Carbon Nanotubes Field Emission X-ray for Research and Clinical Application in Radiation Oncology

Sha X. Chang
University of North Carolina at Chapel Hill

THE UNIVERSITY *of* NORTH CAROLINA *at* CHAPEL HILL

Disclosure:

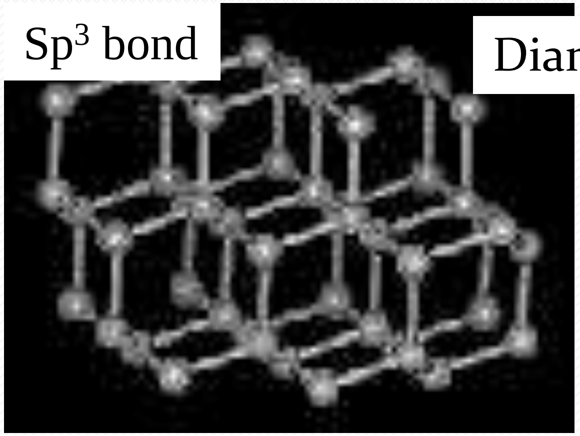
- Co-inventor of patents on field emission cathode and/or distributed source based x-ray technologies presented here.

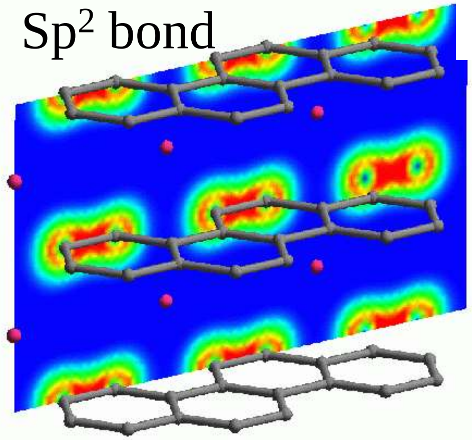
Leaning Objectives:

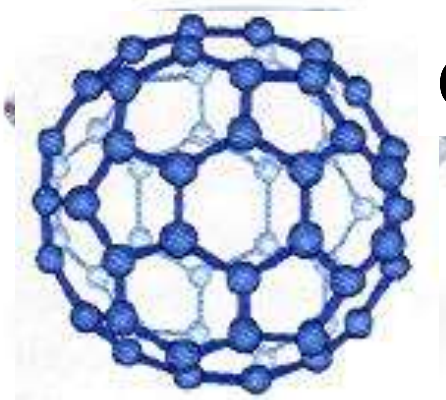
- Understand the principle of carbon nanotube field emission x-ray technology
- Understand the two major advantages of this new x-ray technology - <u>ultra-high temporal resolution</u> and <u>flexibility in distributed source design</u>
- Understand that carbon nanotube field emission x-ray technology has opened up new horizons for novel imaging and therapy device development.

Carbon Nanotubes (CNT)

Different forms of carbon



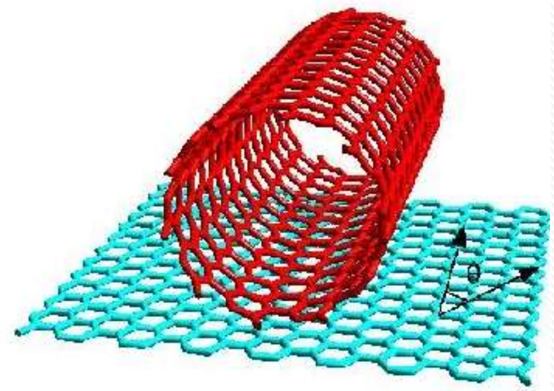


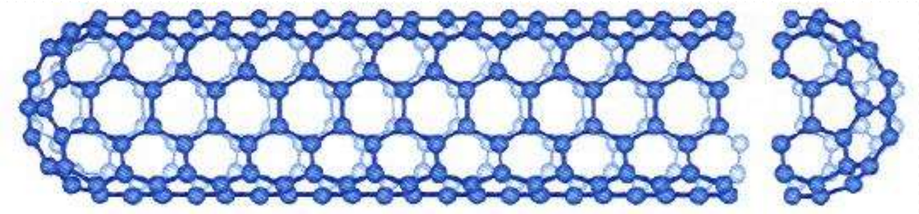


C_{60} "bucky-ball"

- A hollow sphere with 60 carbon atoms
- ~$1x10^{-9}$ m (1nm) in diameter
- (discovered in 1985, Nobel Prize, 1996)

Carbon nanotube: newest form of carbon





(1-50nm in dia., ~1-10μm long graphene tube)

History

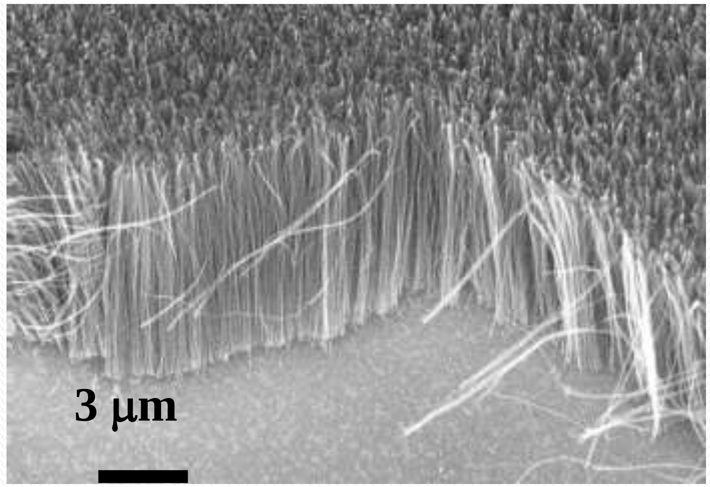
first observed in electron microscope study by Sumio Iijima

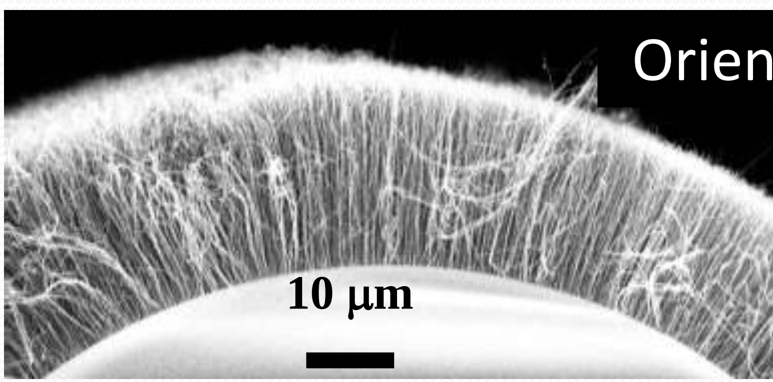
(NEC) in 1991

Unique properties

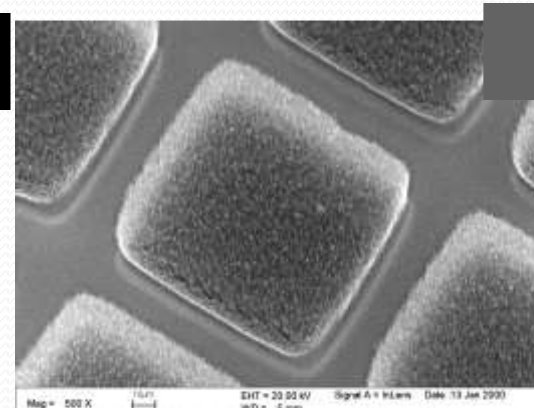
- mechanically strong
- chemically inert
- high thermal conductivity
- high electrical conductivity
- **Excellent electron field emitters**

Controlled and flexible formations of carbon nanotube patterns





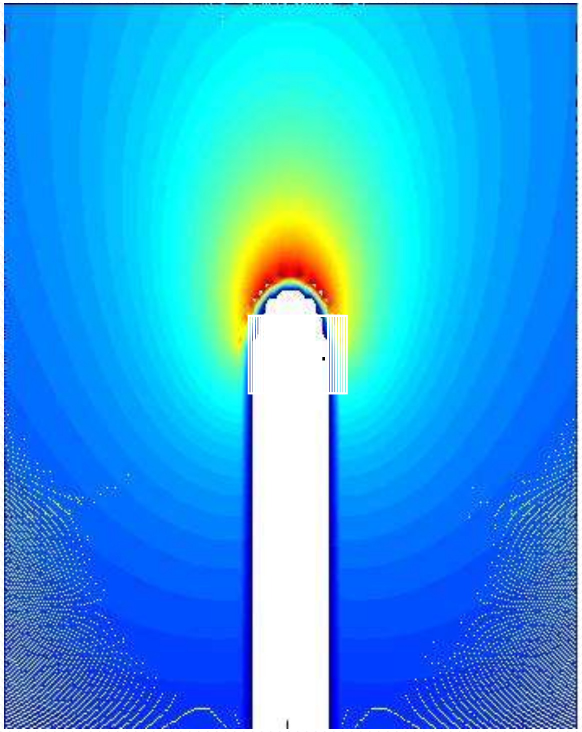
Orientation

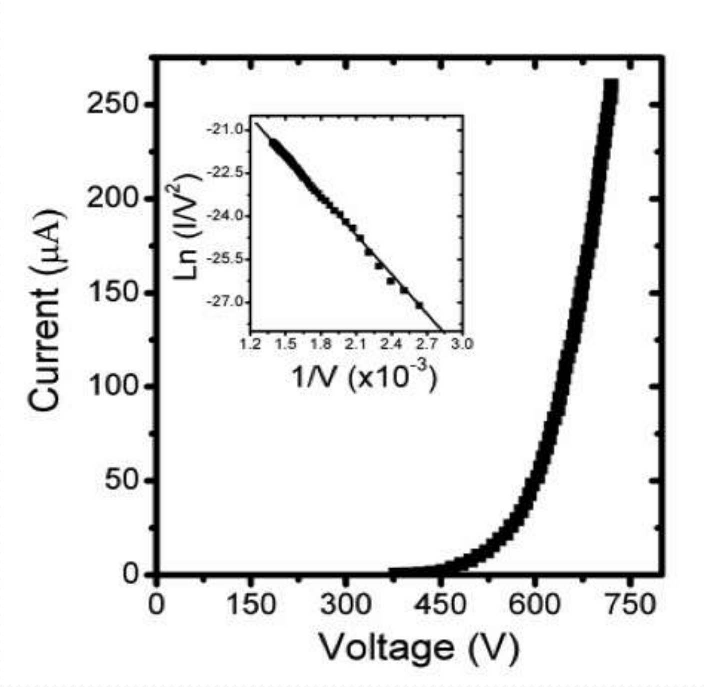


Pattern

Field Emission - cold cathode

Carbon Nanotube (CNT) field emission (cold cathode)





Electron emission

by E field not by heat.

Cold and hot cathode electron emission

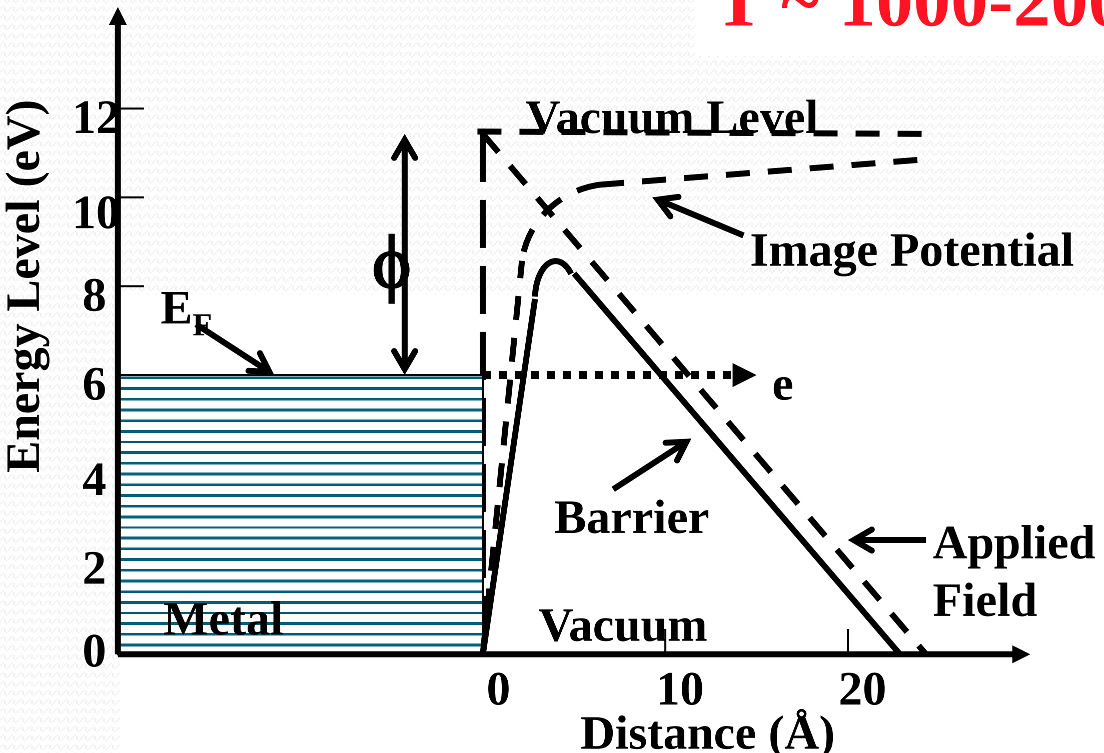
Electron field emission:

$I = a\mathbf{V}^2\exp(-b\Phi^{3/2}/\beta\mathbf{V})$

Thermionic emission:

$J = 120T^2 e^{-\phi/kT}$ [A/cm²]

