Accelerating Innovation

CERN microelectronics technologies for medical applications

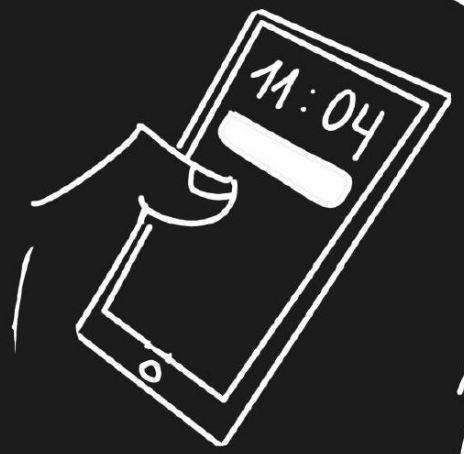
Dr Ana Rita Pinho
Knowledge Transfer Officer, Business Development & Entrepreneurship, CERN

Outline

- Medipix/Timepix family of chips
  - Medipix Collaboration
  - Medical Applications
    - CT
    - Mass Spectrometry
    - Gamma camera for Thyroid diagnostics
    - Beam monitoring in hadron therapy
    - TEM
    - Earth's climate and human health
- FastIC
  - Mass Spectrometry
  - PET
- Dosepix
- Summary and conclusion

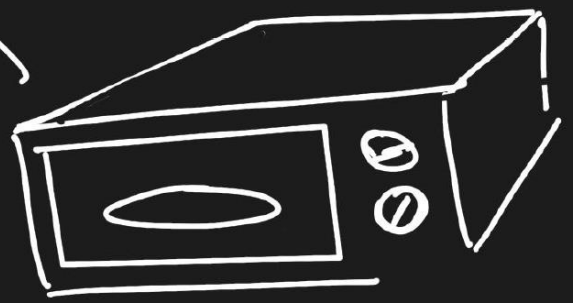
A CHIP IS AN ELECTRONIC DEVICE THAT CAN PROCCESS AND ACT ON DATA.

Not only your phone has chips



But medical equipment...

And many other things you couldn't even imagine...



Your microwave

But do you even know how they work?

Samuel Zaño Álvarez

Chips are made of Billions of transistors which are really tiny devices

Transistors work as switches

Transistors are measured in Nanometers (nm) which are 1 million times less than a mili-meter (mm).

Samuel Zaño Álvarez

The Medipix Collaborations

Almost three decades of turning technology into applications within various domains

Medipix in a nutshell

- A family of pixel detector read-out chips developed by the Medipix Collaborations.
- Hybrid pixel detectors were developed to respond to a need at the LHC: particle tracking in high rate environments.
- Single particle counting detectors have been widely used in education, space science, materials analysis and X-ray applications.
- <u>Collaborations:</u>
  - Medipix2: 17 members
  - Medipix3: 23 members
  - Medipix4: 19 members

Research organisations can still join the Medipix4 Collaboration!

Medipix Collaborations

+10 Medipix/Timepix licencees

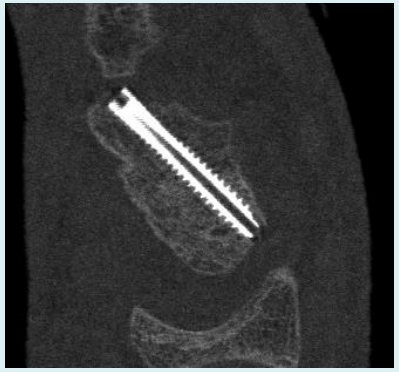
CT

“A computerised tomography (CT) scan uses X-rays and a computer to create detailed images of the inside of the body. ”

Vision

- To be the leader in advanced imaging at point of care.
- Increase access to affordable, accurate and timely diagnosis for the wider community.

Value Proposition



Through clear identification of bone metal interfaces, reduced artifacts and material decomposition (bone density and construction), enable Orthopaedic surgeons to make highly informed decisions without the need for multiple visits, or scans of the patient. Reducing cost, improving success rates and patient satisfaction

Sale portable photon counting CT scanners in pre & post operative space for wrists and lower arms, at point of care.

Medical Applications

Mass spectrometry

“Mass spectrometry imaging visualization of spatial organization and identification of molecular masses from biological surfaces”

Intro to mass spectrometry: applications

Proteomics: protein sequencing, characterisation of proteins and protein complexes, identification of post-translational modifications

Metabolomics: Cancer screening and diagnosis, biomarker discovery, metabolic disorder profiling

Environmental: pesticide screening, pollution monitoring, drinking water testing, trace heavy metal analysis

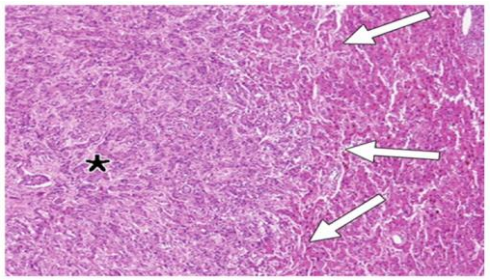
Pharmaceutical: drug discovery, drug metabolism and elimination studies

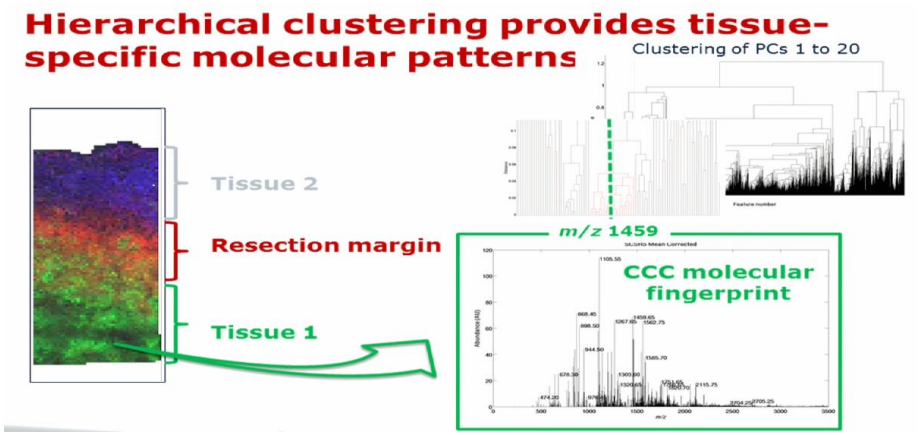
Forensic: analysis of trace evidence, drugs testing, explosive residues

Clinical: disease screening and diagnostic testing, drug therapy monitoring, identification of infectious agents for targeted therapies

Slide: Claire Vallance, University of Oxford

Mass Spectrometry





Images: R, Heeren, Maastricht

- Sarcoma resected from a patient.
- The question the surgeon asks is:

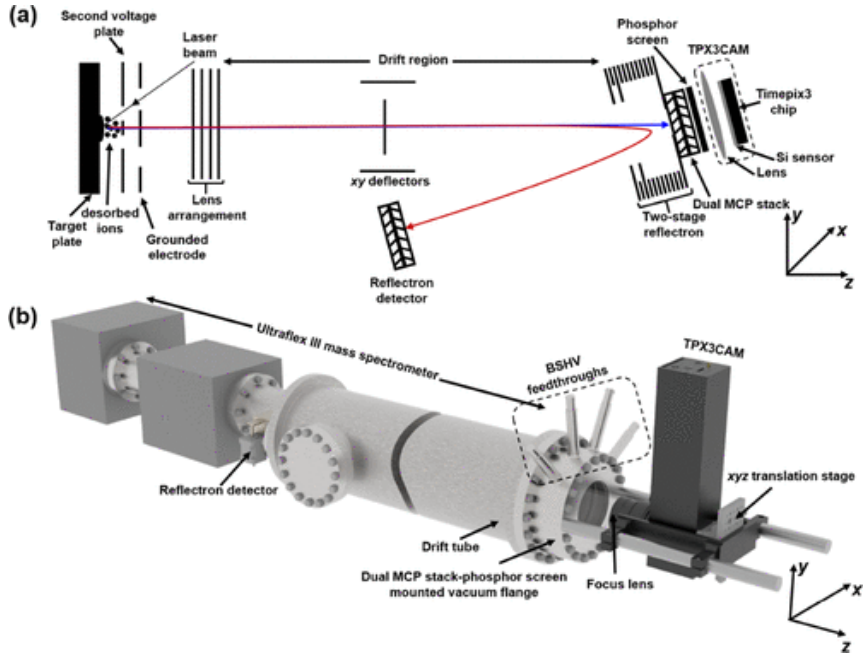
"is it clean"? Are the edges (the margins of the tumor) clean?

- Pathologist has to provide feedback to surgeon based on tissue staining.
- Clear tissue-based diagnosis is difficult.
- Imaging Mass Spectrometry provides access to molecular-based pathology.
- Importance of identifying molecules in their context.

Timepix 3 & 4

Mass Spectrometry

The Timepix (TPX) is a position- and time-sensitive pixelated charge detector that can be coupled with time-of-flight mass spectrometry (TOF MS) in combination with microchannel plates (MCPs) for the spatially and temporally resolved detection of biomolecules.



