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Brain Organoid Cell Type Prediction by Brain Single-cell Atlas Trained Annotation Models

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Understanding human brain development is critical for advancing our knowledge of neurological diseases and potential therapeutic approaches. Human brain cortical organoids, derived from stem cells, present promising in-vitro models that recapitulate many aspects of brain development. Yet, we should map the organoid's temporal and cellular fidelity to actual human brain cell types to validate their utility as models of the human brain. We used our previously constructed developmental human brain single-cell atlas to train two cell-type prediction models: CellTypist and scArches. The models were evaluated by applying them to a publicly available brain organoid dataset of diverse time points of cultivation and comparing the predictions with the original cell types. Both models demonstrated accuracy, with early-stage organoids (2 months) showing the highest consistency with known cerebral cortex cell types. However, misclassifications were observed in the CellTypist model due to ambiguous gene expression without distinct marker genes, and scArches consistently predicted stable numbers of radial glia (RG) and neuroblast populations across all time points. Comprehensively, the CellTypist exhibited superior clustering quality while scArches model showed better bio-conservation across time points. By comparing and evaluating the predictions from both models, this study provides critical insights into the strengths and limitations of current brain organoid annotation methods. These models will offer a deeper understanding of how well organoids reflect human brain development, serving as a step toward improving their accuracy and utility in neurodevelopmental research.