With ever-advancing genomic technologies, it has become increasingly clear that cell-to-cell genomic variability is a ubiquitous feature of multicellular systems with importance to numerous phenomena in health and disease. While technologies for single-cell genomics are rapidly improving, though, they are still impractical for the scales needed to characterize genomic heterogeneity of complex mixtures across large patient populations, leaving the field highly dependent on computational inference to fill in the gaps in what it is practical to measure experimentally. Genomic deconvolution and phylogenetic methods have become subfields in themselves for making sense of still-limited genomic data in terms of coherent models of genomic heterogeneity. There is probably no system for which this phenomenon has been more intensively studied than cancers, where cell-to-cell genetic heterogeneity is now appreciated as key to tumor initiation, progression, and response to treatment. This talk will explore computational challenges in reconstructing models of genomic heterogeneity and the evolutionary processes by which it develops, as well as strategies for meeting those challenges, with particular focus on intra-tumor heterogeneity. It will in the process explore computational strategies for various sources of genomic data (bulk, single-cell, and combinations) and examine the tradeoffs between them. It will conclude with consideration of some emerging directions and open problems in studies of heterogeneity in multicellular systems, in cancers and beyond.