Implantable Micro System For *In Vivo* Dosimetry

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In Vivo Dosimetry
outline

- ☐ **In Vivo Dosimetry introduction;** *needs, methods*
- ☐ **Current state-of-the-art technology for IVD;** *initial clinical results*
- ☐ **Proposed novel STFC IVD;** *preliminary work and collaboration*
- ☐ **Summary of the project and CLASP proposal;** *costs and timeline*
- ☐ **Conclusions**

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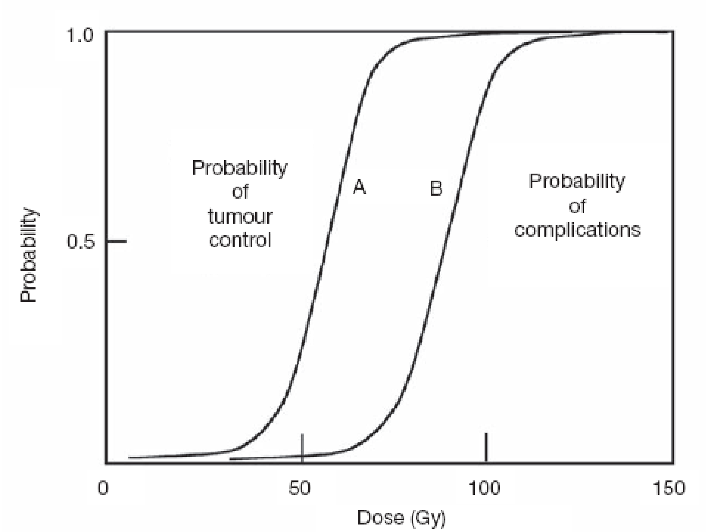
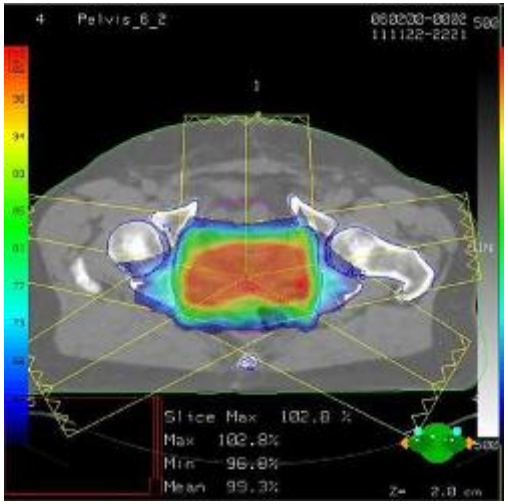
In Vivo Dosimetry
introduction

In clinical field, *In vivo dosimetry* (IVD) is a QA tool used to verify that the expected dose of therapeutic radiation has been delivered during radiotherapy session.

This is of crucial importance when high doses of radiation are used, to ensure that the intended dose has been delivered to the correct position and avoided healthy tissues.



*The **T**herapeutic **R**atio **C**urve shows the probability of disease control and complications. The steepness of the curves requires tight control over the delivered dose of radiation. Usual practice assumes TCP>=0.5 and NTCP<=0.05.*
***ICRU** reports 50 and 61 recommends -5% to +7% max*



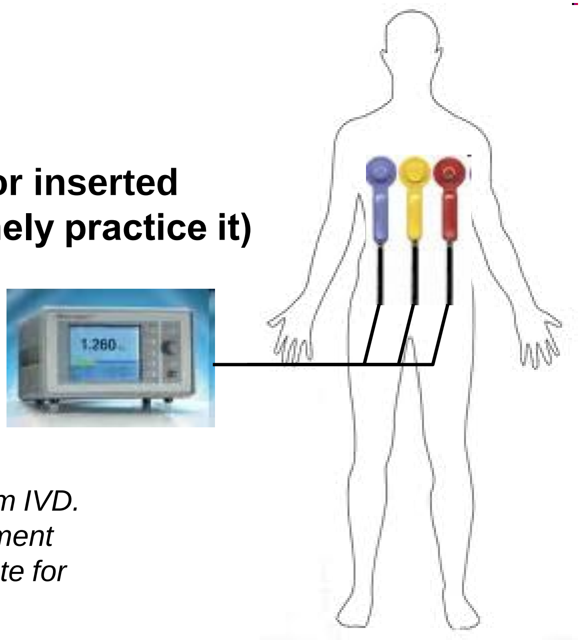
Modern radiotherapy treatments allow delivery of radiation to fixed targets with high accuracy

In Vivo Dosimetry
methods

Advanced methods of radiation delivery (3D CRT or IMRT) rely on SW planning and allow in principle accurate delivery of high doses of radiation to more targeted areas, but they suffer from uncertainties due to:

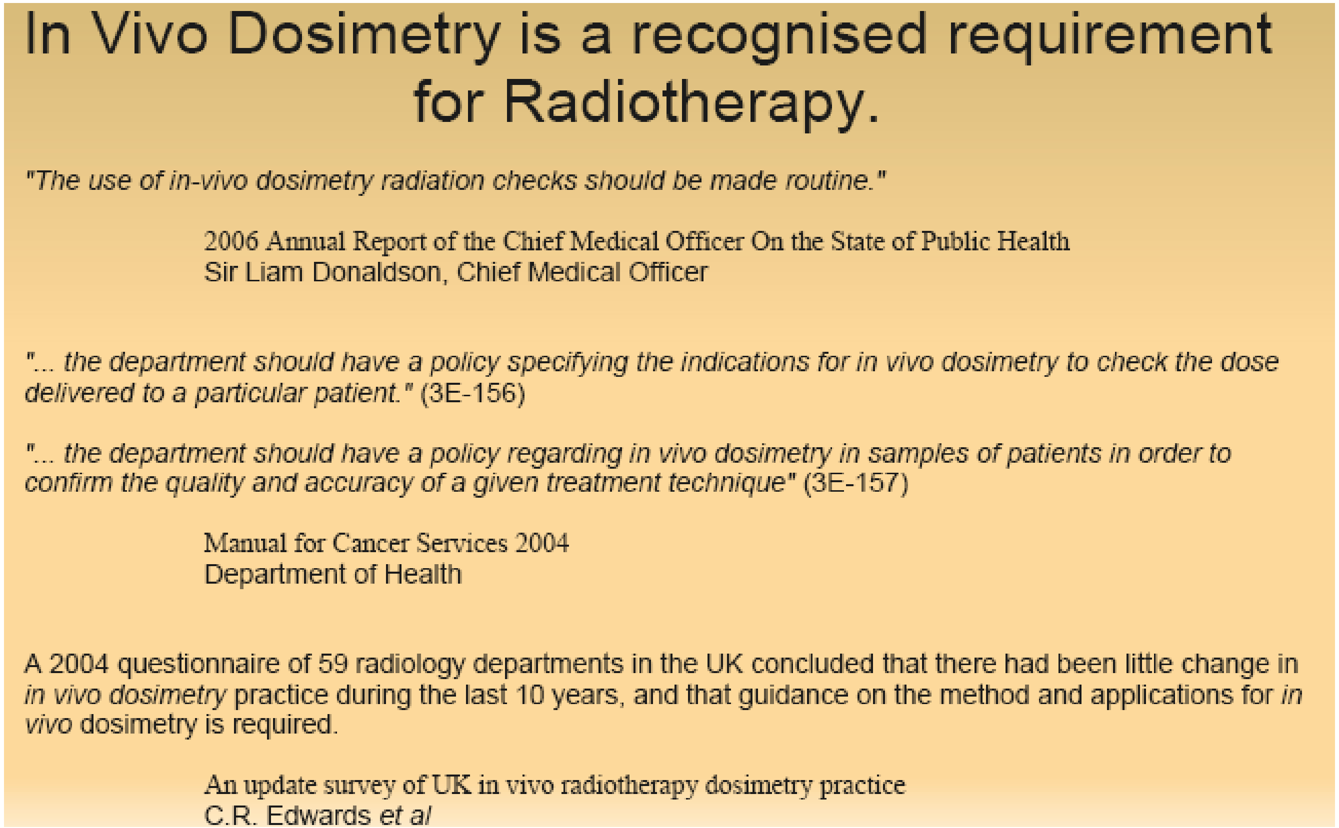
☐ Internal motion of body's organs (breathing)
☐ Motion of the patient
☐ Random and systematic errors of the machines
☐ Tissues non-homogeneity
☐ Changed size of the target

IVD is usually performed using diodes, wire-attached to the skin or inserted into body's cavities (currently only 30/40% of centres in UK routinely practice it)



Skin surface measurements are the most common method to perform IVD. The measurement is usually performed at the beginning of the treatment only, as their use increases the time of treatment. Cannot compensate for most of the uncertainties outlined above.

In Vivo Dosimetry
needs and requirements



In Vivo Dosimetry is a recognised requirement for Radiotherapy.

"The use of in-vivo dosimetry radiation checks should be made routine."

2006 Annual Report of the Chief Medical Officer On the State of Public Health
Sir Liam Donaldson, Chief Medical Officer

"... the department should have a policy specifying the indications for in vivo dosimetry to check the dose delivered to a particular patient." (3E-156)

"... the department should have a policy regarding in vivo dosimetry in samples of patients in order to confirm the quality and accuracy of a given treatment technique" (3E-157)

Manual for Cancer Services 2004
Department of Health

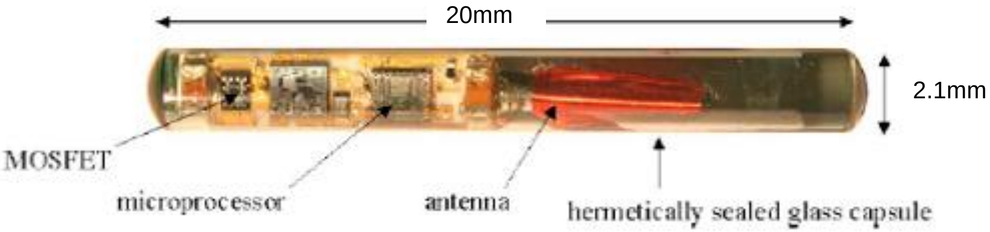
A 2004 questionnaire of 59 radiology departments in the UK concluded that there had been little change in *in vivo dosimetry* practice during the last 10 years, and that guidance on the method and applications for *in vivo* dosimetry is required.

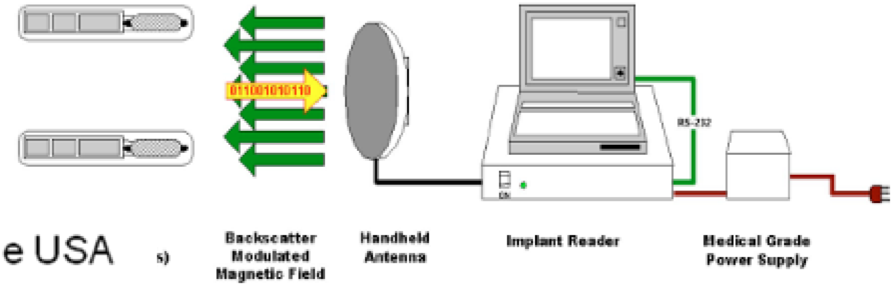
An update survey of UK in vivo radiotherapy dosimetry practice
C.R. Edwards *et al*

- **Currently ~50% patients undergo radiotherapy**
- **IVD as QA routine is supported by many clinicians in UK and abroad**
- **Need for small devices, accurate (~%) and inexpensive to guarantee improved treatments**

In Vivo Dosimetry
current state-of-the-art

- **Implantable IVD from *Sicel*: FDA clearance in 2009 for use in breast and prostate radio treatment (clinical studies available)**





Used at 29 centres in the USA

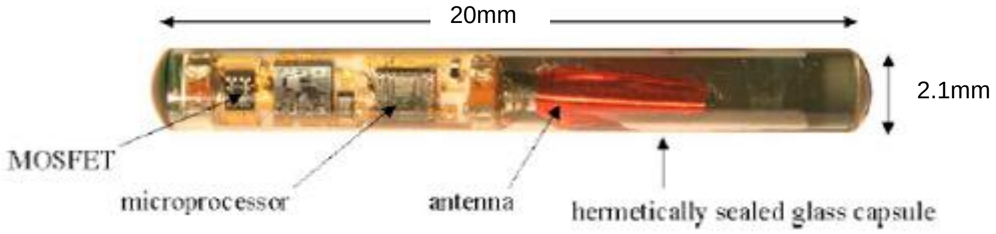
Item	Price
DVS Dosimeter Kit (2 per box)	$1,200
DVS/HFT Dosimeter Kit (2 per box)	$1,200
DVS Reader System	$19,750

