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Dear Editor,

We submit our manuscript entitled “**MeLSI: Metric Learning for Statistical Inference in Microbiome Community Composition Analysis**” for consideration as a Methods and Protocols article in mSystems.

Current microbiome beta diversity analysis relies on fixed distance metrics (Bray-Curtis, Euclidean, UniFrac) that treat all taxa uniformly. This approach cannot adapt to dataset-specific signal structure and may miss subtle but biologically meaningful differences. We present MeLSI, a machine learning framework that learns data-adaptive distance metrics while maintaining rigorous statistical inference through permutation testing.

MeLSI integrates ensemble metric learning with PERMANOVA-based hypothesis testing. The method provides interpretable feature importance weights that identify which taxa drive group separation, addressing a key limitation of black-box machine learning approaches. Comprehensive validation demonstrates proper Type I error control, competitive statistical power across synthetic benchmarks, and superior performance on real microbiome datasets (Atlas1006, DietSwap).

The method is implemented as an open-source R package with comprehensive documentation and reproducible validation code (DOI: 10.5281/zenodo.17714848). We believe this work will be of broad interest to the mSystems readership and addresses an important methodological gap in microbiome analysis.

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Sincerely,

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