Why Timepix?

- Timepix is noise-hit-free. As a result, every recorded "hit" is the result of an actual ion arrival event at the detector, and thus constitutes a real signal that contributes to the intensity of the particular m/z value. A single ion extracted from a tissue can be identified;
- The ability to acquire high-quality spectra at low MCP gains allows to increase the lifetime of the MCP and reduces the dead time due to MCP depletion;
- All data generated is digital, this means that the pathologist does not look at the microscope anymore but has access to digital molecular information, leading to improving the quality of the diagnosis.

Anal. Chem. 2023, 95, 2, 1470−1479
Publication Date:December 27, 2022
https://doi.org/10.1021/acs.analchem.2c04480

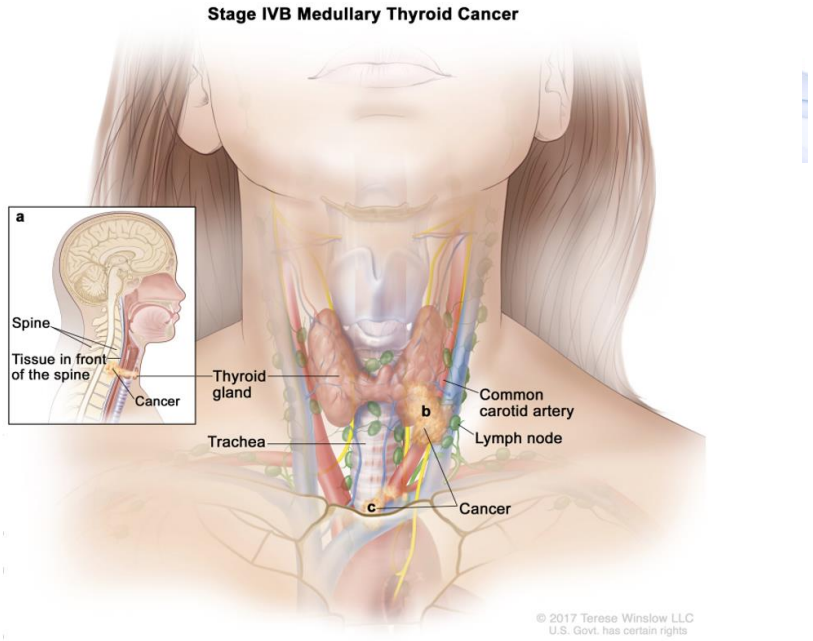
Gamma camera

“A Gamma Camera is a device, which is used as an imaging technique to produce functional scans of the brain, lungs, thyroid, liver, skeleton, gallbladder and kidneys”

Gamma camera application: Thyroid diagnostics

Thyroid cancer diagnostics and treatment monitoring:

- The second most frequent cancer for women (after breast cancer)
- Current imaging methods offer resolution of about 12 mm in 2D
- Technology allows
  - 5 times better resolution and 3D (2.5 mm)
  - 4 times lower dose



Courtesy of D. Turecek, Advacam s.r.o

Timepix 3

FN MOTOL

CZECH METROLOGY INSTITUTE

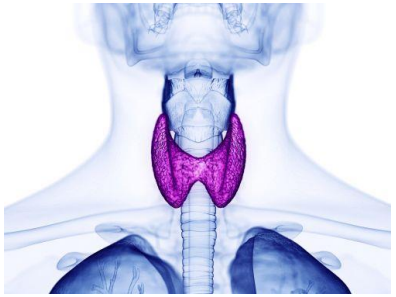
CAPI CENTER FOR ADVANCED PRECLINICAL IMAGING

radalytica One machine rules them all !

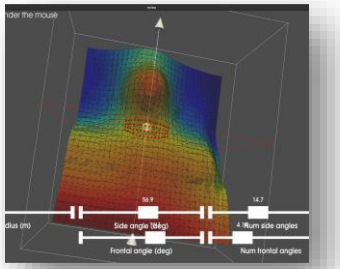
FIRST FACULTY OF MEDICINE Charles University

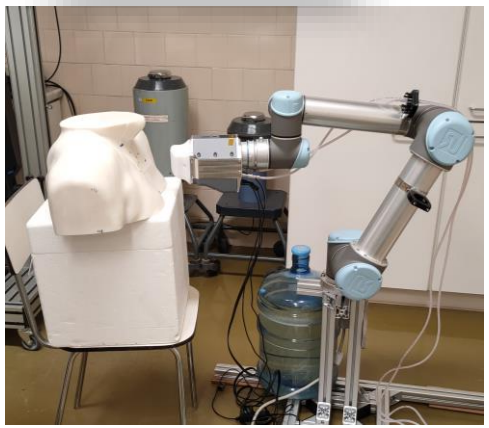
ThyroPIX: could particle cameras help with thyroid gland cancer treatment?

- **Aim:** develop a mobile robotic imaging camera for the thyroid gland and small organ imaging using nuclear medicine methods. This has potential applications in both diagnostic and therapeutic procedures in medicine.

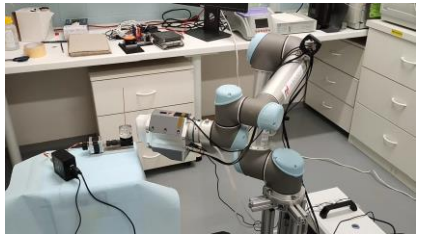


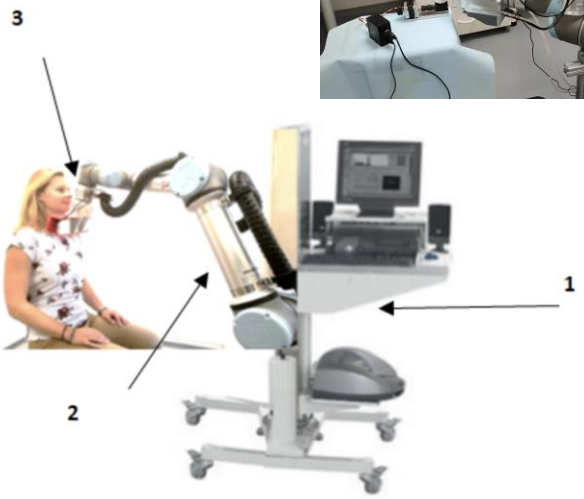
- **Technology:** Mobile Compton camera based on Timepix3 technology for monitoring thyroid gland cancer treatment





- **The main advantages** of ThyroPIX are:
  - Single-photon detection of gamma photons in fully-spectral mode (**Timepix3**);
  - **High activity radionuclide** accumulated in target volume imaging for treatment verification;
  - Detection of **high photon fluxes;**
  - **High spatial resolution** imaging unavailable with current state-of-art gamma cameras using collimators;
  - **Lowering of diagnostic activities** due to high detection efficiency;
  - **Shortening acquisition times** due to high detection efficiency;
  - Combination of planar and tomographic imaging (2D and SPECT) thanks to robotic arm implementation;
  - **Mobile** camera concept.





Timepix 3

FN MOTOL

CZECH METROLOGY INSTITUTE

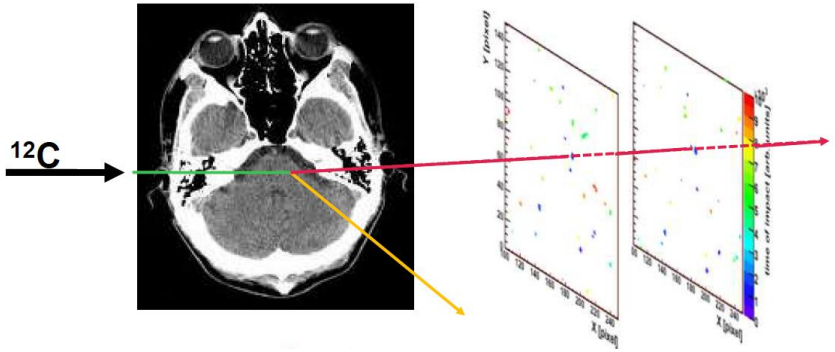
CAPI
CENTER FOR ADVANCED PRECLINICAL IMAGING

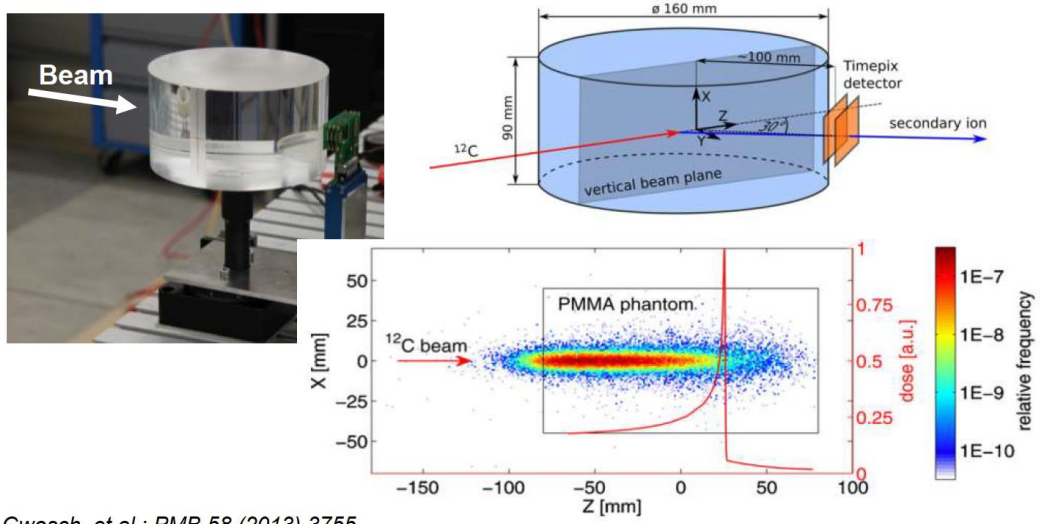
radalytica
One machine rules them all !