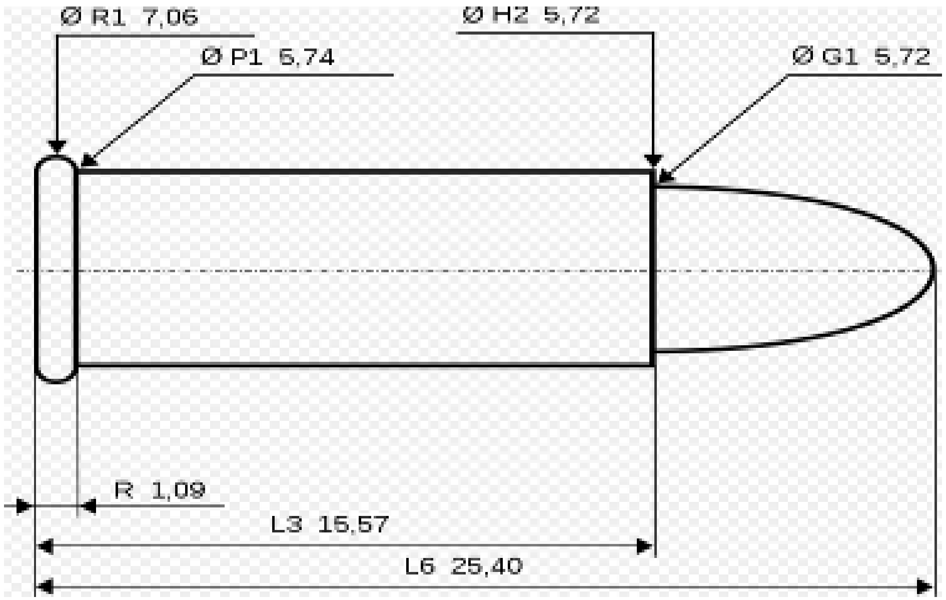
- **The *Sicel* IVD is currently being commercialised in the US at 600$/each**
- **Directory of Radiotherapy centres: UK : 72,USA: 2749**

• *'An Implantable MOSFET Dosimeter for the Measurement of Radiation Dose in Tissue During Cancer Therapy' ,IEEE Sensor Journal, Vol. 8, No.1, Jan 08*

In Vivo Dosimetry
current state-of-the-art

- **Implantable IVD from *Sicel*: FDA clearance in 2009 for use in breast and prostate radio treatment (clinical studies available)**

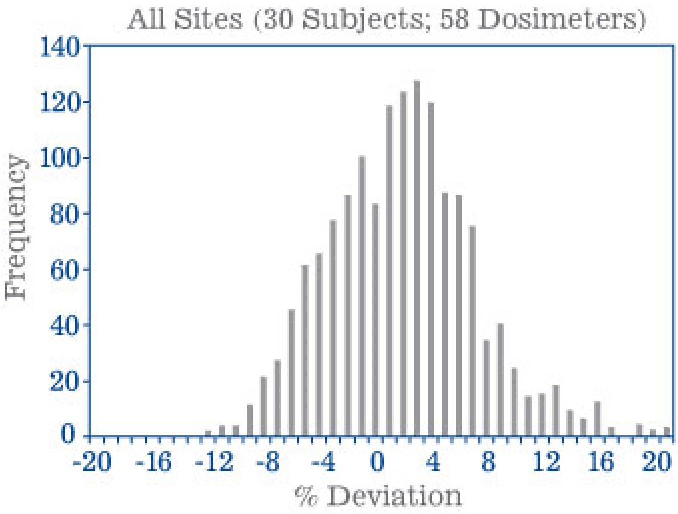




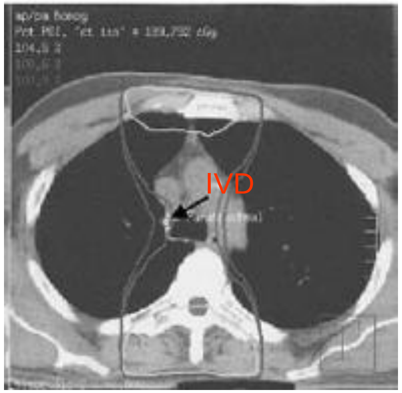
In Vivo Dosimetry
current clinical results

Clinical tests have been performed on patients in US (>60) for a total of 126 dosimeters implanted.

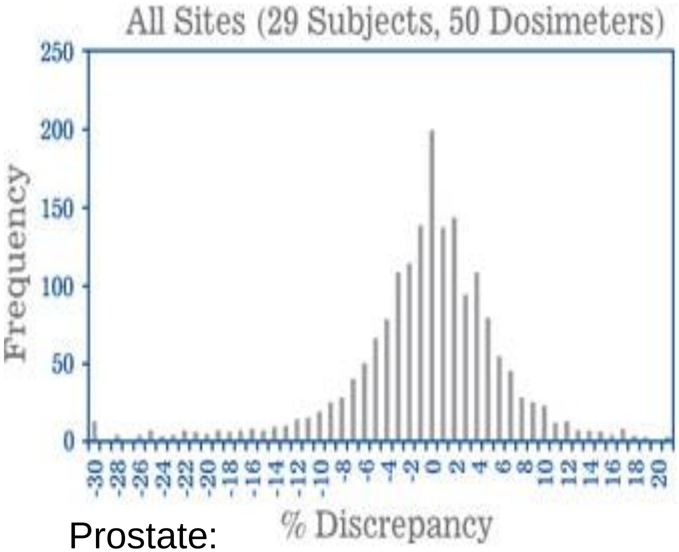
<u>The results show critical discrepancy between PD and actual measured dose</u>



Breast:
∆ from PD >=7% in 21% of cases
∆ from PD >=5% in 40% of cases



CT scans showing the IVD



Prostate:
∆ from PD >=7% in 22% of cases
∆ from PD >=5% in 36% of cases

- *'Initial clinical results of an in vivo dosimeter during external beam radiation therapy', C. Scarantino et al., Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 2, pp. 606–613, 2005*

- *'The observed variance between predicted and measured radiation dose in breast and prostate patients utilizing an in vivo dosimeter', Scarantino cw, prestidge br, anscher ms, ferree cr, kearns wt, black rd, bolick ng, beyer gp. int. j radiation oncology biol. phys., 2008. vol. 72, no. 2, pp 597-604.*

In Vivo Dosimetry
state-of-the-art limits

The Sicel device provides evidence for the need for accurate and more routinely used IVD.

Limiting factors that affect the Sicel device:

☐ **fabricated in hybrid technology: size, reliability and costs;**

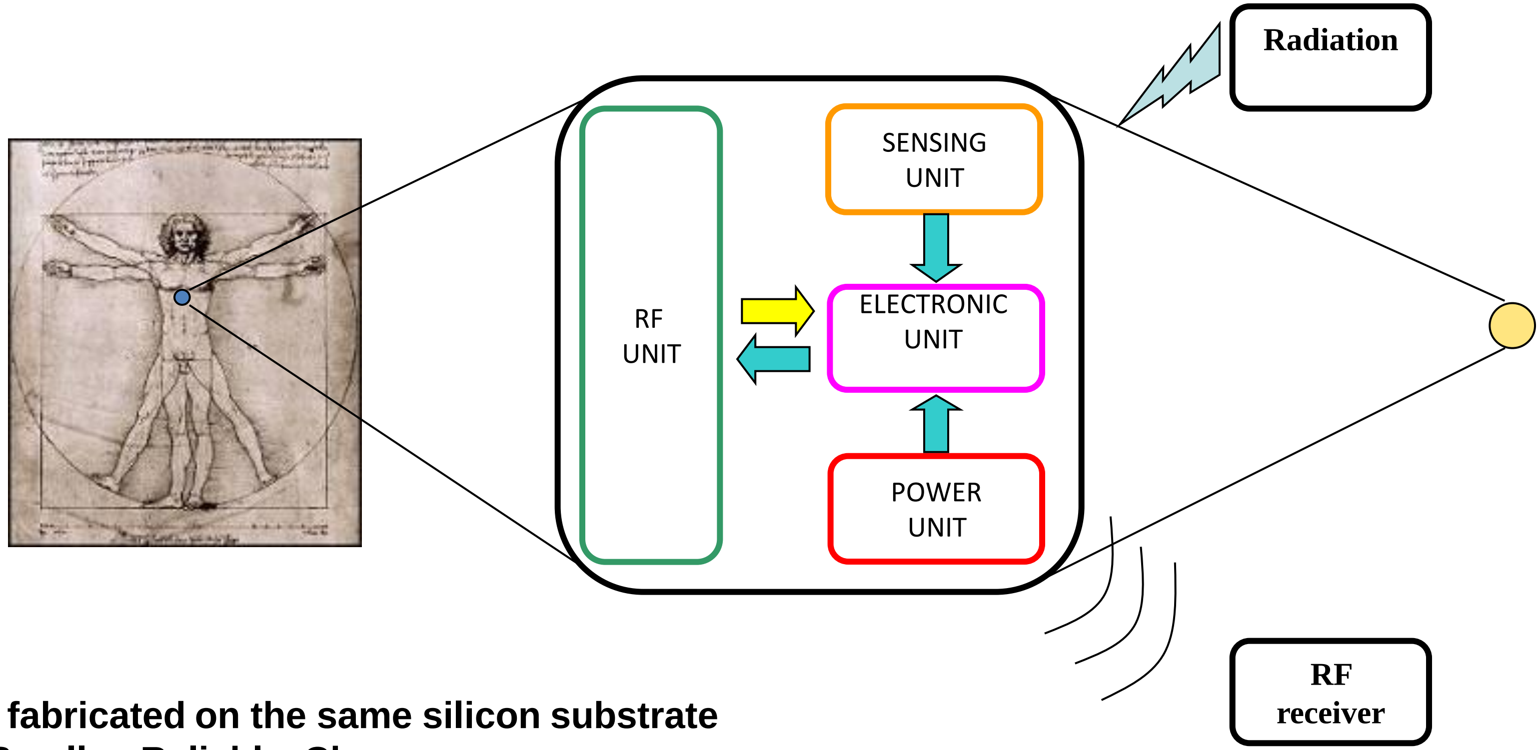
☐ **RF communications relies on back scattering (i.e. near EM field) : short range (15 cm) and not in a standard allocated RF band (MICS);**

☐ **no real time measurement, require manual operation;**

☐ **technology choice (thick SiO_2 MOSFET for radiation sensing): measurements has to be performed soon after the end of the treatment (fade effect due to thermal de-trapping)**

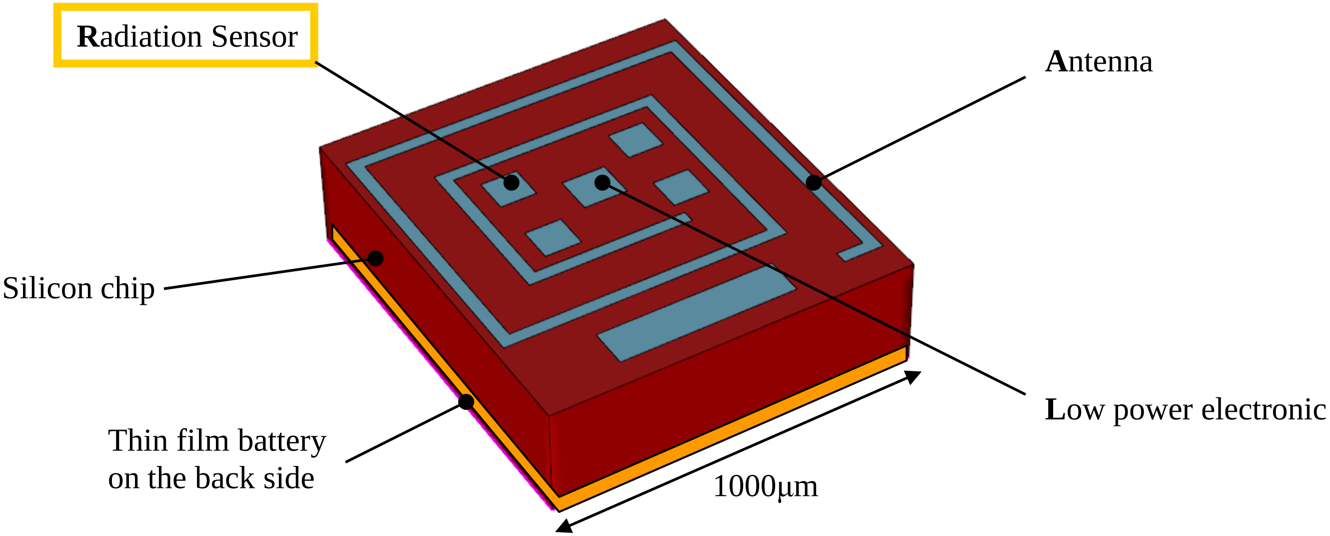
STFC Proposed Monolithic In Vivo Dosimeter

- ❑ **A novel proposed implantable IVD: micro system on a single silicon chip**



- ❑ **An *IVD* fabricated on the same silicon substrate**
  - ➢ **Smaller, Reliable, Cheaper**
  - ➢ **Same or better technical specs of the Sicel IVD**
- ❑ **Technologically advanced: longer RF communication range (~m's) in MICS band (402 – 405 MHz)**
  - ➢ **Can perform RT measurements**
  - ➢ **More than one device could be implanted to give a better representation of dose field**

