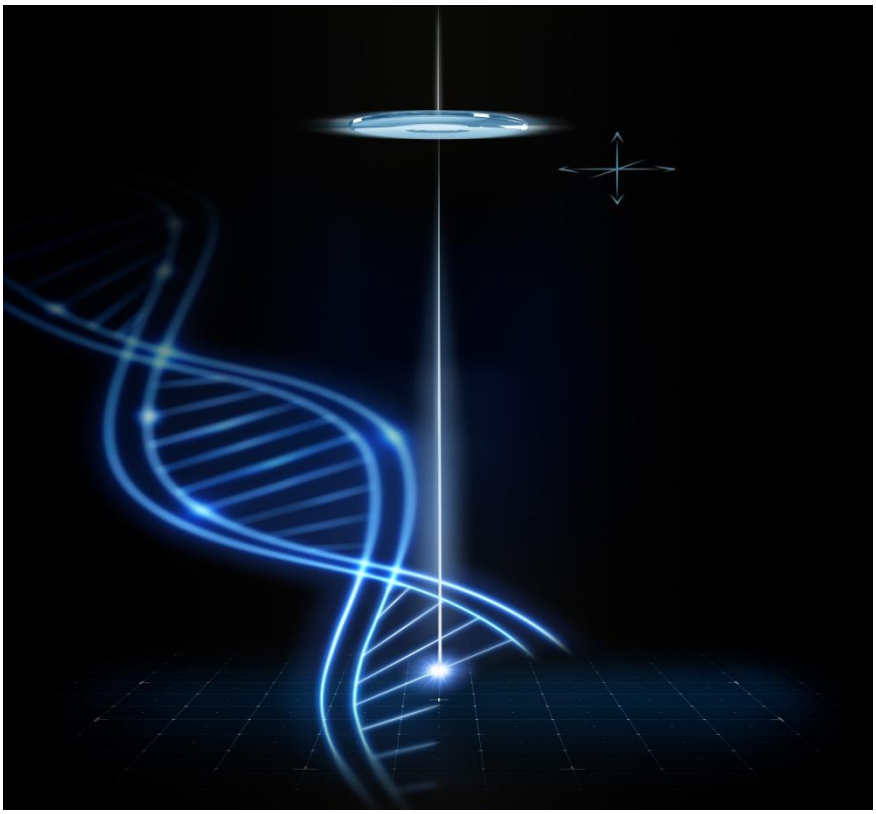
Genome Sequencing - Sequencing-by-Synthesis Method

Precision drives for fast and precise flow cell scanning in XYZ-directions and Piezo-based flow actuators for flow cells & other microfluidic cartridges



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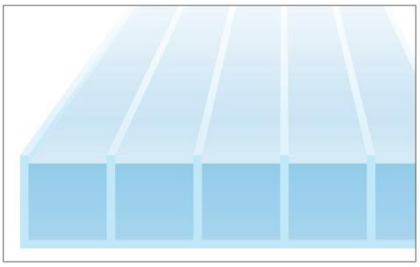
Sequencing-by-Synthesis Method

The Sequencing-by-Synthesis method, also known as Solexa-Illumina-method, is the most widespread method among all Next-Generation-Sequencing methods (NGS). It was used to identify the RNA fingerprint of the SARS-COV2 virus in January 2020 in a research institute in Wuhan. Since then, this RNA fingerprint measurement has frequently been repeated in research institutes all over the world. And today this NGS method is used worldwide day-by-day to continuously monitor the SARS COV2 virus for mutations.

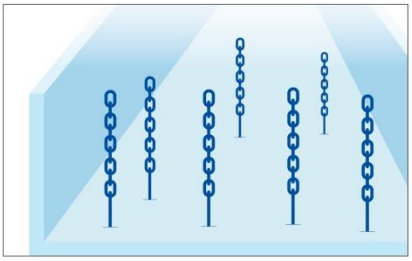
In addition to microfluidic flushing and washing cycles, as also used by the other methods, e.g. the semiconductor-method and the nanopore-method, the Sequencing-by-Synthesis method is based on very precise and fast XYZ-optical image scanning of the whole sample area.