FIRST FACULTY OF MEDICINE
Charles University

Beam Monitoring

Carbon Therapy beam monitoring





Gwosch et al.: PMB 58 (2013) 3755

Hadron Therapy

- *Precise delivery of radiation dose in a tumor area*
- *Essential to monitor beam in real time*
  - *To avoid overdose on critical organs or underdose in tumor*
- *Timepix-based camera allows to reconstruct trajectory of secondary particles*
- *As an alternative to PET*
- *Verification in real time of the beam delivered to the patient: beam range, width and shifts in the lateral direction*

Verification in real time of the beam delivered to the patient: beam range, width and shifts in the lateral direction

Timepix & Timepix 3

Slide courtesy of M. Martisikova, German Cancer Research Centre, Heidelberg

TEM

Impact of Medipix technology in TEM

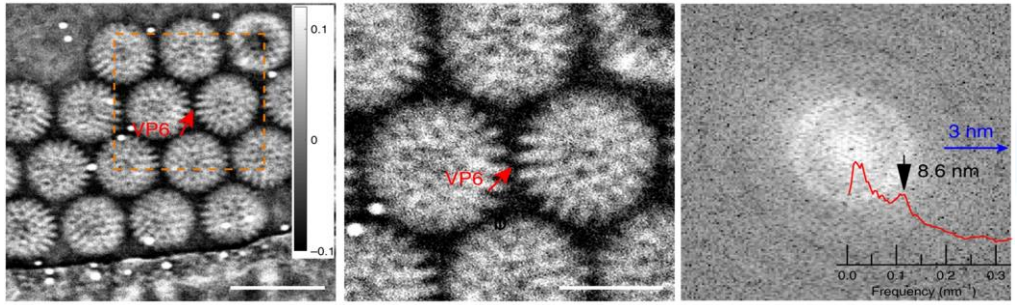
>70
Merlin EM sold

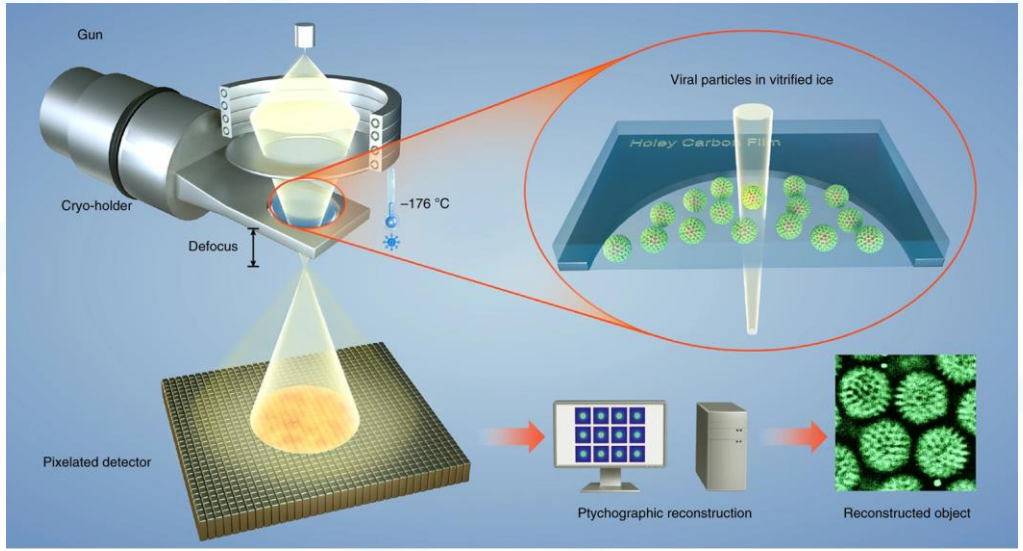
>70
Publications

nature
Microscopy AND Microanalysis
scientific reports
Ultramicroscopy
ACS Chemistry for Life®
nature COMMUNICATIONS
APS physics

Low dose biological imaging - MerlinEM tested as base of next generation technique

- MerlinEM used in Cryo-STEM, low dose defocused ptychography
- Sensitive sample can be scanned in low dose conditions (this case 5.7 e/Å^2)
- Phase recovered by iterative reconstruction





Under CC 4.0 from Zhou L. et al. Nat Commun 11, 2773 (2020)

Medipix 3

Imaging of HIV-1 virus-like particles under low-dose conditions JEOL GrandARM with MerlinEM, 300 kV, ePSIC, Diamond Light Source

ePSIC electron Physical Sciences Imaging Centre

diamond®

Earth's climate and human health

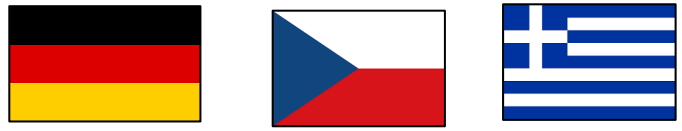
BioSphere project: 2024 measurement campaign

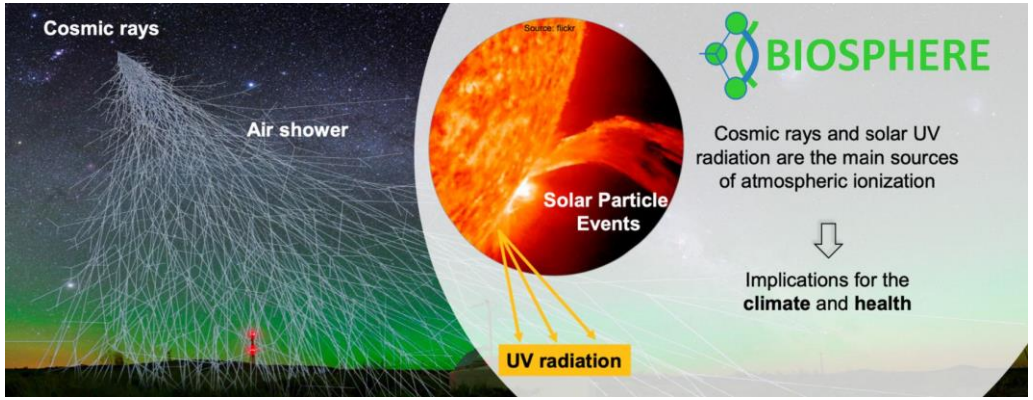
- **Project Aim:** study the relationship and correlation of cosmic radiation in the atmosphere with ozone and UV radiation and their impact on public health and organic life on Earth.

- **Action:** measurement campaign to trace muons, electrons, neutrons, or gamma rays on the ground and in the high-altitude mountains across Europe (Czech Republic, Germany, and Greece)

- **What is Advacam offering**? single-photon counting cameras to precise measures of cosmic rays and solar UV radiation to understand implications for Earth's climate and human health.

Timepix 2





Funded by EURAMET - The European Association of National Metrology Institutes within the Metrology Research Program

Medipix Collaboration: latest updates

Timepix 4 has been processed with TSVs & it works!

- 6 R&D licenses have been granted

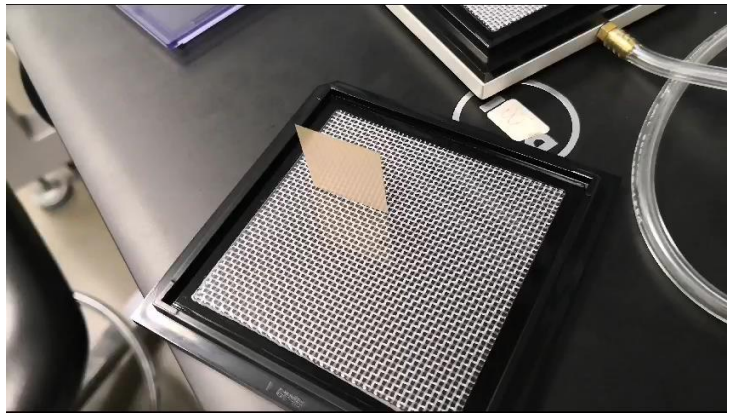
Medipix 4 is working;