Proposed Monolithic In Vivo Dosimeter

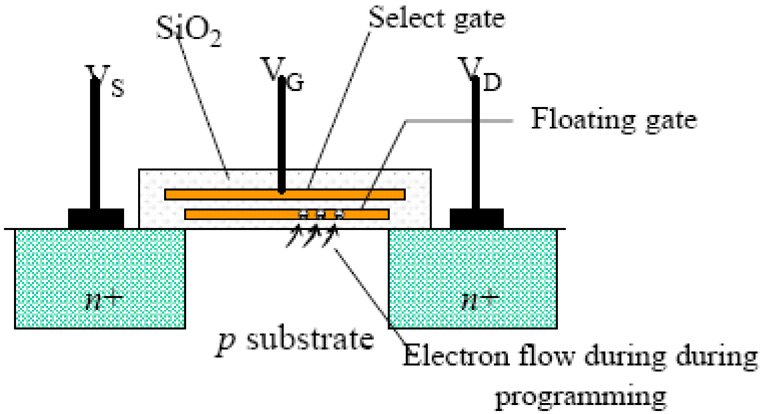


Layout Example of the proposed monolithic IVD

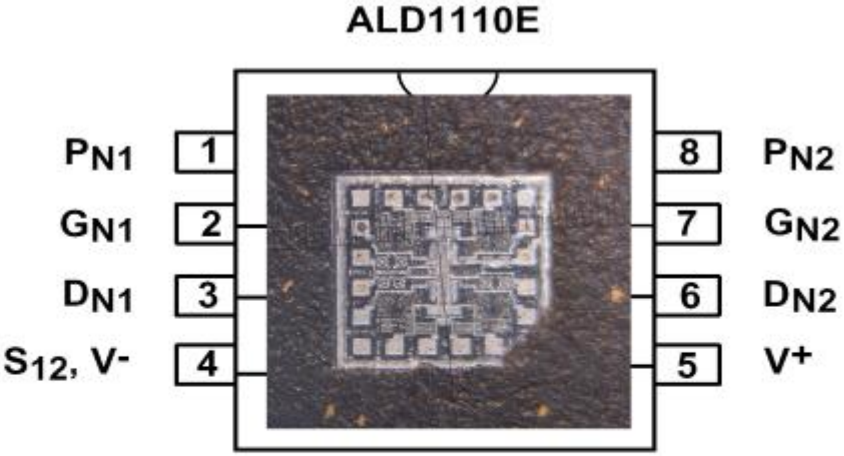
- **Proposed CMOS technology 0.18 µm allows integration of radiation sensors and RF**
- **Power options for the implantable version include thin film battery on the back side**
- **Alternative powering options for surface measurements**

Proposed Monolithic In Vivo Dosimeter
initial works

Radiation Sensor



Evaluation of commercial FG devices

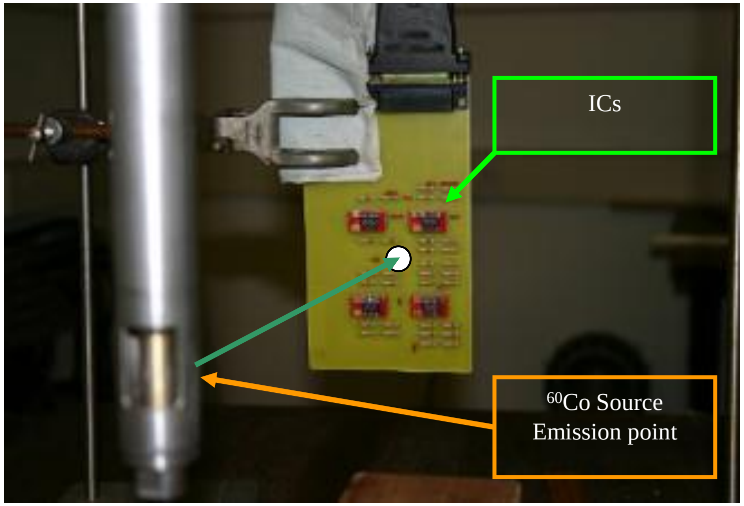


SEM picture of commercial FG device

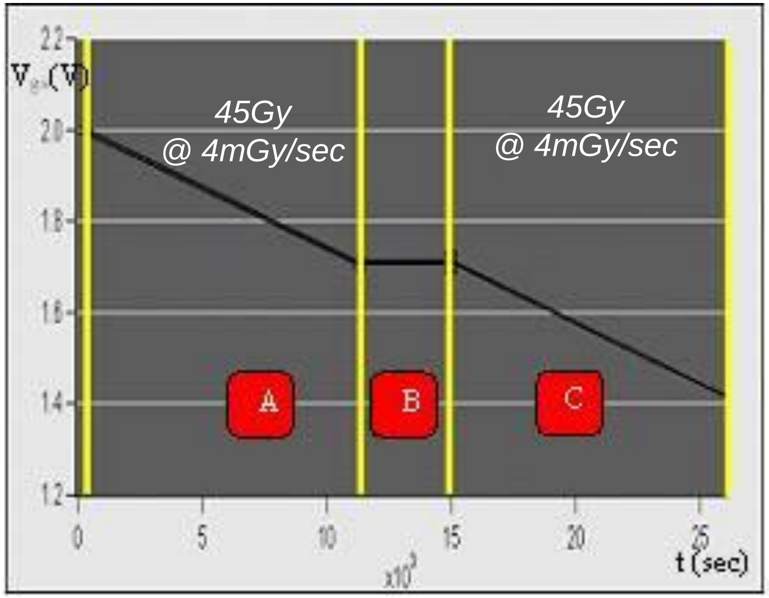
Radiation Sensor study based on floating gate (FG) technology (following a PoC funding from STFC Innovations, Ltd.)

- **studies of commercial FG devices**
- **only one family of FG devices is commercially available for analogue applications**
- **custom technology, rather old**

Proposed Monolithic In Vivo Dosimeter initial works



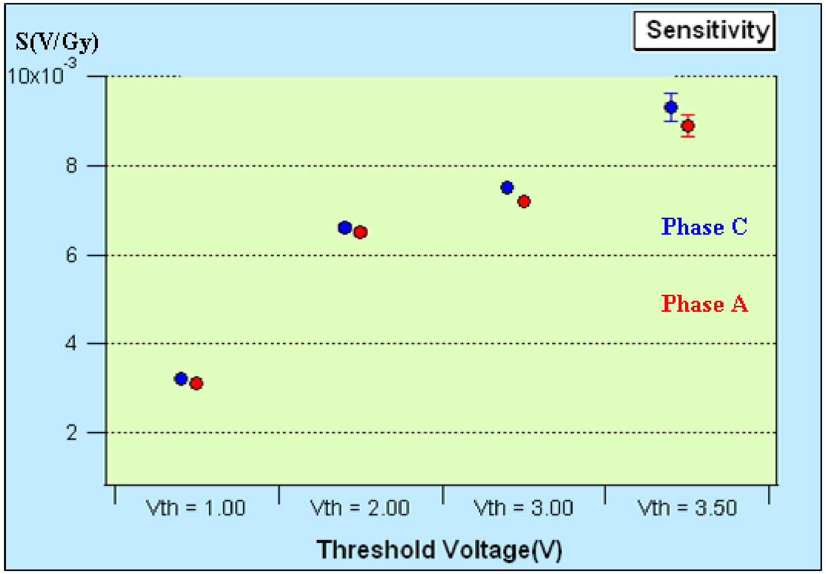
Gamma irradiation of devices



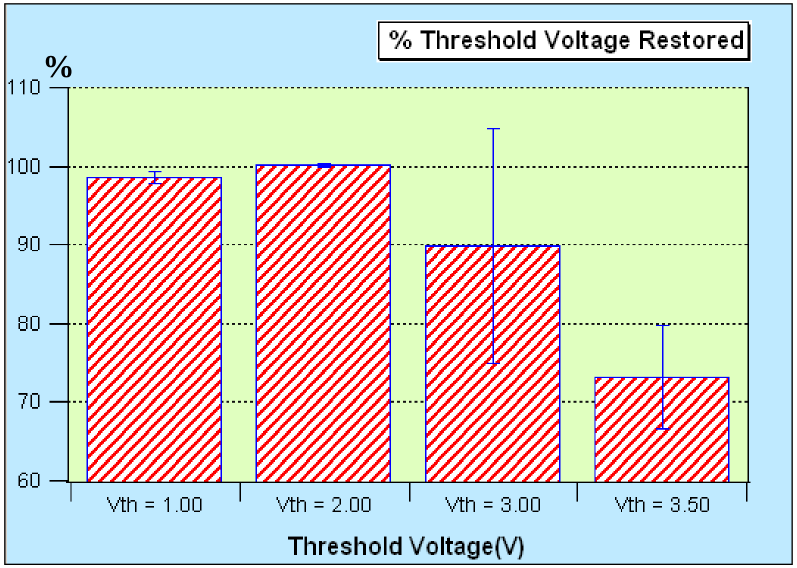
RT V_{gs} *voltage shift during irradiation*

- **commercial FG devices were ^{60}Co irradiated @ Brunel University**
- **dose of radiation up to ~ 90 Gy**

Proposed Monolithic In Vivo Dosimeter
initial works



Average sensitivity (V_{th} vs. V_{thinit})



Average of % of V_{th} recovery vs. V_{thinit}

- ☐ **The commercial FG devices show too little sensitivity**
- ☐ **noise ~ 200 μV pk-pk**
- ☐ **Evidence of radiation damage (trapped charge in SiO_2)**

- *G. Villani et al., 'Evaluation of commercial programmable Floating Gate devices as radiation dosimeters', published on JINST, February 2009*

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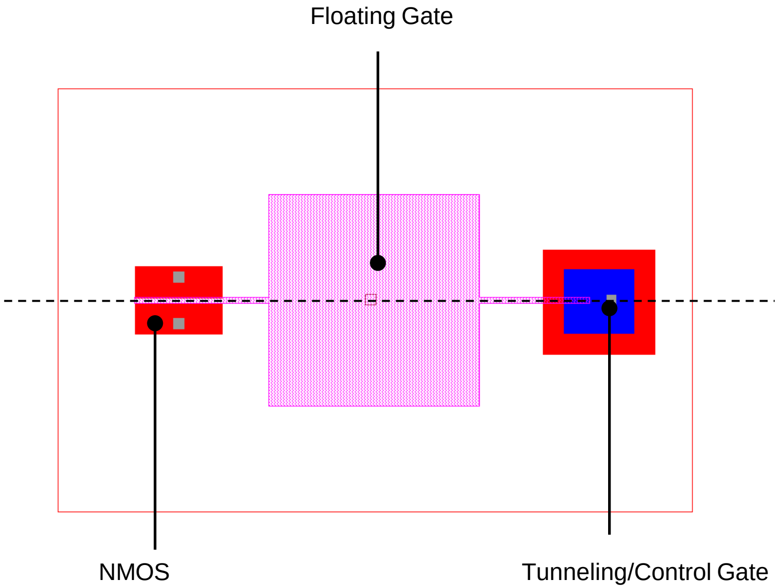
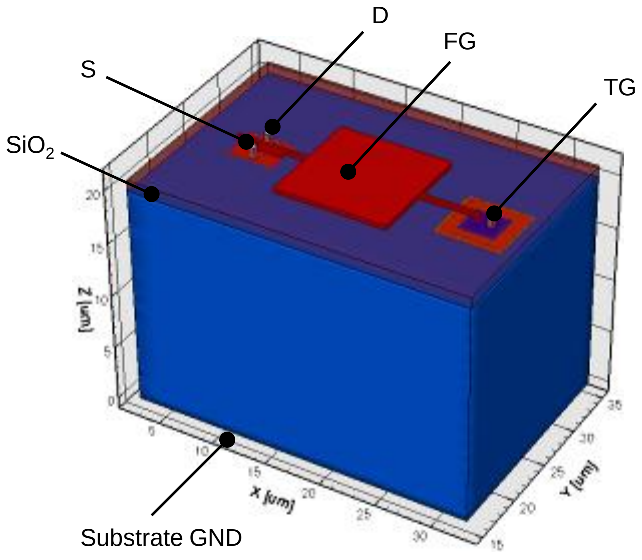
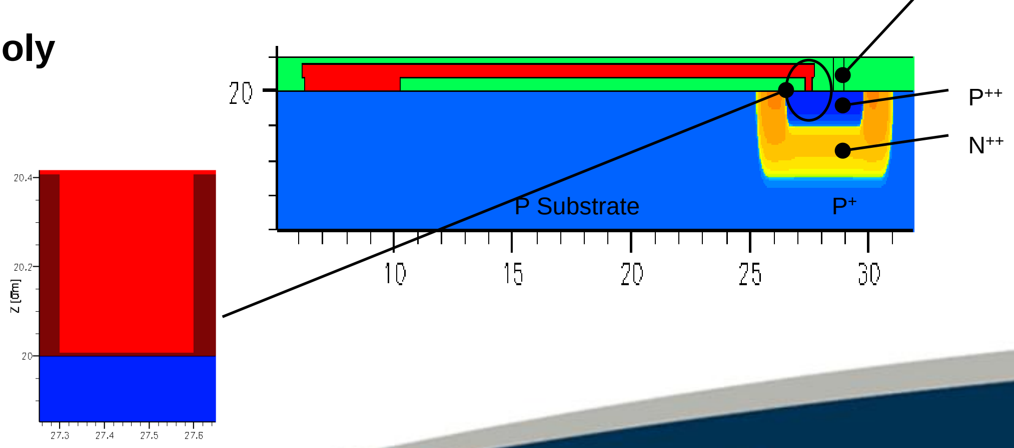
Proposed Monolithic In Vivo Dosimeter
Radiation sensor design







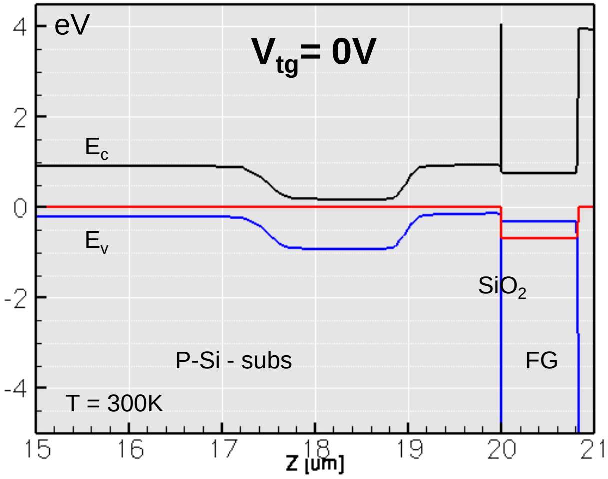
Radiation sensor from a standard dual poly CMOS process used for NVM memory