T ~ 1000-2000ºC



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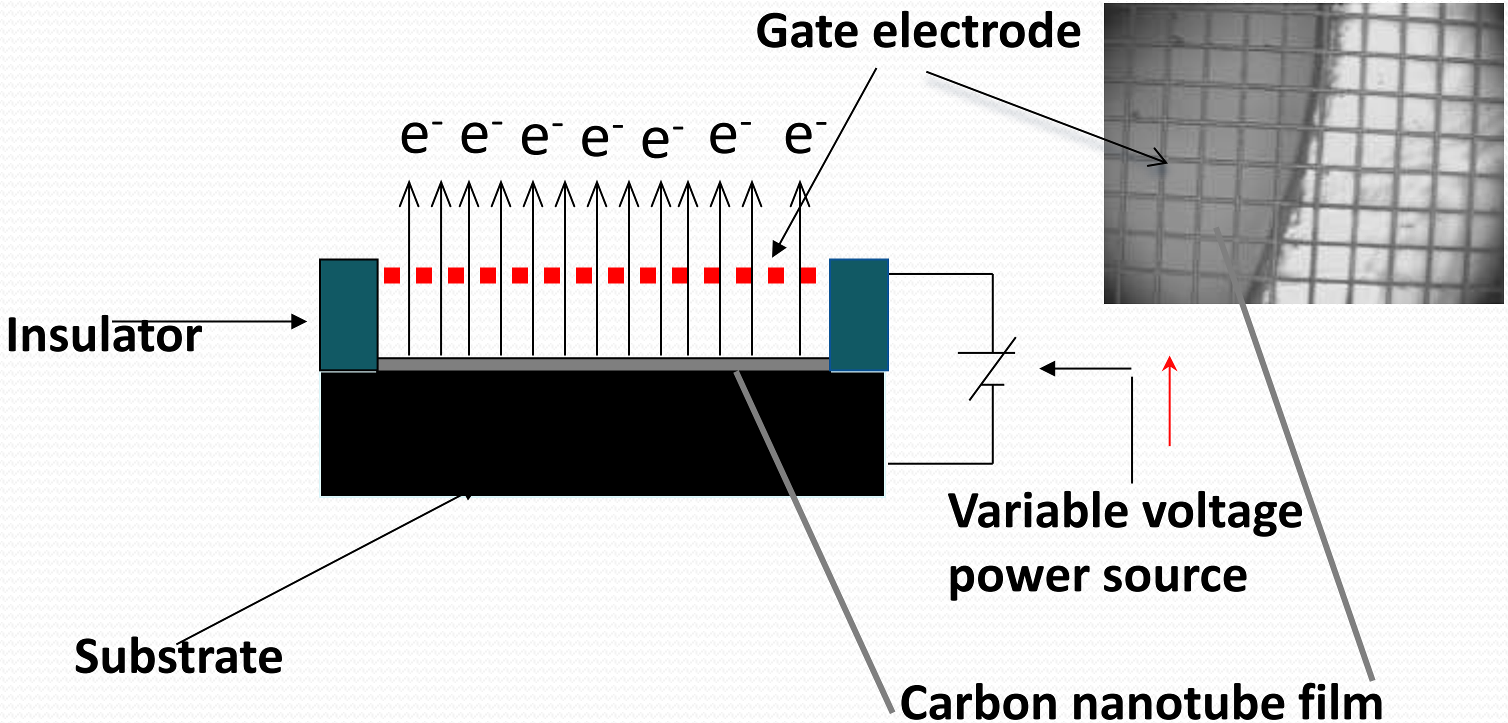
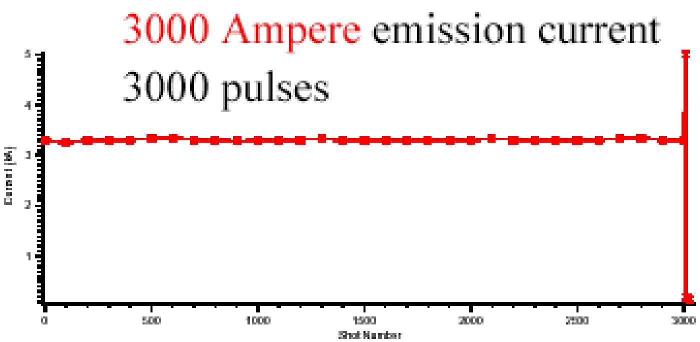
Basic CNT cathode structure



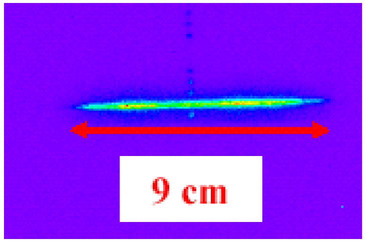
X-ray & β-ray on chip technology

Spontaneous control of x-ray production

High emission current

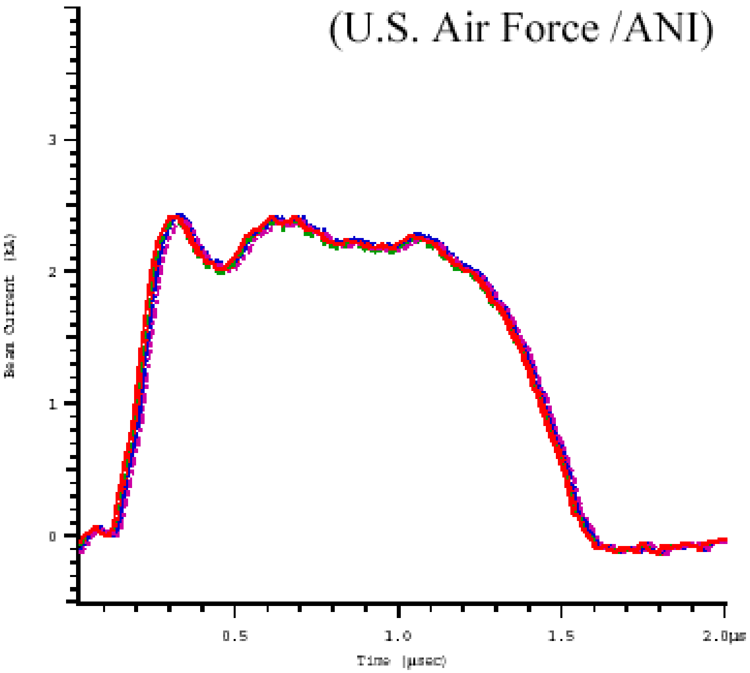


Uniformity at 2000 Ampere emission current at 220 kV



ANI- Air Force

8 cm diameter cathode
2000A peak emission current
µsec pulses width



Advantages of CNT cathodes

Hot vs. cold cathode x-ray technology

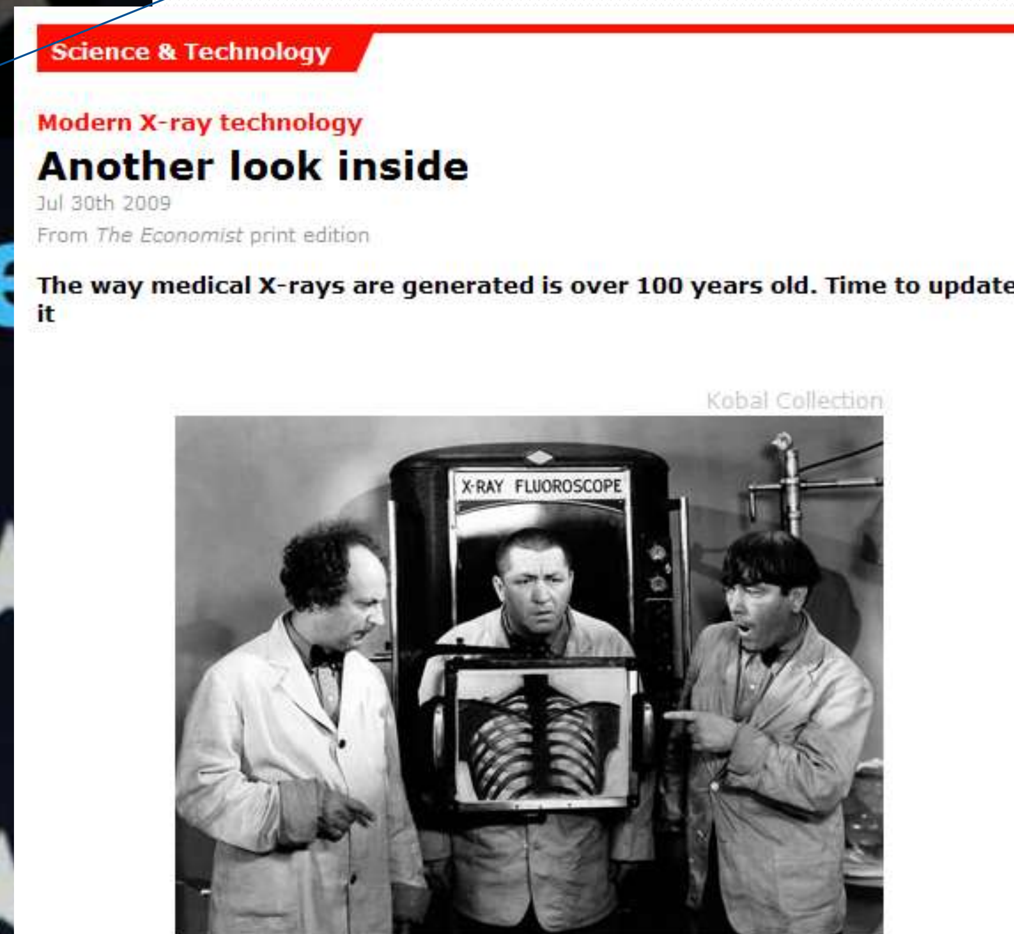
Cold Cathode	Hot cathode
High temporal resolution	
Distributed source design	
	Mature technology
	Readily available
Lower energy consumption	

CNT-Field Emission X-ray Technologies developed by our multidisciplinary group in collaboration with industry in the past decade

- Imaging
  - X-rays
  - Micro-CT
  - Nanotube Stationary Tomosynthesis (IGRT)
  - Stationary Breast tomosynthesis
- Therapy
  - Single cell and tissue irradiator
  - Small animal RT
  - Compact microbeam radiation therapy technology

Media coverage of our work (Nature News, The Economist, Science and Technology, German Public Radio,..)

“ Reinventing the X-ray”



Science & Technology

Modern X-ray technology

Another look inside

Jul 30th 2009

From *The Economist* print edition

The way medical X-rays are generated is over 100 years old. Time to update it

Kobal Collection

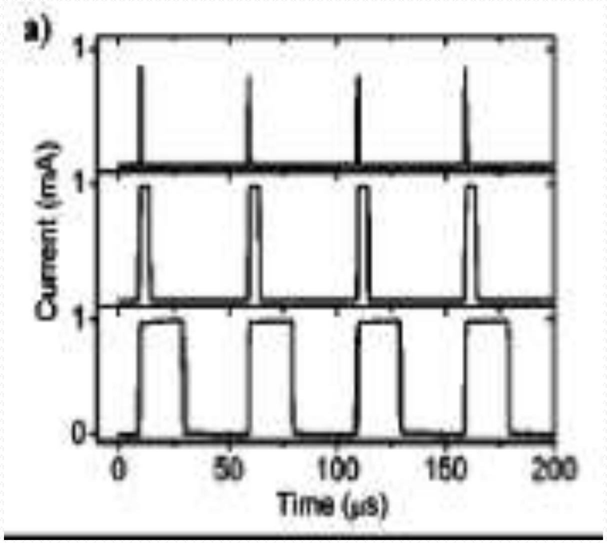
First CNT x-ray medical image (2002)

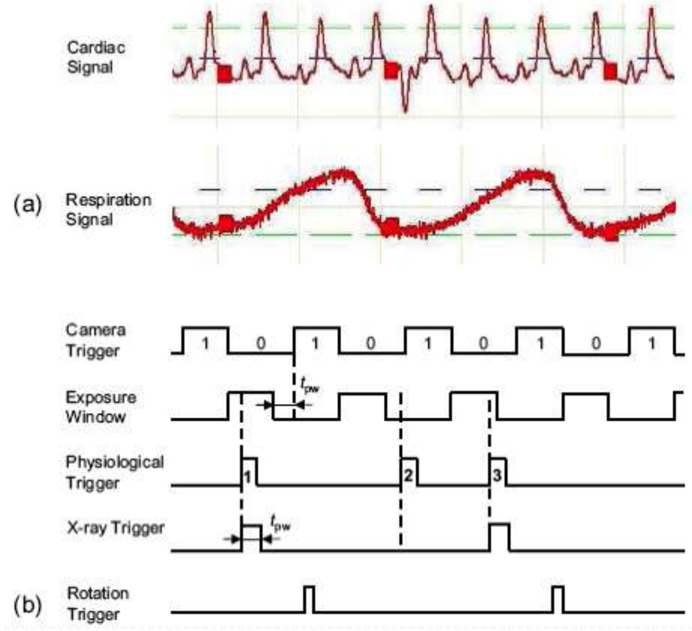
G. Z. Yue et al, Appl. Phys. Lett. 81, 355, 2002

"One of the highlights in physics research"
- Physics News in 2002.

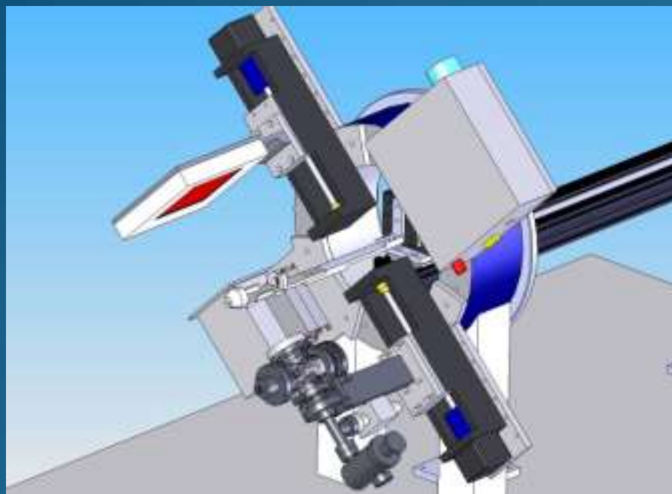
Important Point 1:

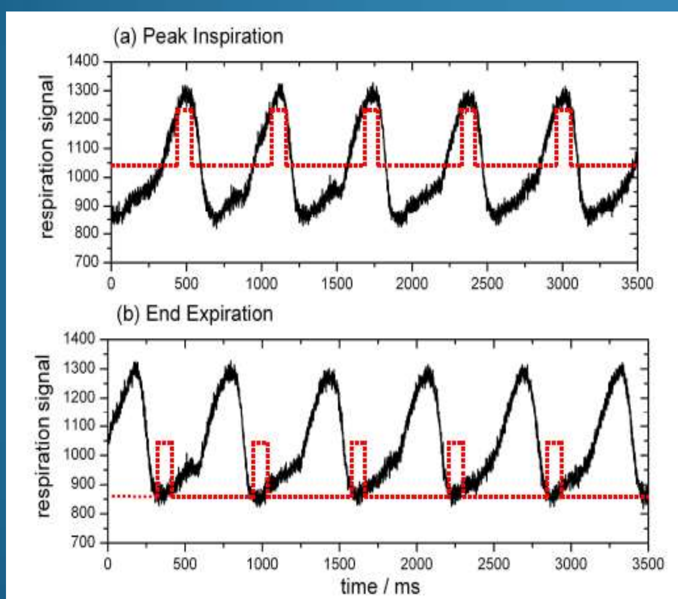
CNT cold cathode x-ray source has intrinsic high temporal resolution and can be gated by arbitrary signal (w/o dark current).

