Submission to PLOS Computational Biology

Dear Editors,

We are pleased to submit the manuscript entitled **“Pathway Identifiability under Partial Metabolomics via JL-Stabilized FGW Alignment and Measurement-Driven Disambiguation”** for consideration in *PLOS Computational Biology*.

Metabolomics studies rarely achieve full pathway coverage, yet pathway-level interpretations are often reported as if all relevant metabolites were observed. In practice, missing panel measurements and limit-of-detection censoring introduce structural ambiguity at key branch points, where multiple, mechanistically distinct pathway behaviors remain equally compatible with the same data. Existing computational approaches typically address this problem by imputing missing metabolites or enumerating plausible completions, strategies that either collapse uncertainty into point estimates or become intractable while obscuring why a pathway is ambiguous.

In this work, we propose a unified computational framework that treats partial observability as a first-class object of inference rather than a preprocessing nuisance. Pathways are represented as condition-aware graphs containing both observed and latent metabolite nodes, with missingness encoded explicitly as uncertainty in node features. We compare pathway states across conditions using a geometry-aware alignment operator based on fused Gromov–Wasserstein optimal transport, stabilized via Johnson–Lindenstrauss projections to ensure reproducible behavior under sparse, high-dimensional features. Pathway underdetermination is quantified using a composite functional that combines alignment instability, transport entropy, and a computable growth-based proxy capturing how rapidly uncertainty expands with missing coverage.

A central contribution of the manuscript is the operationalization of experimental design. We introduce a computable measurement-impact estimator that ranks candidate metabolites by their expected ability to reduce pathway ambiguity, without enumerating latent states. Importantly, we validate both identifiability diagnostics and measurement recommendations using a falsifiable synthetic masking protocol with regret-based metrics, explicitly testing whether recommended measurements reduce ambiguity more than alternatives when revealed. This evaluation loop provides a principled and reproducible way to assess pathway identifiability claims under partial metabolomics.

We believe this work is well aligned with the scope of *PLOS Computational Biology*. It addresses a pervasive biological problem—structural ambiguity in pathway interpretation under incomplete measurements—using transparent computational methodology, with explicit assumptions, reproducible evaluation protocols, and openly available code. While motivated by metabolomics, the framework generalizes to other partially observed biochemical networks where identifiability and experimental design are central concerns.

The manuscript is original, has not been published previously, and is not under consideration elsewhere. All authors have approved the submission and declare no competing interests.

Thank you for your consideration. We would be pleased to address any questions or revisions.

Sincerely,

Anas Enoch
Independent Researcher