

Massively parallel oligonucleotide synthesis on a microchip based on the μParaflo™ microfluidics technology

Massive Parallel Synthesis

The scientists and engineers at our technology partner, Atactic Technologies, have developed platform technologies that encompass a new class of microfluidic μParaflo™ reaction devices, an advanced digital light synthesizer apparatus, and picoliter scale biochemical processes. The functionalized μParaflo™ chips are particularly suited for applications where small sample consumption, contamination-free, and performance-reproducibility are primary concerns.

This technology enables the massively parallel synthesis of high quality DNA and RNA oligonucleotides as well as peptides and peptidomimetics in picoliter-scale reaction chambers.

PicoArray Reactor

The microfluidic PicoArray reactor is made from silicon using standard microelectronic fabrication procedures. The reactor contains three topographical features: pico-reaction chambers, fluid microchannels, and inlet/outlet through holes. The chip contains 128 x 31 (total 3698) individual reaction chambers, each with an internal volume of 270 pl. The fluid microchannels are of a tapered shape that was derived from a fluid mechanical model to produce a uniform flow rate across all reaction chambers. This technology enables a high density of uniform spots.

Digital Photolithographic Device

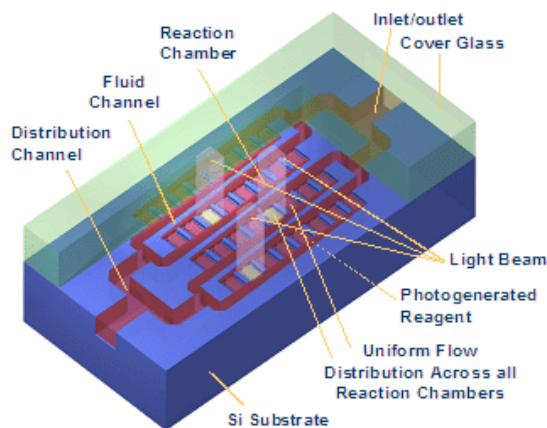
A significant improvement in making photolithography a practical method for combinatorial chemical synthesis is the introduction of the digital optical device for light patterning projection onto a reaction surface. This technology allows parallel synthesis of a large number of different molecules on the same reaction surface without the need for the expensive, inconvenient microfabricated photomasks previously used. Custom sequences can be synthesized by simply reprogramming the computer controlling the digital optical device.

Photo Generated Acid (PGA) Deprotection

A PGA precursor is fed into the microfluidic chamber prior to the light irradiation step to create the acid which removes the acid labile DMT protecting group. This process is simple in that it does not require an electrochemical surface or specialty monomers with photolabile protecting groups (PLPG).

Electrochemical deprotection methods require a complex circuitry of electrodes that can withstand contact with the strong organic reagents through multiple synthesis cycles. Another limitation of deprotection with electrodes is that side reactions can occur on the electrode surface. The need for specialty PLPG monomers means no flexibility for creating content variations in the sequences. Studies show the reaction efficiency is much lower than standard monomers and they have been known to give rise to randomized misincorporation or insertion errors lowering sequence fidelity.

PGA deprotection allows parallel synthesis with conventional chemicals and supplies, following well established synthesis processes. The quality of the synthesis reaction is greater than 98.8% ASWY and this approach is very flexible because virtually any modified monomer can be used creating a wide array of non-regular oligonucleotides.



PicoArray Reactor

Clear Advantages

- The synthesis method is suitable for different classes of molecules, such as oligonucleotides, peptides, or their analogs
- The synthesis can be performed in a regular research laboratory
- The synthesis efficiency can be optimized to be comparable with conventional synthesis
- It offers flexibility in the sequences to be synthesized – editing the changes in sequence text files to create different chips easily
- The overall consumption of chemicals (in synthesis) and samples (in assays) is significantly reduced to the level of sub-nanoliter to picoliter per assay
- The microfluidic reaction chambers are particularly suited for parallel biochemical reactions
- The liquid delivery to the microchip is simple (parallel flow through the inlet and outlet holes), can be automated, and there is little chance of ambient contamination
- The spot density of the chip can be ten-fold higher than that of spotted chip

Further Reading

Technology and Application Articles

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