Francesco Mancini

BioMerieux Italia s.p.a
A presentation of the company R&D

PIONEERING DIAGNOSTICS

BIOMERIEUX

Francesco Mancini

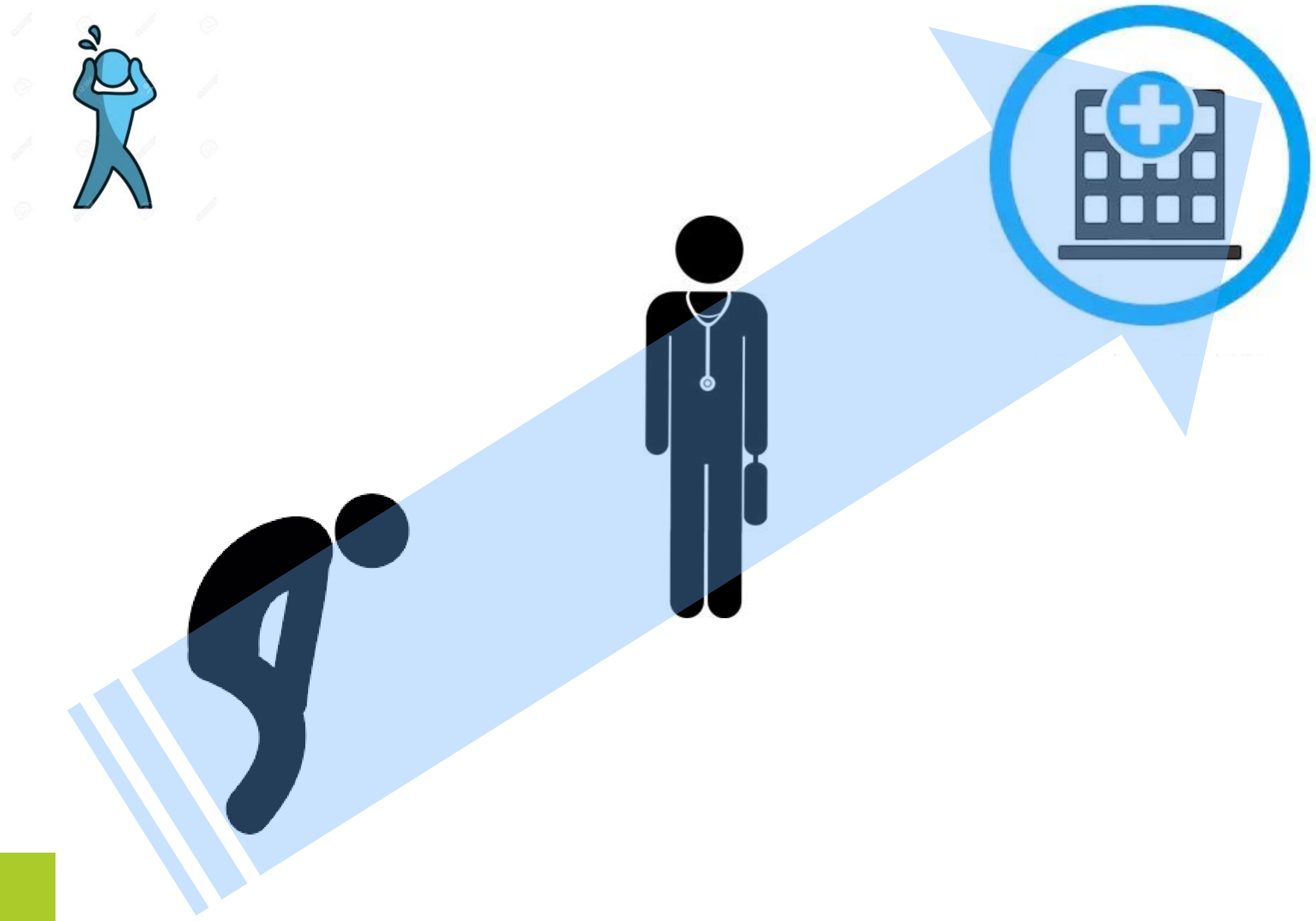
Electronic Department Manager

francesco.mancini@biomerieux.com

BIOMERIEUX

MISSION

WHAT IS CLINICAL DIAGNOSTIC ?



WHAT IS CLINICAL DIAGNOSTIC ?

Human
matrix

-Blood
-Saliva
-Urine
-Stools
-…

Reagent
Kit

? Healthy ?

NOT ONLY CLINICAL ….

FOOD Quality Control

COSMETICS Quality Control

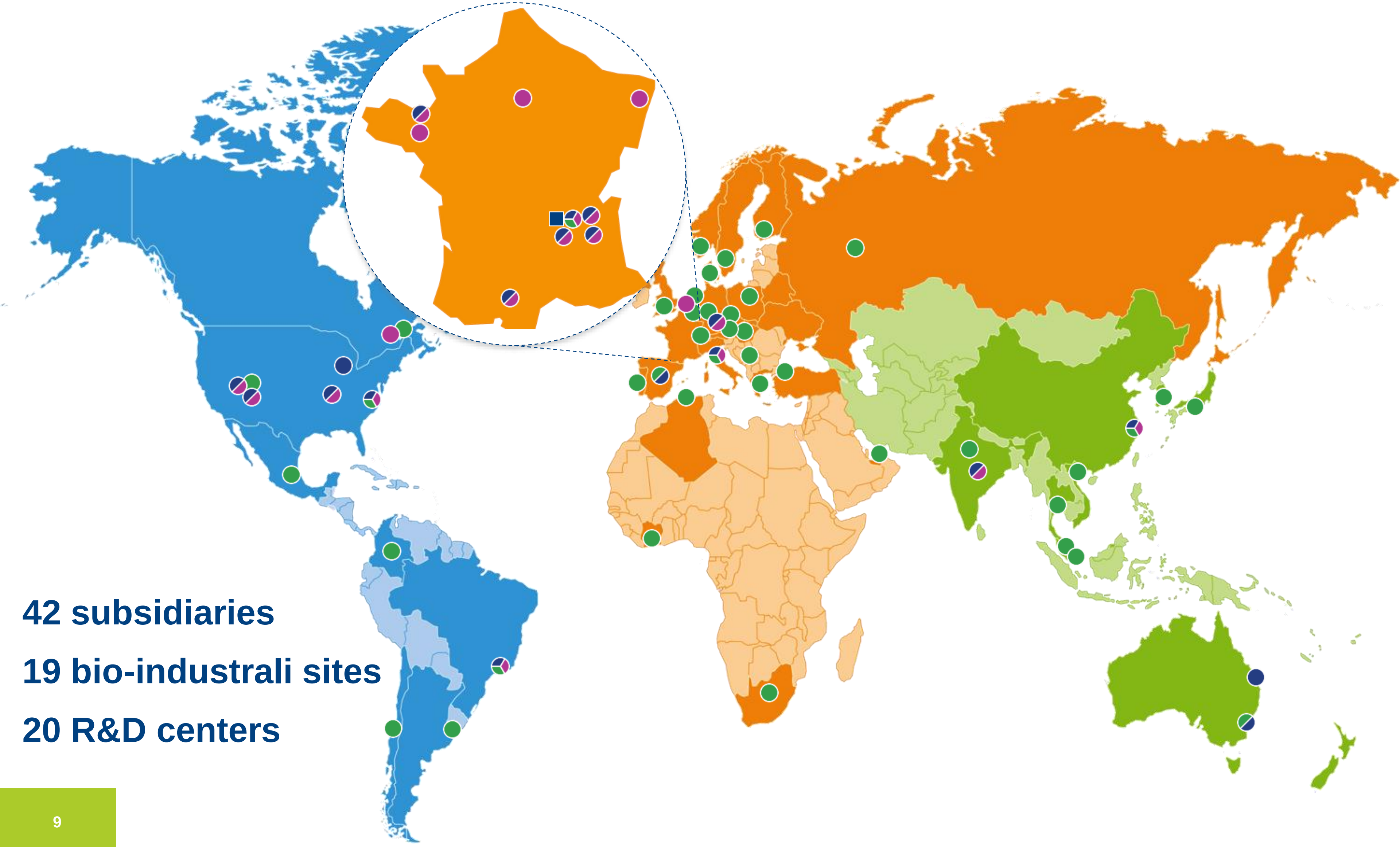
PHARMA Quality Control

ORGANIZATION

BIOMERIEUX GROUP

Headquarters	Lyon - France
Employees	~ 11.000
Revenue	~ 2.4 Billions €

GEOGRAPHICAL LAYOUT



42 subsidiaries

19 bio-industrali sites

20 R&D centers

BIOMERIEUX ITALIA

Location	Ponte a Ema
Employees	~ 240
R&D employees	~ 27

BIOMERIEUX ITALIA

Human Resources

Administration

Finance

Marketing & Sales

Purchasing

Tenders

R&D

Manufacturing

Support

Refurbishment

Customer Care

WareHouse

Quality Assurance

Supply Chain

BIOMERIEUX ITALIA

R&D

(Instrument Development)

Manufacturing

(Instrument Assembling and Testing)

No Reagent Development

R&D

SYSTEM

REAGENTS

INSTRUMENT

USER INTERFACE

NETWORK

SYSTEM PROJECT

BUSINESS OPPORTUNITY

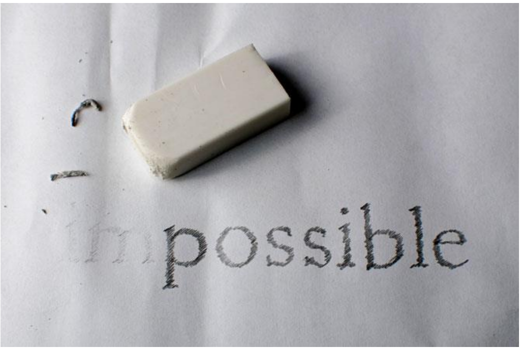
FEASIBILITY

DESIGN & VERIFICATION

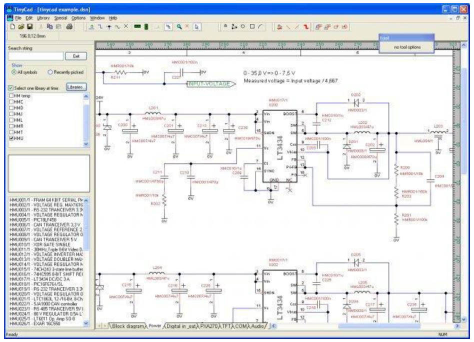
VALIDATION

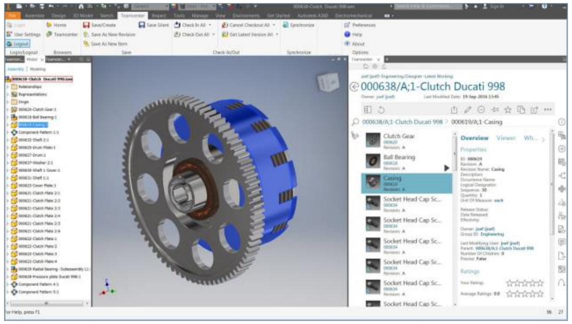
LAUNCH & POST-MARKET

R&D - MISSION

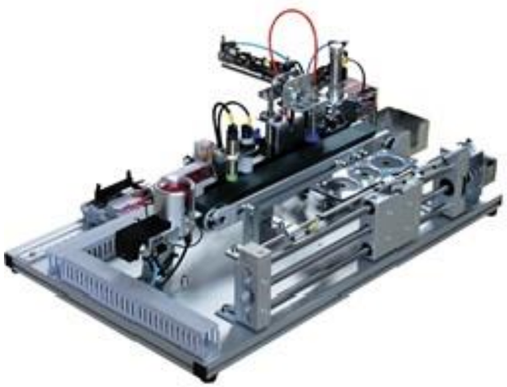


Feasibility





Design and Industrialization



Prototyping

Integration & Verification

Certification

R&D - POSITIONS

Mechanic Design Department

- Feasibility
- Mech. Design
- Workshop

Electronic Design Department

- Feasibility
- FW Design
- HW Design

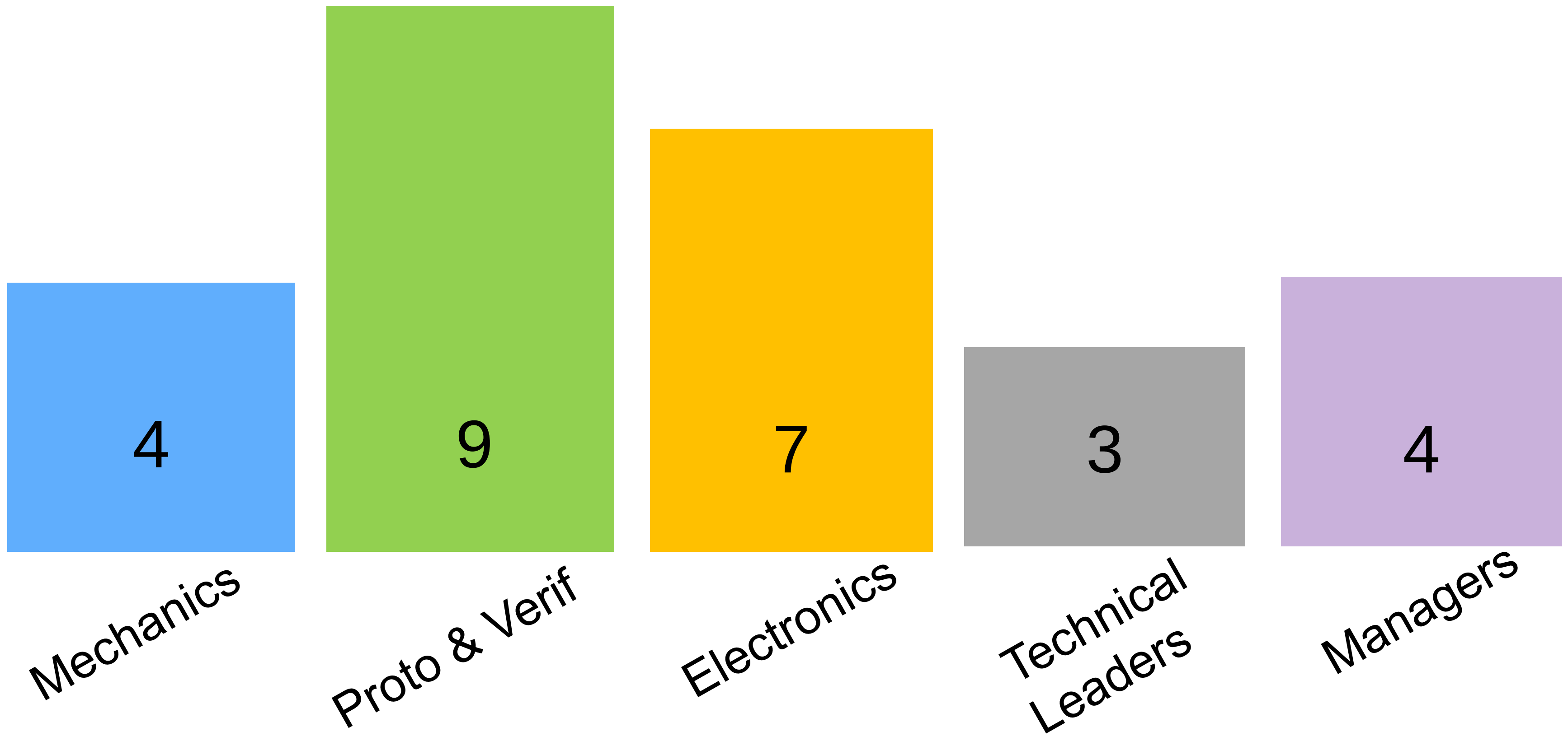
Technical Leaders (Project Coordinators)

