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Research Topic: Pre-Flight Causal Multi-Omic Prediction Of Spaceflight-Induced Biological Age Acceleration
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Abstract:
Within just 7 days of spaceflight, astronauts experience an average 1.91 year increase in epigenetic age acceleration. The extent of this rapid age acceleration during missions differs significantly among individuals, with its underlying causes remaining unexplored. No framework currently exists to predict the pre-flight vulnerability of each individual to this effect and existing research only accounts for single-modality biomarkers such as DNA methylation without incorporating inter-omic molecular mechanisms. By synthesising pre-flight multi-omic molecular profiles (epigenomic, proteomic, metabolomic and immune cell composition data), this project proposes a multi-omic machine learning approach to model and predict individual trajectories of biological age acceleration pre-spaceflight. This framework aims to assist personalised risk assessment and the creation of targeted countermeasures, thereby enhancing the feasibility of future long-duration human space exploration.

Introduction:
Manned deep-space missions projected for the 2030s will expose astronauts to prolonged microgravity, cosmic radiation and ciradian disruptions, posing significant risks to crew health and performance. However, current space medicine approaches, including epigenetic clocks such as Horvath's DNAm age and DunedinPACE, are unable to forecast the severity of these effects on each astronaut's biological aging before launch. This concern is observable in short-duration missions, including the Axiom-2 mission, during which astronauts experienced an average 1.91 year increase in biological age acceleration within a week of spaceflight, suggesting significant physiological impact. While NASA's Twins Study had found that some spaceflight-induced biological changes partially reverse after landing, others such as adverse atherosclerotic and cognitive effects do not fully reverse and hence, can lead to long-term damage. Notably, existing research has also documented individual variation in biological aging rates for astronauts under identical mission conditions but has not accounted for its dependence on molecular interactions across omic layers. This inhibits effective pre-flight forecasting and individualized risk stratification by preventing pre-flight causal multi-omic prediction of spaceflight-induced biological age acceleration.

Literature Review:
Multi-omic profiling has been validated as an approach for characterising biological aging through studies demonstrating that integrated molecular signatures can predict physiological age more accurately than when analysed in isolation (Saleh et al., 2024). In space medicine, epigenetic clocks including Horvath's DNAm age and DunedinPACE have been successfully applied to astronaut cohorts, with studies establishing rapid epigenetic age acceleration during spaceflight (Fuentealba et al., 2026). However, these tools remain retrospective and lack comprehensiveness as they do not incorporate cross-omic signals (Pierson Smela et al., 2025). While recent research has begun applying comprehensive multi-omic analysis to spaceflight (da Silveira et al., 2020), they do not predict individual aging trajectories from pre-flight baselines and therefore, cannot generate risk forecasts pre-launch for each astronaut, which limits such tools from supporting more informed decision making.

Methodology:
To begin with, pre-flight molecular data spanning 5 modalities (epigenomics, proteomics, plasma metabolomics, urine metabolomics and immune cell composition) will be collected from these

publicly available datasets: SOMA- Inspiration4 (OSD-569 to OSD-656), the NASA Twins Study (Garrett-Bakelman et al., 2019), the China Manned Space Program cohort (Zhang et al., 2025), AX-1 dataset based on microgravity-induced pain (NASA OSD-903), Axiom-2 biological age dataset (Fuentealba et al., 2026), and the GEO GSE74708 dataset- covering approximately 39 astronauts from which only data samples collected within a 60-day pre-launch window will be used. For systematic harmonisation, all methylation data will be restricted to 452,000 CpG sites shared across arrays and each modality will then be cleaned to remove low-quality samples and to correct probe-type bias using BMIQ followed by normalization through preprocessFunnorm. Protein data below detection limits will be filtered out and metabolomic abundance will be normalized via log6 transformation, after which Probabilistic Quotient Normalization and Pareto Scaling will be conducted, followed by ComBat batch correction using cohort as the batch variable. Without this step, technical inconsistencies across processing laboratories could be mistaken for biological signals, thereby making the cross-cohort analysis invalid. Features from each omic layer will then be selected through variance filtering, univariate Spearman association screening and LASSO regression for each modality. These features will be integrated via Multi-Omics Factor Analysis (MOFA+) to identify latent biological factors that capture shared variance across modalities, producing interpretable representations of each astronaut's pre-flight molecular state for input to 3 parallel predictive models: Elastic Net, Random Forest and Gaussian Process Regression. The corresponding outcome, delta epigenetic age acceleration, shows the change from baseline pre-flight age acceleration to the observed maximum, which will be computed across 7 fully-validated epigenetic clocks with PCGrimAge as the primary measure (Higgins-Chen et al., 2022). To evaluate model performance, nested Leave-One-Out Cross-Validation (LOOCV) will be used to accommodate the limited cohort sizes and to compare them against 2 null baselines: mean outcome prediction and chronological age prediction, both of which must be outformed by our model. Furthermore, model robustness should be assessed through sensitivity analyses using alternative epigenetic clocks; concordance checks between ComBat-corrected and uncorrected analyses; and stratified analyses separating the short-duration ($\leq$14 days) missions from long-duration ($\geq$14 days) missions. Furthermore, to assess causal relationships, a Double Machine Learning framework (Chernozhukov et al., 2018) will be applied to the MOFA factor scores. This two-stage residualisation, with bootstrapped confidence intervals, will isolate each biomarker's causal contribution to the aging trajectory from confounding inter-omic effects. The framework will generate 3 final outputs: an individualised pre-flight biological age acceleration prediction, a personalised risk stratification score and a validated set of biomarkers. These outputs would allow for informed mission planning and targeted pre-mission countermeasures, creating an active decision-support system.

Conclusion:

This study presents a pre-flight multi-omic prediction framework that reorients space medicine's approach to biological aging by generating an individualised aging estimate, personalised risk stratification score and a panel of validated causal biomarkers to guide pre-mission planning. Its feasibility is supported through freely accessible datasets, validated modelling strategies and baseline comparisons to prevent overclaiming. Future work can extend this model by incorporating longitudinal pre-flight sampling for temporal dynamics, additional omic layers (including microbiome composition) and more uncertain molecular profiles to improve predictive performance. Ultimately, such individualised pre-flight biological risk tools will transform space medicine research from retrospective analyses to actionable insights.

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