

Novel methods and compositions for rapid and highly efficient nucleic acid sequencing based upon hybridization with two sets of small oligonucleotide probes of known sequences are disclosed. Extremely large nucleic acid molecules, including chromosomes and non-amplified RNA, may be sequenced without prior cloning or subcloning steps. The methods of the invention also solve various current problems associated with sequencing technology such as, for example, high noise to signal ratios and difficult discrimination, attaching many nucleic acid fragments to a surface, preparing many, longer or more complex probes and labeling more species.