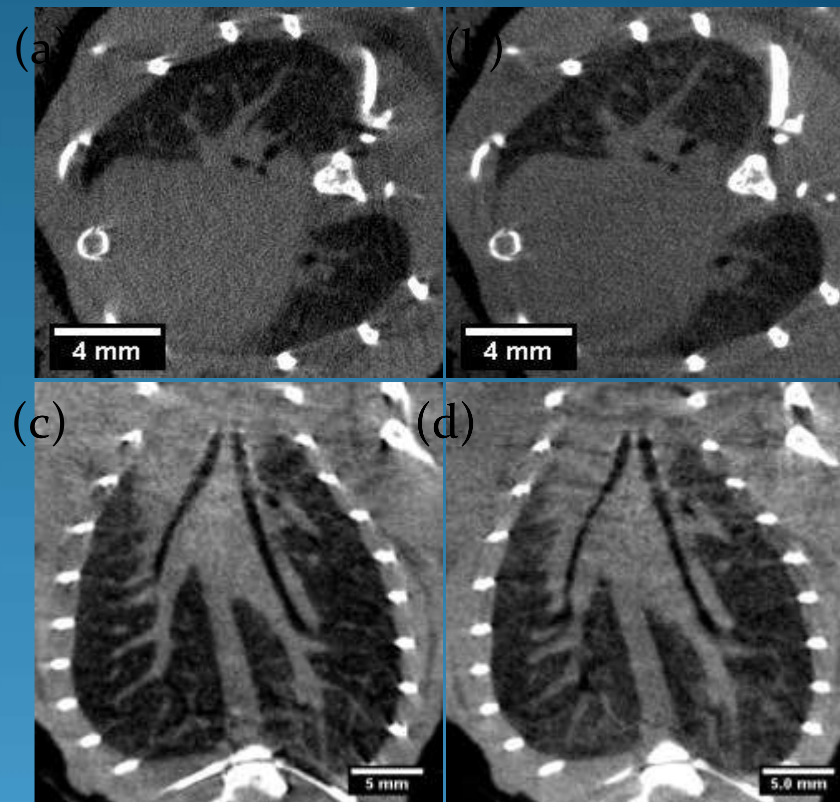


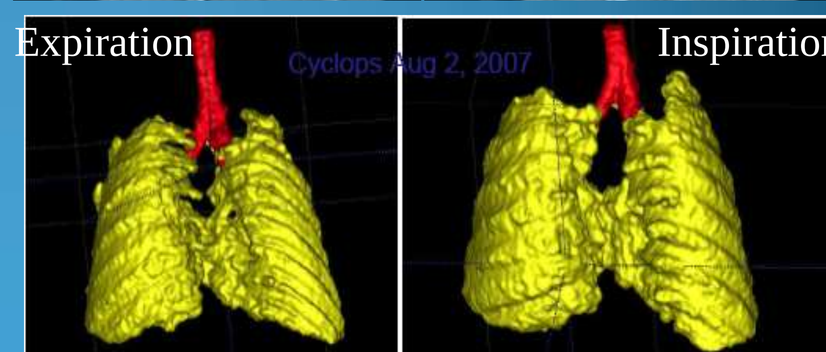


CNT micro-CT (Respiratory-gated)



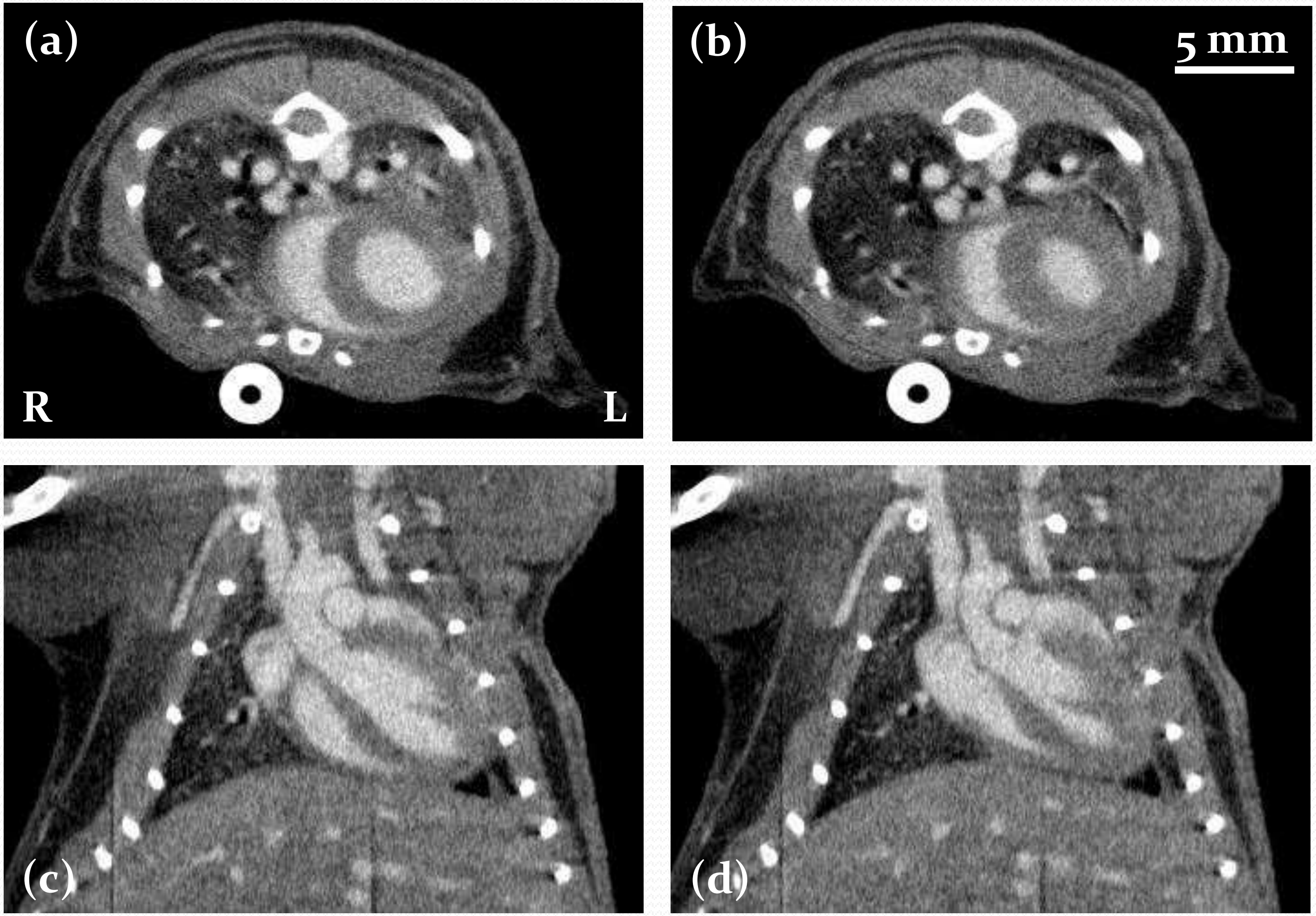






G. Cao et al. SPIE Medical Imaging 2008; G. Cao et al. Phys Med Biol 2009

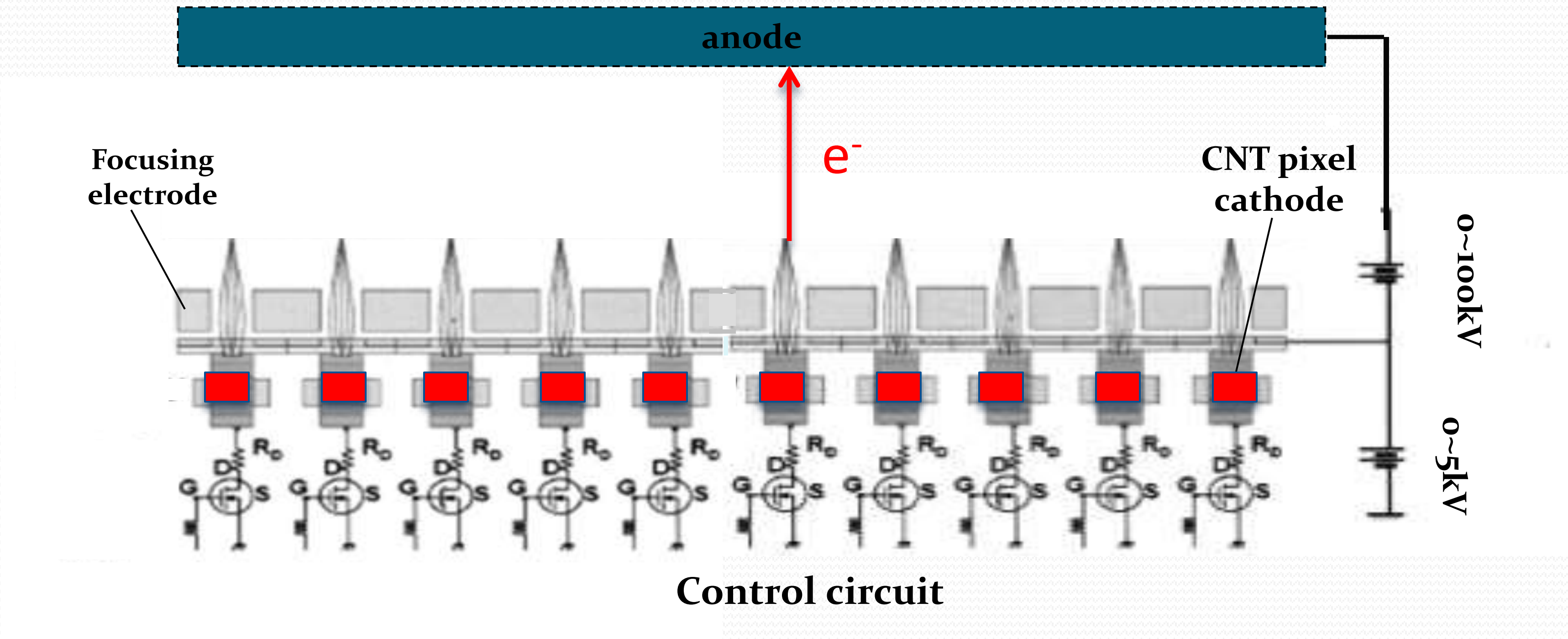
CNT micro-CT: mouse **cardiac-gated** CT



Yueh Lee (UNC) unpublished

Important Point 2:

CNT cathode x-ray technology is ideal for distributed source design



Multi-pixel x-ray source technologies

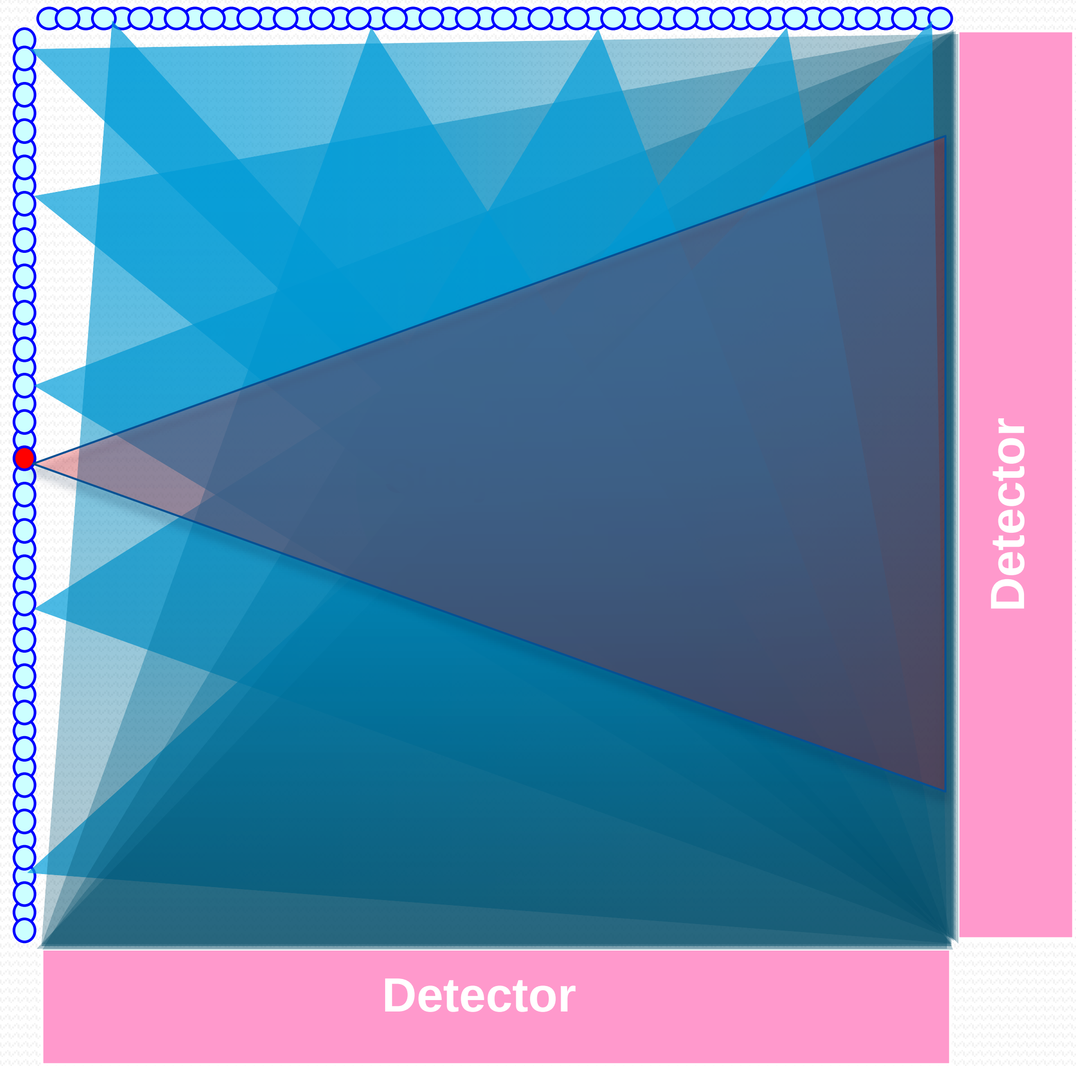
Stationary CT

- Stationary Tomosynthesis (breast and IGRT)

- Micro-RT

- Single cell irradiator

- Microbeam



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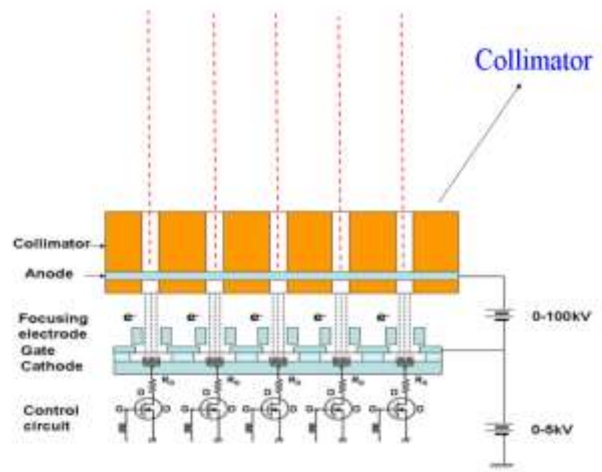
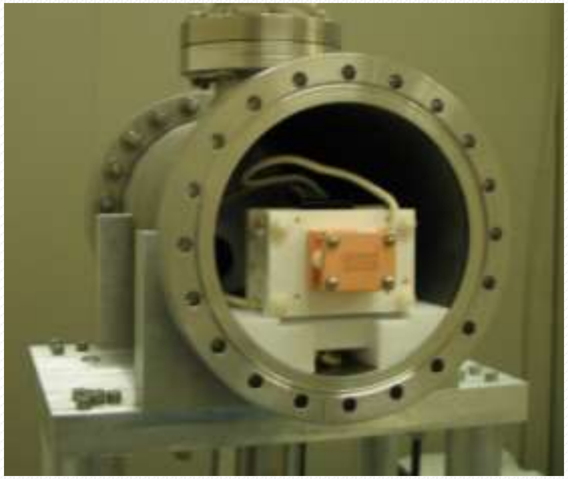
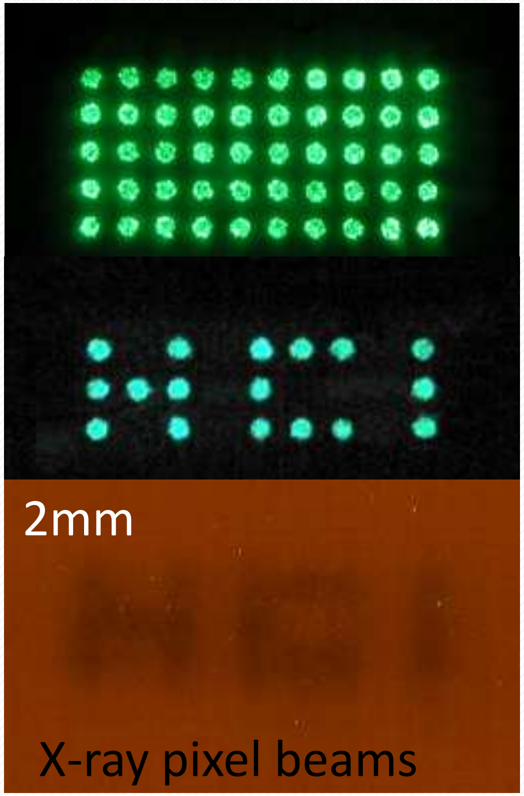
multi-pixel x-ray CNT micro-RT