Prototyping and Verification Department

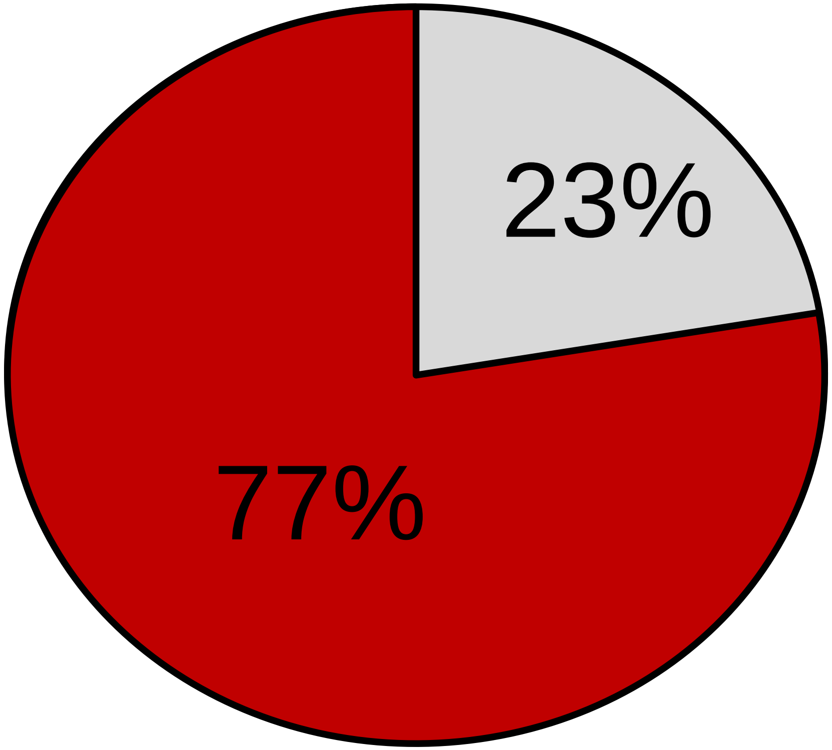
- Feasibility
- Safety
- Prototyping and bio-Integration
- EMI/EMC testing
- Instrument Verification

R&D - COMPOSITIONS

27 People



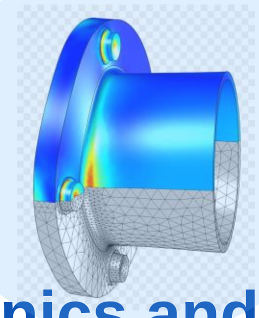
R&D - COMPOSITION



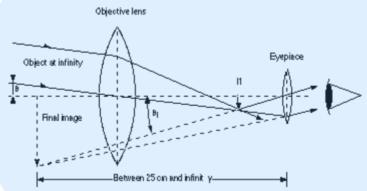
Industrial High Schools

Mechanical Engineers
Biomedical Engineers
Electronics Engineers
Informatic Engineers
Physicists
Biologists

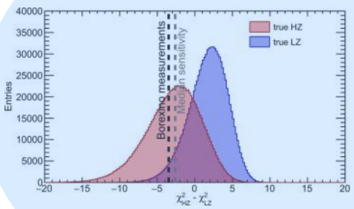
R&D – SOME TECH INSIGHT



Mechanics and Materials



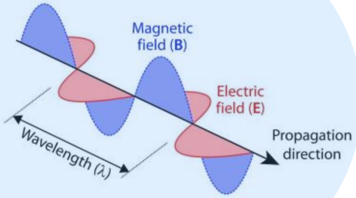
Physics (Optics)



Statistics

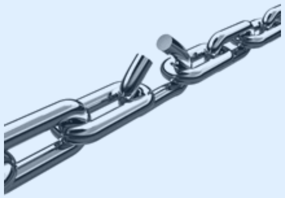
Fluidics

Electronics



Electromagnetics

Coding



Reliability

Algo & Processing

DESIGN OF A FLUORESCENCE DETECTOR

DIAGNOSTIC PRINCIPLE

EBV Reagent Kit

EBV ?!

BIOCHEMICAL REACTIONS

Final chemical Compound

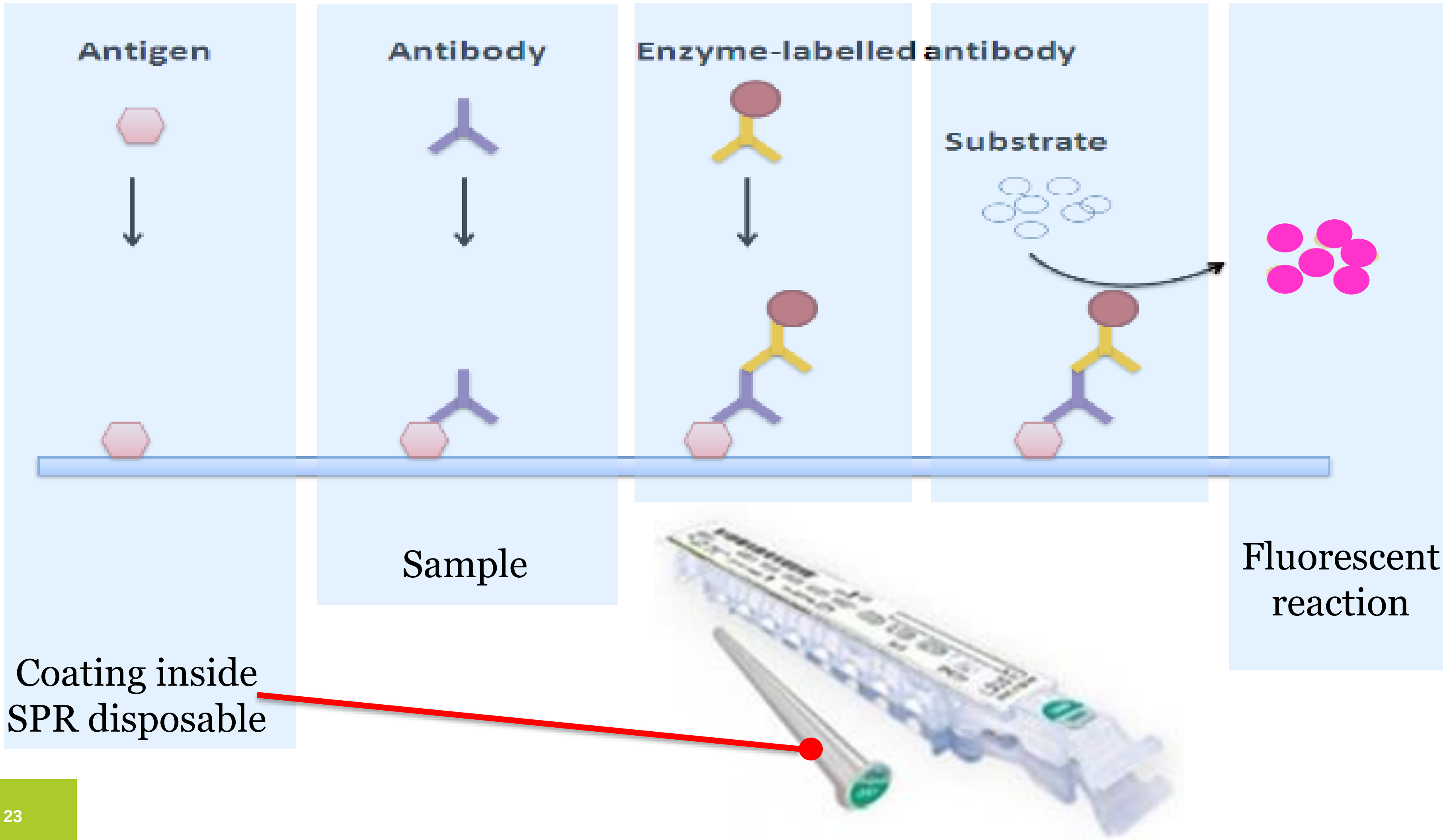
Compound contains fluorescent/chemiluminescent molecules whose concentration is proportional to initial EBV concentration

Compound is lit up and return light intensity is measured

Measure is proportional to EBV concentration

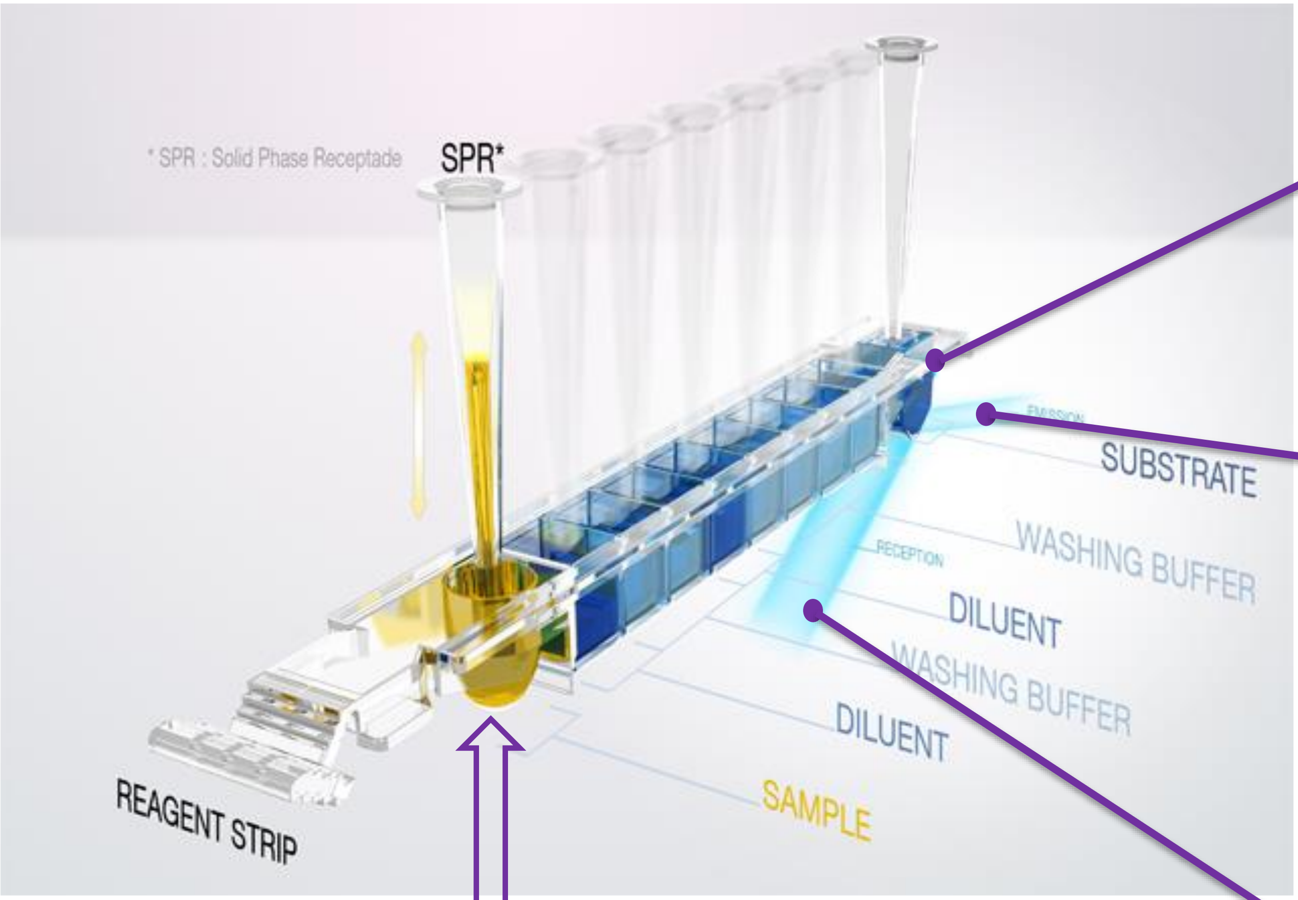
DIAGNOSTIC PRINCIPLE

E.L.I.S.A. : Enzyme Linked ImmunoSorbent Assay



DIAGNOSTIC PRINCIPLE

Final Compound



Re-emitted Light to be read WL = 450 nm

Liquid Sample

Source Light WL = 365 nm (UltraViolet)

DETECTOR SYSTEM

Old

- Expensive product
- No Bill Of Material control
- Lamp Single Supplier
- Partially prone to noise
- Analog technology
- Low stability of impulse peak

