

Abstract. Micro-indels are small insertion or deletion events (indels) that occur during genome evolution. The study of micro-indels is important, both in order to better understand the underlying biological mechanisms, and also for improving the evolutionary models used in sequence alignment and phylogenetic analysis. The inference of micro-indels from multiple sequence alignments of related genomes poses a difficult computational problem, and is far more complicated than the related task of inferring the history of point mutations. We introduce a tree alignment based approach that is suitable for working with multiple genomes and that emphasizes the concept of *indel history*. By working with an appropriately restricted alignment model, we are able to propose an algorithm for inferring the optimal indel history of homologous sequences that is efficient for practical problems. Using data from the ENCODE project as well as related sequences from multiple primates, we are able to compare and contrast indel events in both coding and non-coding regions. The ability to work with multiple sequences allows us to refute a previous claim that indel rates are approximately fixed even when the mutation rate changes, and allows us to show that indel events are not neutral. In particular, we identify indel hotspots in the human genome.