Electron pixel beams

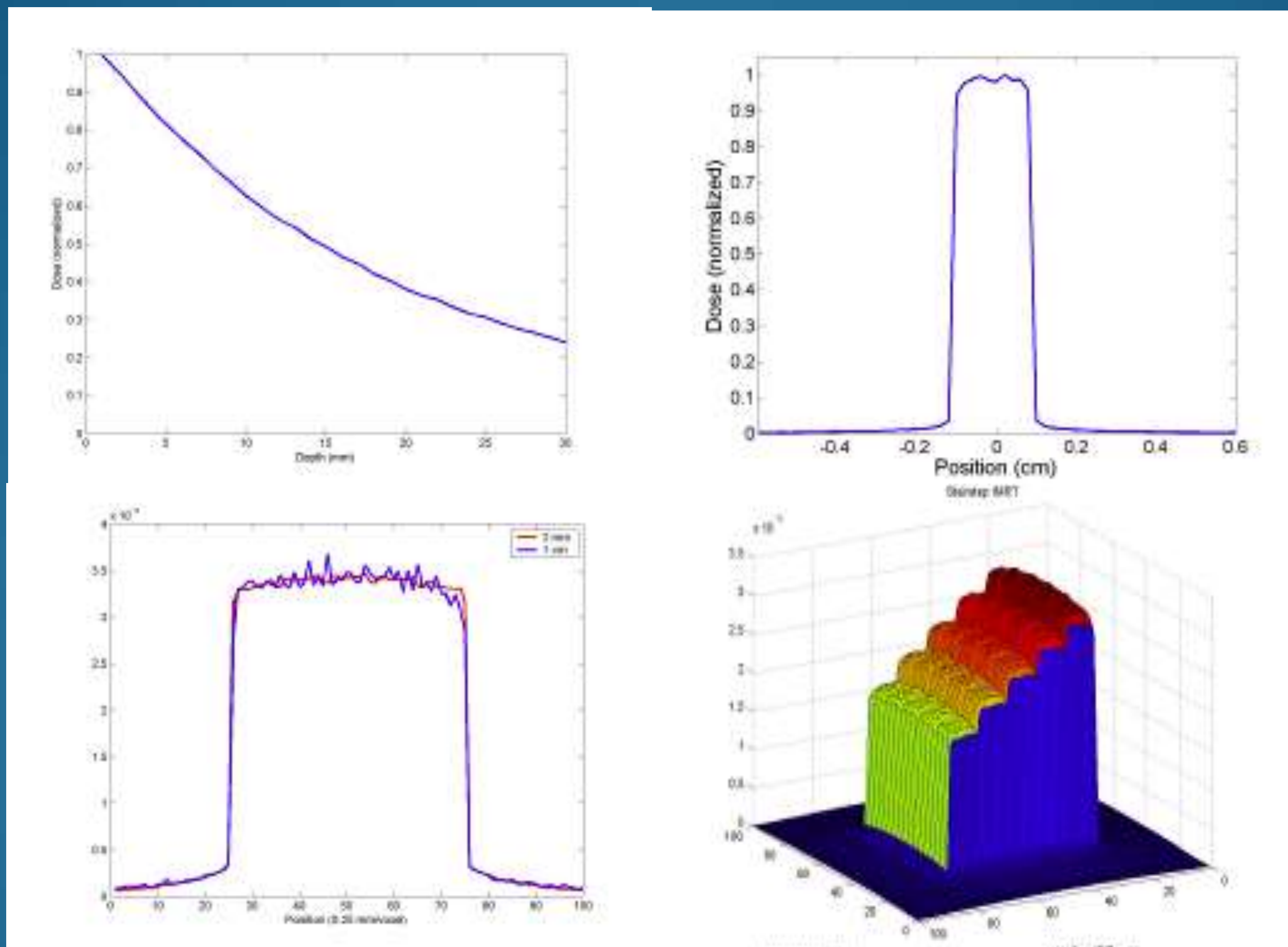


X-ray pixel beams

Monte Carlo dose calc.

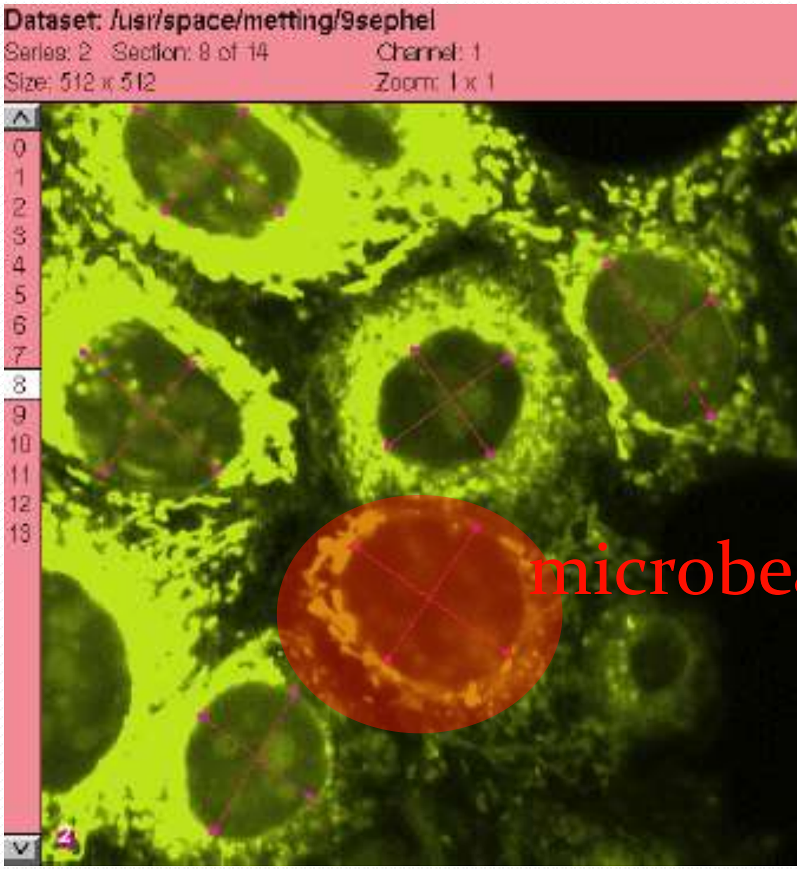
Electronically *shape RT field and IMRT*

Micro-RT dosimetry: Monte Carlo Simulation



Schreiber and Chang (2008)

CNT field emission Single Cell Irradiation (SCI)



(HeLa and mouse macrophase cell image by John Miller of PNNL).

- Selectively irradiate specific cells in Petri dish
- Onboard microscope reveals information about how cells, DNA, and proteins respond to a range of different local radiation stresses (different doses, dose rates, patterns, etc.)

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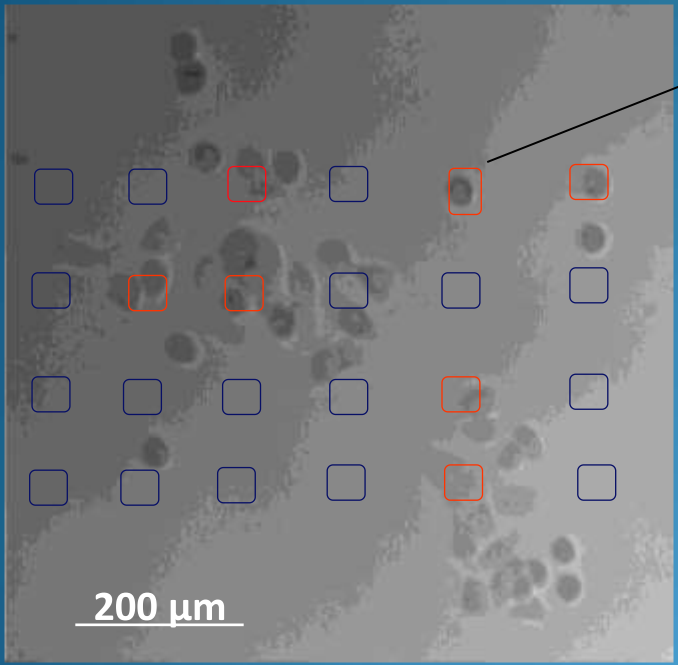
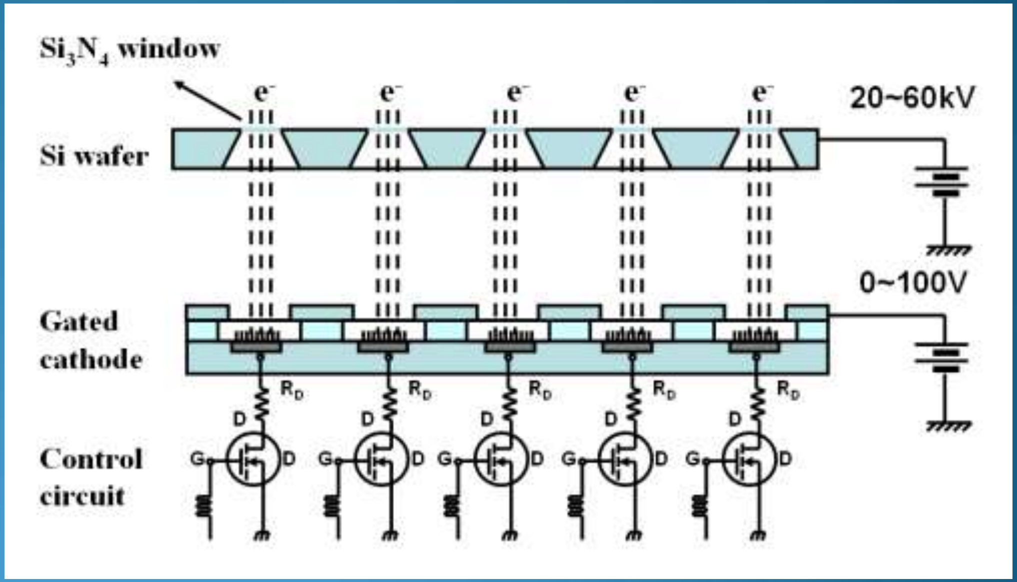
Multi-pixel array single cell irradiator (proposal)



Microscope image of human pancreatic cells (Capan-1) in petri dish.

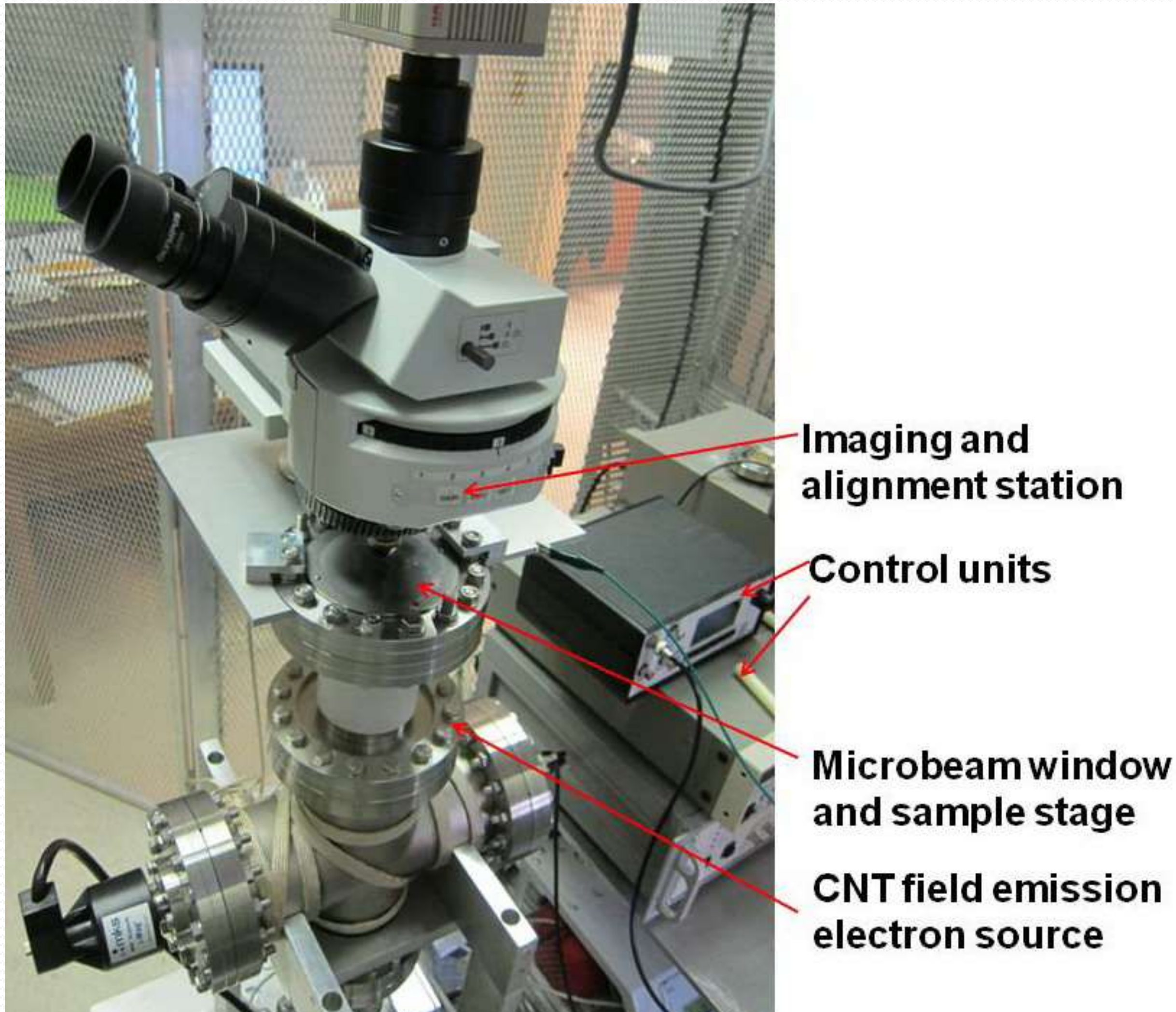
28 µm microbeam



Schematic of the prototype CNT field emission multi-pixel microbeam array.