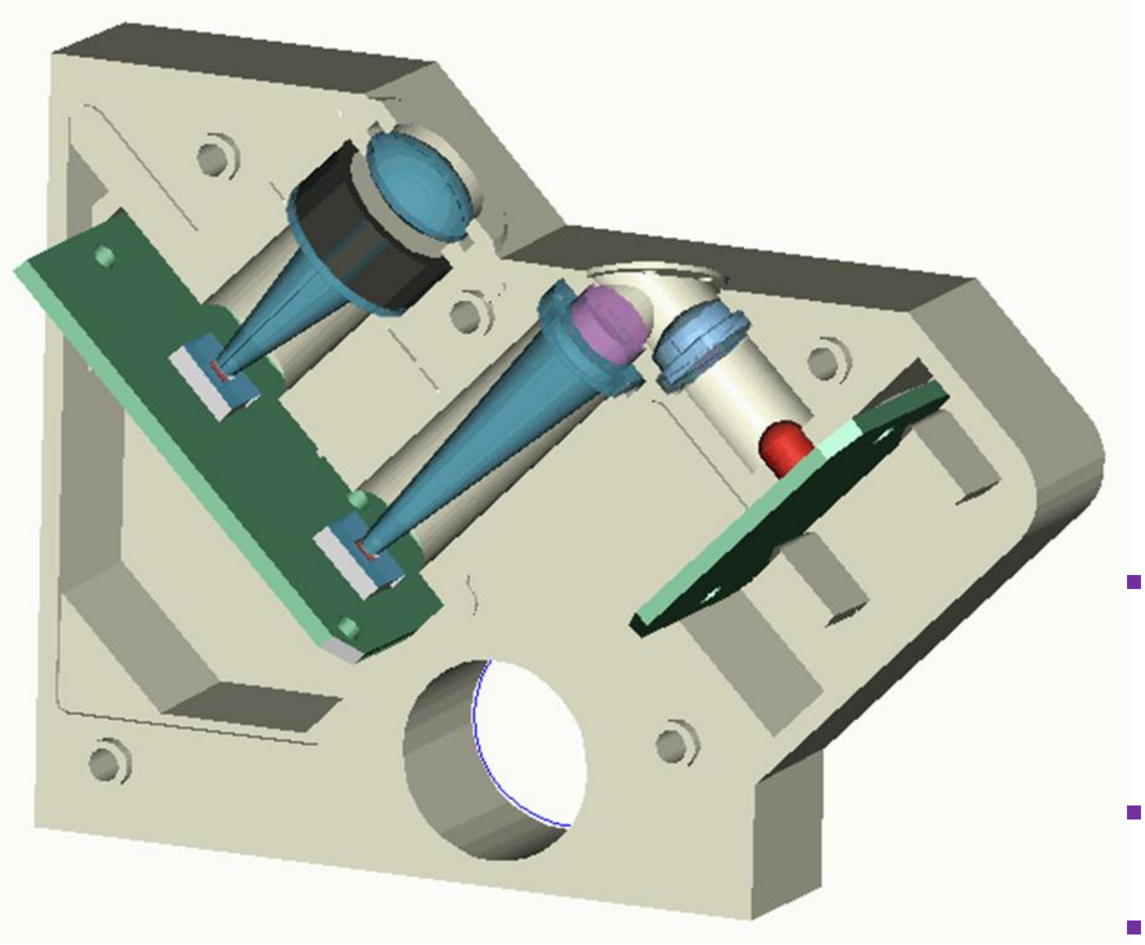
New (Goals)

- Cost reduction
- Bill Of Material control
- Owner of the system
- Increase SNR
- Digital technology
- Same performances (At least)

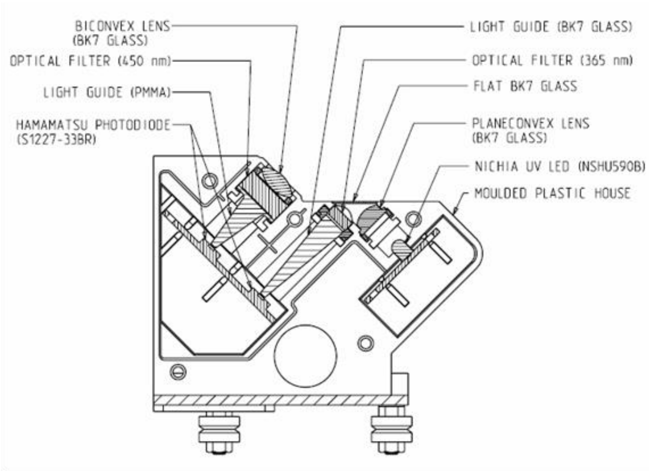
+

- Wider range of measurement
- Back compatible

DETECTOR SYSTEM

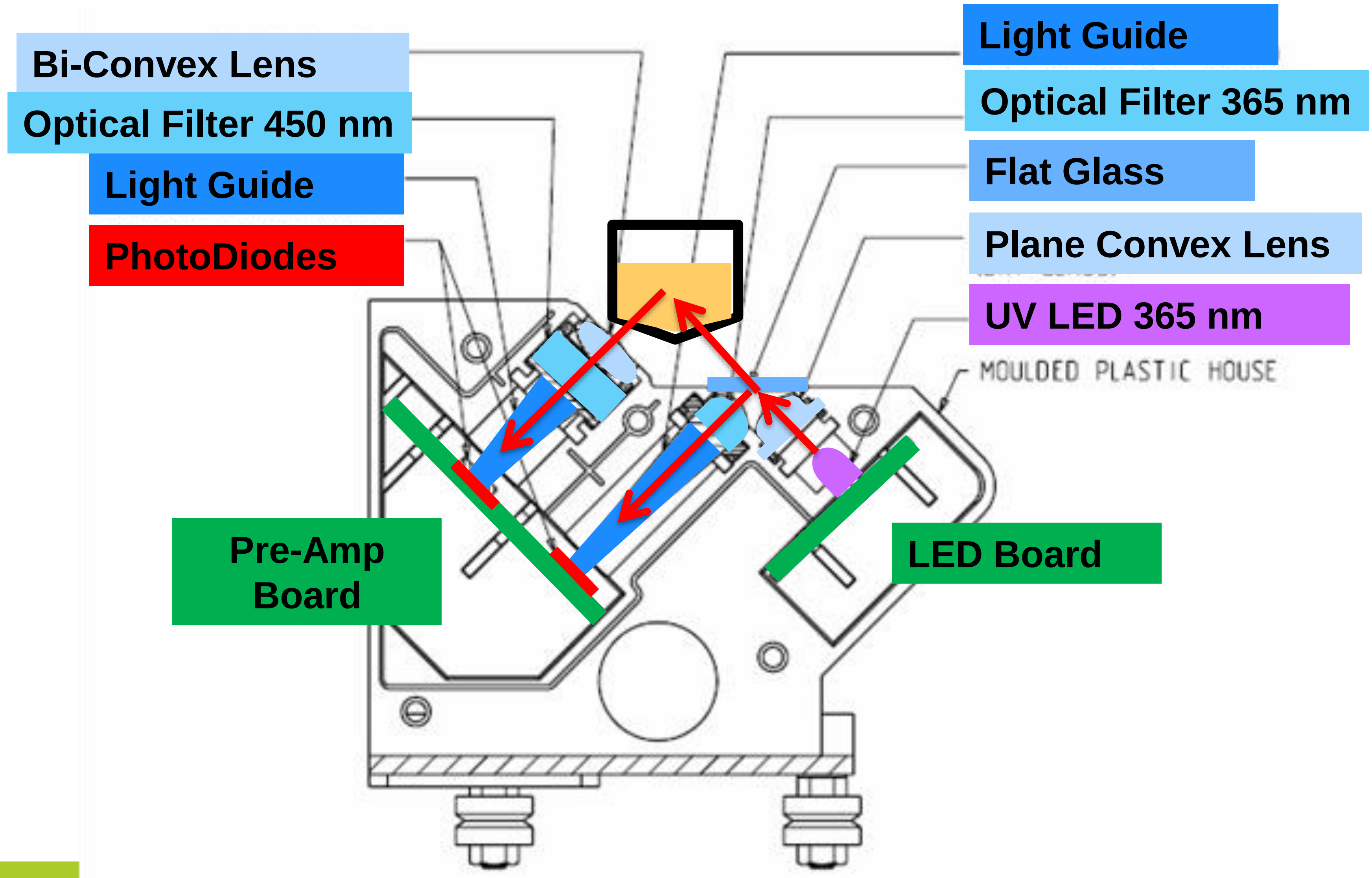


Two moulded shells sub-assembly

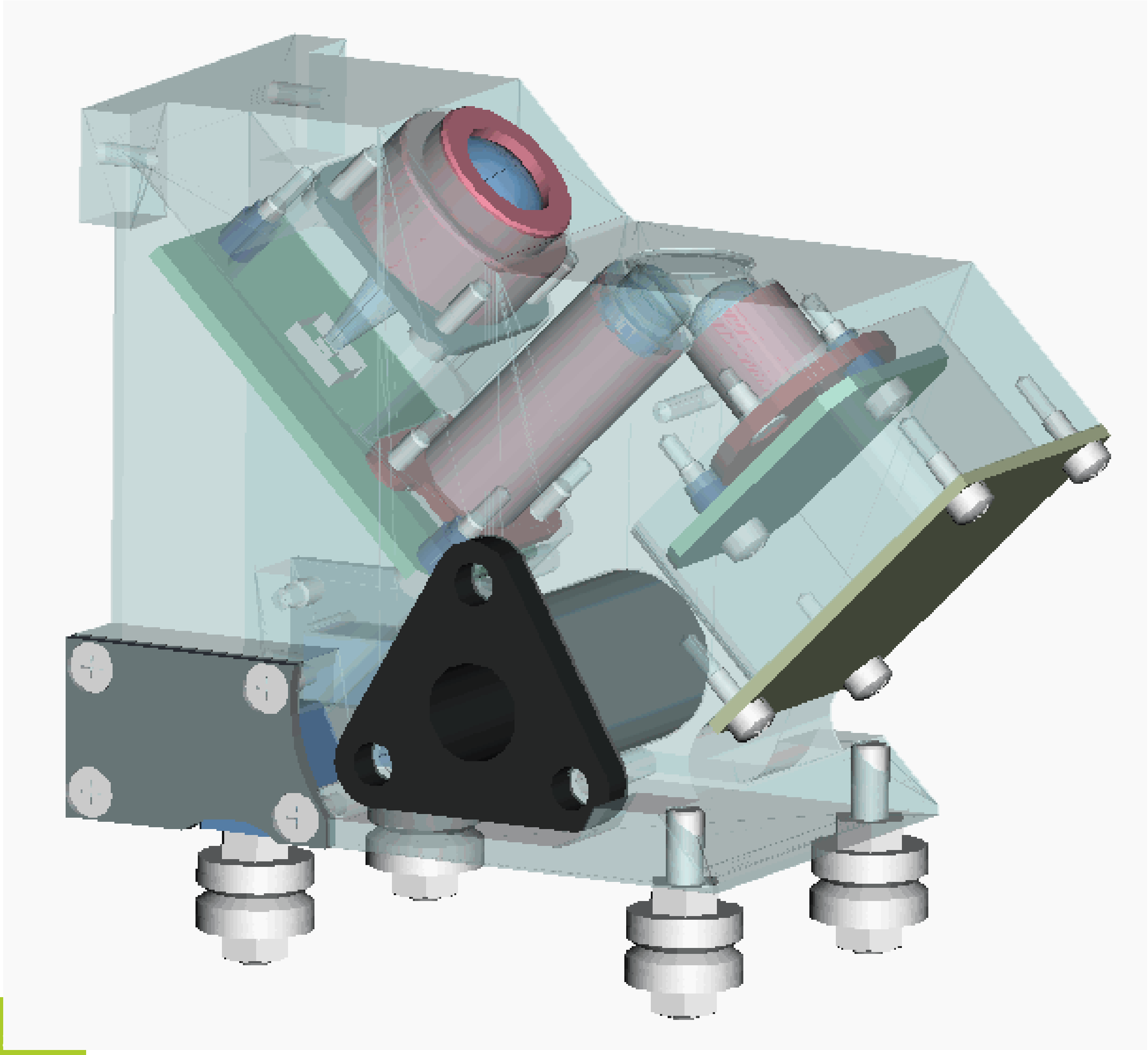


- Optical design in collaboration with INOA (Istituto Nazionale di Ottica Applicata)
- Started from old optical design
- Replacement of Xenon Lamp with UV LED
- Very compact mechanical design – Complex Mould