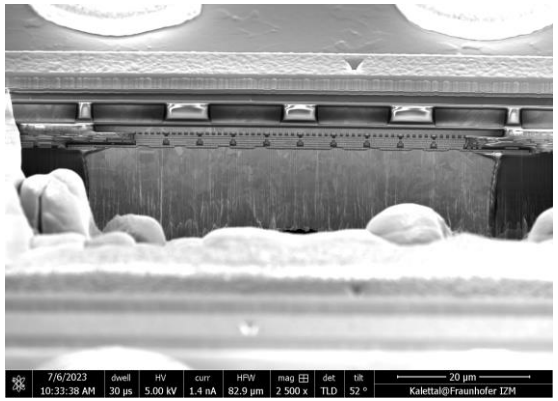
- Starting to think about tech transfer

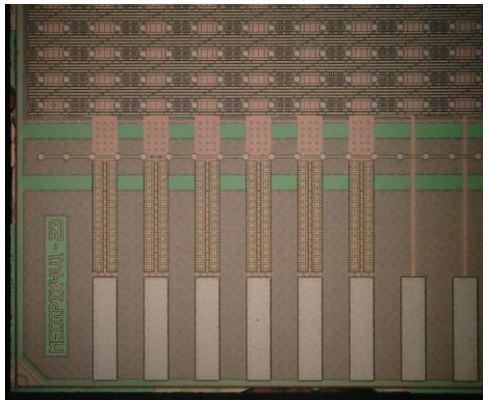
Timepix 4:
available for R&D licensing

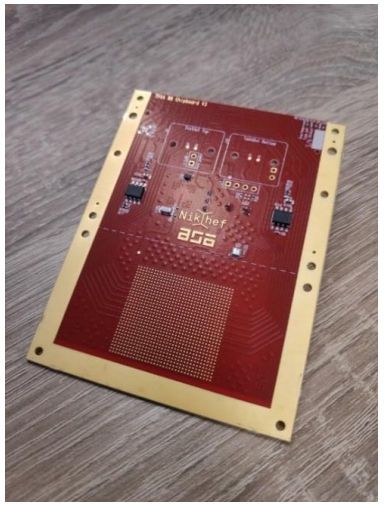
Medipix 4:
coming up in 2024

TPX2, TPX3, MPX3:
available for commercial licensing







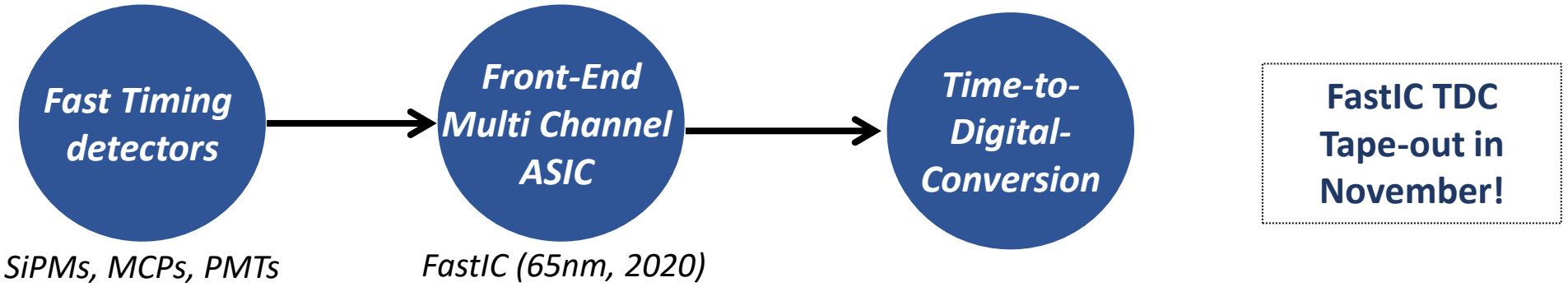


*Picture courtesy: J. Alozy & Viros

FastIC Project

FastIC (65nm CMOS) is a chip for the read-out of fast radiation detectors providing particle time of arrival and energy information. The chip has applications in medical and biomedical fields, e.g. for

Time-of-Flight Positron Emission Tomography (PET), mass spectrometry or fluorescence detection in biological samples.



FastIC TDC Tape-out in November!

Highly configurable:

- Singled ended, differential & summation of 4 single-ended channels (+/-) to explore benefits of segmentation of detector areas;
- Large range of input capacitances;
- Large dynamic range (with positive and negative polarity readout).

Mass spectrometry with Chemistry Dep Univ Oxford

Goal: proof-of-principle that (expensive and fragile) MCP can be removed, allowing lower vacuum conditions and opening the door to portable applications.

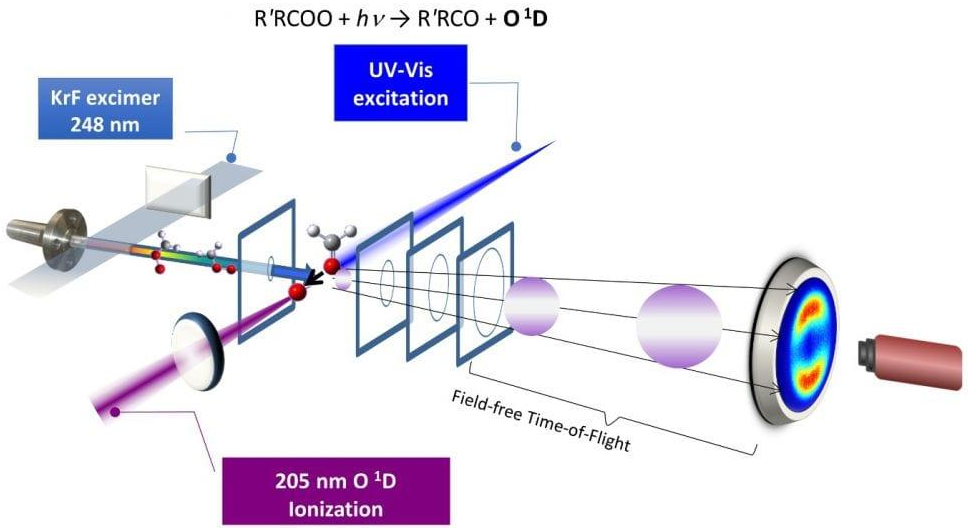
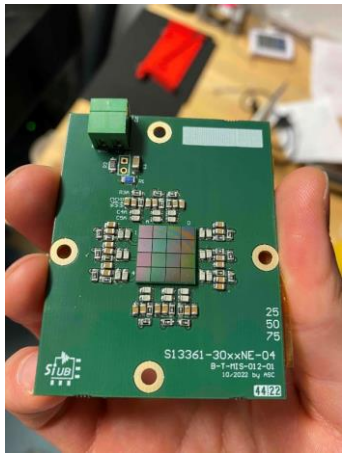
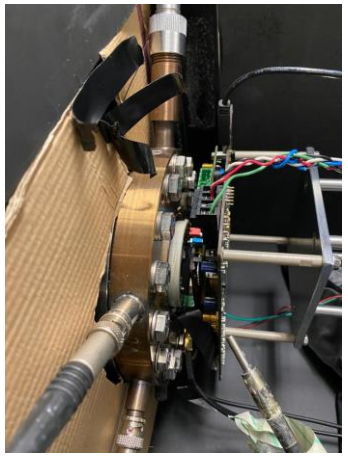
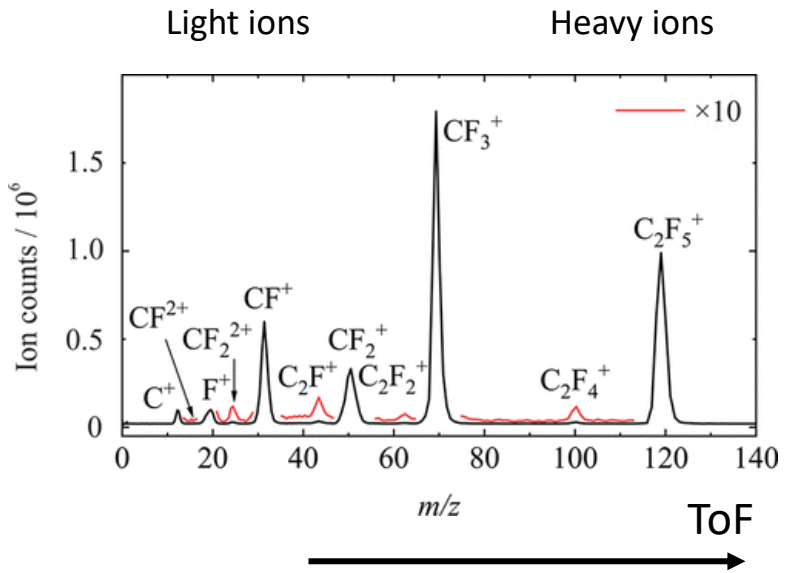
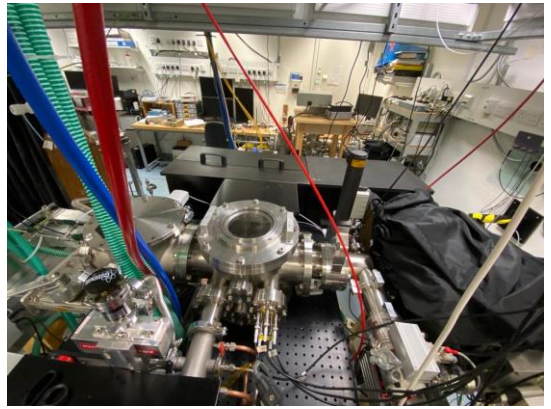


Image: https://web.sas.upenn.edu/lestergroup/velocity-map-imaging/







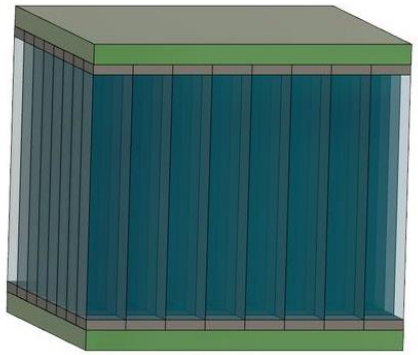


FastIC+

Tests for the evaluation of FastIC, coupled to an array of SiPMs, in ToF Mass Spectrometry November 2022.