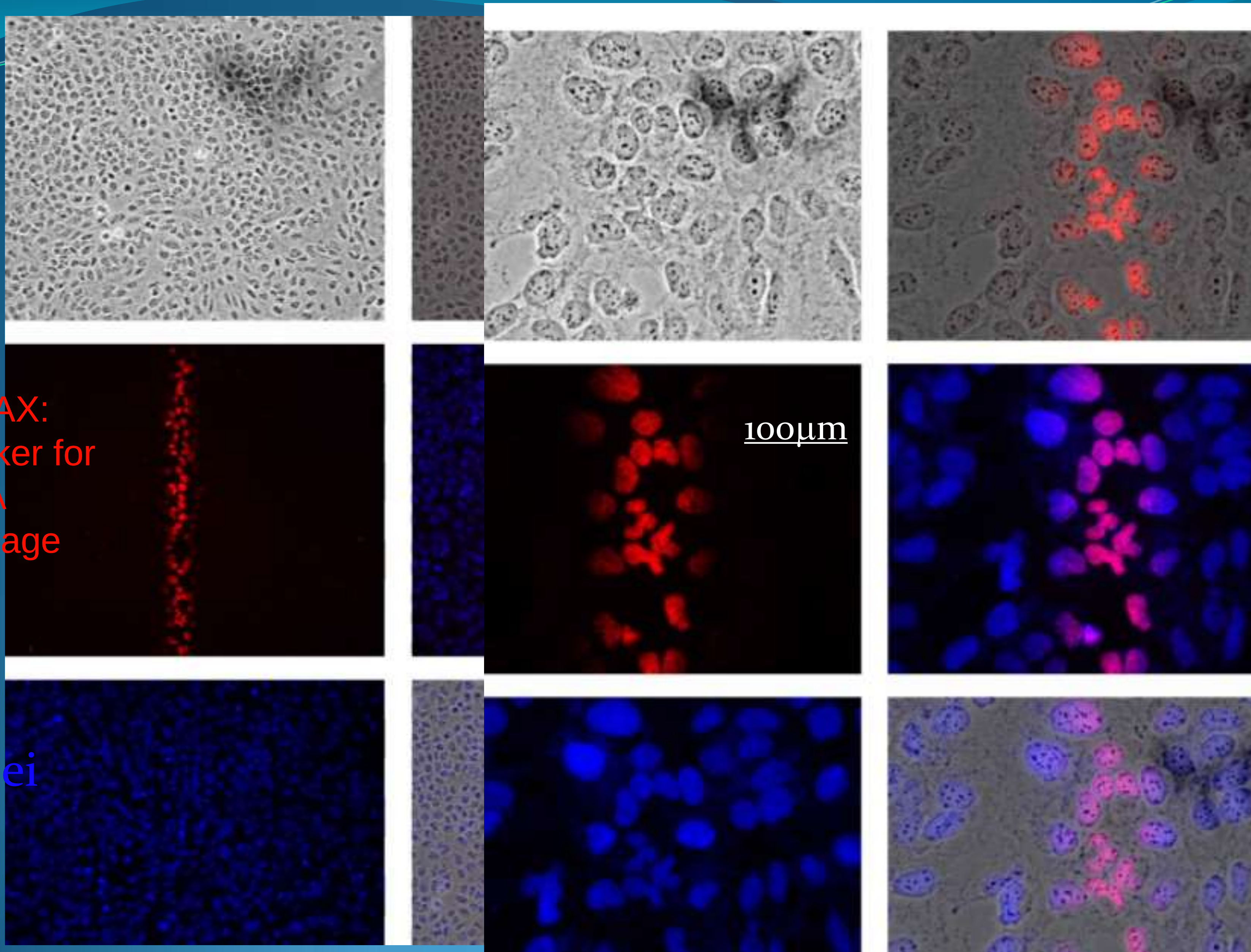
(Bordelon et al Rev. Sci. Instru.2008))

CNT cellular irradiation system

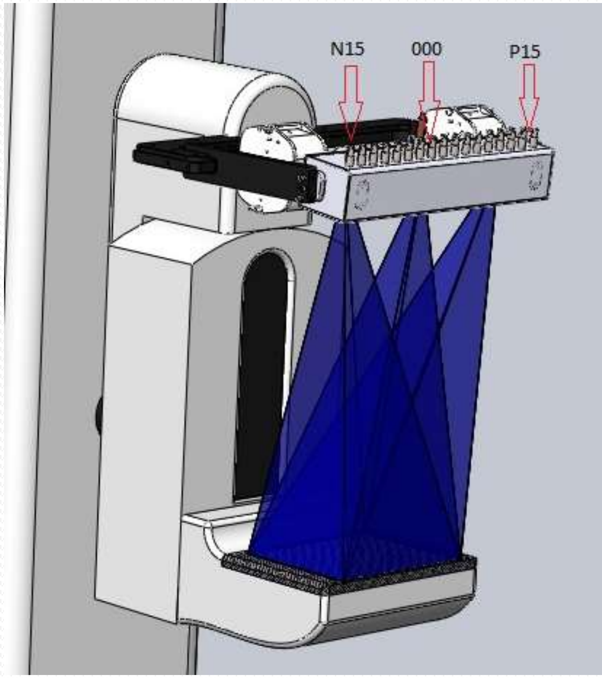


γH2AX: marker for DNA damage

nuclei



Stationary breast tomosynthesis
via
CNT multipixel source array x-ray tube (UNC, Xinray)



Rotating gantry tomosynthesis scanner

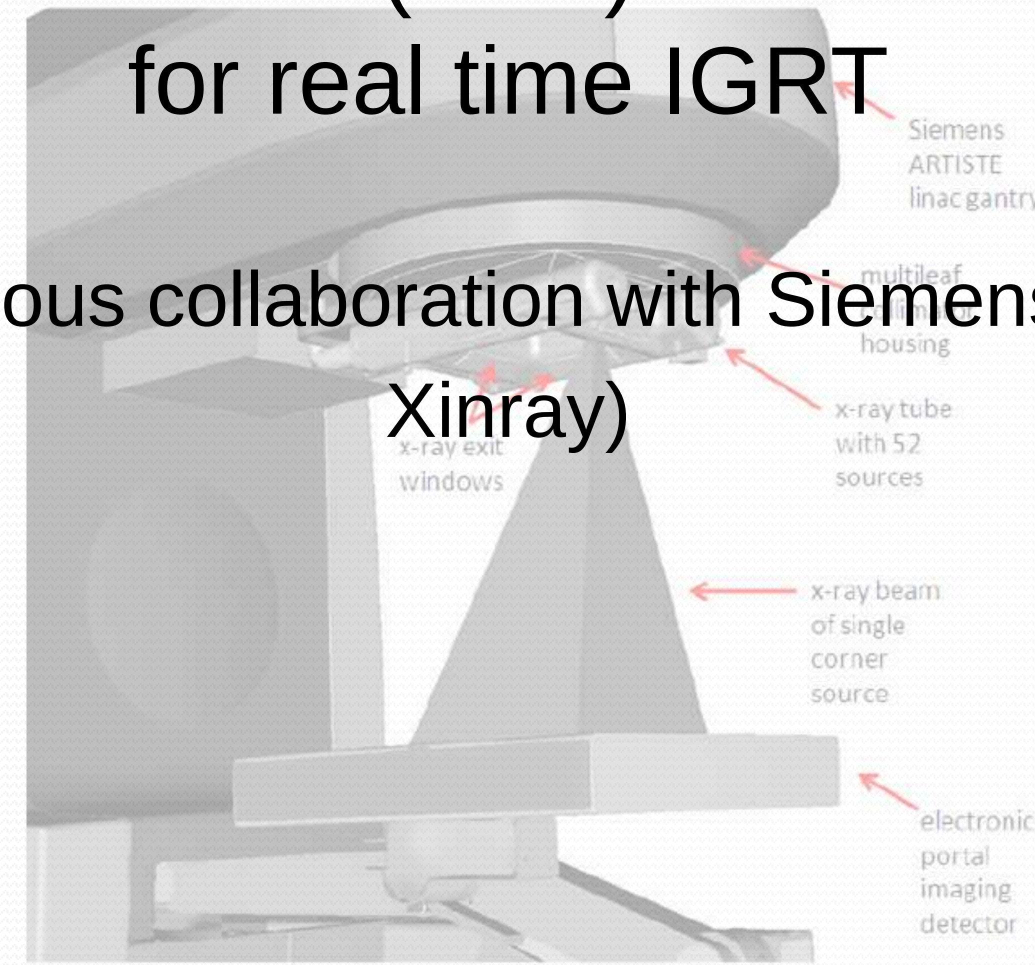
Hologic Selenia Dimension Tomosynthesis scanner installed in our lab (Jan 2011)

CNT Stationary tomosynthesis system

CNT x-ray source array system in clinical use (clinical trial July 2013)

Nanotube Stationary Tomosynthesis (NST) for real time IGRT

(Previous collaboration with Siemens and Xinray)



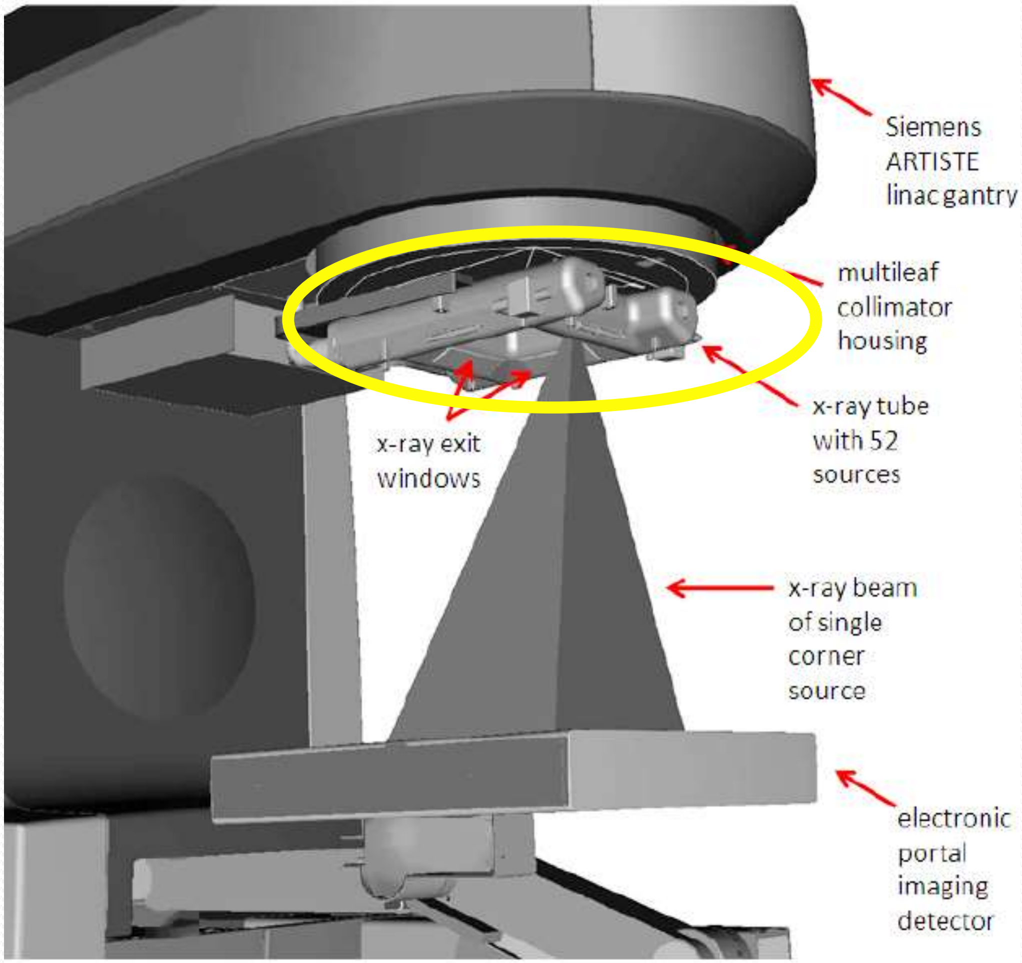
State-of-the-art IGRT

Limitations:

Motion blur and 3D imaging interferes therapy

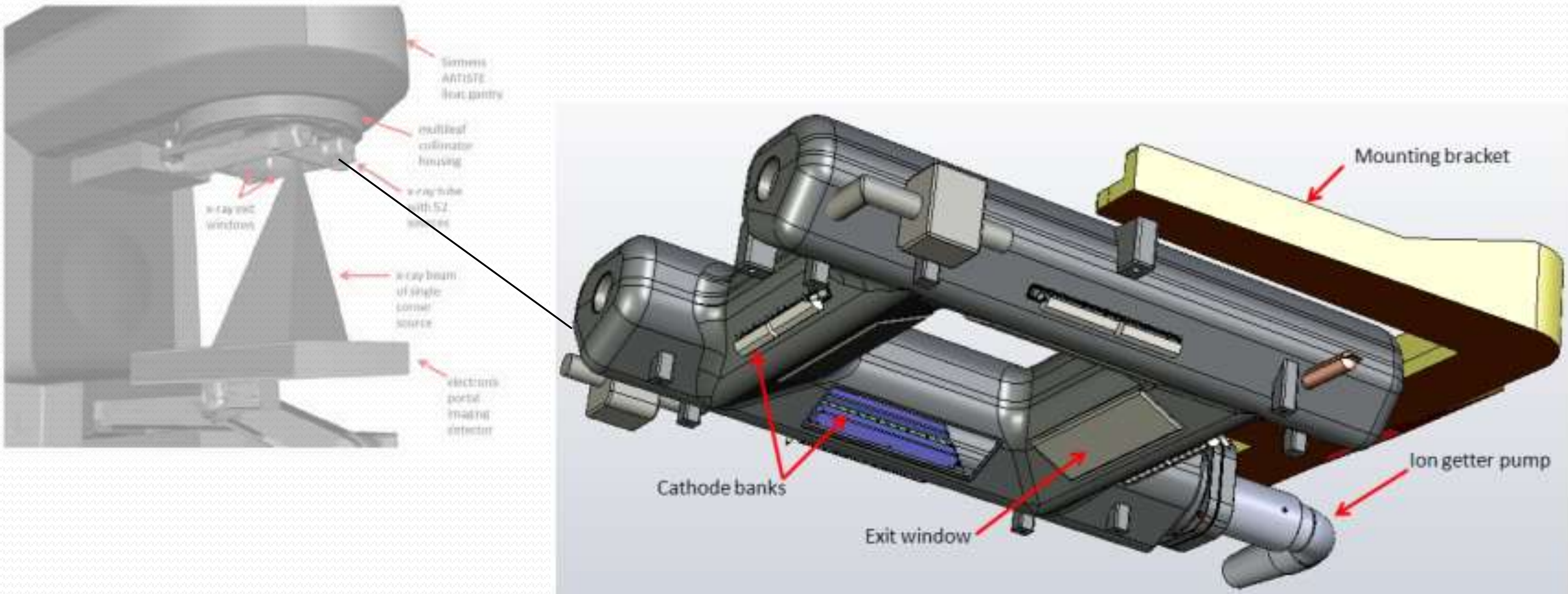
Nanotube Stationary tomosynthesis IGRT

Sylvia Sorkin Greenfield Award (Best Paper Published in *Medical Physics in 2009)*



(Maltz, et al Med Phys 2009)