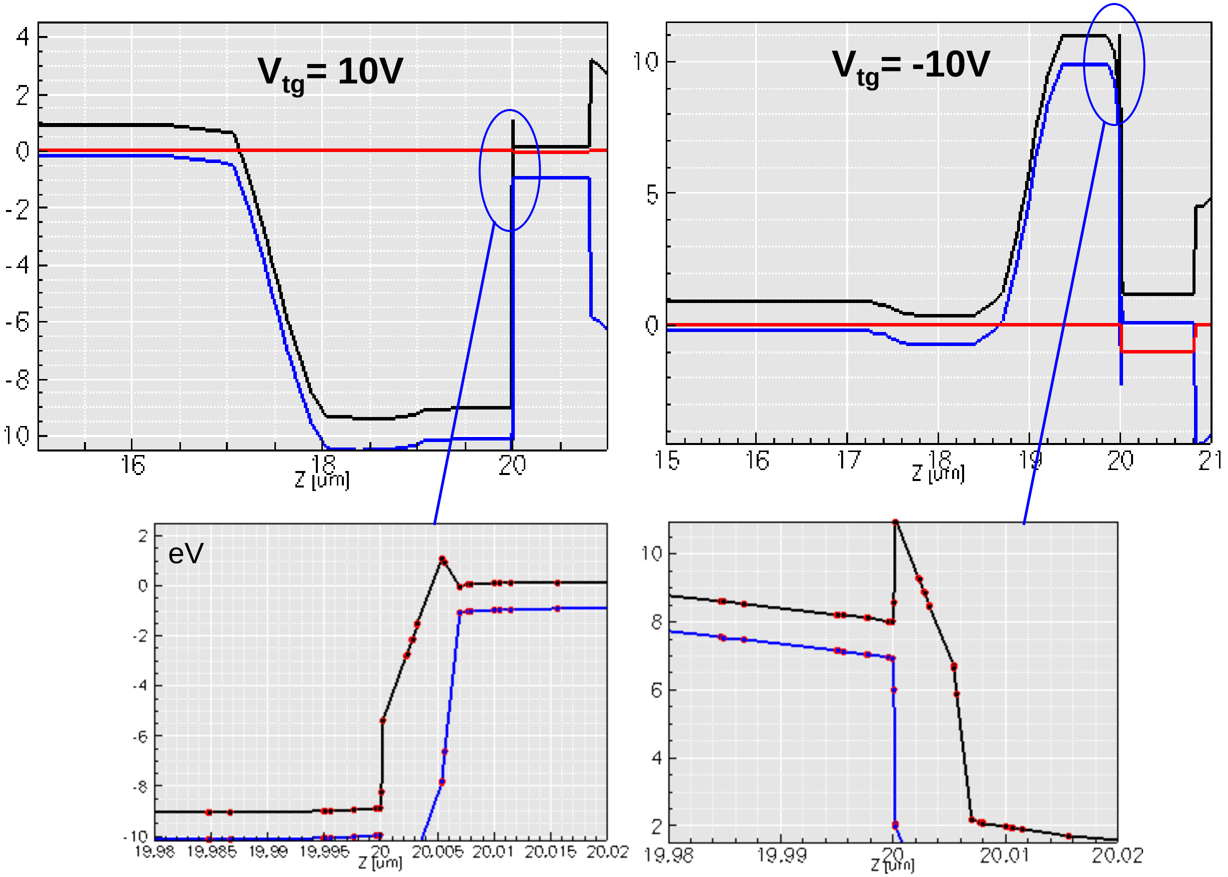
Collaboration with TOWER Jazz foundry

The programming pin acts as the Gate of the MOSFET

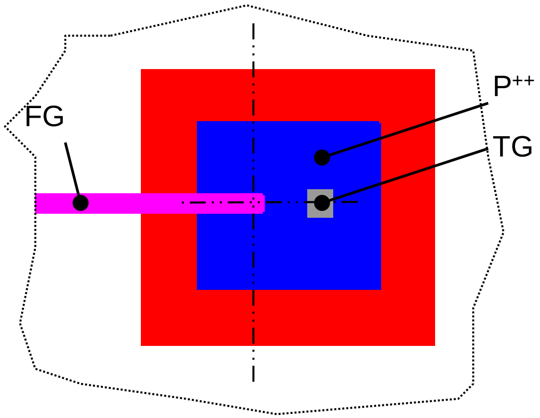
Charge tunneling @ ~ 10 V

Proposed Monolithic In Vivo Dosimeter
Radiation sensor design





Tunneling through SiO_2 is enabled by applying a voltage bias to TG



X section through tunneling area
(subs = 0V, D = S = 0V)

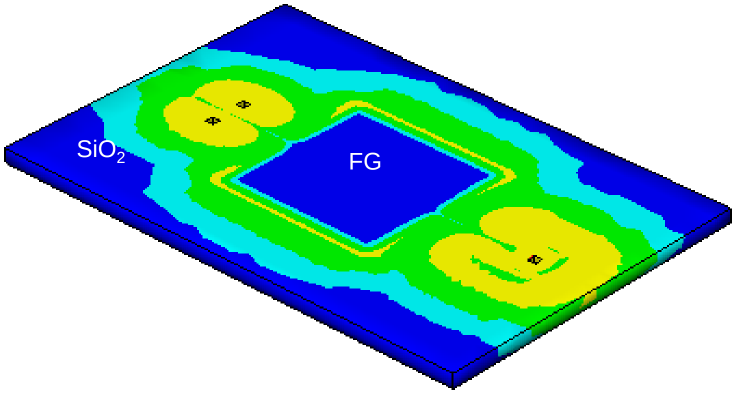
Band diagrams

Debye length ~ 5nm

Proposed Monolithic In Vivo Dosimeter
Radiation sensor design

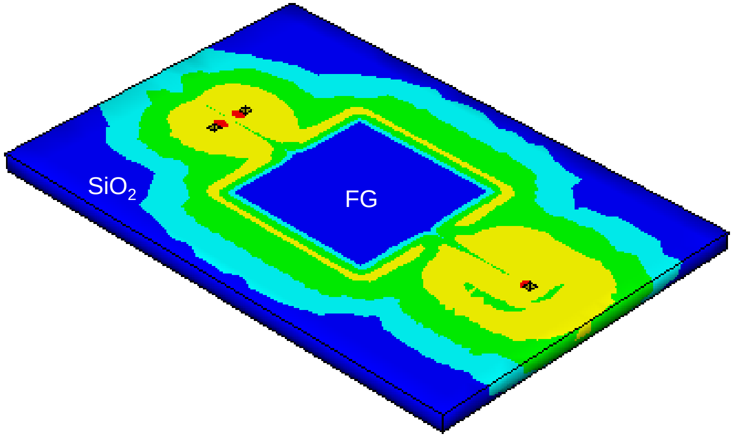
Q_{fg}= 0C

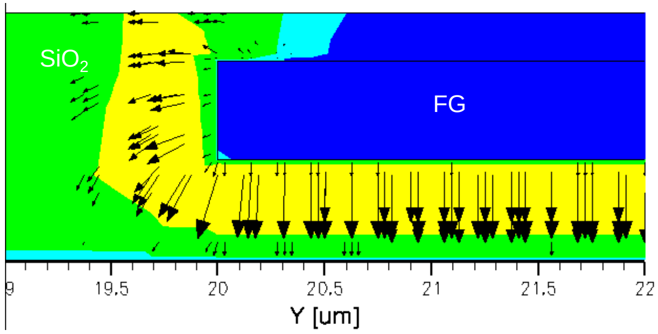
Φ_{FG}= -0.228V



Q_{fg}= -4fC

Φ_{FG}= -0.506V



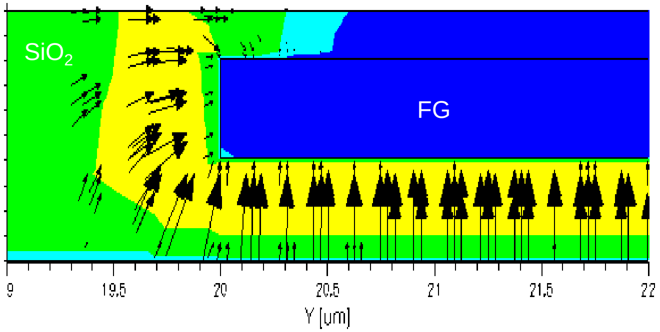


kV/cm

🟨 1<F<10

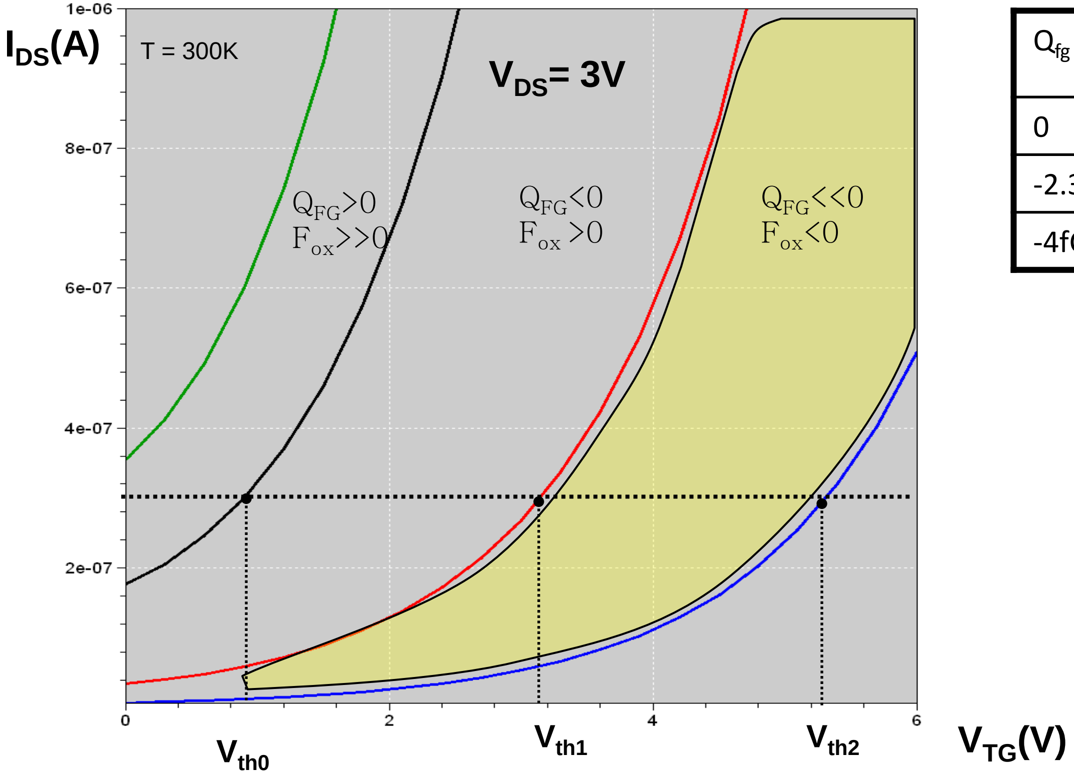
🟩 0.1<F<1

🟦 0.01<F<0.1



The intensity and direction of the SiO_2 electric field can be changed with Q stored in FG

Proposed Monolithic In Vivo Dosimeter
Radiation sensor design

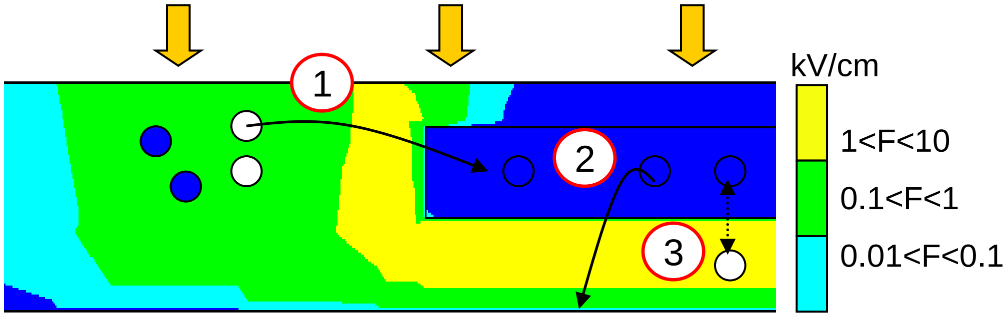


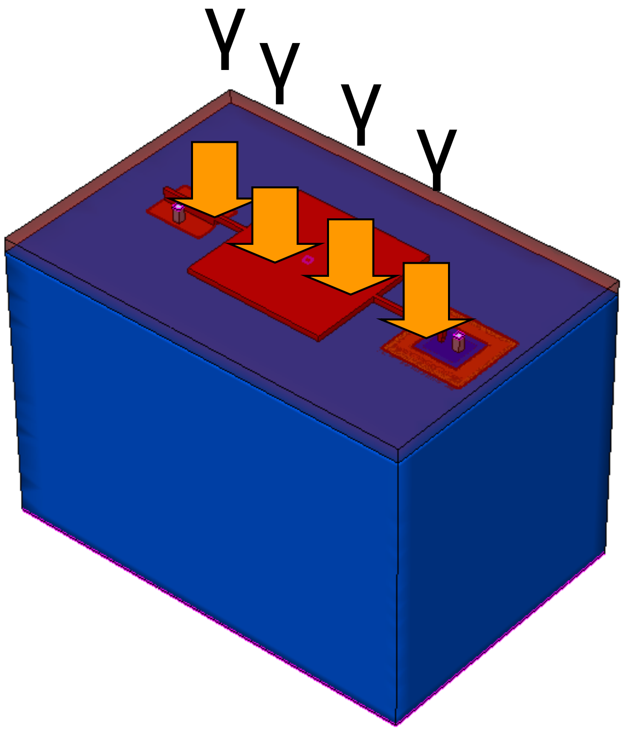
Q_{fg}	V_{th} (I_{ds}=0.3uA @ V_{ds} =3V)
0	0.898
-2.368fC	3.139
-4fC	5.307