ERC project: CHLOE-PET

(CHerenkov Light mOdulE for time-of-flight Positron Emission Tomography)



- ERC Starting Grant based on FastIC+
- PI Gerard Ariño-Estrada
- Improvement in time resolution and spatial resolution by almost a factor 10.

Novelty:

- Use Cherenkov light as a prompt time source;
- Use a dual-ended photodetector readout **based on the FastIC+** to maximize light collection and provide 3D segmentation;
- Employing photodetectors with small pixel pitch.

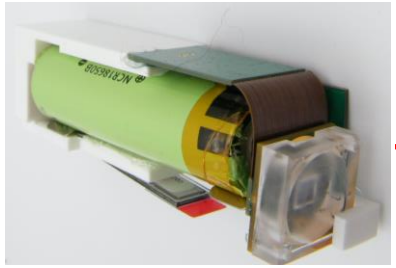
Goal:

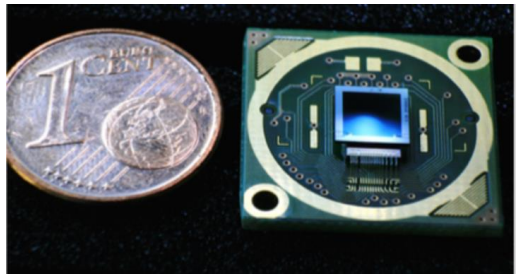
- Improve early detection of tumors down to 2 mm in size, such as in lung, breast, and prostate;
- Allow the diagnosis and study of other diseases such as Alzheimer's with much better imaging accuracy, among other applications.

FastIC+

The first electronic eye lens dosimeter for interventional radiology

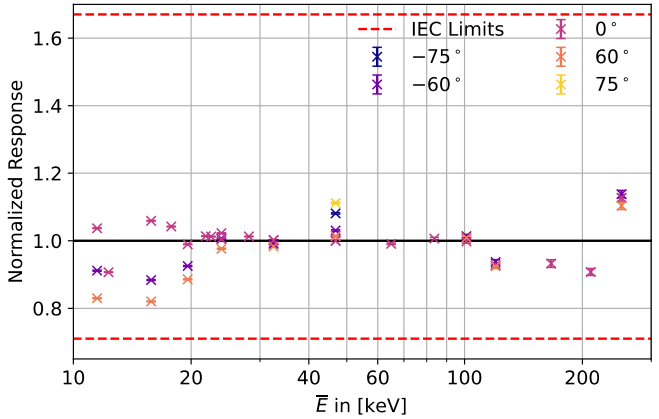
Foldable Readout electronics with battery and Bluetooth communication





DOSEPIX

Excellent dose response close to 1.0 from 0° to 75° angle of incidence



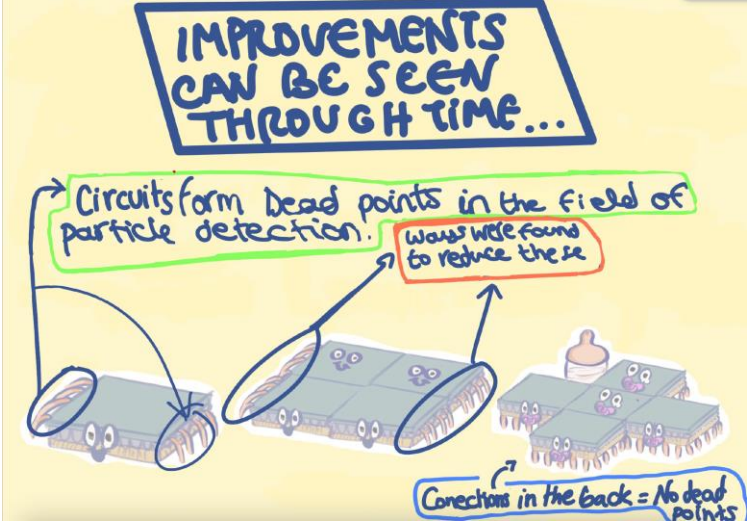
Measured in collaboration with German National Metrology Institute PTB

Dosepix

FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG

Physikalisch-Technische Bundesanstalt
Nationales Metrologieinstitut

Summary and conclusion



- **Computed Tomography**:
  - Medipix3 can bring high spatial resolution, material identification and quantification and beam artefact reduction;
  - Medipix 4 will also be a great chip for CT: 4-side buttable;
- **Mass Spectrometry:**
  - Benefits from the highly parallel and noise-hit-free Timepix detectors;
  - FastIC can replace MCP;
- **Gamma cameras** can be used for Thyroid diagnostics;
- **Beam Monitoring:** detectors are being explored to monitor dose deposition in ion beam therapy;
- **TEM:** Medipix 3 for low dose biological imaging ;
- **Earth & Human Health:** single-photon counting cameras to measure cosmic rays and solar UV radiation;
- **PET:** readout **based on the FastIC+** to maximize light collection and provide 3D segmentation;
- **Eye lens dosimetry** for the medical staff in interventional radiology using Dosepix.

CERN Microelectronics technologies are being used in many different medical applications across the World. The new chips under development will expand the portfolio.

CHIPS ARE EVERYWHERE AND WILL CONTINUE TO PLAY A FUNDAMENTAL ROLE IN OUR FUTURE

LET'S IMPROVE

WOULD YOU LIKE TO TAKE PART?

Samuel Ceballos Álvarez

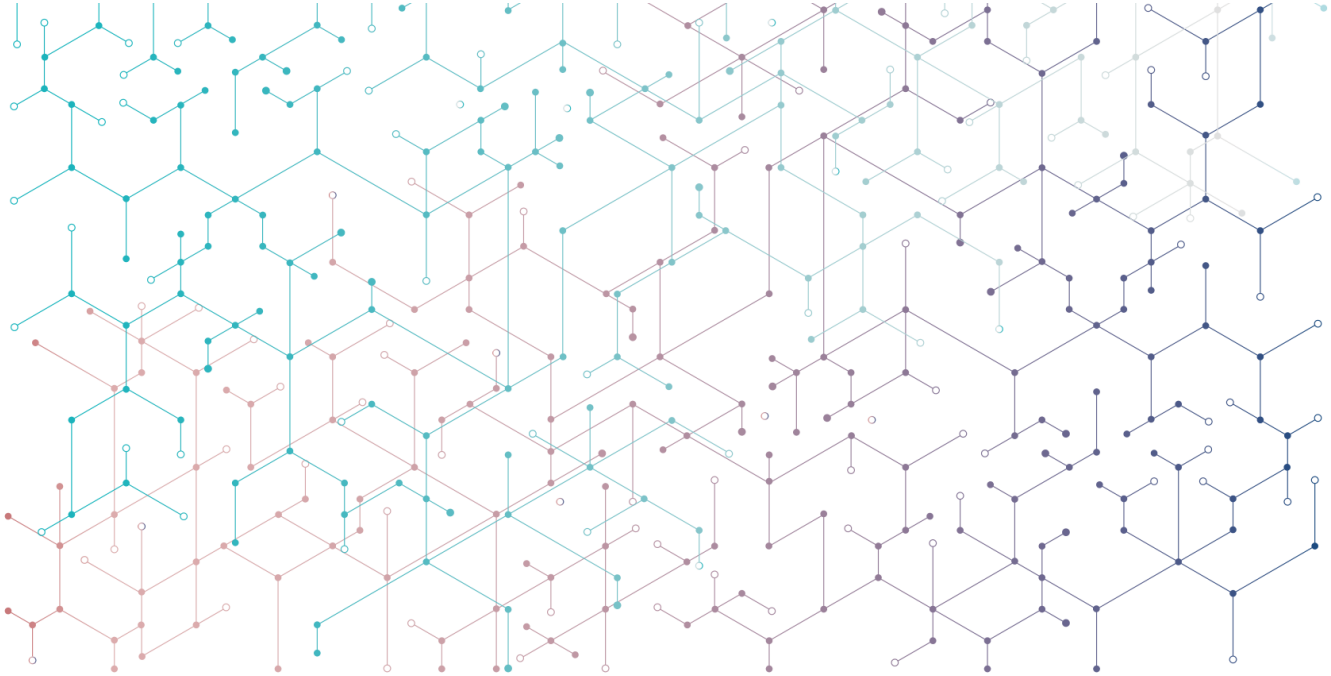
CERN

medipix collaboration

THANK YOU

Get in touch!

ana.rita.pinho@cern.ch



With thanks to the CERN community for the daily support of the Organisation's KT mission!