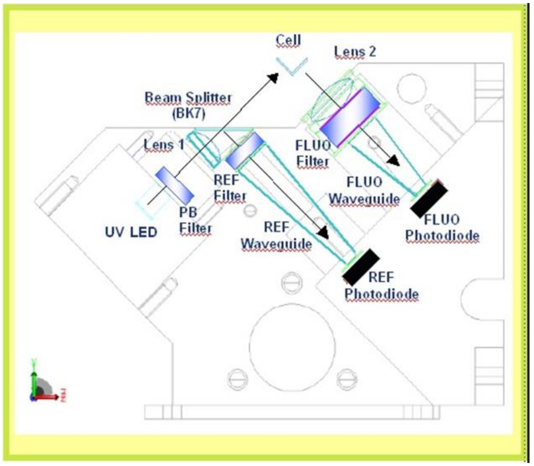
DETECTOR SYSTEM



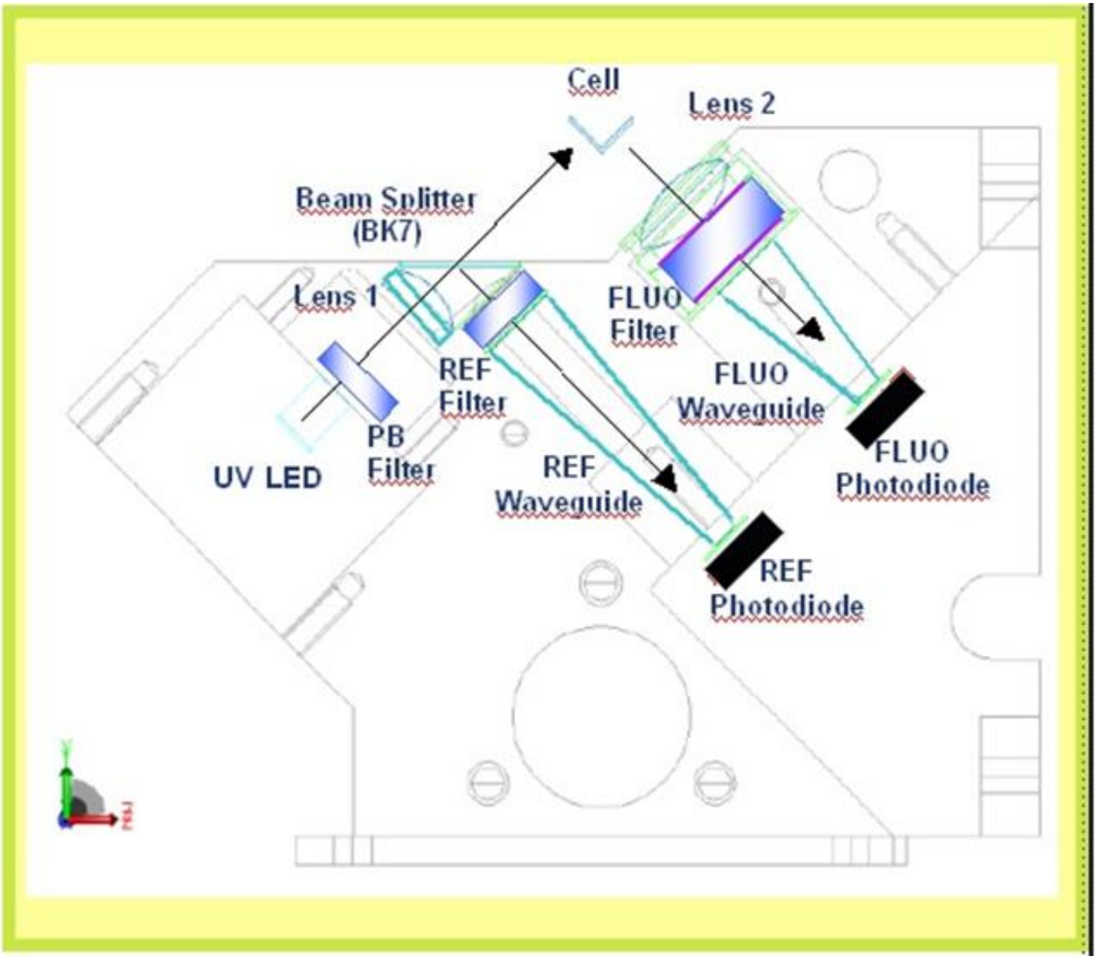
DETECTOR SYSTEM



3D CAD FULL MODEL



DETECTOR SYSTEM



Fluorescence values are always measured against a reference source signal

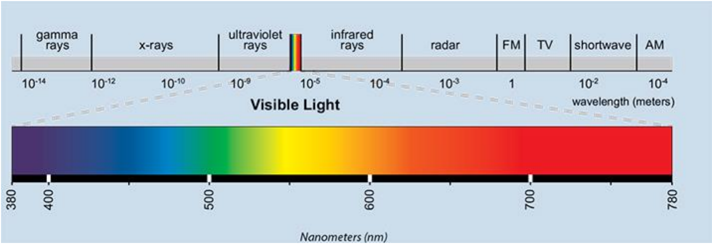
Furthermore the source light can vary due to:

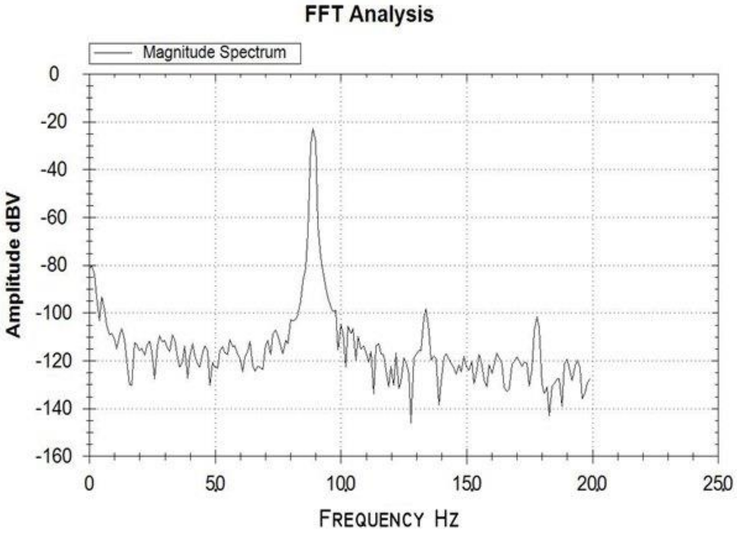
- **Temperature effects on LED and electronic components**
- **LED aging**

The reference channel measure provides a normalization value for the fluorescence channel measure compensating the above effects

DETECTOR SYSTEM

In order to increase the SNR the noise coming from external undesired light source had to be reduced.
EX: Electronic noise
EX: Artificial light ripples («neon» tubes)
EX: Ambient light



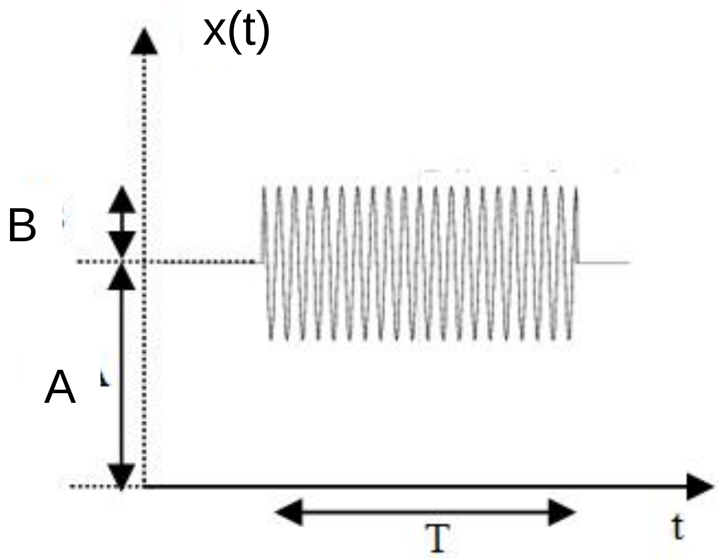


Electronic noise and ambient light can be considered as white
Artificial light ripple noise is not white: noise contribution is more relevant at lower frequencies

Band separation through LED source AM modulation (no lamp) + bandpass filtering

DETECTOR SYSTEM - TRANSMITTER

The source impulse is a sinwave of limited duration T



$$x(t) = [A + B \sin(2\pi f_0 t)]\, rect_T(t)$$

Where:

f_0 = 2 KHz

T = 15,5 ms

A = 15 mA

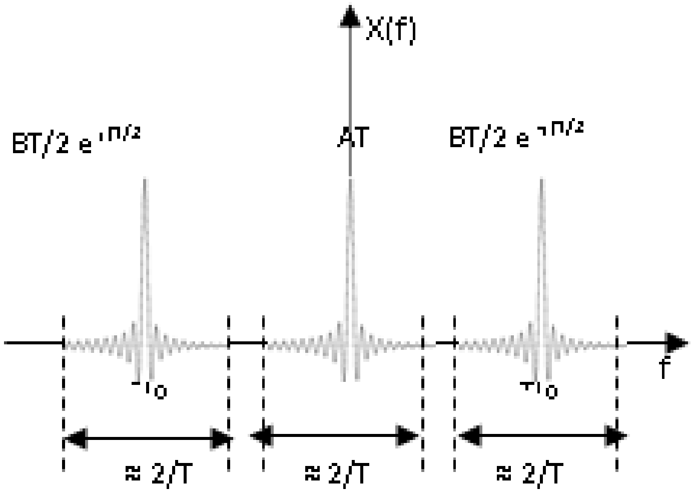
B = 10 mA

This is the representation of the LED current since the current is proportional to the emitted light amplitude

The constant A current is necessary for the LED polarization in order to reach a suitable working point.
The sinusoidal signal is then modulated with a constant amplitude B signal.
The B value is the informative part of the signal, the amplitude of the meaningful current impulse.

DETECTOR SYSTEM – TRANSMITTER

$$x(t) = [A + B\cos(2\pi f_0 t - \pi/2)]\,\mathrm{rect}_T(t)$$
$$X(f) = AT\,\mathrm{sinc}(fT) + BT/2\,(e^{-j\pi/2}\,\mathrm{sinc}[(f-f_0)T] + e^{j\pi/2}\,\mathrm{sinc}[(f+f_0)T])$$



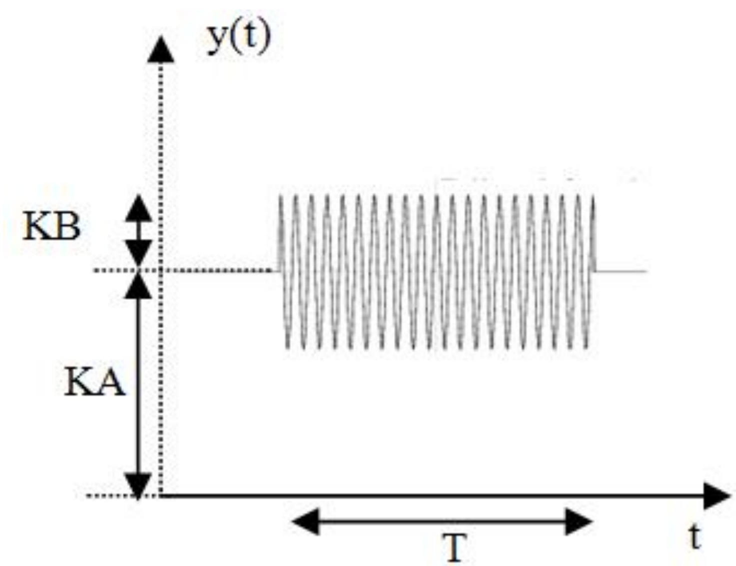
Spectrum of the source impulse signal at the LED input (hence the modulated output light)

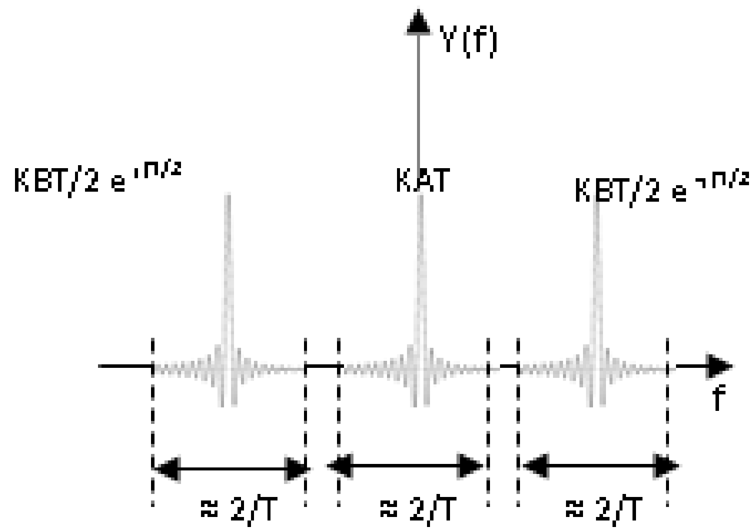
The constant polarization part «A» is spectrally placed in base band but doesn’t have any informative relevance.

The relevant informative part «B» is now spectrally placed around the f0 frequency, hence overlapped to a much lower noise contribution from artifical external light (the electronic white noise and ambient light noise are still present)

DETECTOR SYSTEM - RECEIVER

Under the hypothesis of a no distortion channel (just attenuation and a phase shift φ)





$y(t) = K_A\,rect_T(t) + K_B\,[\cos(2\pi f_0 t + \boldsymbol{\varphi})]\,rect_T(t)$

$Y(f) = K_A T\,sinc(fT) + K_B T/2[e^{j\varphi}\,sinc[(f-f_0)T] + e^{-j\varphi}\,sinc[(f+f_0)T]$

$f_0 = 2$ KHz

$T = 15{,}5$ ms

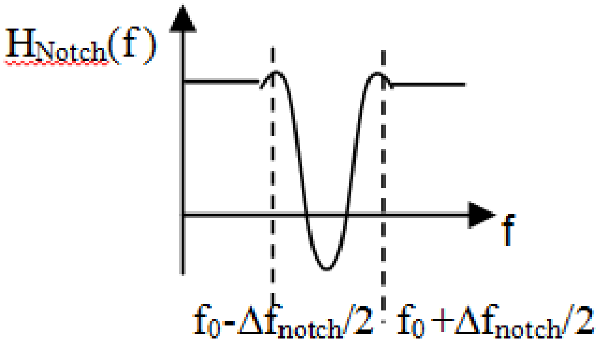
$\varphi = \Delta - \pi/2$

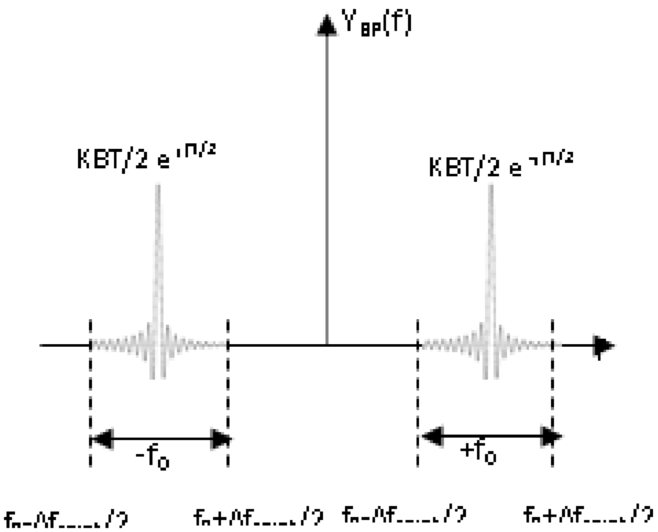
Current signal at the photodiode output

DETECTOR SYSTEM - RECEIVER

Before demodulation the received signal is filtered with a pass band filter centered in f_0 and having 200 Hz of cut-off bandwidth

