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Equi-UMI pooling for cost-effective AIRRseq

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The adaptive immune receptor repertoire (AIRR) forms the foundation of adaptive immunity and offers vast potential for diagnostic and prognostic applications. However, sequencing AIRRs poses significant technical challenges due to the immense diversity of unique receptors, the requirement to accurately assess relative clonal abundances, and the wide size variability between samples. Conventional next-generation sequencing (NGS) library pooling methods, which rely on equimolar pooling, are inefficient for AIRR studies with samples differing greatly in receptor diversity. This often leads to either excessive sequencing costs or biased subsampling.

To address this, we present Equi-UMI pooling, a new strategy that equalizes the expected number of reads per unique molecular identifier (UMI) across samples. By estimating UMI counts prior to sequencing, libraries are pooled in proportion to their expected information content rather than molarity. In a proof-of-concept study of 96 samples averaging 200,000 UMIs each, sequencing at six reads per UMI achieved uniform coverage while reducing total read requirements from over 800 million to ~100 million, cutting costs by 86%. The method also demonstrated robustness against technical subsampling biases.

Equi-UMI pooling thus enables accurate, bias-free AIRR sequencing at substantially reduced cost and effort, expanding accessibility of repertoire analysis to resource-limited research settings.

Thomas-Wolf Verdonckt is a virologist and immunologist specializing in next-generation sequencing (NGS) applications for immunological and viral research. His work focuses on the development and optimization of sequencing methodologies for highly diverse biological systems, particularly adaptive immune receptor repertoires (AIRRs). He has contributed to improving experimental designs and data analysis workflows that enhance the accuracy, efficiency, and interpretability of immune repertoire sequencing.

Drawing on a strong background in both molecular biology and computational analysis, Thomas-Wolf bridges wet-lab protocol development with bioinformatic innovation. His recent work introduced the *Equi-UMI pooling* strategy, a novel approach that significantly reduces sequencing costs and mitigates bias in AIRR profiling. His broader research interests include viral immunodynamics, repertoire evolution, and scalable NGS workflows for translational immunology.

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