Special thanks to M. Campbell, R. Ballabriga, T. Michel, and Medipix Collab & licensees

Subscribe the KT newsletter

@cern-innovation-partnerships

@CERNVenture

Find out more at kt.cern

Follow us on social media

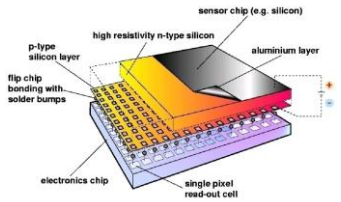
#CERNKT

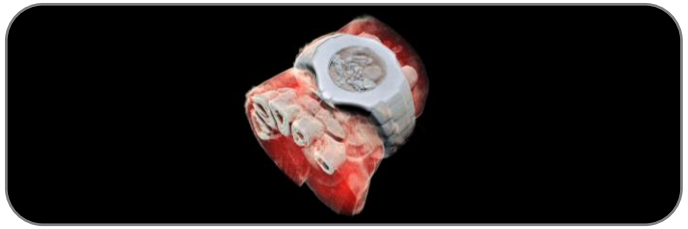
Medipix/Timepix detectors

- Medipix and Timepix families are hybrid pixel detector readout chips with complementary signal processing chain
- Medipix
  - Imaging applications
  - Camera mode with global Shutter
  - Pixels count number of events above threshold within Acquisition time (multiple thresholds)
  - Frame-based readout
  - Event by event on pixel processing possible (for example for Charge Sharing Correction)
  - Ability to deal with high fluxes (more suitable for photons)
- Timepix
  - Tracking applications
  - Global Shutter
  - Pixel registers Time and Energy, and sends the information to the periphery (single threshold, Time-over-Threshold)
  - Data push readout
  - Offline processing (for example for Charge Sharing Correction or sub-pixel resolution)
  - Lower flux rate capability

Medipix & Timepix Chip Families

A family of pixel detector read-out chips for particle imaging and detection developed by a consortium lead by CERN.





Medipix acts as a camera taking images based on the number of particles which hit the pixels when the electronic shutter is open.

- MPX3 permits colour imaging and dead time-free operation.
- Charge summing & allocation at the pixel level = proper binning of the energy of incoming photons.
- Two counters in each 55µm pixel = one counter is being read out, while the other is counting.
- Up to 8 counters are available per pixel.

The Medipix chip family aims at frame-based imaging and spectroscopic x-ray imaging.

Timepix that can accurately measure time, allowing direct reconstruction of the 3D track of passing charged particles.

			Timepix3 (2013)	Timepix4 (2018/19)	
Technology			IBM 130nm – 8 metal	TSMC 65nm – 10 metal	
Pixel Size			55 x 55 µm	55 x 55 µm	
Pixel arrangement			3-side buttable 256 x 256	4-side buttable 512 x 448	3.5x
Sensitive area			1.98 cm^2	6.94 cm^2	
Readout Modes	Data driven (Tracking)	Mode	TOT and TOA		
		Event Packet	48-bit	64-bit	33%
		Max rate	< 43 Mhits/cm^2/s	178.8 Mhits/cm^2/s	4x
	Frame based (Imaging)	Mode	PC (10-bit) and iTOT (14-bit)	CRW: PC (8 or 16-bit)	
		Frame	Zero-suppressed (with pixel addr)	Full Frame (without pixel addr)	
		Max count rate	82 Ghits/cm^2/s	~800 Ghits/cm^2/s	10x
TOT energy resolution			< 2KeV	**< 1Kev**	2x
Time resolution			1.56ns	**~200ps**	8x
Readout bandwidth			≤5.12Gb (8x SLVS@640 Mbps)	≤81.92 Gbps (16x @5.12 Gbps)	
Target global minimum threshold			<500 e^-	<500 e^-	

Motivation

Modern radiology can diagnose most medical conditions.

However, it is not provided:

- when the patient needs it most
- where the patient is
- in an affordable way

The New York Times

TRILOBITES

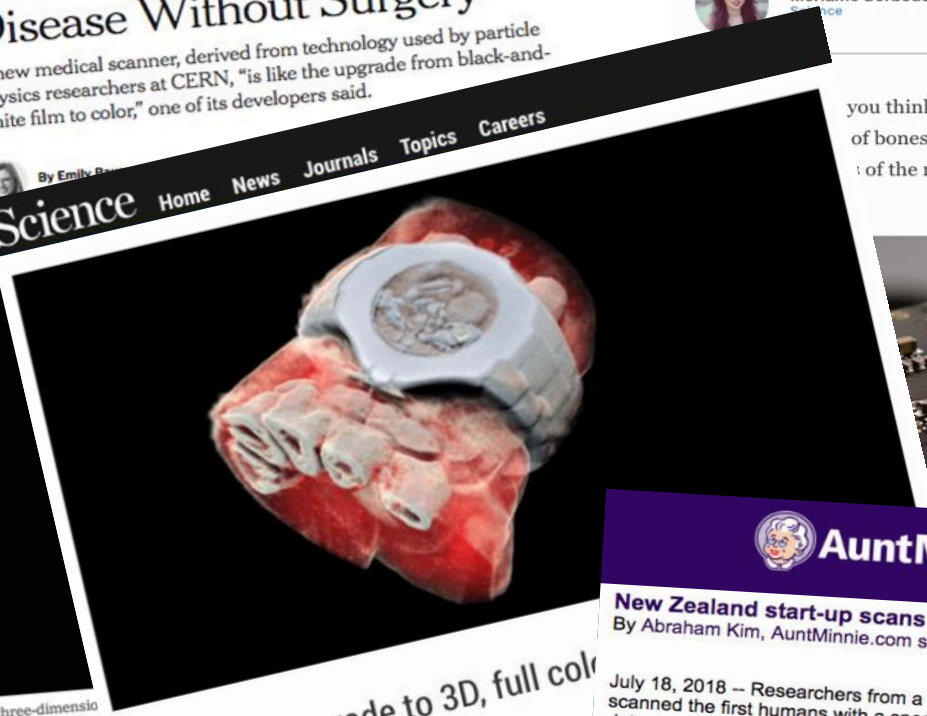
3-D Color X-Rays Could Help Spot Deadly Disease Without Surgery

A new medical scanner, derived from technology used by particle physics researchers at CERN, "is like the upgrade from black-and-white film to color," one of its developers said.

By Emily Ba

A three-dimensio
developed by Dr.

Science Home News Journals Topics Careers



X-rays get upgrade to 3D, full col

By Frankie Schembri | Jul. 18, 2018 , 4:10 PM

Forbes Billionaires Innovation Leadership

1,240 views | Aug 1, 2018, 12:21am

CERN Technology Used To Create First Ever 3D Color X-Ray

Meriame Berboucha Contributor

you think of an x-ray image, you probably think of a black
of bones. But now imagine a world where x-ray images
of the rainbow. Don't know abo hat's right

AuntMinnie.com

New Zealand start-up scans 1st humans with spectral CT

By Abraham Kim, AuntMinnie.com staff writer

July 18, 2018 -- Researchers from a start-up company in New Zealand have scanned the first humans with a spectral CT scanner based on solid-state digital detectors. The technology produces color images at much higher levels of resolution than traditional CT scanners and, thus, may improve diagnosis.

MENU nature International journal of science

News & Comment Research

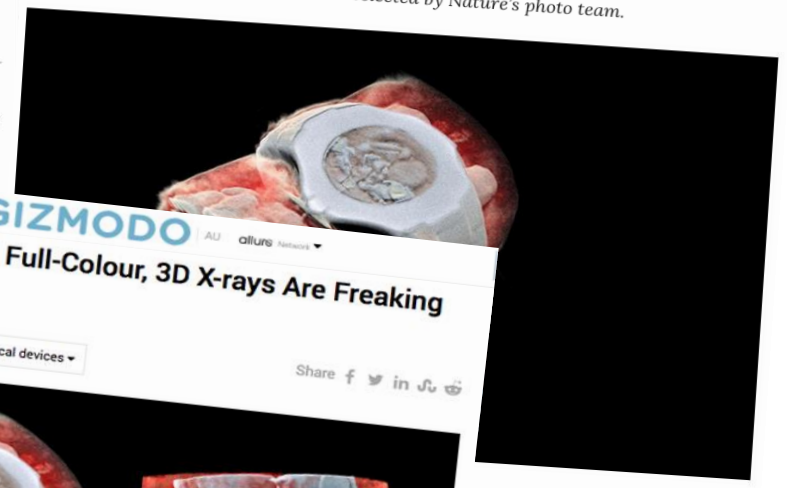
News Opinion Research Analysis Careers Books & Culture

Search E-alert

NEWS · 03 AUGUST 2018

Whales, scales and moons — July's best science images

The month's sharpest science shots — selected by Nature's photo team.



ped a technology that
nmercialized by MARS
originally developed
chip detects and counts
run through powerful
differentiate bones,