Multi-pixel source array x-ray tube

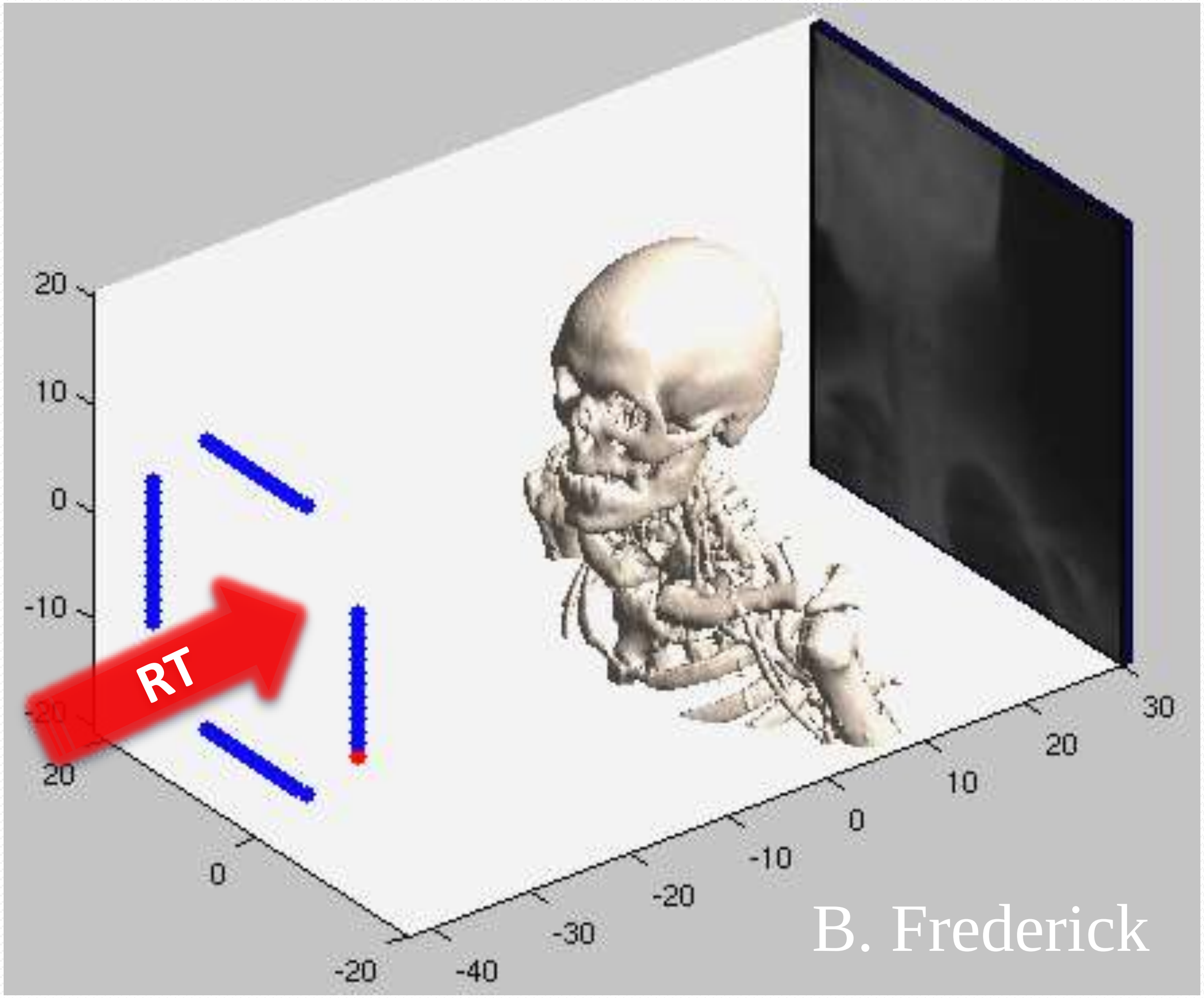


52 individually controlled kV x-ray sources

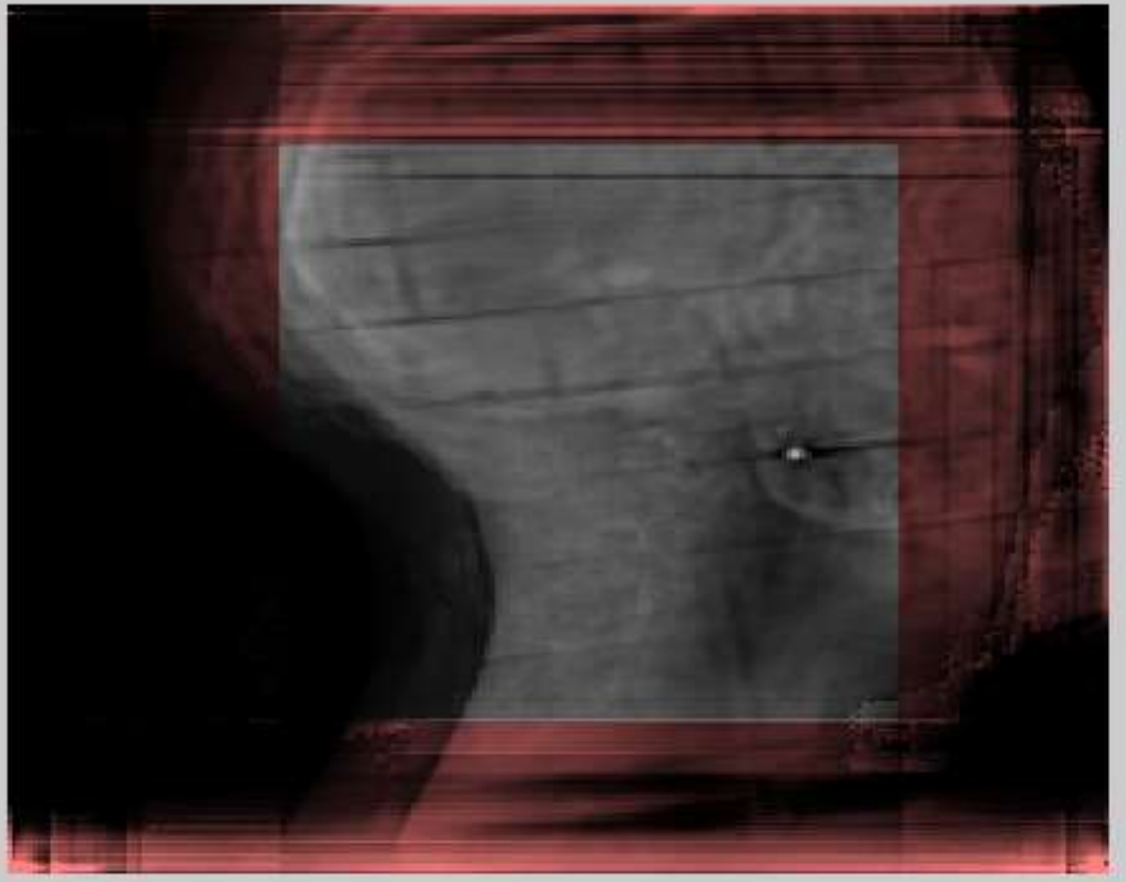
Nanotube Stationary Tomosynthesis

52 pixel source imaging:

- ***Real-time electronic "scan"***
- ***Imaging does not interfere with treatment delivery***

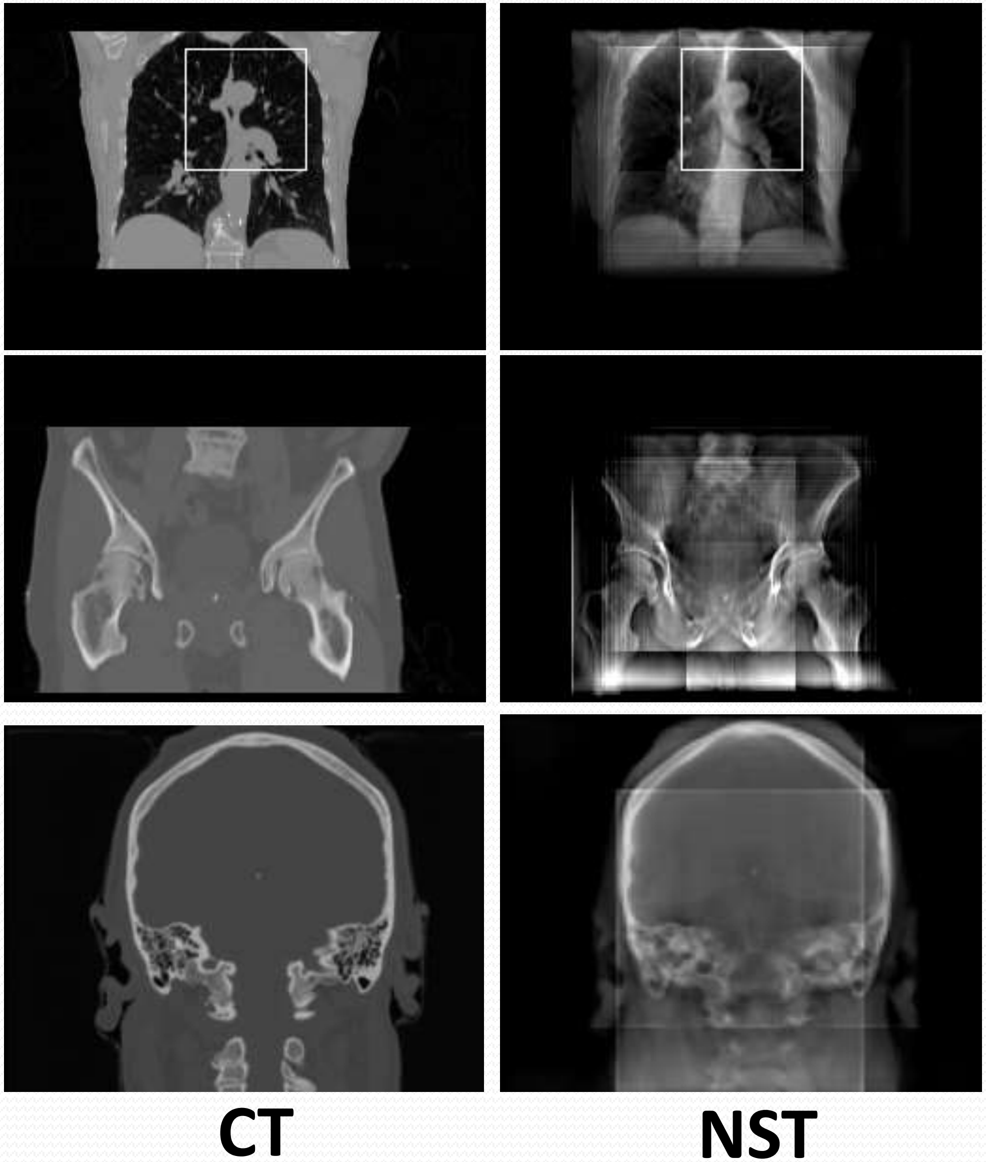


First Prototype NST tomosynthesis image (courtesy of Siemens)



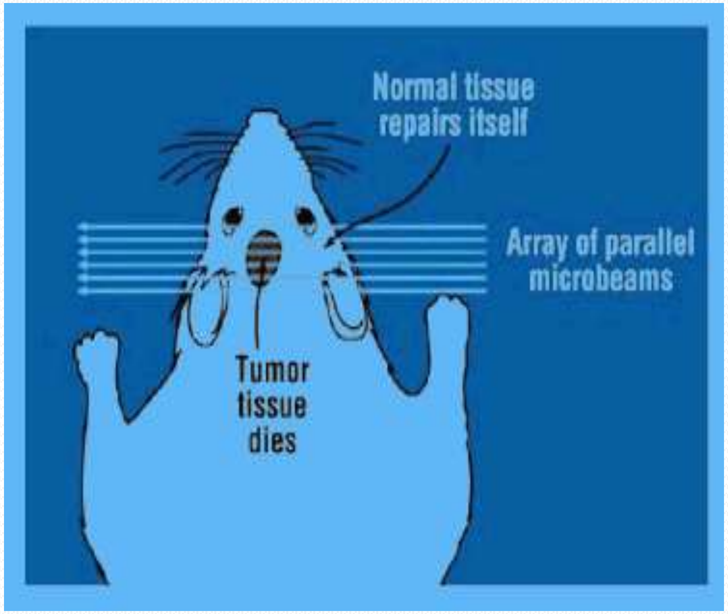
Treatment sites studied

- Lung
- Prostate
- Head & neck



Microbeam Radiation Therapy

It intrinsically eradicate tumor and spare normal tissue in animal experiments.



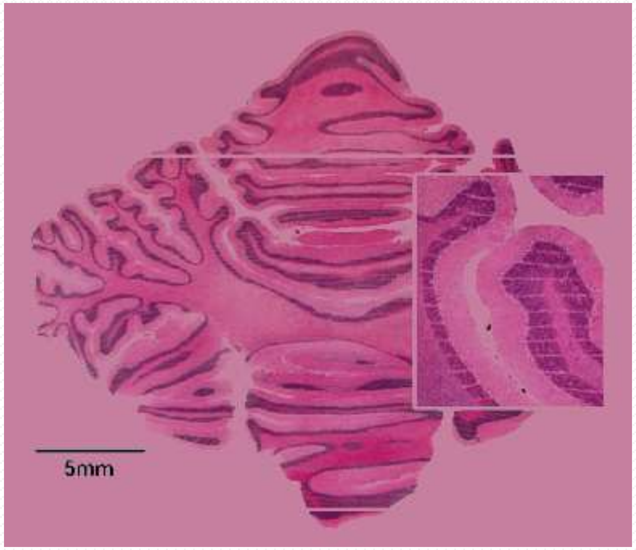
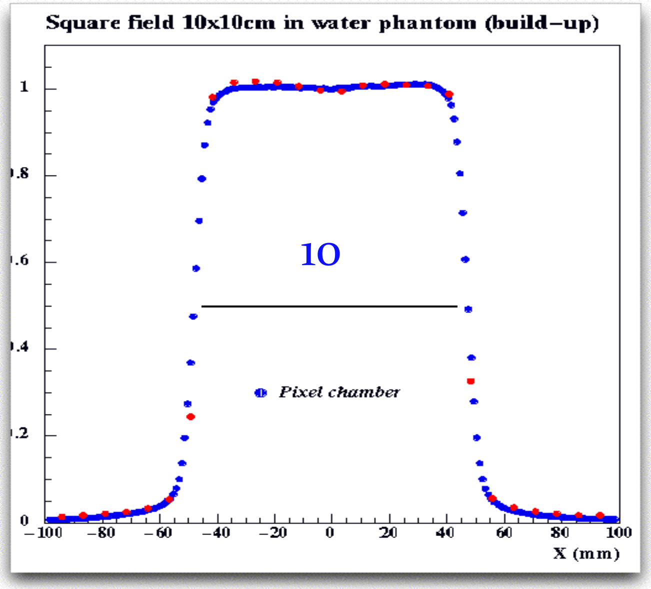


Fig.3. (a) Horizontal section of the cerebellum of a piglet of 15 months after irradiation with a skin entrance dose of 300 Gy. Some cells and their nuclei directly in the path of microbeams were destroyed. There was n o tissue destruction present, nor were there signs of hemorrhage [Blattmann et al]

Conventional RT (uniform)

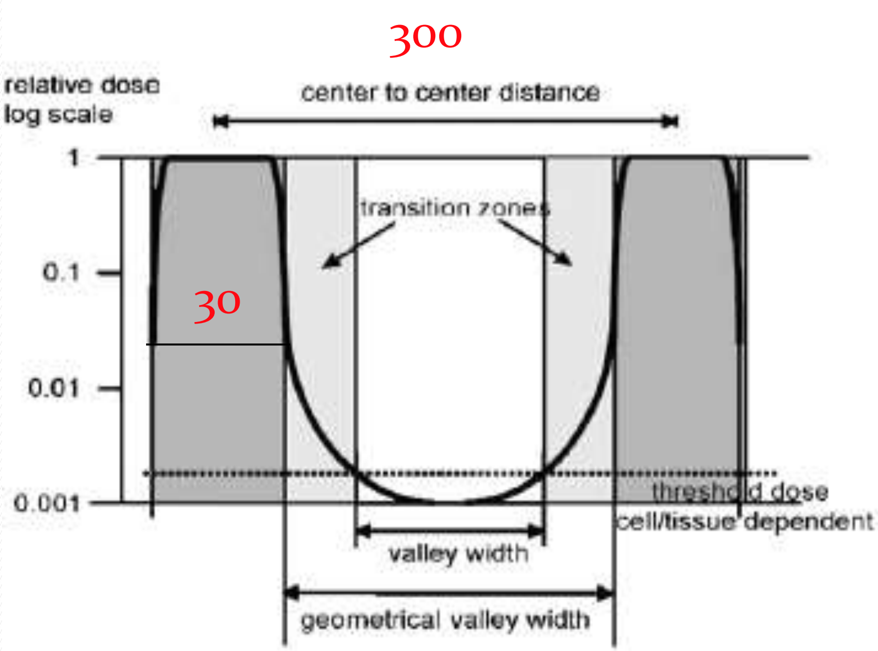


Unit: cm

2Gy x 30

5Gy/min

MRT (discrete)



Unit: μm

200Gy x 1

100Gy/s

Hair regrowth post MRT

(EMT-6 mouse mammary tumor model BNL Dilmanian et al).

