A077 · Statistical detection of drivers of hematopoietic differentiation from lentiviral integration site datasets

Presenter: Giacomo Ceoldo — Boston Children's Hospital - Harvard Medical School

Authors: Giacomo Ceoldo, Danilo Pellin

Session: Day 2 · Fri Oct 2, 2026 · 2:15–4:15 PM

Integration site datasets, obtained from blood samples for clone tracking of individuals treated with lentiviral gene therapy, offer important insights into human hematopoiesis. In particular, the long follow-up period of gene therapy patients allows the study of long-term effects on hematopoietic reconstitution for various genetic diseases. Clinical applications include the discovery of novel drivers of hematopoietic differentiation, whose effects may be enhanced by interactions with an integrated transgene. Identifying such drivers may contribute to the development of more specific therapies targeting disease-relevant hematopoietic subtypes.

We are developing algorithms to detect and test genomic windows with a rate of lentiviral integration, clone survival, or clone fitness higher than the baseline, or with large differences in rates across two or more groups (cell types, clinical trials). The first phase (window detection) is based on fused lasso estimation, which is extended to generalized linear models (with the response function depending on the rate type) and includes covariates to account for dataset heterogeneity (patient- or cell-type-specific effects). For multi-group analyses, the fused lasso graph penalty is extended to sparse graphs of integration sites.

The second phase consists of formally testing the set of windows selected in the first phase, in order to identify those with a statistically significant effect and provide a biological interpretation of the results. The test statistics we are developing are permutation-based, to account for misspecification of the generative model (regression-based approximations of hematopoiesis). We are currently analyzing all published integration site datasets from gene therapy clinical trials.