The charge stored in the FG allows to change the threshold voltage in both directions

Proposed Monolithic In Vivo Dosimeter
Radiation sensor design

The deposited radiation in SiO_2 alters the internal electric field (F_{ox}): this affects the electrical characteristics of the device (V_{th})



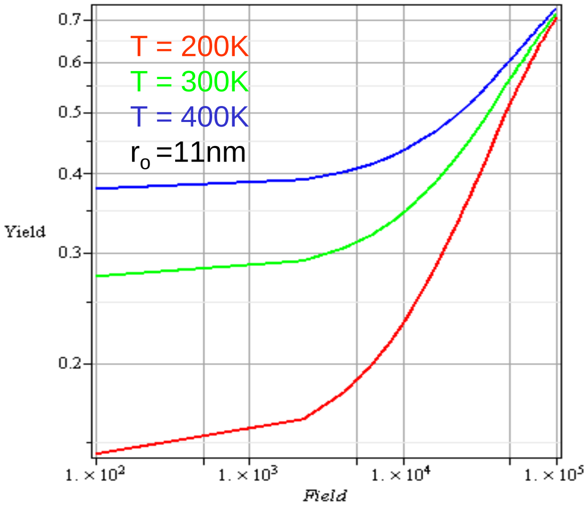


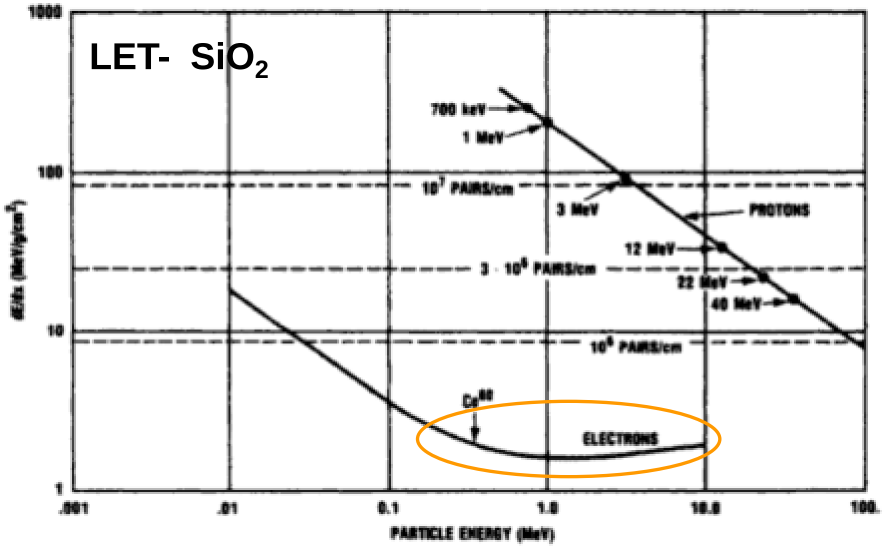
Three main mechanisms of radiation sensing:

1. FG discharge via <u>charge injection</u>
2. FG discharge direct
3. Holes trapping (requires knowledge on SiO_2 processing)

FG discharge by holes collection from SiO_2, generated by gamma radiation

Proposed Monolithic In Vivo Dosimeter
Radiation sensor design





low LET particles: Onsager model

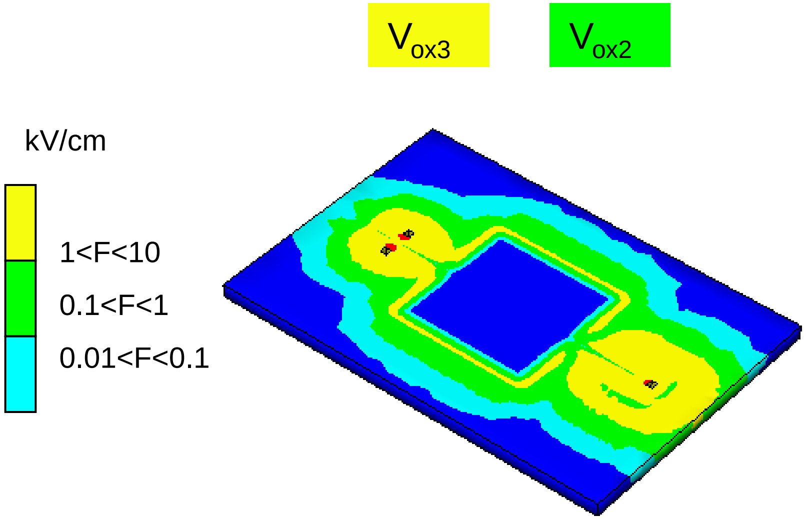
$$Y(F_{ox},T,r_o) = K^{-1}e^{(-A)}e^{(-K)}\sum_{m=0}^{\infty}\frac{A^m}{m!}\sum_{n=0}^{\infty}\sum_{l=m+n+1}^{\infty}\frac{K^l}{l!}$$

probability of an electron escaping recombination

$$K = \frac{qF_{ox}r_o}{kT}$$

$$A = \frac{r_c}{r_o}, r_c = \frac{q^2}{4\pi\varepsilon_{SiO_2}kT}$$

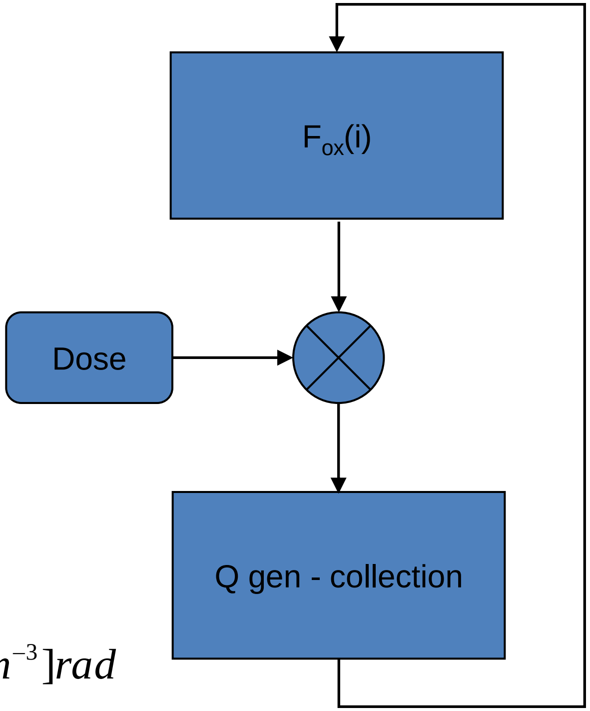
Proposed Monolithic In Vivo Dosimeter
Radiation sensor design



$$Q_{coll} = Q_{rad} \cdot \sum_i V_{oxi}(i) \cdot Y_{ox}(i) \quad ,i > 1$$

$$Q_{rad} = \frac{D \cdot \rho_{SiO_2}}{W_{SiO_2}} = \frac{6.24 \cdot 10^7 \left[MeV \cdot g^{-1}\right] \cdot 2.2 \left[g \cdot cm^{-3}\right]}{17 \left[eV\right]} \cong 8[\mu m^{-3}]rad$$

The collection of holes by FG generated in SiO_2 is a function of F_{ox}



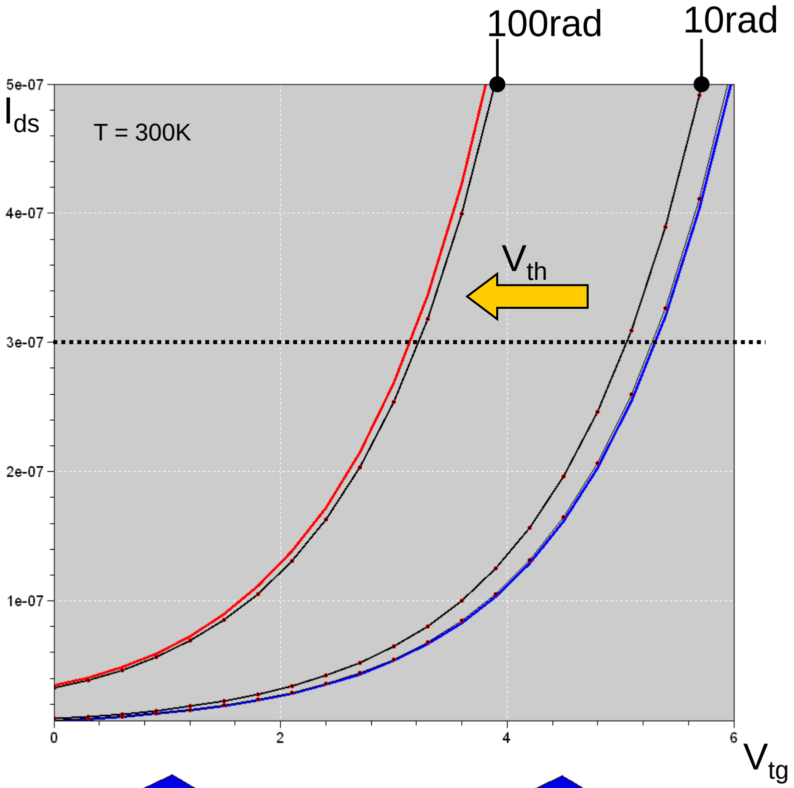
$F_{ox}(i)$

Dose

Q gen - collection

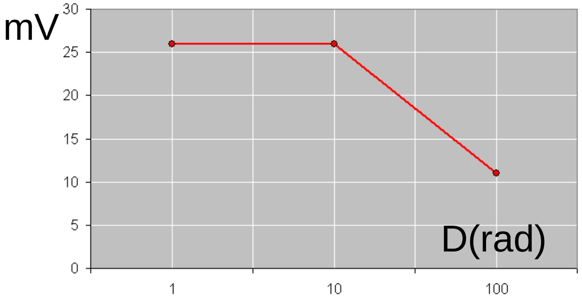
The F_{ox} is updated after new charge collection to estimate effect of decreasing FG charge

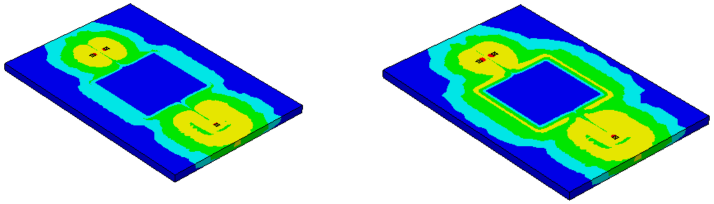
Proposed Monolithic In Vivo Dosimeter
Radiation sensor design



D	Vth @ Ids=0.3µA
0	5.307
1rad	5.281
10rad	5.056
100rad	3.214

D	Sensitivity (ΔVth/rad)@ Vds=3V
0	26mV
10rad	26mV
100rad	11mV



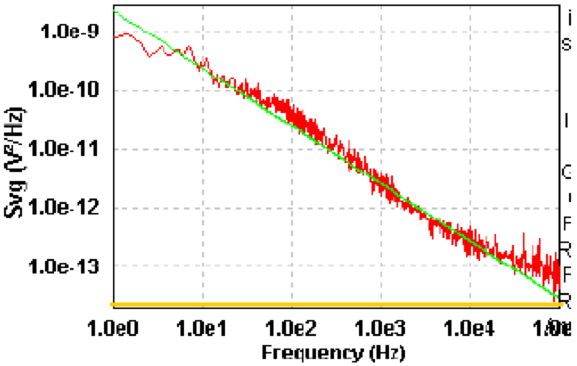


The sensitivity decreases as the FG discharges

Proposed Monolithic In Vivo Dosimeter
Radiation sensor design

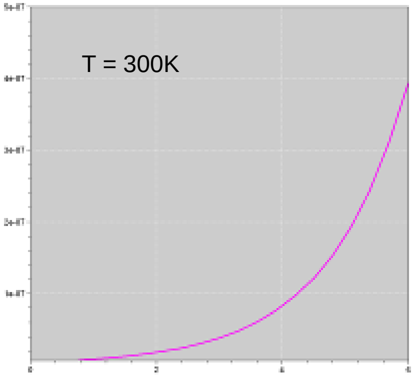
The gate referred noise of the device has estimated spectral density:

$$v^2_{noise} = 4kT\frac{2}{3}\frac{1}{g_m} + \frac{K_f}{WL}\frac{1}{f^{\alpha}} \cong 4.8e-14 + \frac{2.5e-9}{f^{0.8}} \Rightarrow \int_{1e-3}^{10} v_{noise} df \cong 330\,\mu Vrms$$



