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A Rapid Method for Simultaneous Chemical Synthesis of Oligonucleotides in Large Nufiber

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A RAPID METHOD FOR SIMULTANEOUS CHEMICAL SYNTHESIS OF OLIGONUCLEOTIDES
IN LARGE NUMBER

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Summary : A rapid manual method is described for simultaneous synthesis of over one hundred oligonucleotides on a microscale by the phosphotriester approach on cellulose paper.

With the increasing need for synthetic oligonucleotides in molecular biology it became necessary to develop a simple, rapid, inexpensive technique for synthesis and purification of a large number of unique oligonucleotides. The phosphotriester approach was used : The solid support was paper disks stacked into 4 glass columns (one for each monomer to be added) placed in parallel in a continuous-flow system controlled by gas pressure. Anhydrous solvents, protected mononucleotides as triethylammonium salts and 5'-O-DMT-2'-déoxynucleoside 3'-O-succinates were obtained commercially and used without additional purification. By use of the catalyst 1-methylimidazole, with MSNT as condensing agent the coupling reaction was 15 min with an average efficiency of 90 % per step. The same catalyst was used to couple deoxyribonucleoside succinates to the cellulose support and lead to a loading of 80 $\mu\text{mol/g}$ paper. Based on 50 nmol scale the yields for 17-20 mers were on average 10 %, an amount sufficient for most purposes. In the synthesis of 125 oligomers, the assemblies were carried out in 3 days. The majority of this time was spent on sorting the disks. Purification was performed by HPLC and polyacrylamide gel electrophoresis. The latter procedure offers the advantage that many oligomers can be purified simultaneously. The numerous oligonucleotides synthesized and purified by the described method were biologically active in different experiments.