A072 · Reconstructing Intra-Tumor Fitness Landscapes from scSeq CNA Genotypes via Simulation-Based Bayesian Inference and Deep Learning

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Chromosome-arm copy-number alterations (CNAs)—gains and losses of entire chromosome arms—are pervasive drivers of tumor evolution, yet quantifying the fitness effects of CNAs remains challenging. Recent advances in single-cell sequencing (scSeq) enable high-resolution profiling of CNAs across intra-tumor clonal populations, potentially providing a window into the underlying phenotypic diversity within tumors and enabling its inference through computational approaches.

Phenotypic effects of alterations at different loci are often assumed to be independent, simplifying calculations but neglecting epistatic interactions and synthetic lethality, both of which are prevalent in cancer clonal populations. Inferring selection coefficients for entire CNA genotypes is substantially more challenging, particularly because mechanistic models of clonal evolution typically yield intractable likelihoods, precluding standard likelihood-based inference.

We present a likelihood-free, simulation-based inference (SBI) framework for estimating genotype-specific selection coefficients from single-snapshot clonal CNA profiles. Using synthetic data generated by agent-based simulations, we train a normalizing-flow neural posterior estimator to map observed CNA profiles to calibrated posterior distributions over their associated fitness coefficients, thereby amortizing inference across new observations without requiring additional simulations.

On simulated data, our primary model, CloneMLP-NPE, yields well-calibrated posterior distributions over fitness coefficients. Its posterior-mean estimates recover a substantial fraction of the variation in true fitness coefficients (R^2 = $ 0.34–0.62; Pearson correlation up to 0.79), outperforming several baseline approaches. Together, these results demonstrate the potential of SBI as an uncertainty-aware likelihood-free approach for inferring intra-tumor fitness landscapes from scSeq data.

Reconstructing Intra-Tumor Fitness Landscapes from scSeq CNA Genotypes via Simulation-Based Bayesian Inference and Deep Learning

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