$H_{BP}(f) = 1 – H_{Notch}(f)$





Considering an ideal passband filter:

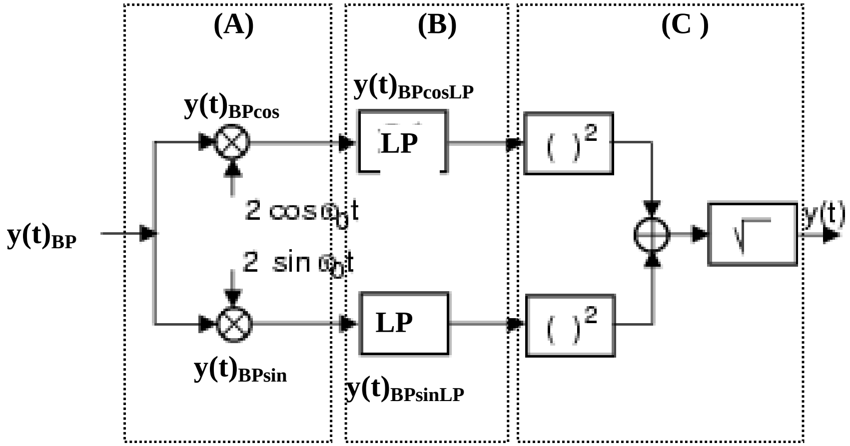
$Y_{BF}(f) = K_B T/2[e^{j\varphi} \mathrm{sinc}[(f-f_0)T] + e^{-j\varphi} \mathrm{sinc}[(f+f_0)T]$

DETECTOR SYSTEM - RECEIVER

In the time domain we have therefore :

$y_{BF}(t) = K_B\,[\cos(2\pi f_0 t + \boldsymbol{\varphi})]\,\mathrm{rect}_T(t) = K_B\,\mathrm{rect}_T(t)\cos(\boldsymbol{\varphi})\cos(2\pi f_0 t) - K_B\,\mathrm{rect}_T(t)\,\sin(\boldsymbol{\varphi})\,\sin(2\pi f_0 t)$

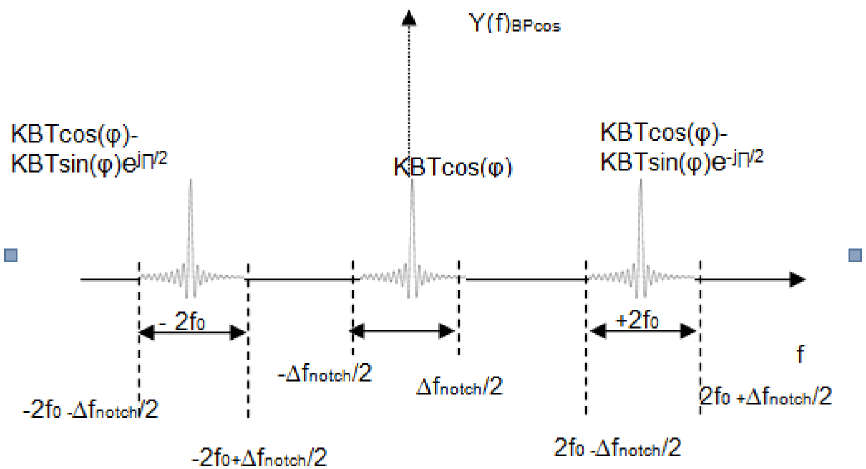
In order to get rid of the uknown phase shift a Phase-Quadrature demodulation is done

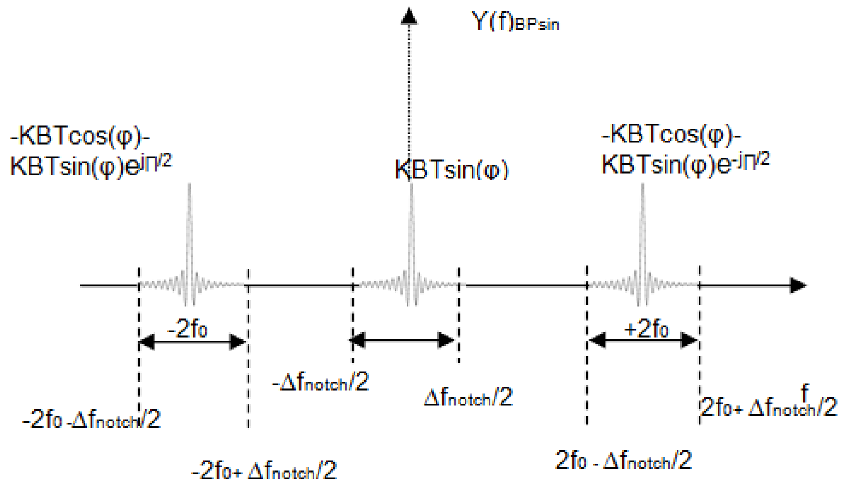


DETECTOR SYSTEM - RECEIVER

$y_{Dcos}(t) = K_B\,[\cos(2\pi f_0 t + \boldsymbol{\varphi})]\,rect_T(t) = [K_B\,rect_T(t)\cos(\boldsymbol{\varphi})\cos(2\pi f_0 t) - K_B\,rect_T(t)\sin(\boldsymbol{\varphi})\sin(2\pi f_0 t)] * 2\cos(2\pi f_0 t)$

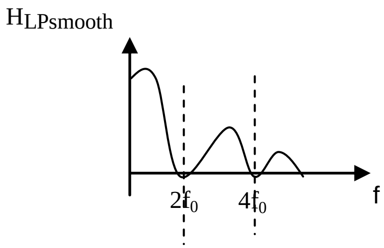
$y_{Dsin}(t) = K_B\,[\cos(2\pi f_0 t + \boldsymbol{\varphi})]\,rect_T(t) = [K_B\,rect_T(t)\cos(\boldsymbol{\varphi})\cos(2\pi f_0 t) - K_B\,rect_T(t)\sin(\boldsymbol{\varphi})\sin(2\pi f_0 t)] * 2\sin(2\pi f_0 t)$



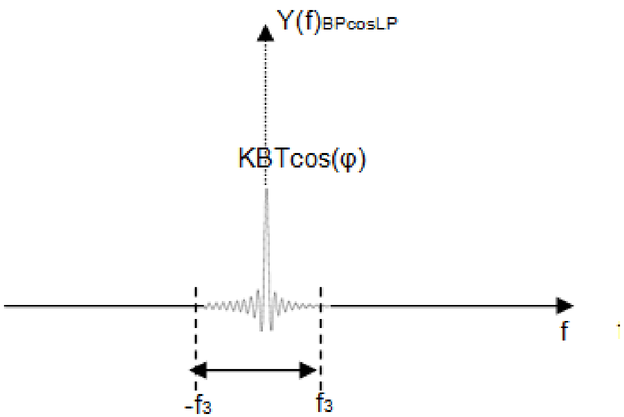


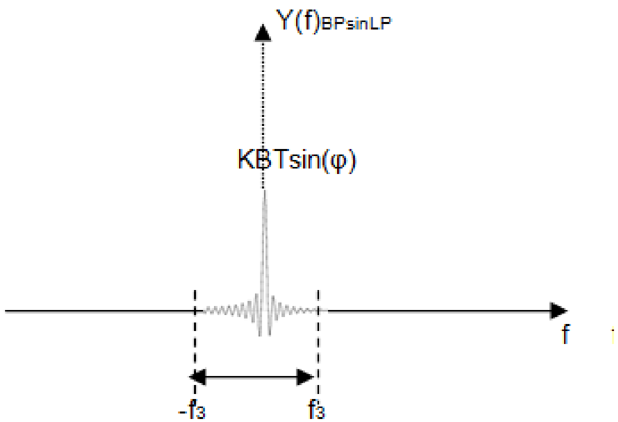
DETECTOR SYSTEM - RECEIVER

In order to get the baseband spectrum the signal is filtered through a low-pass filter $H_{LP}(f)$ with 110 Hz cut-off frequency + a smooth low-pass mobile windowing filter $H_{LPsmooth}$ (average of the last 20 samples)



$$Y_{DcosF}(f) = Y_{Dcos}(f)H_{LPsmooth}(f)H_{SM}(f) = K_B\, T \cos(\boldsymbol{\varphi})\, \mathrm{sinc}(fT)$$
$$Y_{DsinF}(f) = Y_{Dsin}(f)H_{LPsmooth}(f)H_{SM}(f) = K_B\, T \sin(\boldsymbol{\varphi})\, \mathrm{sinc}(fT)$$





$$y_{DcosF}(t) = K_B\, \mathrm{rect}_T(t) \cos(\boldsymbol{\varphi})$$
$$y_{DsinF}(t) = K_B\, \mathrm{rect}_T(t) \sin(\boldsymbol{\varphi})$$

DETECTOR SYSTEM - RECEIVER

The final module is then computed :

$$Y(t)_{mod}(t) = \mathrm{sqrt}[\,(K_B\, rect_T(t))^2 \cos^2(\boldsymbol{\varphi}) + (K_B\, rect_T(t))^2 \sin^2(\boldsymbol{\varphi}))] =$$
$$= \mathrm{sqrt}[\,K^2_B\, rect^2_T(t)\,(\cos^2(\boldsymbol{\varphi}) + \sin^2(\boldsymbol{\varphi}))\,] = K_B$$

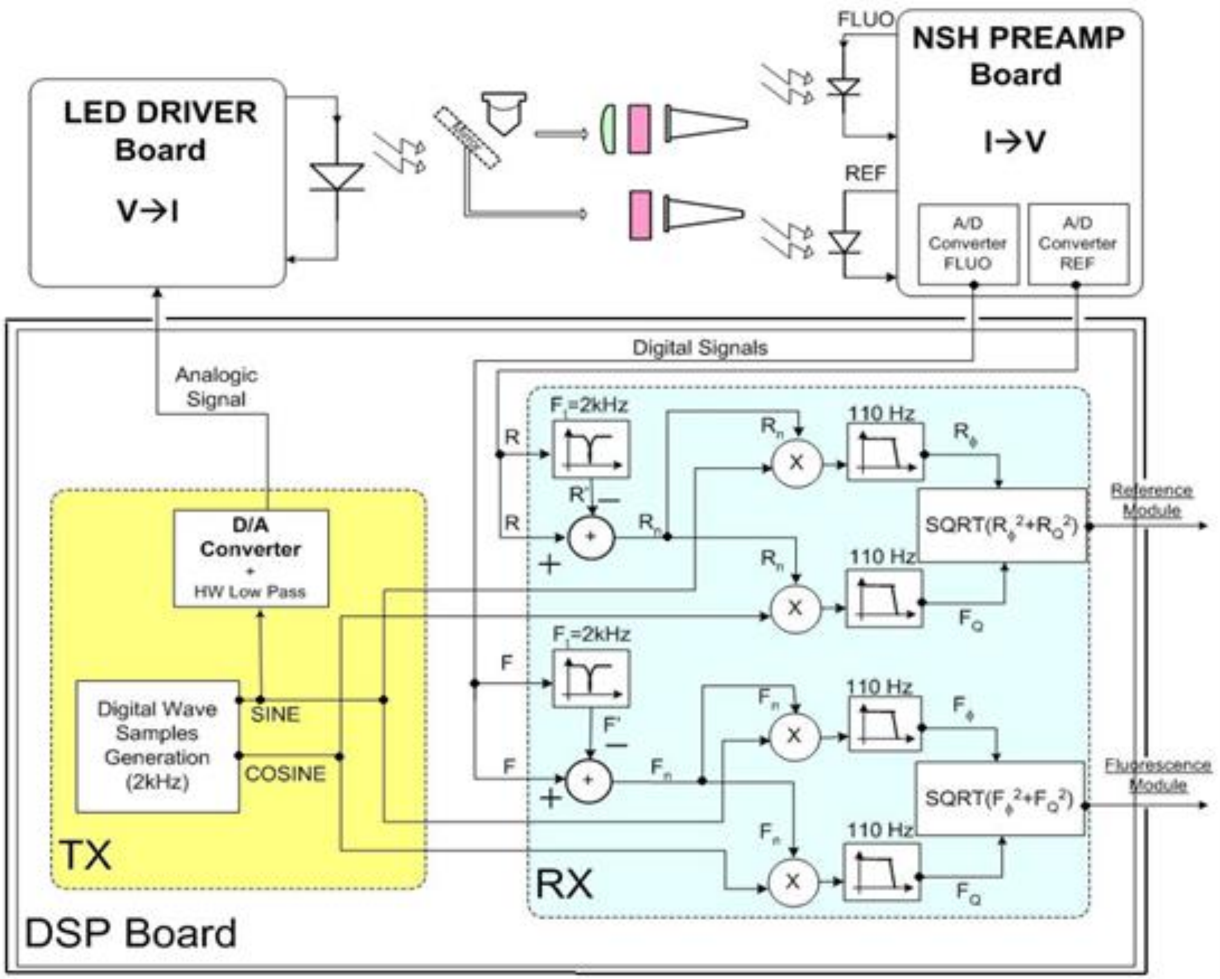
A similar approach is used for the reference channel

Once the normalized ratio is computed this is not in general what we were searching for since the channel attenuations can very among the readers.

A calibration against a known standard is done in order to have a meaningful fluorescence measure in Fluorescence Reference Units (RFU).