Typ. Flicker noise spectrum

W/L = 10/0.18



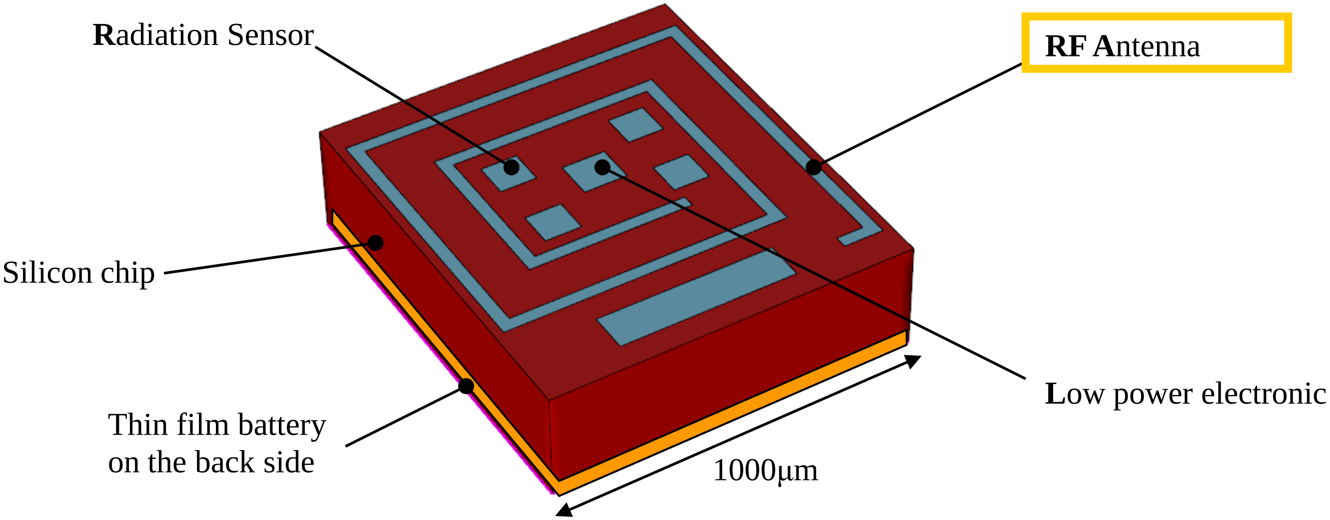
$g_m(V_{th}) \approx 2.3e\text{-}7A/V$

D	Sensitivity (ΔVth/rad)@ Vds=3V, T = 300K)	Max resolution (Rad)
0	26mV	0.0384
10rad	26mV	0.0384
100rad	11mV	0.091

Assuming a minimum readout time of 10 readings/sec over a period of 1hr and 3 times the RMS value as minimum detectable V_{th} change gives the resolution in rad of the device

- *G. Villani et al., 'Simulation of a Floating Gate Device in standard CMOS process for Dosimetry application', published on PoS(RD09)023*

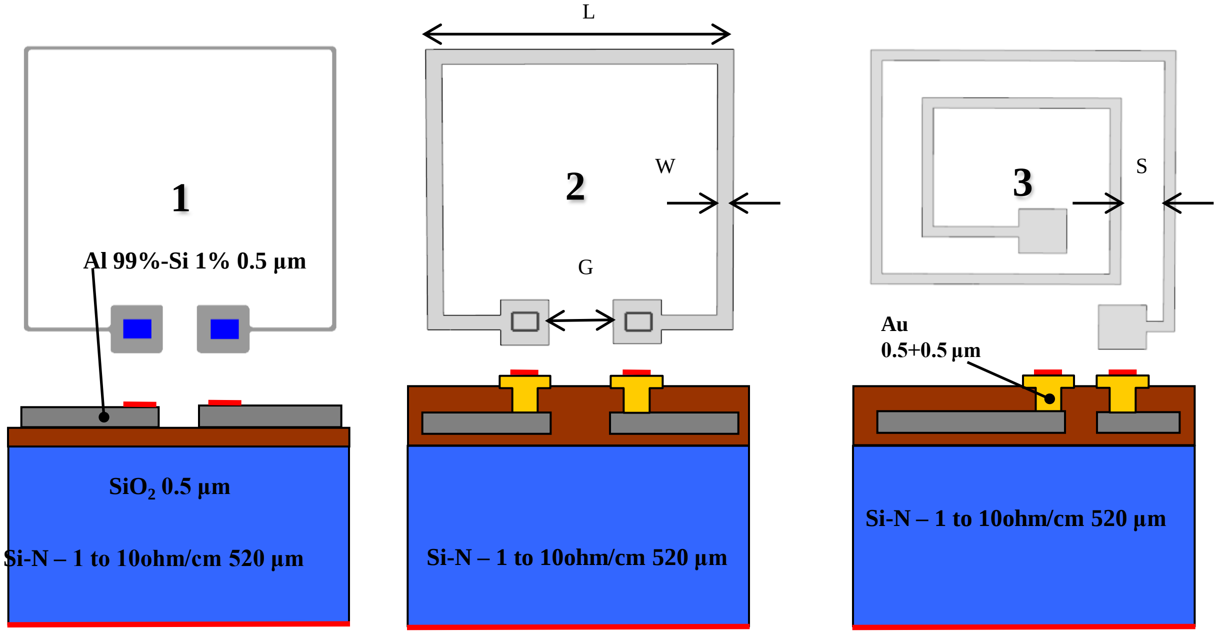
Proposed Monolithic In Vivo Dosimeter
RF transmission



Layout Example of the proposed monolithic IVD

- **Proposed integrated micro RF TX to transmit wirelessly information of dose of radiation**
- **Performance studies of integrated antennas on chip (ANTs)**

Proposed Monolithic In Vivo Dosimeter
RF antennas



Investigation of micro-antennas on chip – fabricated at MNTC STF RAL

Integrated antennas studies following a PoC funding from Innovations Ltd.

- **3 different layouts designed at RAL PPD**
- **Fabrication at MNTC STFC RAL**
- **Layout resembling those obtainable from CMOS foundry**

Proposed Monolithic In Vivo Dosimeter
RF antennas

Vector potential
$A = A(J, \mathbf{x})$

$$H = \frac{1}{\mu}\nabla \times A$$

$$E = \frac{1}{j \cdot \omega \cdot \varepsilon}\nabla \times H$$

$$S = \frac{1}{2}E \times H^*$$

$$P_{rad} = \lim_{r \to \infty}\int S \cdot r^2 \cdot \sin(\Theta)\, d\Theta d\Phi$$

$$\eta = \frac{R_{rad}}{R_{rad} + R_{loss}}$$

~ 1.7e-6

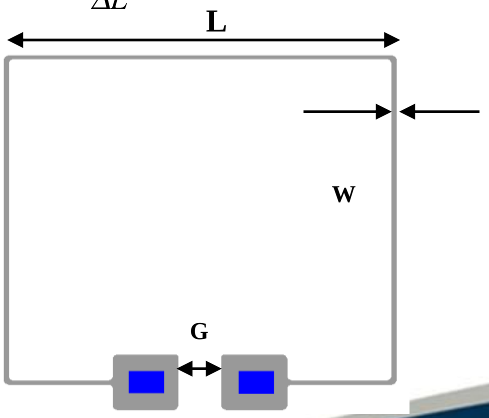
- **The performances of a layout are estimated from first principles, by solving ME using Maple , under some simplifying assumptions**
- **The efficiency of the antenna is defined as the ratio of radiation resistance over total resistance**
- **Skin effect negligible**
- **Resonant frequency of the layout estimated from TCAD simulations**

$$R_{rad} = \frac{10}{60}\frac{\Delta L^2 k^3}{\pi\, \varepsilon\, \omega}\left[\left(1+\frac{1}{10}k^2\Delta L^2\right)B^2 + \left(-2+\frac{3}{10}k^2\Delta L^2\right)B + \left(1+\frac{6}{10}k^2\Delta L^2\right)\right]$$

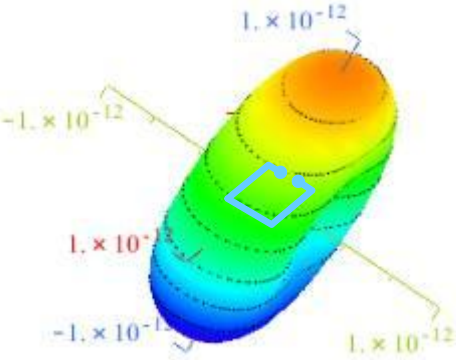
$$\Delta L = L - w$$

$$k = \frac{2\pi}{\lambda}$$

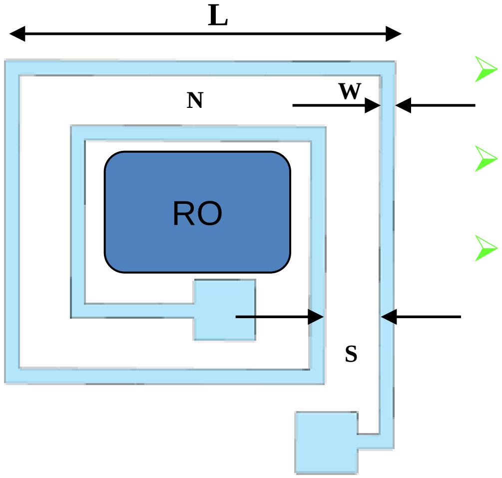
$$B = \frac{\Delta L - G}{\Delta L}$$



ANT1 I_{in} = 1 mA



Proposed Monolithic In Vivo Dosimeter
RF antennas



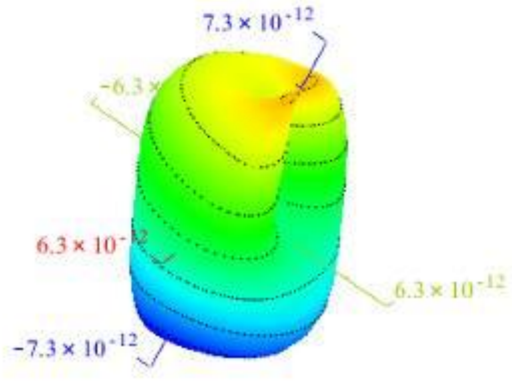
- **Increasing the number of loops increases the radiation resistance, but also the ohmic losses**
- **Also a minimum space within the ANT is required to accommodate the readout**
- **An optimum layout (N, S, W) guarantees the highest efficiency η**

$$R_{rad} = M_1 N^5 + M_2 N^4 + M_3 N^3 + M_4 N^2 + M_5 N$$

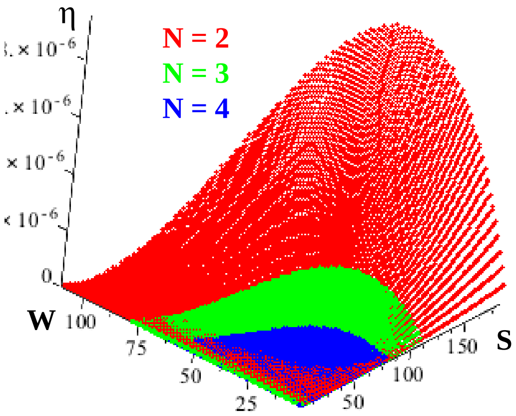
$$M_1 = \frac{8 a^4 k^5}{15 \pi \omega \varepsilon}$$

$$M_2 = -\frac{a^4 k^5}{3 \pi \omega \varepsilon} \left(\frac{7}{2} + 4 a^{-1} \Delta L \right)$$

⋮

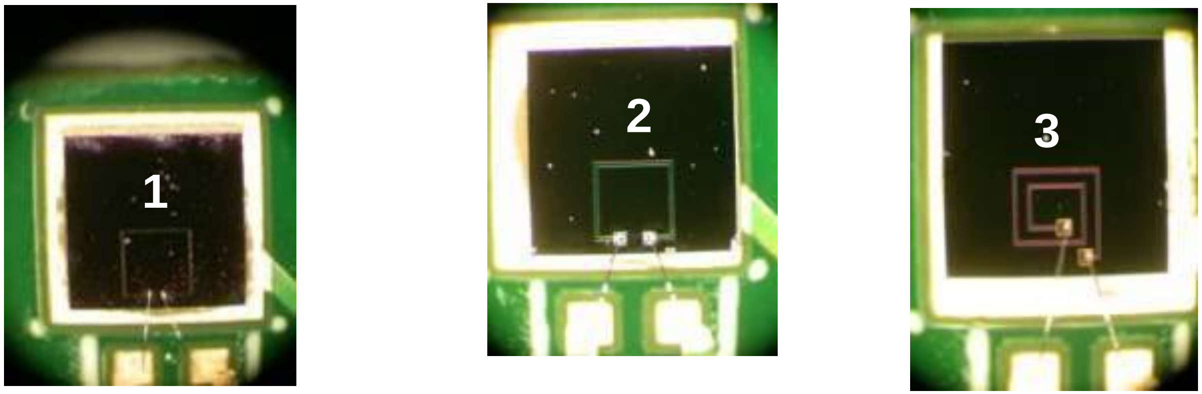


ANT3 I_{in} = 1 mA



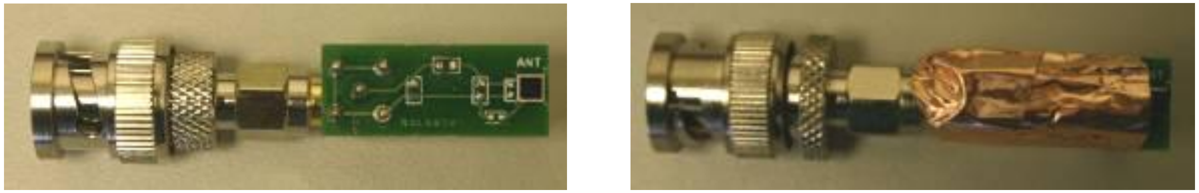
N = 2	S = 125; W = 35; **η = 9.4e-6**
N = 3	S = 75; W = 25; **η = 2.4e-6**
N = 4	S = 54; W = 19; **η = 9.4e-7**

