Advancing Microarray Technology: Efficient Design of Sequence Libraries Covering All k-mers with Degenerate Characters to Improve Interaction Measurement

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Microarray technologies are used to understand the driving forces in genomics and proteomics through high-throughput measurements of interactions among DNA, RNA, peptides, and proteins. Universal microarrays use sequence libraries that include all k-mers, sequence variants of length k, to enable comprehensive, universal, and unbiased measurements of these interactions. Libraries that maximize k facilitate discovery of new interactions and reveal binding properties at greater detail; however, because of the exponential growth in k of such libraries and the limited size of microarrays, developing an efficient universal library for higher k values is difficult. This project introduces a novel way to generate compact designs of sequence libraries by utilizing degenerate characters that represent all characters in the alphabet Sigma. Because multiple sequences without degenerate characters can be represented by a sequence with a degenerate character, the universal library size can theoretically be significantly reduced. A greedy algorithm was developed where optimal local steps are chosen to generate the smaller library sets and a condition of at most one degenerate character in every k-mer is utilized. The new sequence libraries approach the theoretical lower bounds and achieve nearly 1/|Sigma| of the original sizes for DNA, RNA, and amino acid libraries. In addition, through simulation of a protein-DNA binding experiment using the sequence libraries that incorporated the degenerate character, accurate binding scores were acquired for high-affinity k-mers. These resulting sequence libraries provide the first step towards efficiently incorporating degenerate characters into libraries and towards improved understanding of fundamental cellular processes.

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