale-appropriate representations, as a visually rich companion rather than independent confirmation of the electrical result. A whole-body CT age clock over 1227 examinations localizes aging anatomically and identifies the skeleton as a structural bridge organ (Fig. 5a, Fig. 5b); a brain-imaging arm rebuilds an image-derived disagreement coordinate from 220 real T1 volumes and finds it elevated in older brains (Fig. 5c). Separately, an exploratory Zoonomia-HAR screen generated ranked skeletal-lineage hypotheses but no enrichment near skeletal GWAS loci ($p = 0.24$); no regulatory discovery is claimed. These arms are exploratory and are labeled as such; they illustrate that the coordinate view recurs across scales without asserting that any one of them re-proves the perturbation direction.

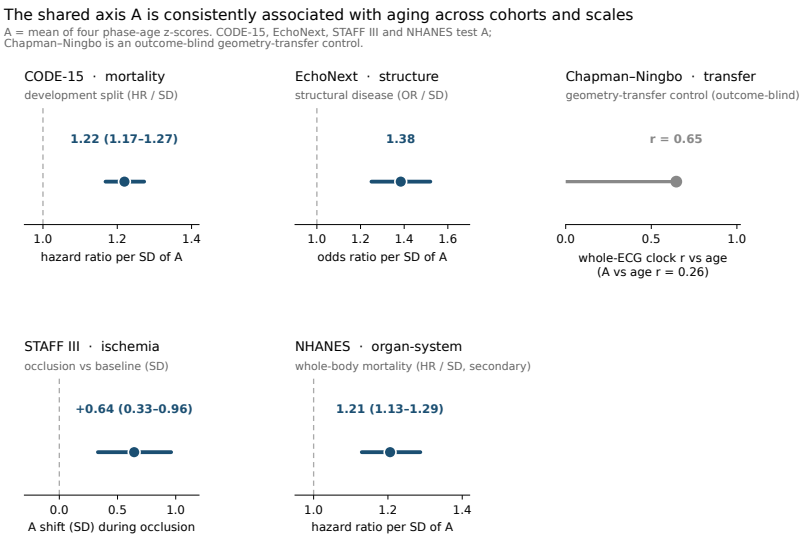

Figure 4: The shared axis A is consistently associated with aging across cohorts and scales. Development mortality, geographic reconstruction of the underlying whole-ECG clock, and whole-body organ-system aging (NHANES) all point the same way. A is the part of the decomposition that behaves like a conventional biological-age summary.

What the result is. The locked mortality test rejected the original hypothesis that the unsigned magnitude of phase disagreement carried incremental prognostic information. Controlled perturbation then revealed a different possibility: the radius preserves distance but cannot represent orientation. An exploratory I_{Kr}-aligned projection retained one such direction and showed adjustment-dependent external phenotype support. This does not establish a clinical biomarker or a universal biological-age axis. It demonstrates that biological-age representations can contain structured coordinates that disappear when reduced to a single scalar. The honest negative (D is null on its confirmatory test), the honest hedge (direction-derivation is exploratory under multiplicity; the external cohort provides conditional phenotype support) and the honest limitation (the transported association is rhythm-context dependent) are part of the result, not footnotes to it.

Frozen record and code. Every headline quantity is drawn from a versioned, content-hashed artifact; the geometry, the I_{Kr} scorer and the protocol lock were frozen before the outcomes reported here were read. "Prespecified" throughout means this content-hash-locked, outcome-blind commitment, not a public timestamped registration. Source cohorts are open where licensing permits (CODE-15, SaMi-Trop, PhysioNet ecg-arrhythmia, NHANES, LEMON); access-controlled arms (EchoNext, AABC) contributed only aggregate results. Full methods, the claim-to-artifact ledger and the 56-page technical manuscript are in the repository.

