Titel:

Reconstructing Clonal Evolution: Bioinformatic Challenges and Perspectives

Abstract:

To understand the development of a tumor over time, it is important to consider its clonal evolution. It allows us to characterized the clones on a mutational level, and to study their rise and fall. Resistant subclones may be detected before relapse, which gives chance to adjust therapy and – in the end – improve survival. However, the actual reconstruction of clonal evolution is challenging.
We consider the main challenges in the preparatory step of mutation calling as well as in actual reconstruction of clonal evolution.
Regarding mutation calling, we address SNV and indel calling, which is challenging with respect to the detection of low-frequency variants, filtration of artifacts, filtration of polymorphisms and the handling of low coverage. Copy number variant (CNV) calling is often complicated by unavailable control samples, presence of whole-exome or even just targeted sequencing data, high false-positive rates and imprecise estimates of the coordinates of CNVs as well as the percentage of affected cells. Deriving the cancer cell fractions (CCFs) from given variant allele frequencies (VAFs) is – in the presence of CNVs – not straightforward, as VAFs have to be adjusted.
Regarding the actual reconstruction of clonal evolution, we present a systematic nomenclature to categorize clonal evolution at two time points. Tree reconstruction is complicated by the presence of many algorithms with similar limitations, e.g. the development of independent subclones is usually not supported and the provided CCFs are considered fixed, which results in too many clusters and much too complicated trees. We show how manual reconstruction of clonal evolution trees is possible. Finally, we consider visualization and show how fishplots can be drawn in the presence of many subclones and few time points, applying our novel approach of estimating development of clones over time and the effect of therapy.