An «open circuit» reading is done before each fluorescence reading in order to get rid of the offset

DETECTOR SYSTEM – HW/FW

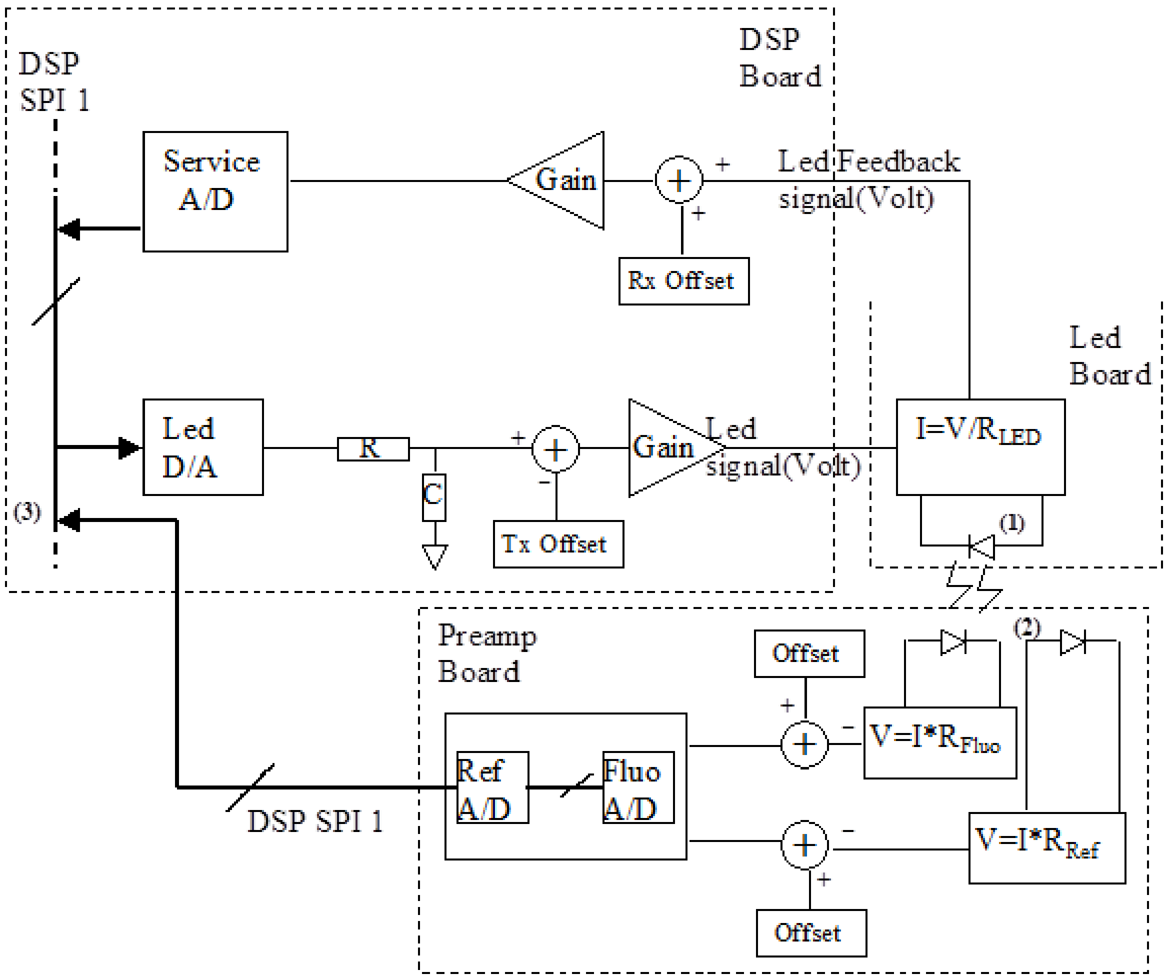


Three HW boards are in charge of the detection process:

a) LED Board
b) Pre-Amp Board
c) DSP Board

The DSP board FW is in charge of the transmission-reception synchronization and the whole processing

DETECTOR SYSTEM – HW/FW

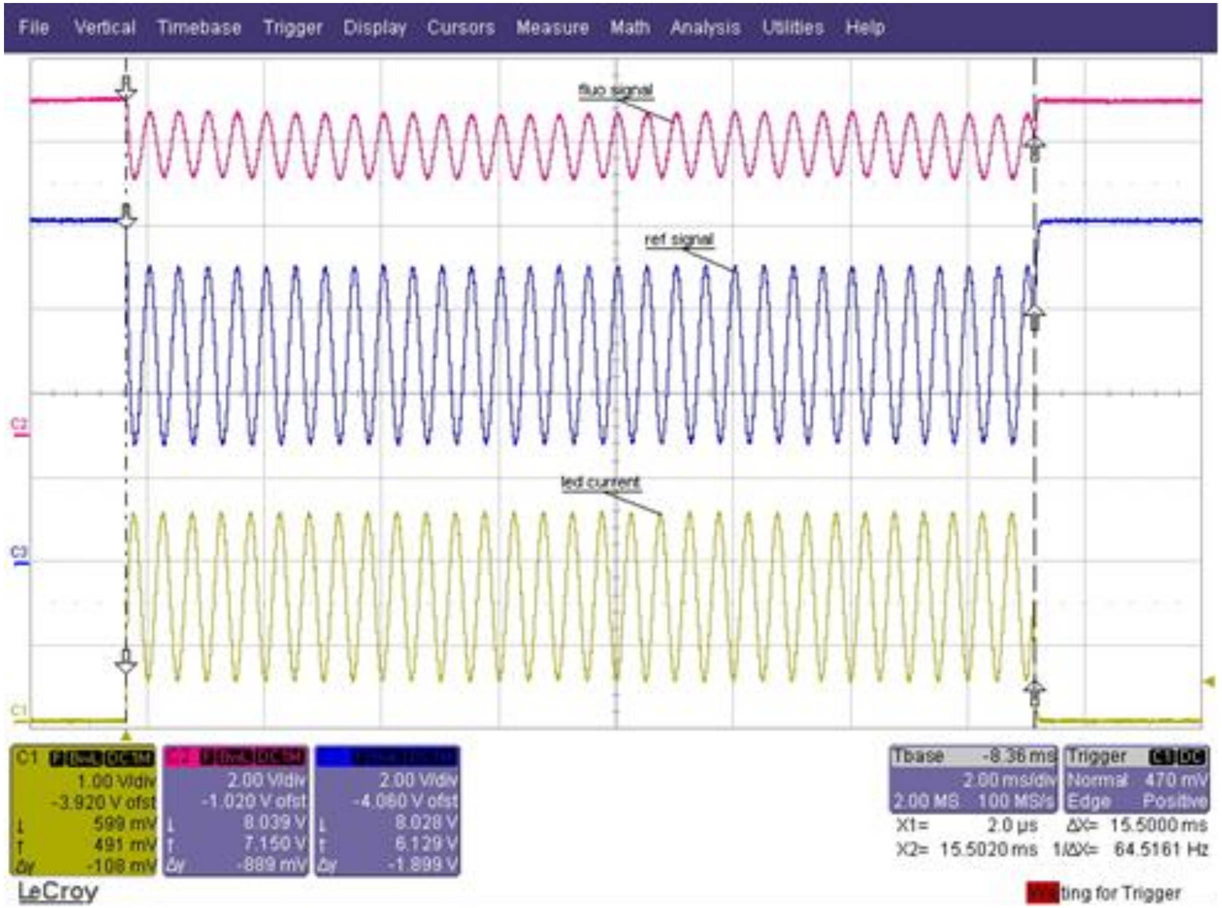


A 16 bit D/A is used to create the sin wave analog differential signal fed to the LED

Two 16 bit A/D are used to acquire the output signals (voltage) of the photodiodes