GIZMODO AU allure Network

The World's First Full-Colour, 3D X-rays Are Freaking Me Out

Andrew Liszewski
Jul 13, 2018, 9:00pm · Filed to: medical devices

Share

CT versus MARS

Traditional CT

- 200-500um spatial resolution
- Metal implants are a problem
- Moderate power x-ray tube

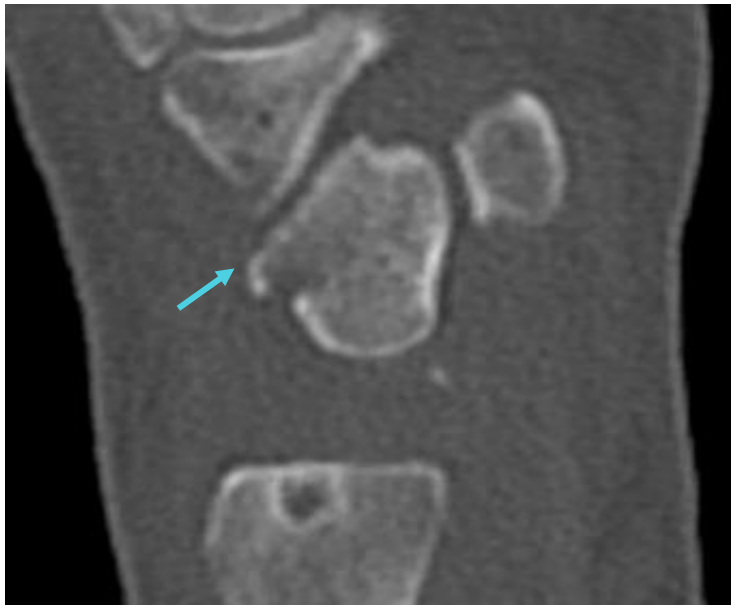
MARS

- 90um resolution
- Fewer metal artefacts
- Low power x-ray
    - Lower dose
    - Less x-ray shielding

MARS scanners

MARS SPCCT Imaging technology is in concept development for human use. It is not a product and is not cleared or approved by the US FDA or any other regulator for commercial availability outside of New Zealand

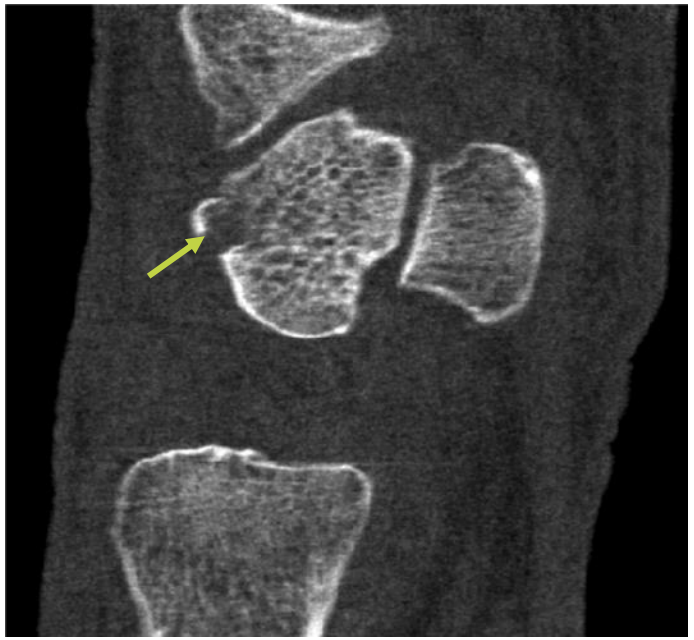
CT versus MARS



Standard CT
300um

Spatial resolution

Triquetrum fracture

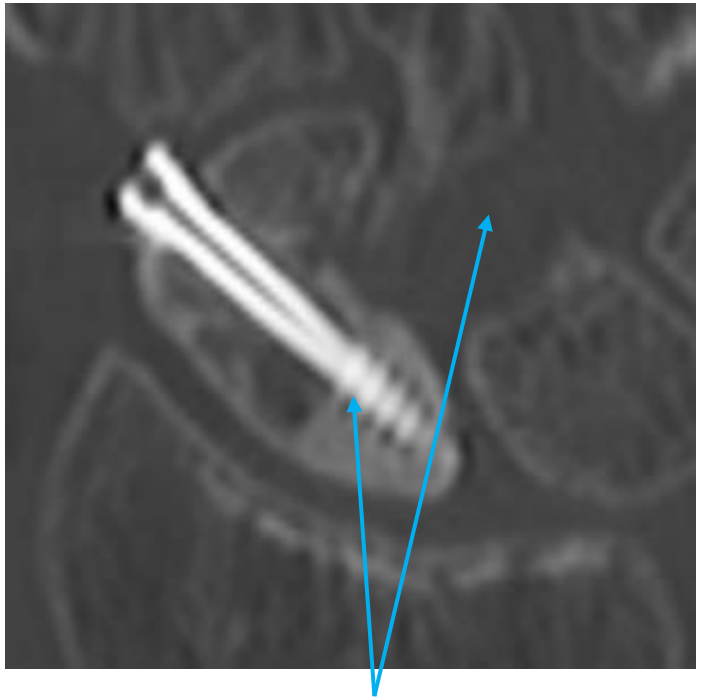


MARS
90um

MARS SPCCT Imaging technology is in concept development for human use. It is not a product and is not cleared or approved by the US FDA or any other regulator for commercial availability outside of New Zealand

CT versus MARS

Standard CT



Metal artifact hides the bone-metal interface

Metal artefact

MARS

The bone-metal interface is visualised enabling assessment of peri-implant infection and osteolysis

MARS SPCCT Imaging technology is in concept development for human use. It is not a product and is not cleared or approved by the US FDA or any other regulator for commercial availability outside of New Zealand

MRI versus MARS

MRI for soft tissue

T1 weighted MRI *(same patient)*

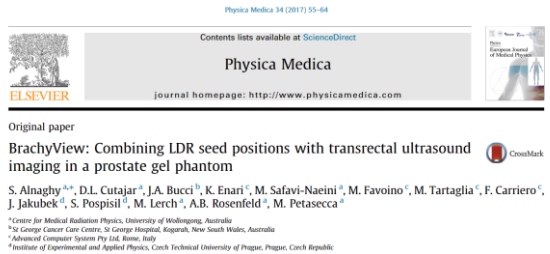
MARS for soft tissue

MARS energy channel fused with lipid map

MARS SPCCT Imaging technology is in concept development for human use. It is not a product and is not cleared or approved by the US FDA or any other regulator for commercial availability outside of New Zealand

Brachytherapy

- Is a procedure that involves placing radioactive sources inside your body to treat cancer.
- Permanent prostate brachytherapy involves placing many radioactive seeds within the prostate to treat prostate cancer.
- Brachyview is a miniaturized Timepix-based gamma camera developed at the Centre for Medical Radiation Physics (CMRP), University of Wollongong.
- It allows to determine the position of the sources and the dose delivered. (The imaging is combined with TRUS Transrectal ultrasound which gives anatomical information, avoiding the commonly used CT).


Physica Medica 34 (2017) 55–64

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Original paper

BrachyView: Combining LDR seed positions with transrectal ultrasound imaging in a prostate gel phantom

S. Alnaghy[a,*], D.L. Cutajar[a], J.A. Bucci[b], K. Enari[c], M. Safavi-Naeini[a], M. Favoino[c], M. Tartaglia[c], F. Carriero[c], J. Jakubek[d], S. Pospisil[d], M. Lerch[a], A.B. Rosenfeld[a], M. Petasecca[a]

[a] Centre for Medical Radiation Physics, University of Wollongong, Australia
[b] St George Cancer Care Centre, St George Hospital, Kogarah, New South Wales, Australia
[c] Advanced Computer System Pty Ltd, Rome, Italy
[d] Institute of Experimental and Applied Physics, Czech Technical University of Prague, Prague, Czech Republic

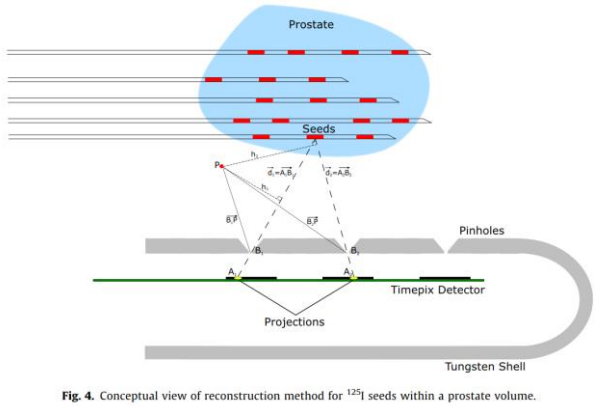
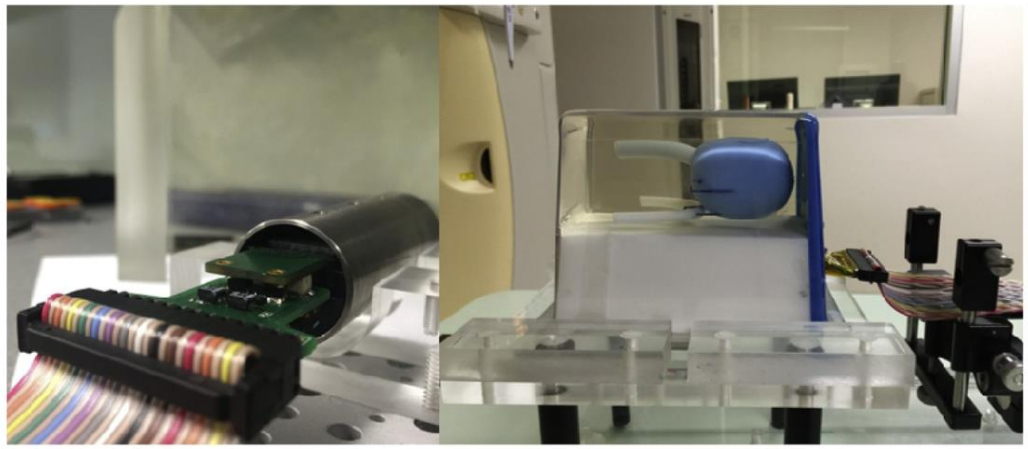


Fig. 4. Conceptual view of reconstruction method for ^{125}I seeds within a prostate volume.