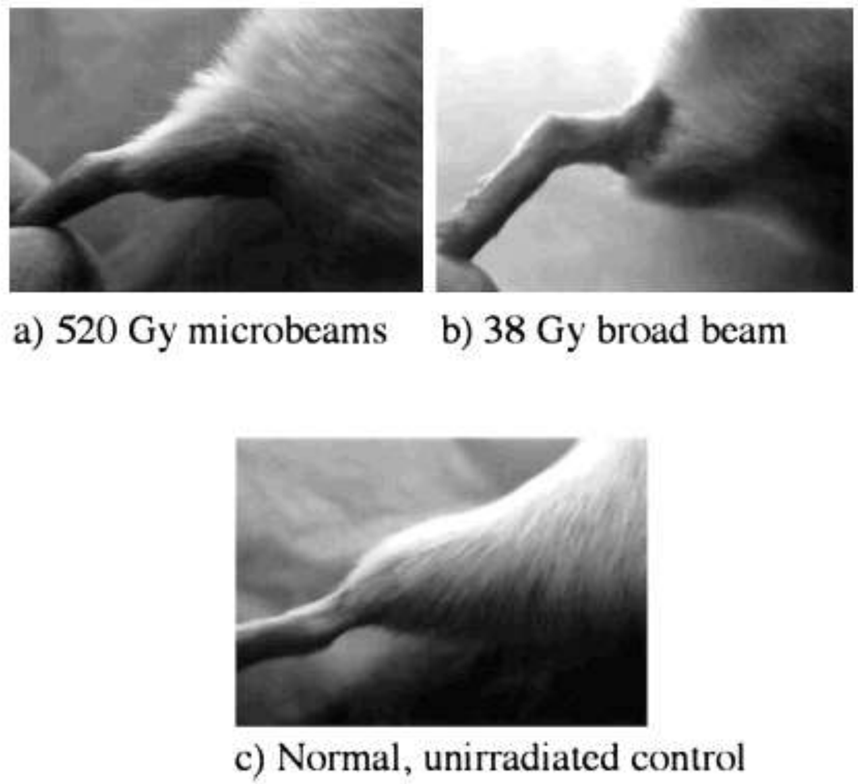


Fig. 8. Long-term (>6 months postirradiation) hair regrowth in mice irradiated with cross-planar microbeams of 520 Gy in each array **(a)** and a broad beam of 38 Gy **(b)**; a normal, unirradiated mouse leg of the same age is shown in **(c)** for comparison.

Bottlenecks for MRT human use

- Lack of clear understanding of MRT working mechanism
  - Bystander Effect
  - Tumor microvasculature
- Lack of widely available MRT delivery devices
  - Only synchrotron facility based MRT
  - A few in the world
  - No human MRT system

CNT field emission compact MRT*

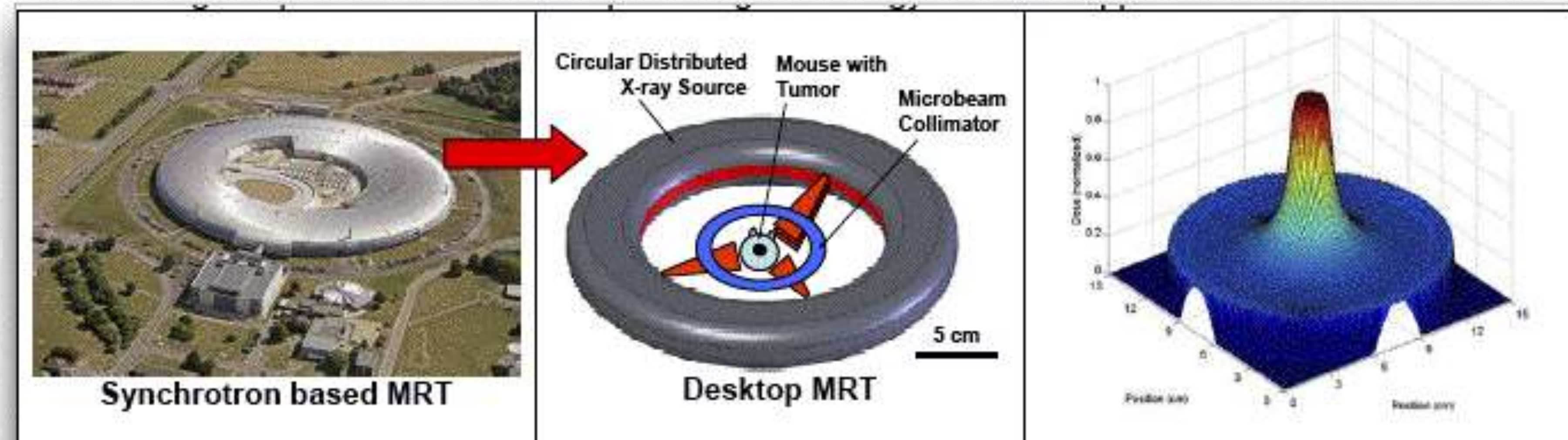


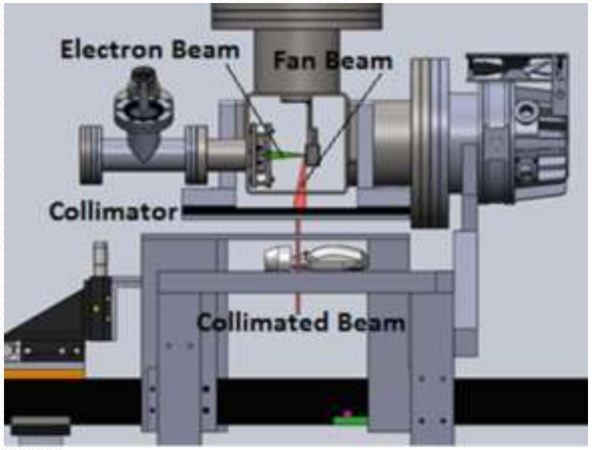
Figure 2: Left: an aerial view of a synchrotron facility currently used for MRT. Middle: The proposed *desktop* MRT system with a carbon nanotube x-ray source array for high-dose-rate parallel micro-planer radiation from all directions surrounding the treatment object. Right: Dose distribution from a ring of 200 kV microbeam sources in a 15 cm diameter cylindrical water phantom, which approximates the size and composition of a pediatric cranium.

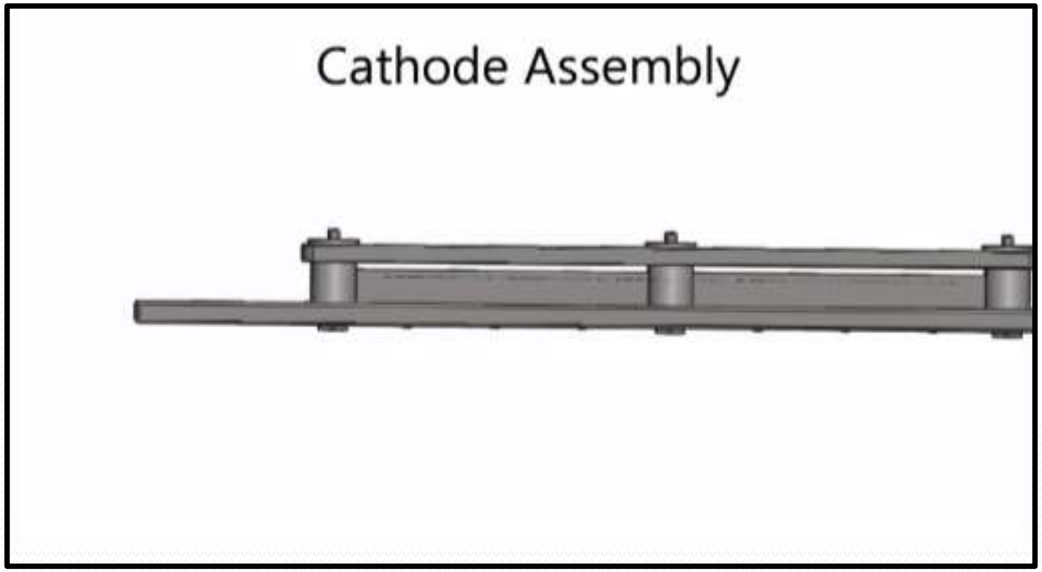
Goal is to design, develop, demonstrate feasibility of a compact MRT system that can produce MRT radiation similar to MRT of a synchrotron facility.

- Patent application filed by Chang and Zhou (Jan. 2009)

Desktop MRT Irradiator

- CNT field emission cathodes directly control x-ray generation
- Allows for geometric flexibility, compact size, low cost
- 5 line sources collimated to 280 um microbeam
- 160kVp, 1.1 Gy/min, PVDR~17
- Electronic control → radiation gated to arbitrary signal





Prototype CNT MRT device design

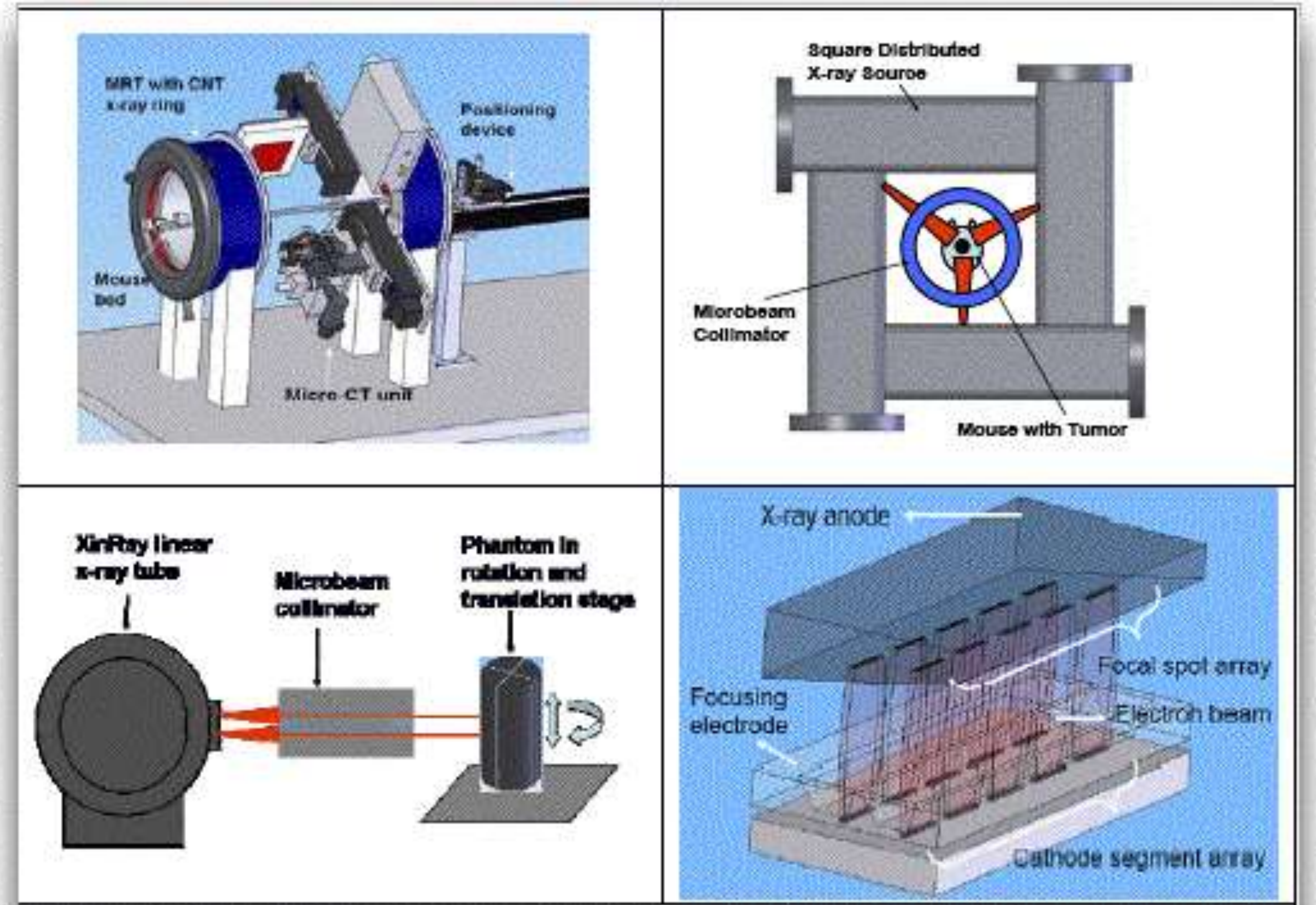
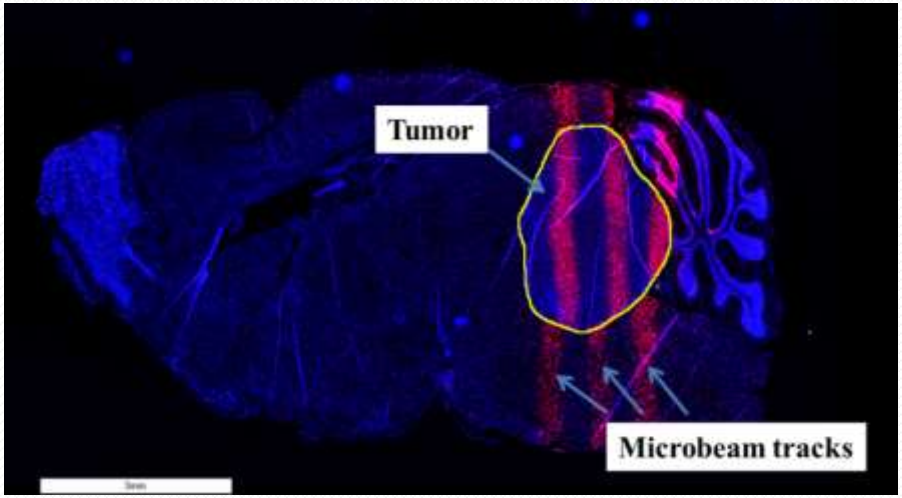
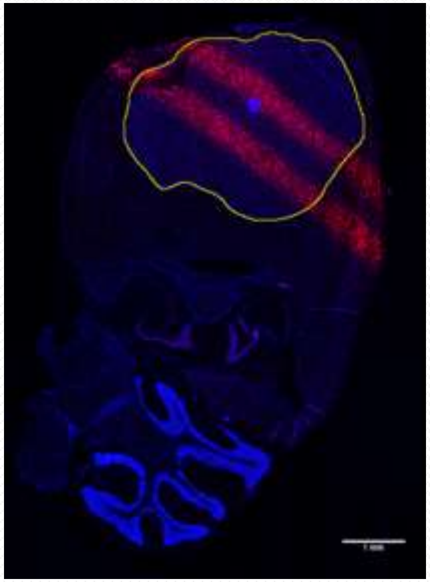


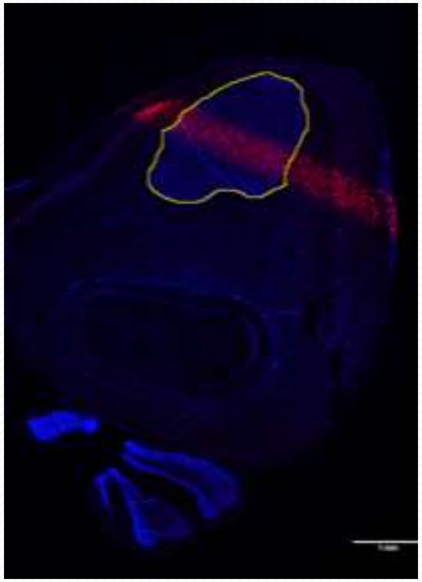
Figure 4. Top-left: Proposed image guided MRT system for preclinical studies. Top-right: An overview of the first prototype MRT x-ray source where x-ray radiations are produced simultaneously from four sides (10cm in lenghth) of the square source array. Bottom-Left: the cross-section view of the MRT system. X-rays from the sources is further collimated by a MRT collimator into an array of microbeams for MRT irradiation. Bottom-right: schematic drawing of cathode-anode structure inside the x-ray tube.