The D/A and the A/Ds are connected through the same SPI bus to the DSP board

DETECTOR SYSTEM – HW/FW



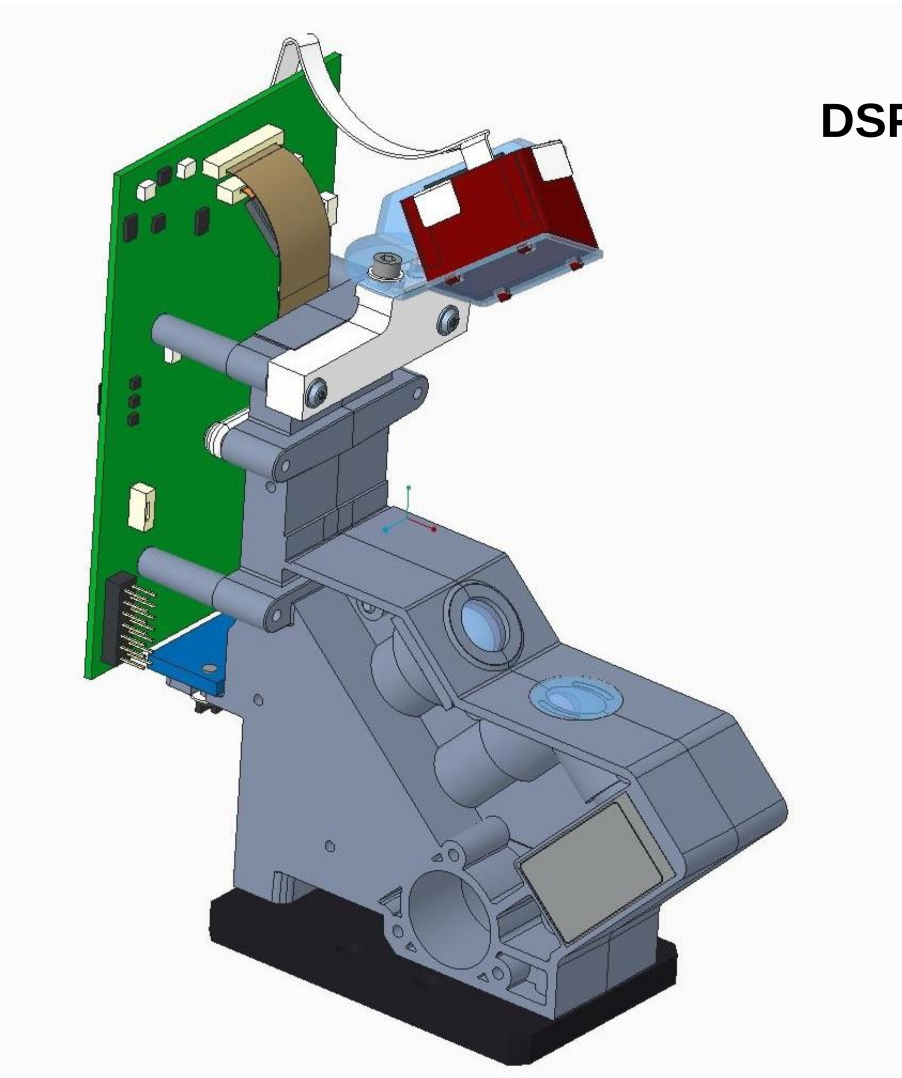
Fluo voltage signal

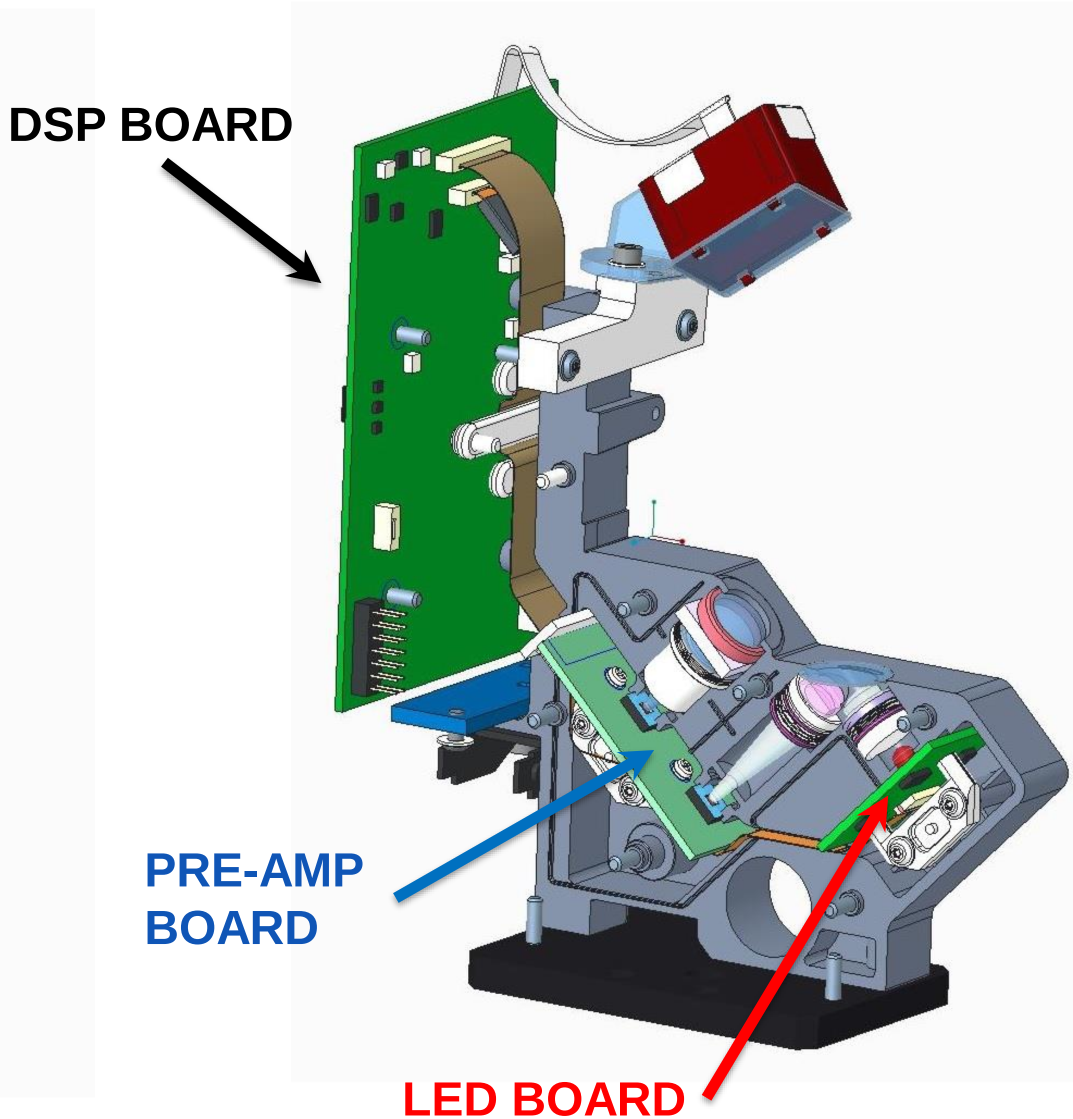
Reference voltage signal

LED current signal

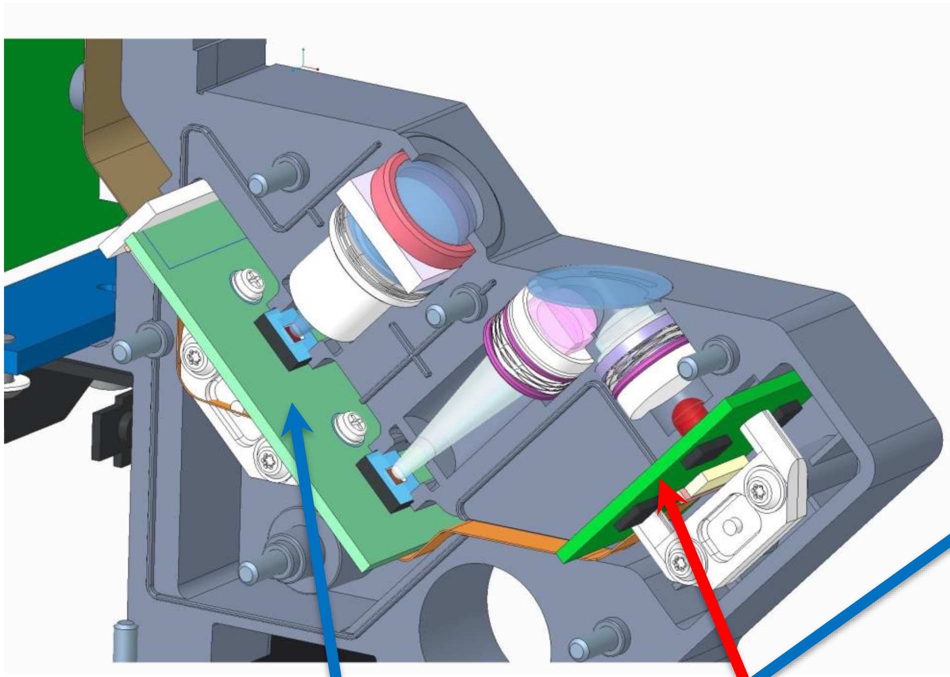
A transmission burst is composed by 31 periods of a 2KHz sin wave.
Each period is made of 40 samples.
Tsample = 12.5 µs (80 KHz)

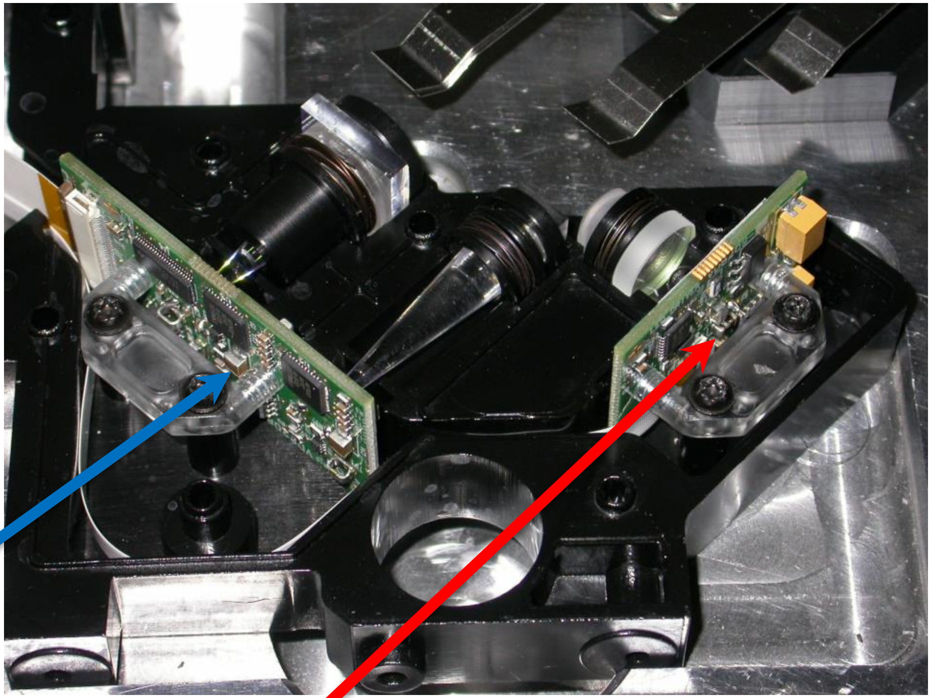
DETECTOR SYSTEM – HW/FW





DETECTION SYSTEM – HW/FW





PRE-AMP BOARD

LED BOARD

DETECTOR SYSTEM – HW/FW

DSP Board (TI TMS320 family)
Core @ 600 MHz
DDR2 Memory
Bare Metal FW (no OS)

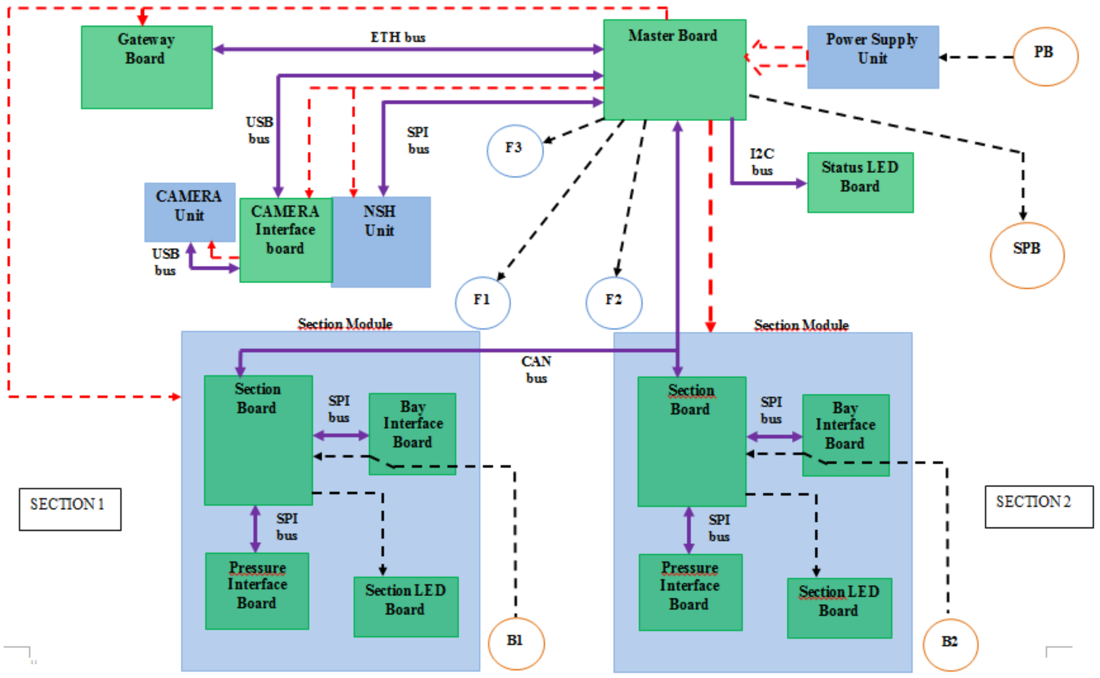
LED Board

Pre-Amp Board

FOCUS ON ELECTRONIC DEVELOPMENT

ELECTRONICS – HIGH LEVEL TASK

Definition of the electronic architecture



Distributed System
-Intelligence
-Data flow and type
-Data storage
-Communication Bus
-Computational power

ELECTRONICS – HIGH LEVEL TASK

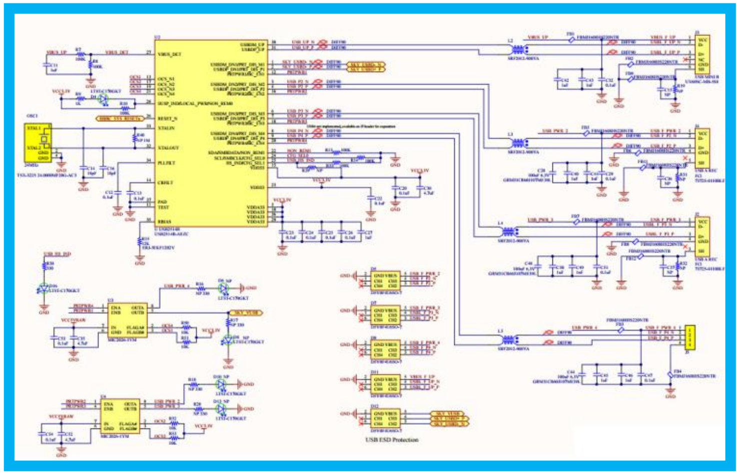
Definition of the ElectroMechanical layout

Industrialization
- Mechanics Interaction
- Manufacturability
- Size
- Costs
- Reliability
- EMI/EMC
- Risk assesement / safety

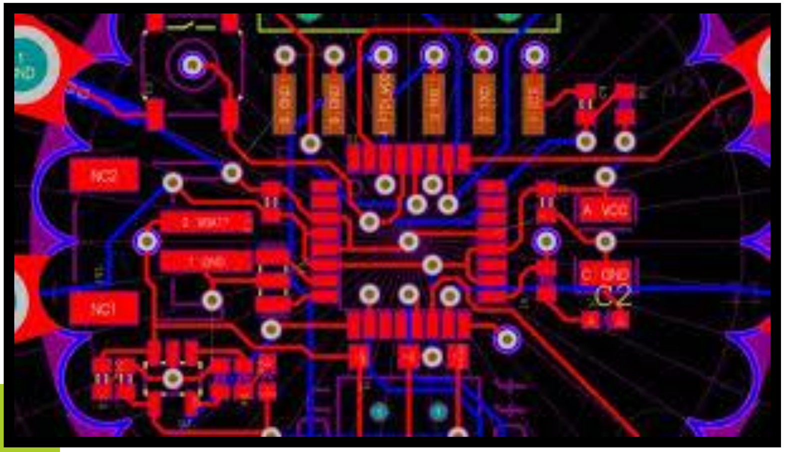
Examples
- Connectors
- Cables
- Shielding and grounding

ELECTRONICS - HW DESIGN

Board Prototyping

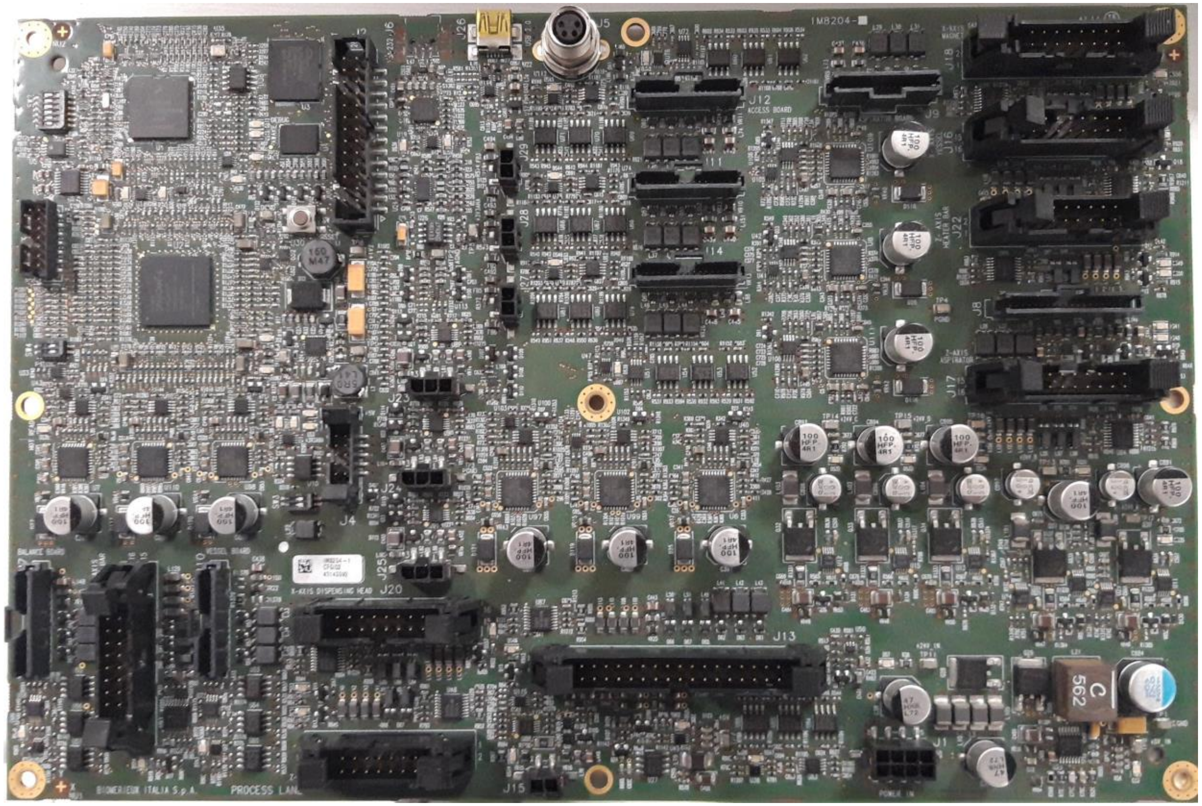


CAD Schematics Design



CAD Routing Design

ELECTRONICS - HW DESIGN



9 Stepper Motors
2 Temperature sens.
2 Heating pads
4 A/D
1 Ultrasonic sens.
1 FAN
4 Load Cells

CAN Bus
RS232 Interface
I2C Interface
SPI Interface

- 32 bit Microcontroller / Flash / RAM / FPGA / EEprom
- 10 Layers

ELECTRONICS – HW/FW

HW/FW

Platform
- Microcontroller
- Microprocessor

Memories
- SRAM / SDRAM
- DDR
- NAND Flash
- NOR Flash
- EEprom

Sensors
- Temperature
- Pressure
- Ultrasonic
- Optical / Hall
- Encoders
- Load Cells