Proposed Monolithic In Vivo Dosimeter
RF antennas



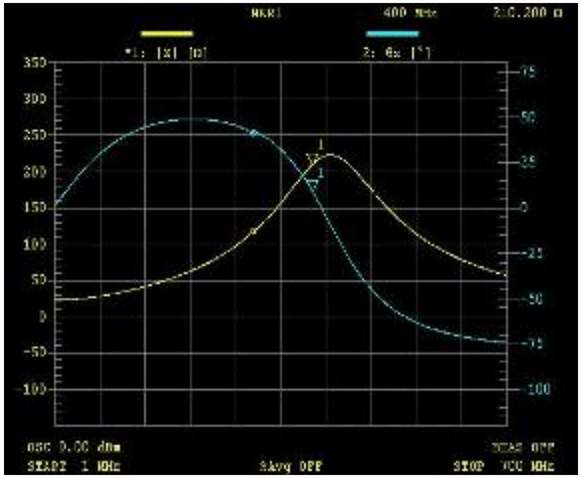
ANTs microphotographs

- **After design and fabrication at MNTC, the ANTs are diced to 2.54 x 2.54 mm^2 , glued onto a PCB and wire bonded for testing**

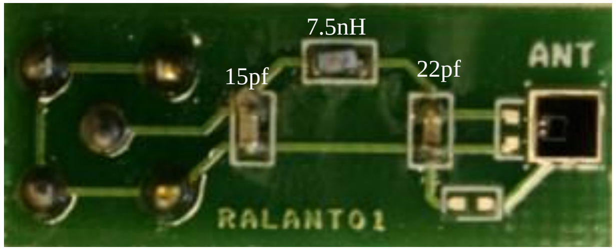


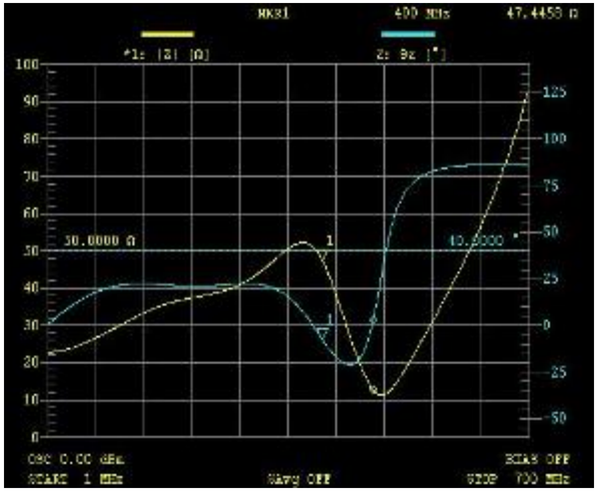
- **A passive network on the PCB allows impedance matching for maximum power transfer**
- **A grounded copper foil around the PCB leaves only the ANT chip exposed during the RF test**

Proposed Monolithic In Vivo Dosimeter
RF antennas



ANT2 Impedance plot unmatched

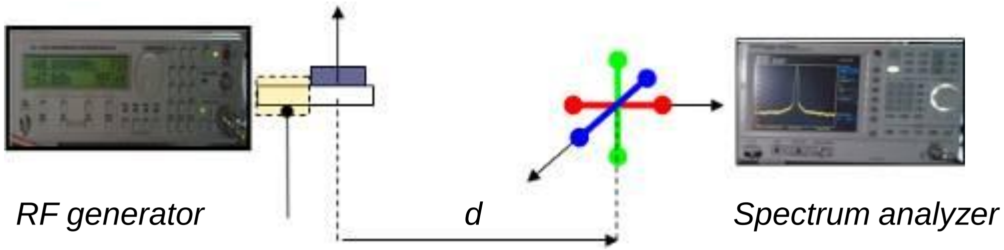


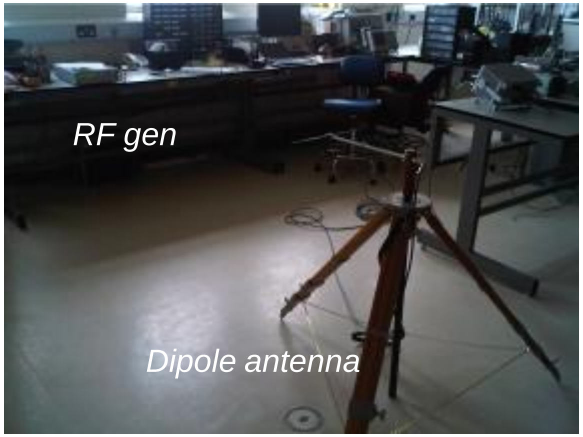


ANT2 Impedance plot matched

- The impedance matching for maximum power transfer @ 400 MHz is obtained using an Agilent E4991A analyzer (on loan)
- Problems of too high impedance of ANT1 (oxidation of exposed Al tracks)

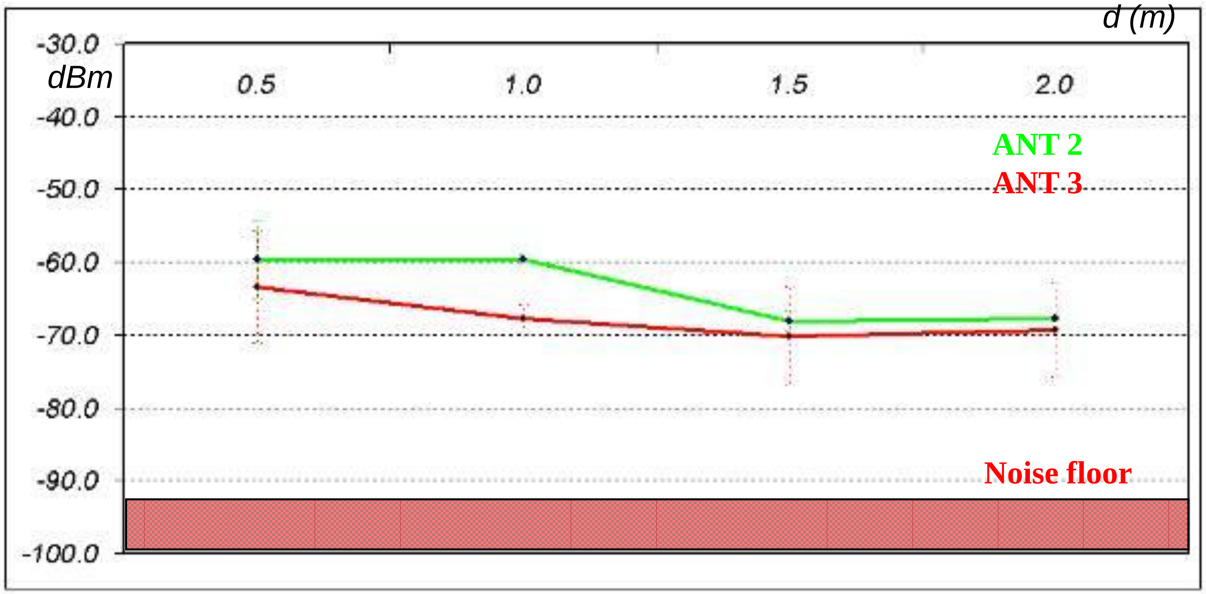
Proposed Monolithic In Vivo Dosimeter
RF antennas





- **The RF test consists of measuring the signal received by a spectrum analyzer coupled to a dipole antenna when driving the ANT with a RF generator**
- **Measurements of signal strength vs. distance and relative orientation for each ANT**

Proposed Monolithic In Vivo Dosimeter
RF antennas



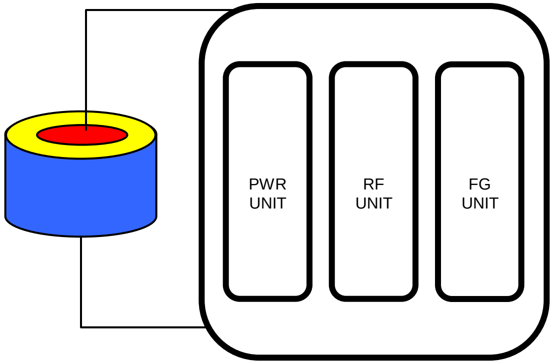
Pin 0 dBm
F = 402 MHz
BW SA = 10 kHz

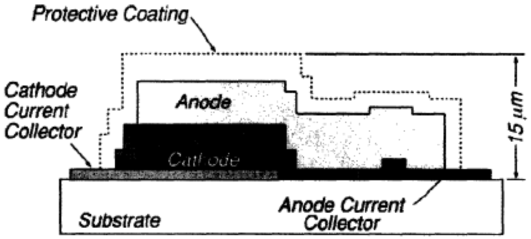
The plot of measured average signal for ANTs devices (layouts 2 & 3) vs. distance. Input power 0 dBm.
For each ANT the signal is averaged over the three different orientations along the Cartesian axes of the receiving dipole antenna and for two different orientations of the ANT (loop magnetic moment pointing perpendicular and parallel to ground).

Proposed Monolithic In Vivo Dosimeter Powering

Option A:

Embedded power source

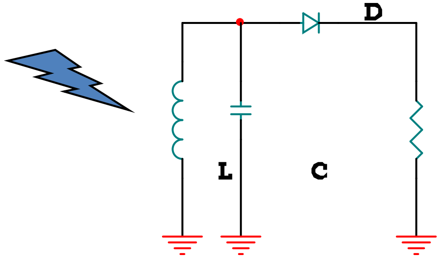




- Thin film batteries of approx 50 µAh/cm^2 fabricated
- They could be attached to the back of the chip
- Collaboration with Brunel Energy group

Option B:

External RF field to power the system



- It depends on the power requirements of the integrated IVD
- Maybe an option at close distance

Proposed Monolithic In Vivo Dosimeter collaboration

Technical collaborations:

☐ **STFC RAL PPD:** *project leading, overall design, testing*

☐ **TOWER semiconductor foundry:** *device fabrication*

☐ **Churchill Hospital Oxford:** *access to radiotherapy facilities, clinical support*

☐ **Bologna University/INFN:** *RF design, testing*

☐ **Brunel University:** *PhD student, testing, design*

☐ **CMRP**, University of Wollongong, Australia: *technical advice*

Financial support and funding for preliminary work:

☐ **STFC Innovations Ltd**

Monolithic In Vivo Dosimeter
CLASP proposal 2010

Objectives of the proposal:

- **Delivery of an industry ready demonstrator to implement a novel implantable In Vivo Dosimeter for radiotherapy treatments**

- **The novel devices for In Vivo Dosimetry will be designed at STFC RAL PPD, which will lead the project, in collaboration with Brunel University, University of Bologna and radiotherapy centres (Churchill Hospital, Oxford). The fabrication will be performed by Tower Semiconductor, Israel**

- **In parallel with the technical development, identification of suitable commercial partners will be pursued**

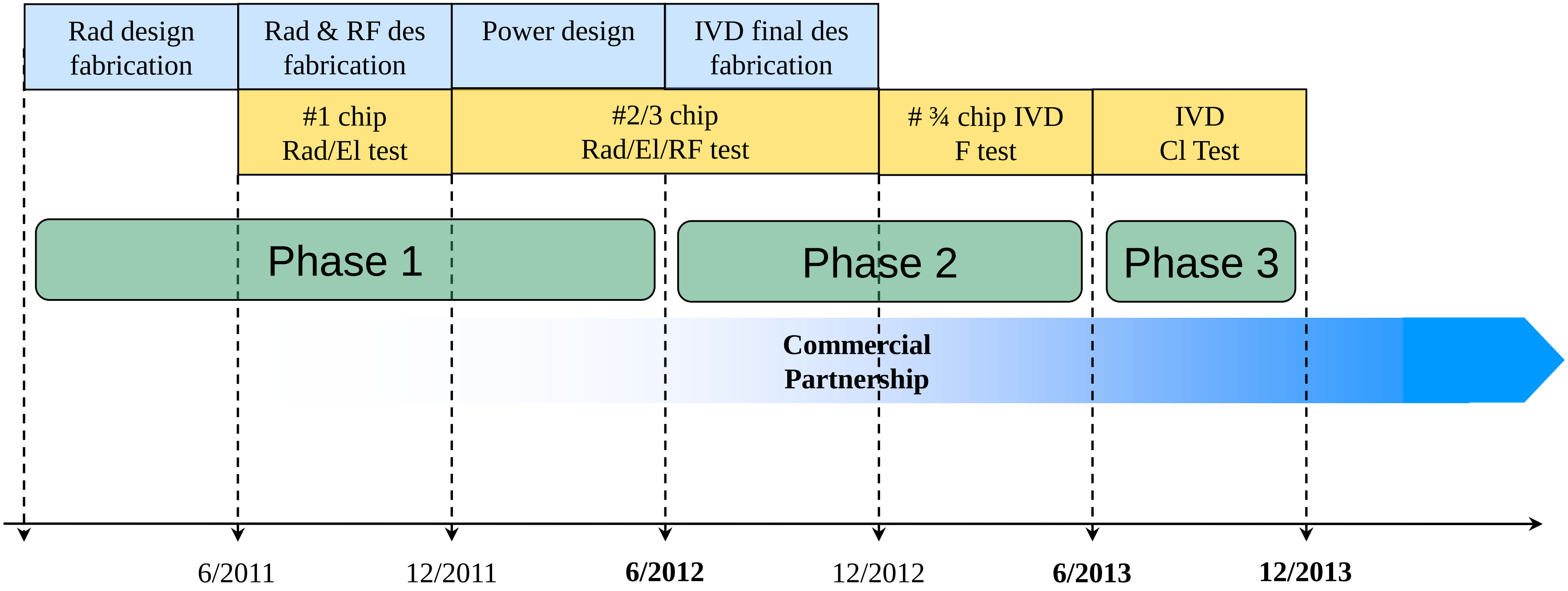
- **If successful further work will be necessary to develop a medical device (biocompatible coating, health and risk assessment etc.)**