Conceptual view of reconstruction method for ^{125}I seeds.



Experimental setup of prototype placed inside prostate gel phantom to image 30 implanted ^{125}I seeds.

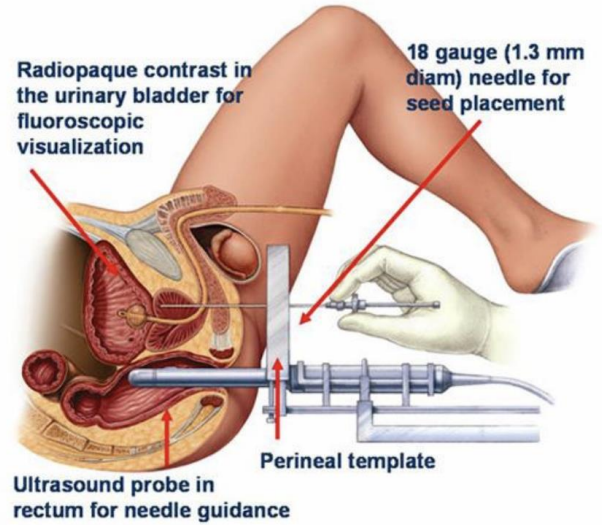


Image: https://www.mayoclinic.org/tests-procedures/brachytherapy/about/pac-20385159

Brachytherapy

UNIVERSITY OF WOLLONGONG AUSTRALIA

What is BrachyView? Novel in-body imaging system developed to provide real-time intraoperative dosimetry for low dose rate prostate brachytherapy treatments.

How? Seed positions can be reconstructed after *in-vivo* implantation using a high-resolution pinhole gamma camera inserted into the patient rectum.

Technology? fully automatic seed centre of mass identification and 3D position reconstruction for real-time applications. The algorithm presented uses a local feature detector, speeded up robust features, to perform detection of brachytherapy seed 2D projections from images, allowing for robust seed identification. It can detect 97% of seeds and correctly match 97% of seeds. The average overall computation time of 2.75 s per image

The proposed algorithm will allow the BrachyView system to be used as a real-time intraoperative dosimetry tool for low dose rate prostate brachytherapy treatments.


IOPscience Journals Books Publishing Support Login

Physics in Medicine & Biology

PAPER

BrachyView: development of an algorithm for real-time automatic LDR brachytherapy seed detection

T Brennen[1,4], L Galli[3], D L Cutajar[1,2], S Alnaghy[1], J Bucci[2], A Bece[2], K Enari[2], M Favoino[3], M Carriero[3], M Tartaglia[3] + Show full author list

Published 4 November 2020 • © 2020 Institute of Physics and Engineering in Medicine

Physics in Medicine & Biology, Volume 65, Number 21

Citation T Brennen *et al* 2020 *Phys. Med. Biol.* **65** 215015

DOI 10.1088/1361-6560/abac9e

› Med Phys. 2015 Dec;42(12):7098-107. doi: 10.1118/1.4935866.

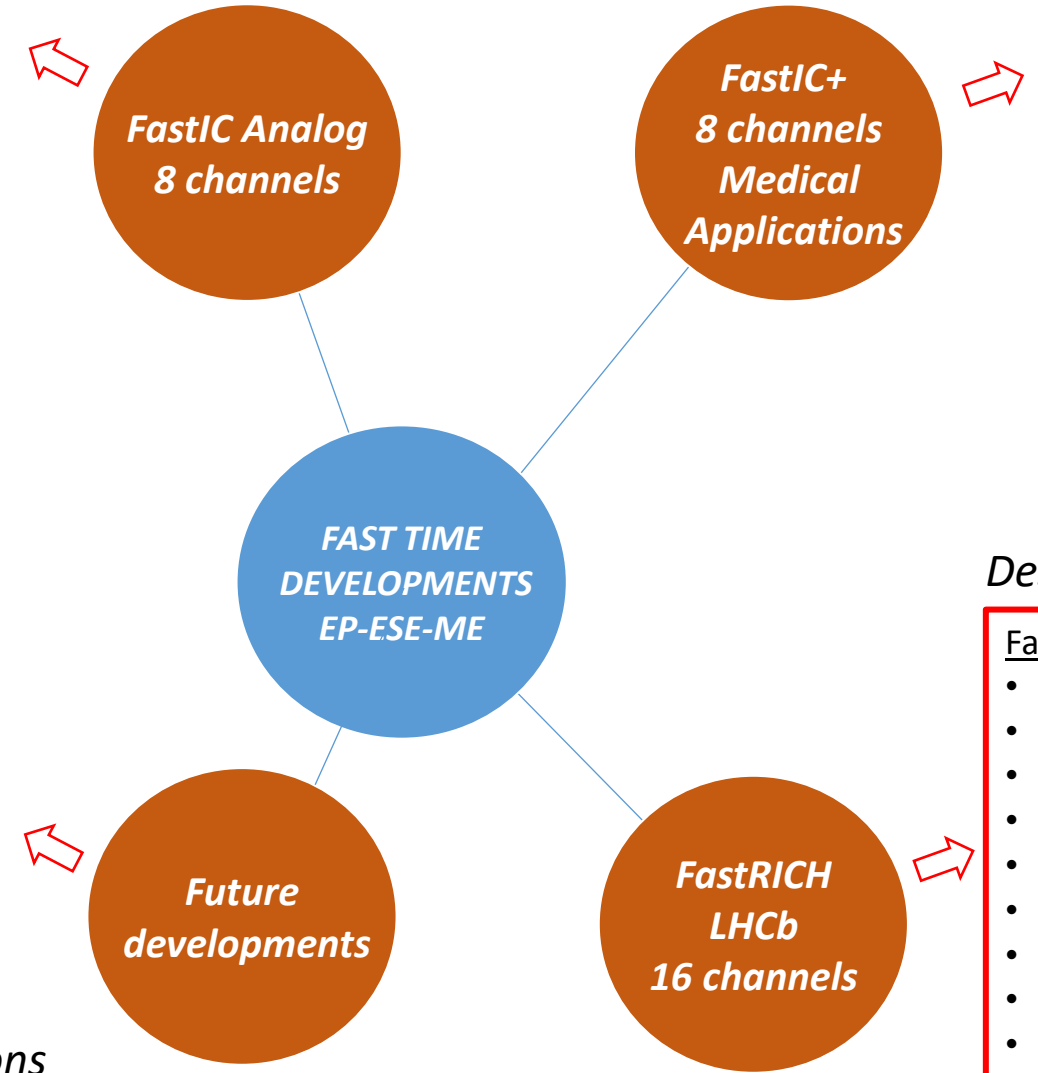
BrachyView, a novel in-body imaging system for HDR prostate brachytherapy: Experimental evaluation

M Safavi-Naeini [1], Z Han [1], S Alnaghy [1], D Cutajar [1], M Petasecca [1], M L F Lerch [1], D R Franklin [2], J Bucci [3], M Carrara [4], M Zaider [5], A B Rosenfeld [1]

Timepix

Design completed (CERN-UB)

FastIC Analog:
- Analog chip
- Generic
- Wide range C_{DET}
- Large dynamic range
- Signal summing
- Used with external TDC
- Not radiation hard



Design ongoing (CERN-UB)

FastIC+:
- Analog and Digital chip
- Generic
- Wide range C_{DET}
- Large dynamic range
- Signal summing
- Used with internal ~25ps bin TDC
- Not radiation hard

Future Roadmap
- Emphasis on module
- Analog and Digital chip
- **Pixelized, Sensor co-design, hybrid integration**
- More channels
- Smaller range C_{DET}
- Large dynamic range
- No signal summing
- Used with internal TDC

Both, HEP and other applications could benefit

Design ongoing (CERN-UB)

FastRICH:
- Analog And Digital chip
- Application specific
- Smaller range C_{DET} (PMTs/Small SiPMs)
- Small dynamic range (single photon operation)
- No signal summing
- Internal TDC (~25ps bin TDC)
- ~2ns Gate (duration/phase programmable)
- CFD
- Radiation hard