Accuracy: Histology Confirmation

- 11 out of 13 experiment mice received all prescribed microbeams on target
- Overall targeting accuracy: ~ 480 µm







- Images: Irradiated U87MG human glioma tumor mice brains with γ-H2AX immunofluorescence staining (4 hrs post-radiation) showing DNA double strand damage by radiation
- beam width 280 µm
- beam c-t-c 900 µm
- Average tumor size: 1.4 mm

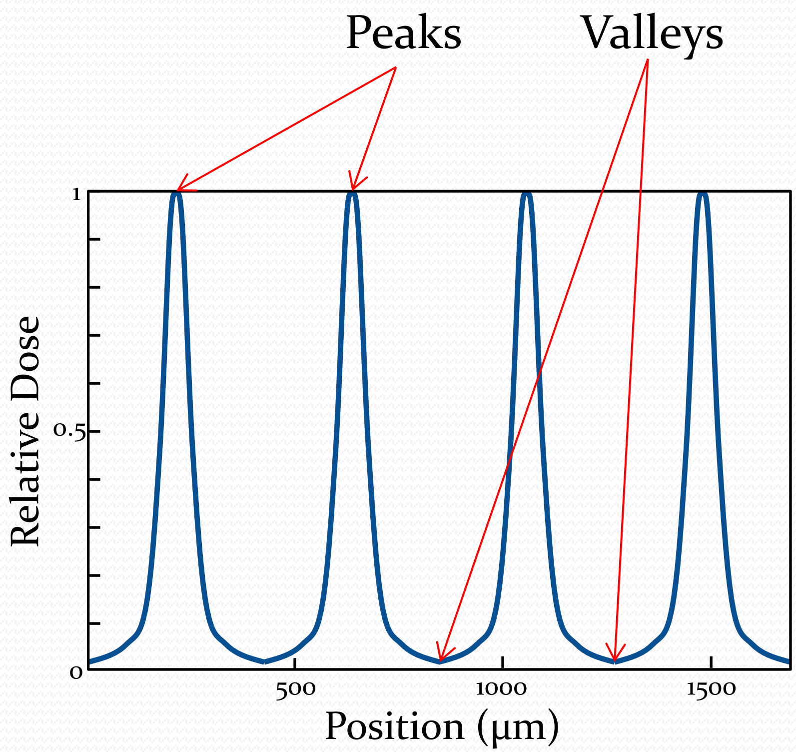
Physiologically Gated Microbeam Radiation Therapy Using Electronically Controlled Field Emission X-Ray Source Array

Pavel Chtcheprov, Laurel Burk, Christina Inscoe, Rachel Ger, Michael Hadsell, Lei Zhang, Hong Yuan, Yueh Lee, Sha Chang, Jianping Lu, Otto Zhou

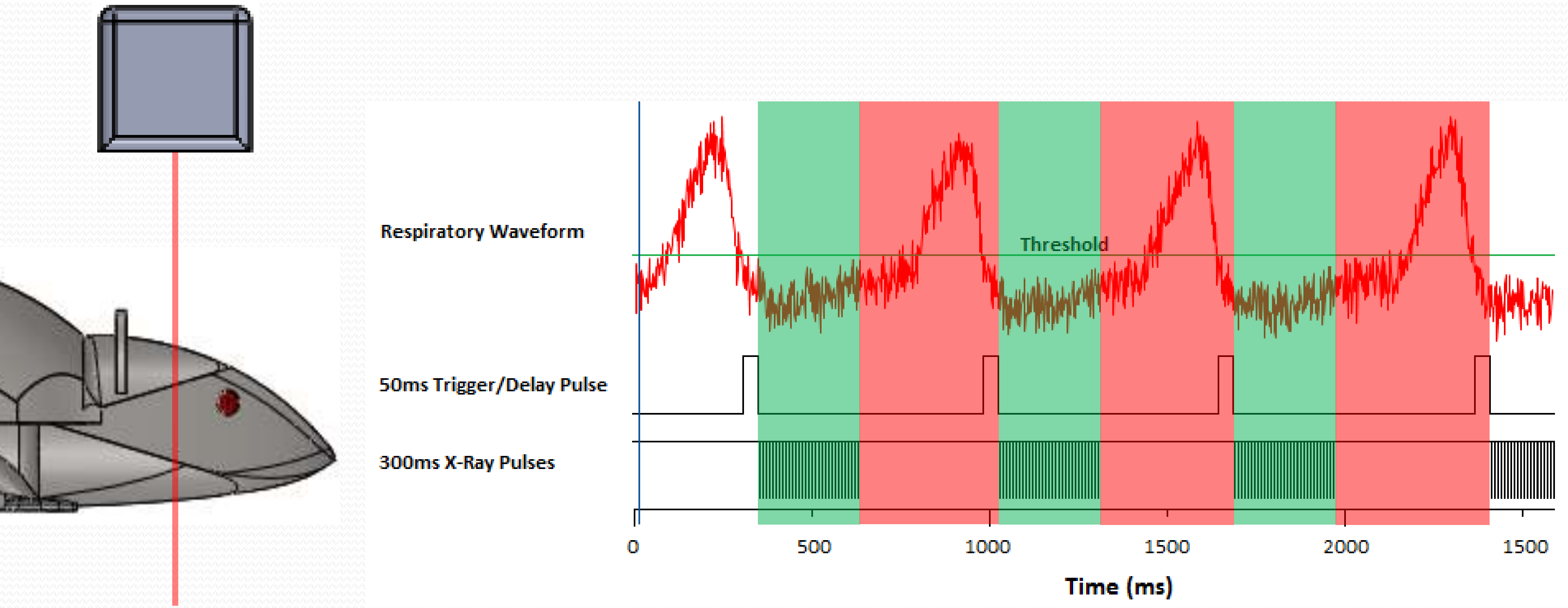
THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

Peak Valley Dose Ratio (PVDR)

- Respiratory motion can deteriorate PVDR significantly
- Respiratory gated MRT to minimize motion effect

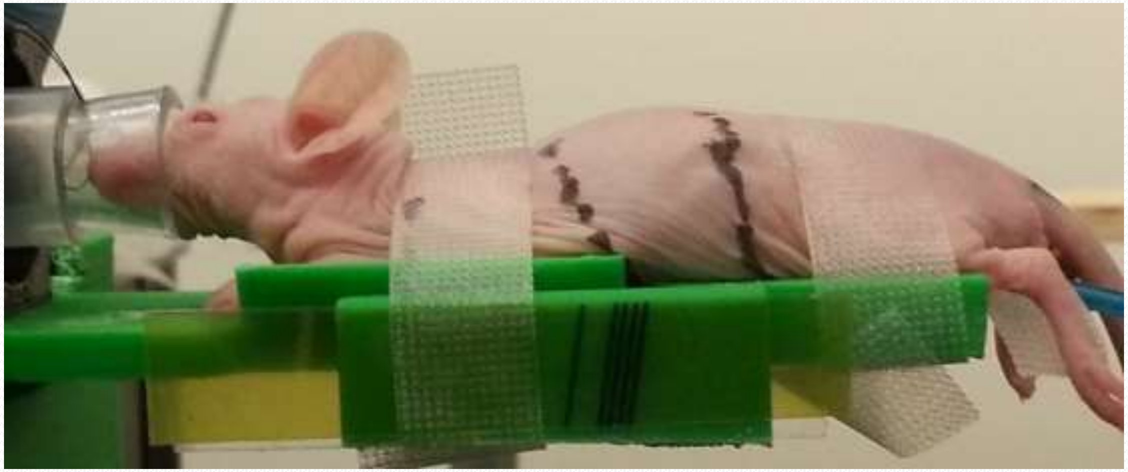


Gated MRT Algorithm

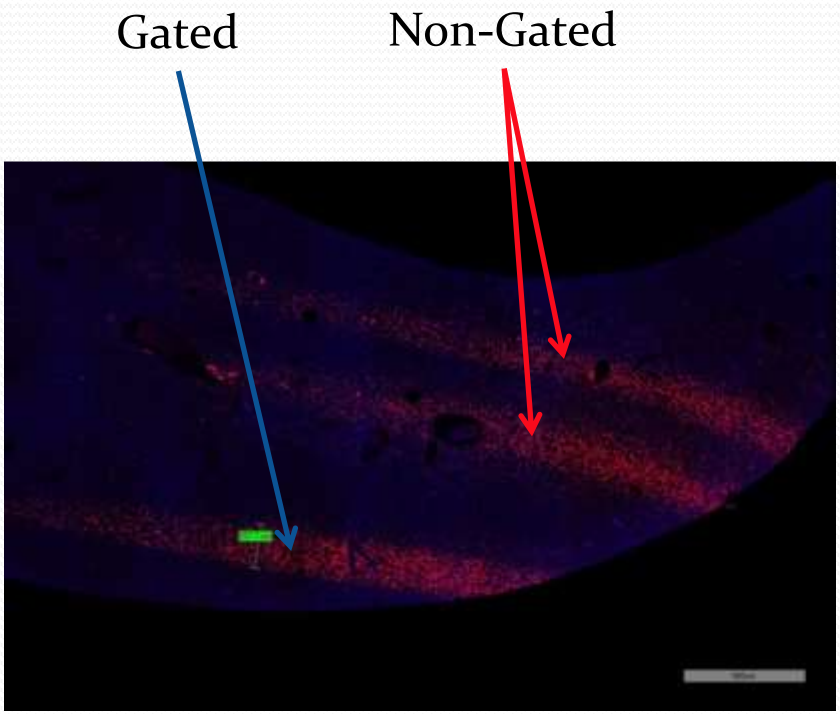


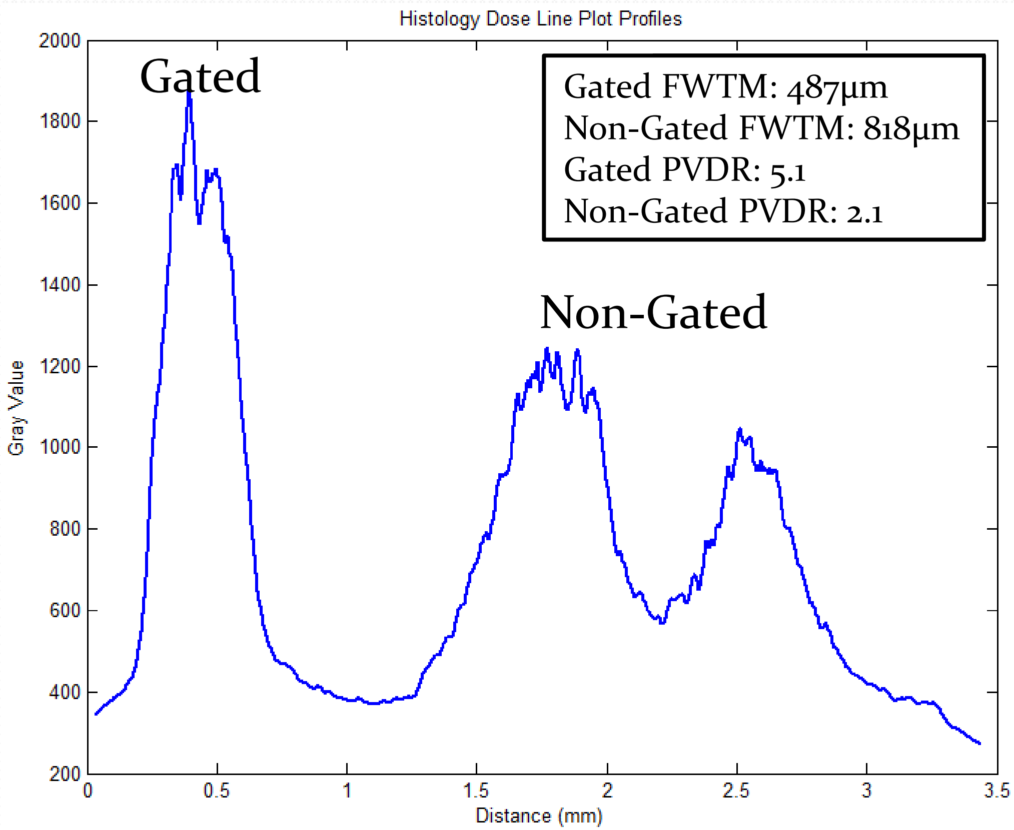
MRT Mouse Liver

- Liver selected due to its large motion during breathing
- Sedated mouse with isoflurane
- Sagittal x-ray projection to determine liver position
- 4 lines total, 14 Gy/line
  - 2 non-gated (10 mins)
  - 2 gated (~33 mins)



Mouse Liver Study Results





gH2AX: DNA damage stain

Leaning Objective Review:

- Understand the principle of carbon nanotube field emission x-ray technology
  - Electric field not thermal controlled electron emission

- Understand the two major advantages of this new x-ray technology:
  - ultra-high temporal resolution and intrinsically gated x-rays
  - flexibility in distributed source design: individually controlled x-ray pixels, non-point sources.

Leaning Objective Review:

- Carbon nanotube field emission x-ray technology has opened up new horizons for novel imaging and therapy device development

  - ✓ Multi-pixel x-ray source array
  - ✓ 3D imaging without mechanical motion
  - ✓ Ultra-high temporal resolution imaging and therapy gated with arbitrary singal
  - ✓ Customized cathode/tube design to fit specific application

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