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Dear Editor,

We are pleased to submit our manuscript entitled "**Comparative analysis of network-based measures for the assessment of drug-induced liver injury: A case study of *Hypericum perforatum***" for consideration as an Original Research Article in *Computational Toxicology*.

Summary. This work addresses a critical methodological problem in network-based toxicology: the instability of proximity Z-scores when comparing compounds with asymmetric target set sizes. Using *Hypericum perforatum* as a controlled case study, we demonstrate that proximity Z-scores can yield misleading rankings due to sample-size-dependent null distribution tightening (the law of large numbers). We show that random walk–based influence propagation provides a more robust framework, and introduce per-target network influence (PTNI) as an effect-size metric for comparative toxicological assessment.

Key Findings.

- Proximity Z-scores are threshold-dependent and reverse compound rankings between STRING confidence levels.
- Influence-based metrics (RWR, EWI) remain stable across network construction parameters.
- Hyperforin targets achieve 3.7-fold greater DILI-directed perturbation efficiency than Quercetin targets, consistent with clinical hepatotoxicity profiles.
- Bootstrap sensitivity analysis excludes target-count confounding as an explanation.

Relevance to Computational Toxicology. Our work directly addresses the journal's focus on computational approaches for toxicological evaluation by:

1. Identifying a systematic artifact in widely-used network proximity metrics.
2. Providing a validated alternative framework (influence propagation + PTNI).
3. Demonstrating practical robustness across multiple validation approaches.
4. Contributing reproducible code and data for the community.

Reproducibility. All code and data are publicly available at: `https://github.com/antonybevan/h-perforatum-network-tox`. Random seeds are fixed (seed=42) throughout, and all software versions are documented.

Declarations. This manuscript has not been published and is not under consideration elsewhere. The author declares no competing interests. No external funding was received. AI-assisted tools were used to support code development; the author takes full responsibility for all content.

We believe this work will be of significant interest to the readers of *Computational Toxicology* as it provides both a methodological advance and a reproducible template for network-based risk assessment.

Thank you for considering our submission. We look forward to your response.

Sincerely,

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