Bus
- CAN
- I2C
- SPI
- USB
- ETH
- RS232

Analog/Digital
- FPGA
- A/D
- D/A
- Amplifiers
- Mux/DeMux
- LEDs

Power
- DC/DC converter
- Stepper Motors
- Linear Actuators
- AC/DC Pumps
- Electrovalves
- Heaters
- Fans
- Peltier

ELECTRONICS – FW DESIGN

BIOMÉRIEUX

FW Development

Bare Metal

C/C++

Real Time OS

MULTI INTEGRITY

Micriµm µC/OS-III™ The Real-Time Kernel

CodeWarrior

QT Creator

IAR SYSTEMS Embedded Workbench®

IAR

Code Composer Studio v5

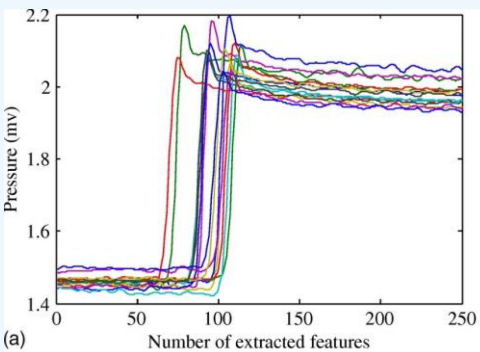
CCS

VIVADO™

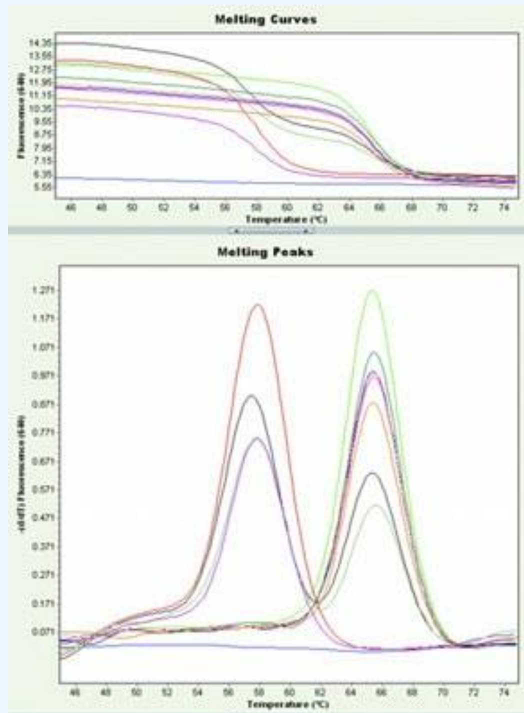
FPGA Xilinx

ELECTRONICS

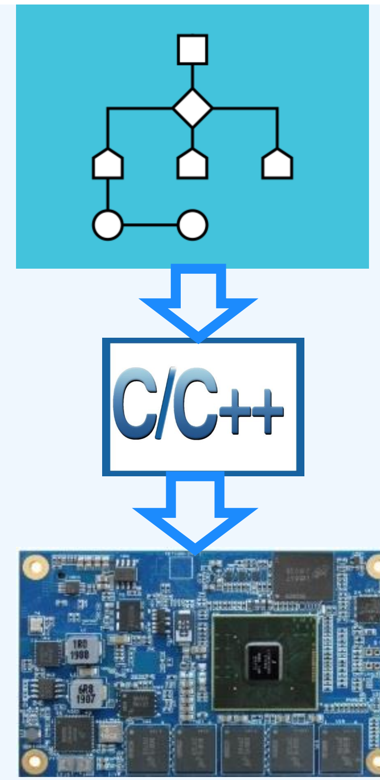
Modeling, Algorithms and Processing



ACQUISITION AND MODELING

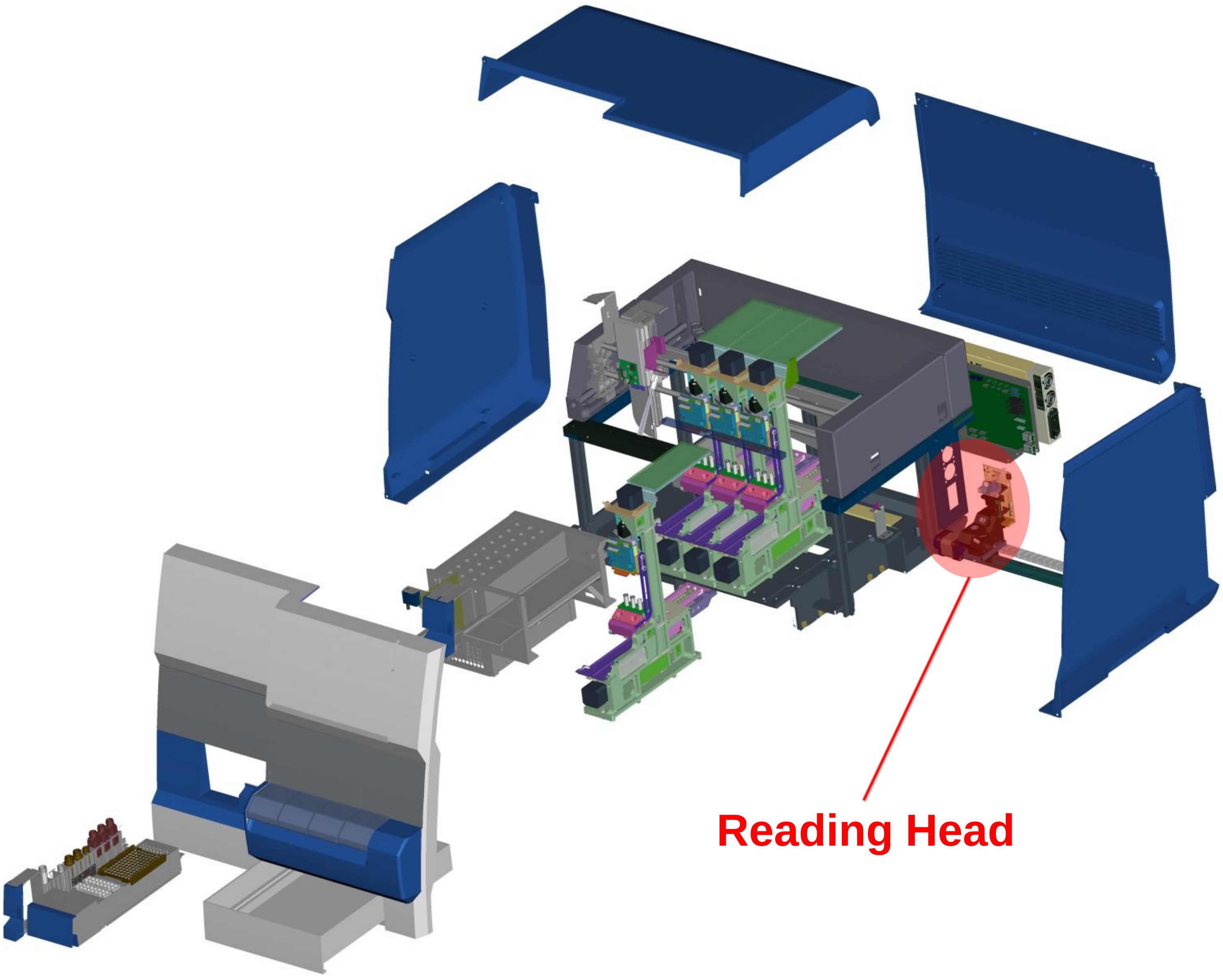


STATISTICAL ANALYSIS AND PROCESSING



ALGORITHM DEFINITION AND PORTING

EXAMPLES

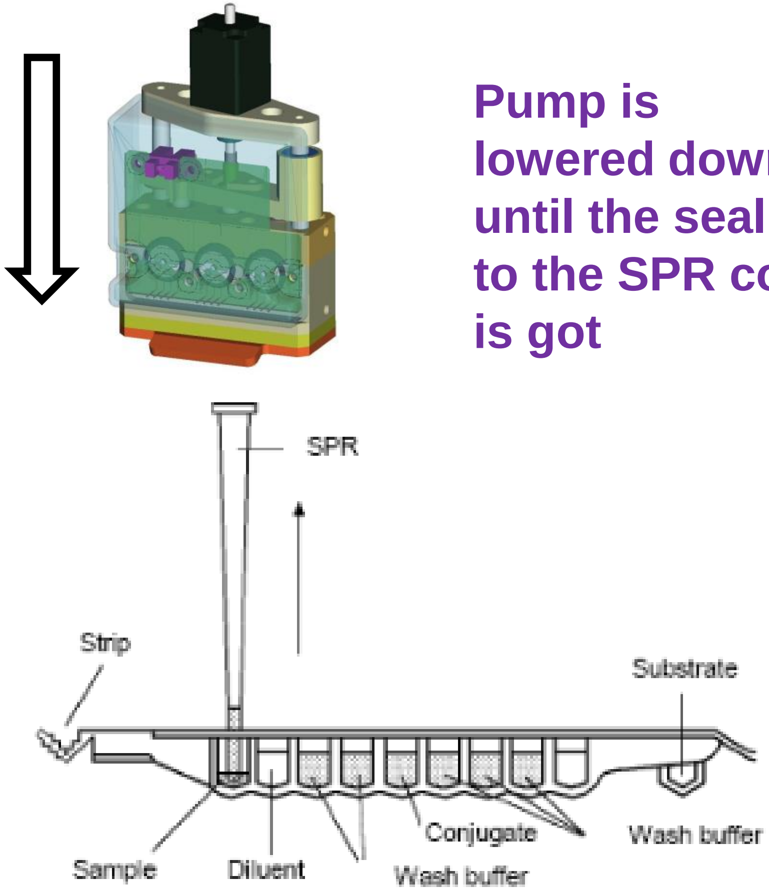


BIOMERIEUX

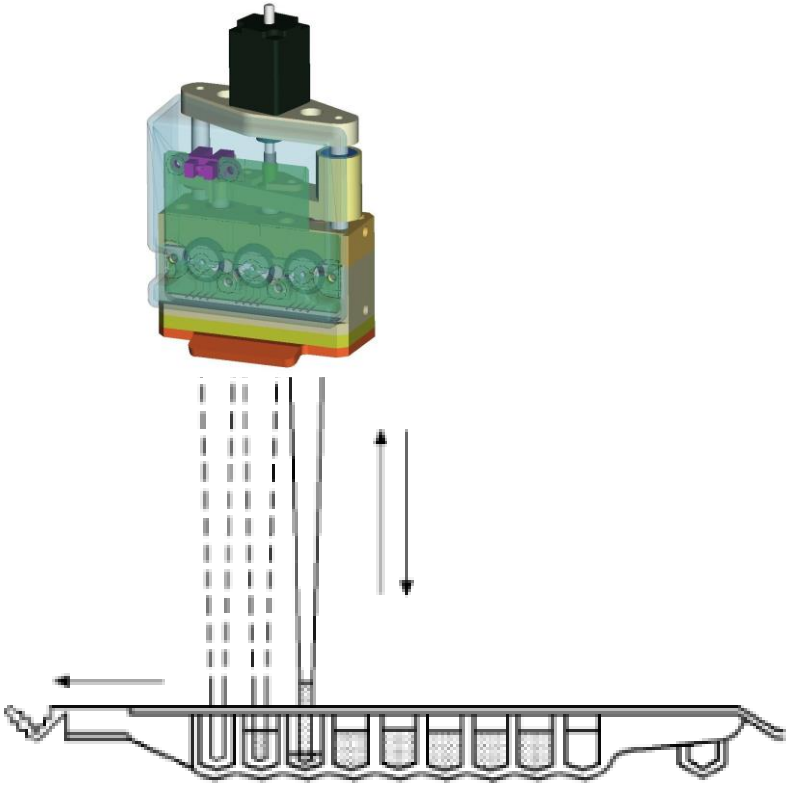
Francesco Mancini
francesco.mancini@biomerieux.com

BACK-UP SLIDES

DIAGNOSTIC PRINCIPLE



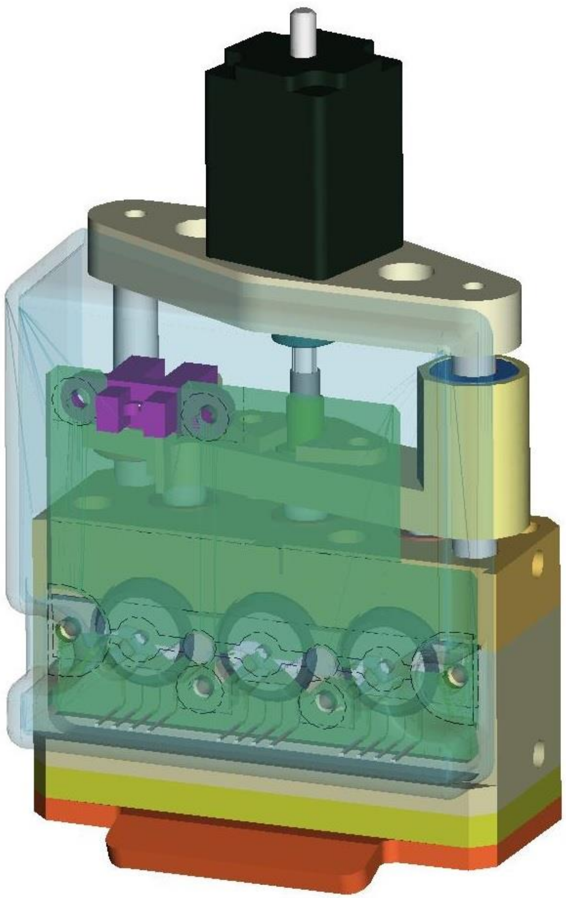
Pump is lowered down until the sealing to the SPR cone is got



Strip tray is moved below the SPR cone to reach the different wells

EXAMPLES

Micro Pump



PIONEERING DIAGNOSTICS