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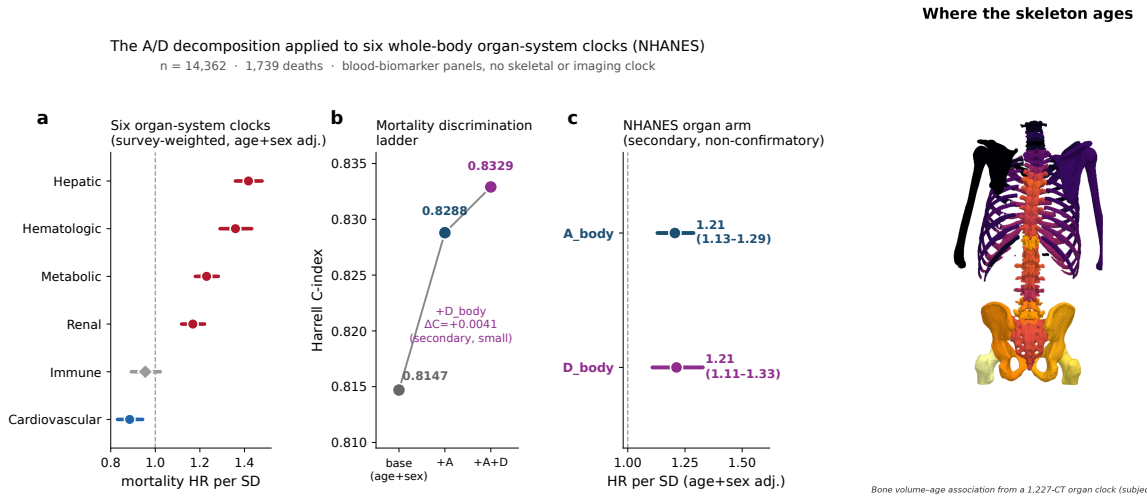
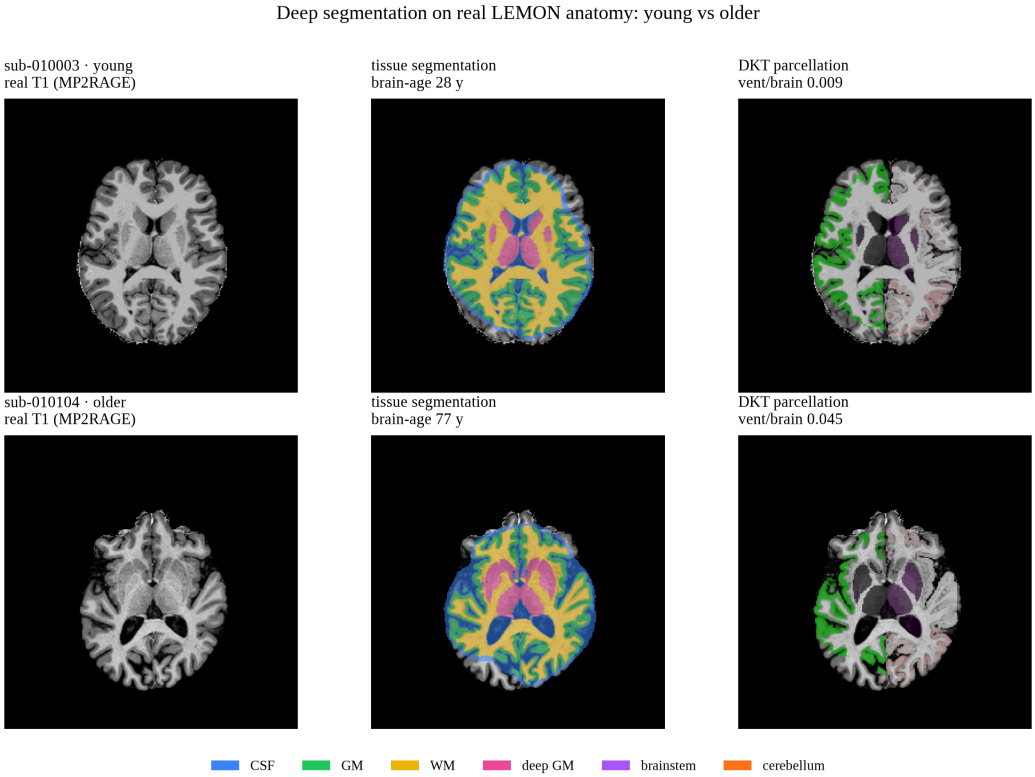
A scalar age gap answers "how old." A controlled perturbation, frozen and transported, begins to answer "old in which direction."



(a) NHANES blood-biomarker organ-system clocks: shared-axis / disagreement structure (14 362 participants).

(b) Whole-body CT organ clock: where the skeleton ages (1227 examinations).



(c) Deep segmentation on two real LEMON T1 volumes: young (sub-010003, 28 y) vs older (sub-010104, 77 y).

Figure 5: The supporting multiscale atlas. Related coordinate-based questions posed at other biological scales using scale-appropriate representations. **(a)** Six blood-biomarker organ-system age clocks in NHANES (14 362 participants) carry a shared axis and a disagreement radius, each adding mortality information (secondary, non-confirmatory). **(b)** A separate whole-body CT age clock over 1227 examinations localizes age-informative structure to the cardiovascular system and the weight-bearing skeleton. **(c)** A brain-imaging arm rebuilds an image-derived disagreement coordinate from 220 real T1 volumes: the older brain shows enlarged ventricles (ventricle–brain ratio 0.045 versus 0.009), widened sulci and thinned cortex, and across all 220 subjects the image-derived disagreement radius is elevated in the older group ($D = 0.52$ versus 0.34, Cohen's $d = 0.84$, Mann–Whitney $p = 4.3 \times 10^{-8}$; the prospective gait-decline test was a prespecified null). All three arms are exploratory and supporting; none is an independent confirmation of the electrical finding.