To reduce turbulence and to achieve laminar flows at high speed flushing and washing cycles, flow cells with several parallel channels are used. Typical channel width is some millimetres. This microfluidic pumping and sucking can be done fast, precise and reliable by piezo-based actuators in form of membrane pump plates, benders or tubes.



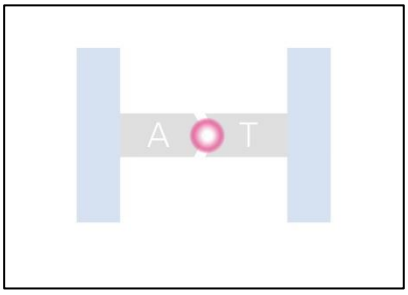
Channels in a flow cell

The whole genome is put to many shorter pieces by the shot-gun technique, these pieces are PCR amplified, then split to single strands (oligo strands) and finally attached to the bottom of the flow cell.



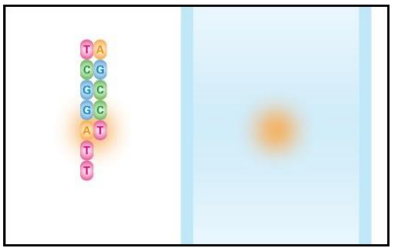
Oligo strands attached to the bottom of a flow cell channel

From here the stepwise recombination of base pairs starts vertically and each recombination is indicated by a fluorescence signal. The base pairs contain four different nucleotides to result in four different fluorescence colors.



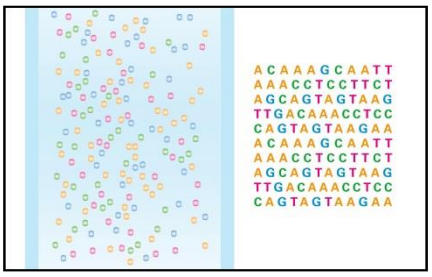
Recombined base pair read out by optical fluorescence signal

After each nucleotide flushing the read-out of the whole flow cell has to be done by a XY-scan with all four laser excitation wavelengths. For this purpose a fast and precise motion drive combination for the laser excitation and read-out in every XY-position and at the correct Z-level is needed. Comprising a Z-focus adjustment in every XY-coordinate and then scanning the XY-plane typically in a meander-like style.



Thymin fluorescence of a base pair at one strand position

This results in a two-dimensional fluorescence data set after each flushing & washing cycle. Each fluorescence signal represents one nucleotide in a recombined base pair.



Resulted data set after one flushing & washing cycle

Motion Solutions from PI

For the XYZ-scanning three drives are needed and typically in addition a rotary drive to correctly position the whole flow cell after cell exchange in the device. This means, in total four precision drives are needed:

- Z-drive (focus drive). Typical requirements are: max. stroke >5 mm; max. speed >25 mm/s; payload >500 g; repeatability <300 nm; accuracy <3 µm

Voice coil drives

- XY-drives (sample stage). Typical requirements are: max. travel range >100 mm x 100 mm; max. speed >200 mm/s; payload >2 kg; repeatability <500 nm; accuracy <3 µm; step & settle in raster scan 1,5 mm in < 40 ms.

3-phase magnetic direct drives, piezo motor stages

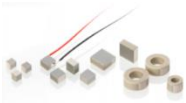
- Rotary-drive (sample alignment after exchange). Typical requirements are: max. stroke >10°; max. speed >5°/s; payload >0,5 kg; repeatability <0,1 mrad; accuracy <1 mrad

DC motor drives, 3-phase magnetic direct drives

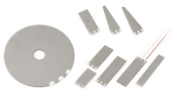
Piezo actuators from PI

- Piezo actuators operate at frequencies of up to several kHz and are ideally suited for milli-, micro- and nanodispensing applications: They can switch valves directly, work against a closing spring or a flexible tube for volume displacement and propel liquids within a microfluidic reaction volume – like a membrane pump.

PICMA® Stack Multilayer Piezo Actuators

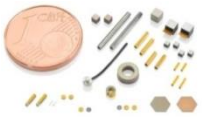


PICMA® Chip Actuators

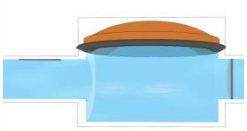


PICMA® Multilayer Bender Actuators

Piezoelectric Components



Miniaturized Piezo Components



Piezo Actuators and Components for Pumping Applications

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