One of the cornerstone in clone-by-clone sequencing involves selecting a minimal tiling path (MTP) from the clones in a genetic library. Due to inevitable noise in restriction fingerprint data, the problem of selecting the best MTP is computationally challenging.

In this paper, we present a novel method that can efficiently select an MTP from a physical map. The method is based on graph-theoretical properties of the underlying clone arrangements in the physical map. We formulate the constraints of the problem in a combinatorial optimization framework that is solved via Integer Linear Programming.

We compare our method with the commonly used software FPC. The results show that MTP produced by our tool covers a higher portion of the genome, even with fewer clones than MTP produced by FPC. Experimental results suggest that if one would use the MTP produced by our method instead of FPC’s in a clone-by-clone sequencing project, one would reduce by about 12% the sequencing cost.