- **total amount requested:**

total amount requested:	**478,281.81GBP (FEC)**
* **device fabrication/equipment :**	**~300,000**
* **staff :**	**~130,000**
* **other recurrent (travel, facilities access) :**	**~ 45,000**

Proposed Monolithic In Vivo Dosimeter Gantt chart

Initial Project's phases



Rad design fabrication

Rad & RF des fabrication

Power design

IVD final des fabrication

#1 chip Rad/El test

#2/3 chip Rad/El/RF test

¾ chip IVD F test

IVD Cl Test

Phase 1

Phase 2

Phase 3

Commercial Partnership

6/2011

12/2011

6/2012

12/2012

6/2013

12/2013

Monolithic In Vivo Dosimeter
CLASP proposal 2010

CLASP reply to the proposal:

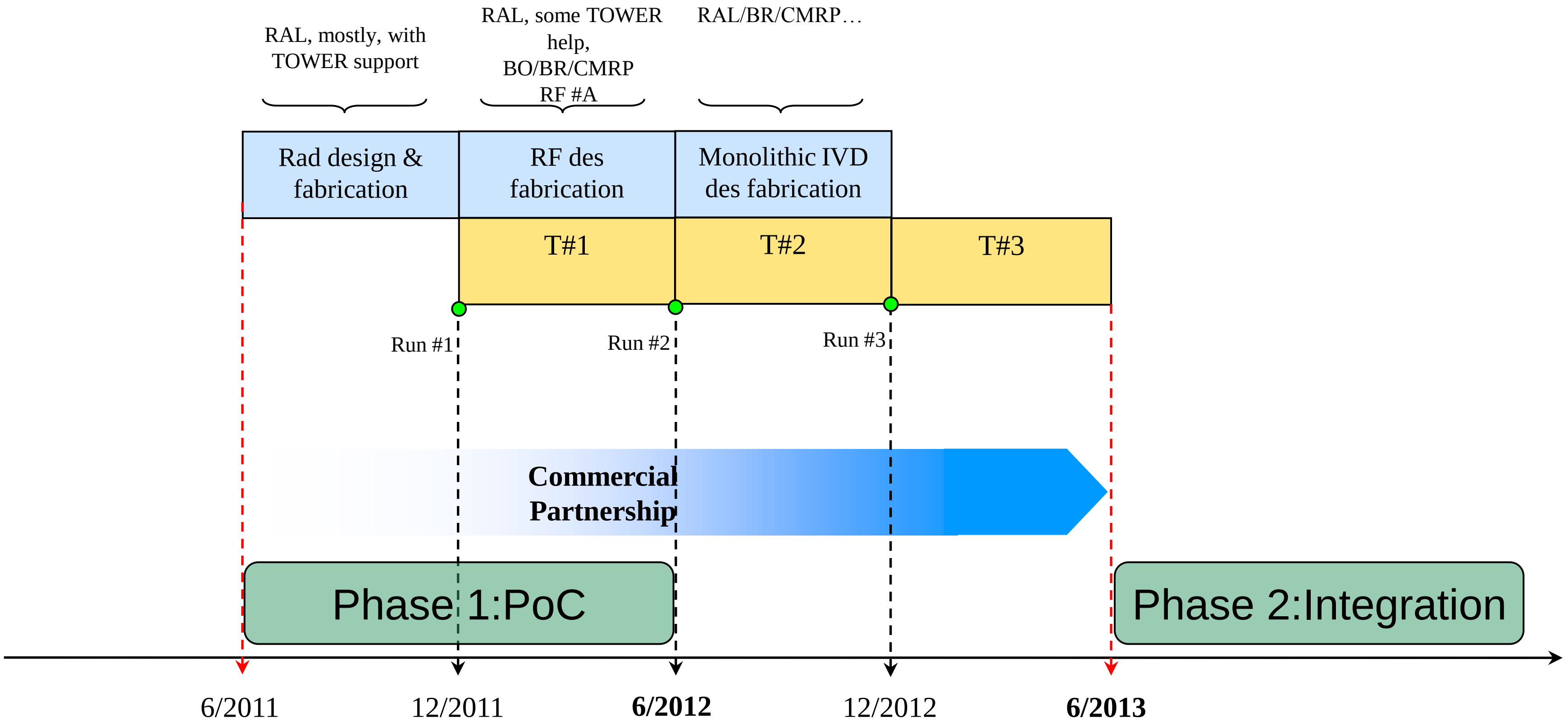
- ☐ **Recommended for support but at reduced funding (~ 200kGBP)** ✓
- ☐ **justify the need for non UK foundry** ✓
- ☐ **Identification of a commercial partner** …

Reply to CLASP by first week of April ,final response expected soon after.

Proposed Monolithic In Vivo Dosimeter Gantt chart

Project's phases – new version : 2 years project

NO embedded power



RAL, mostly, with TOWER support

RAL, some TOWER help, BO/BR/CMRP RF #A

RAL/BR/CMRP…

Rad design & fabrication

RF des fabrication

Monolithic IVD des fabrication

T#1

T#2

T#3

Run #1

Run #2

Run #3

Commercial Partnership

Phase 1:PoC

Phase 2:Integration

6/2011

12/2011

6/2012

12/2012

6/2013

T#1: Run 1 characterization
FG programming, RAD sensitivity

T#2: Run 2 characterization
Oscillations @MICS, RF range vs. power

T#3: Run 3 characterization
Wireless rad sensing

3 MP runs, 180nm
~100k£ (see TOWER quotation)

Monolithic In Vivo Dosimeter

Conclusions

- **Clinical need for In Vivo Dosimetry, stemming from stringent QA in advanced radiotherapy methods, is supported by evidence and requires advanced technological solutions**

- **Currently only one implantable IVD available (US); this market is expected to grow significantly over the next years as radiotherapy treatments will become even more common**

- **In line with a Knowledge Exchange approach, initial studies have been carried out by STFC RAL PPD with collaborating institutes that suggest that a novel implantable IVD is technologically feasible**

- **The proposed novel implantable IVD has been submitted to CLASP which recommended it for further support, subjected to constraints**

- **Estimated starting date this summer**

Backup slides:
Radiation sensors

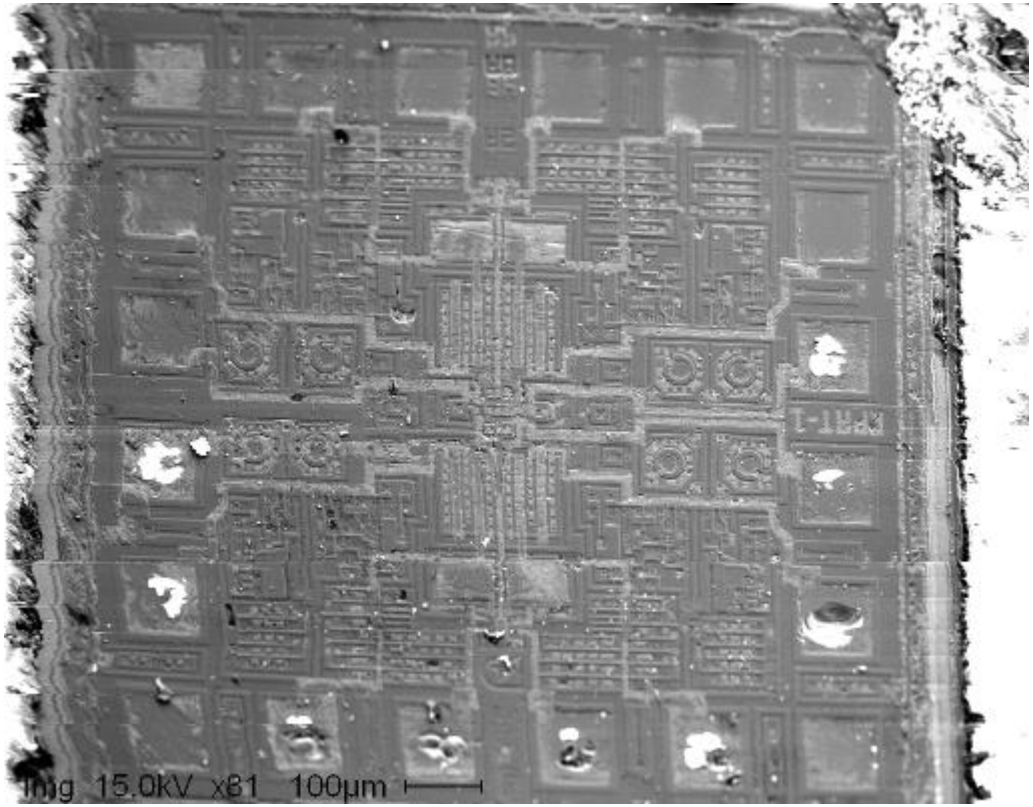
'In-vivo proton beam range verification using implantable MOSFET dosimeters' *Hsiao-Ming Lu FHB Proton Therapy Center, Massachusetts General Hospital, Boston USA*

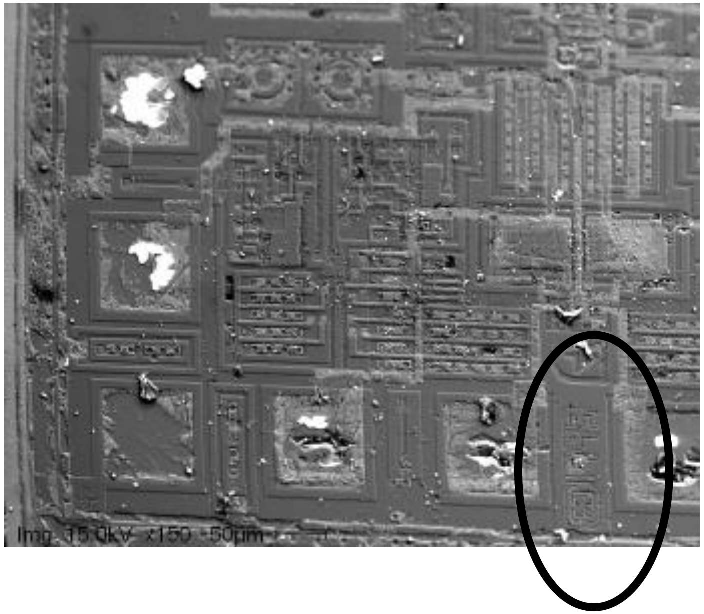
..First tests of Sicel IVD for proton therapy are encouraging, but a limitation comes from the size of the device: a more point-like measurement would be greatly beneficial (private conversation at SSD16).

- ❑ **Implantable IVD from *Sicel*: FDA clearance in 2009 for use in breast and prostate radio treatment (clinical studies available)**
- ❑ **Hybrid design: separate RADFET, readout and RF**
- ❑ **Power delivered via an external RF field, ~15cm range**
- ❑ **20 to 50mV/Gy sensitivity up to 80Gy (non linear, individual device calibration, in the MeV range)**
- ❑ **Fade effect approx 2%/20mins**
- ❑ **1cGy LSB, Total device errors ~ 5%, 2σ**
- ❑ **Operating frequency 133kHz, operating voltage of the implant 5V, backscattering technique (RFID tags)**

- An Implantable MOSFET Dosimeter for the Measurement of Radiation Dose in Tissue During Cancer Therapy ,
IEEE Sensor Journal, Vol. 8, No.1, Jan 08

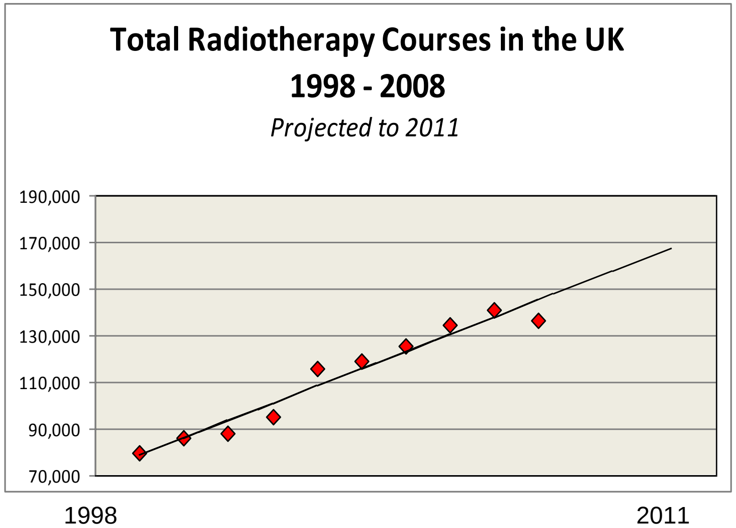
In Vivo Dosimetry
SEM pics





In Vivo Dosimetry market analysis

	UK(2007/2008)		USA(2004)	
Total Number of Radiotherapy patients (2007/ 2008)	136150		1000000	
Number of Dosimeters per Patient	3		3	
Dosimeter Cost	£ 15.00		£ 15.00	
IVD Percentage of Cases	50%	20%	50%	20%
TOTAL SALES	**£ 3,063,375**	**£ 1,225,350**	**£ 22,500,000**	**£ 9,000,000**



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