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

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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 - ultra-high temporal resolution and flexibility in distributed source design
- 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

- **$\text{Sp}^3$ bond**
  - Diamond

- **$\text{Sp}^2$ bond**
  - Graphite

$\text{C}_{60}$ “bucky-ball”
- A hollow sphere with 60 carbon atoms
- $\sim 1\times 10^{-9}$ m (1nm) in diameter
- (discovered in 1985, Nobel Prize, 1996)
Carbon nanotube: newest form of carbon

**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**

(1-50nm in dia., ~1-10μm long graphene tube)
Controlled and flexible formations of carbon nanotube patterns
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:
\[ I = aV^2 \exp(-b\Phi^{3/2}/\beta V) \]

Thermionic emission:
\[ J = 120T^2 e^{-\phi/kT} \text{ [A/cm}^2\text{]} \]
\[ T \sim 1000-2000^\circ\text{C} \]
Basic CNT cathode structure

X-ray & β-ray on chip technology

Spontaneous control of x-ray production
High emission current

3000 Ampere emission current
3000 pulses

Uniformity at 2000 Ampere emission current at 220 kV

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

(U.S. Air Force /ANI)

ANI- Air Force
Advantages of CNT cathodes

Hot vs. cold cathode x-ray technology

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<th>Cold Cathode</th>
<th>Hot cathode</th>
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<td>High temporal resolution</td>
<td>Mature technology</td>
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<td>Distributed source design</td>
<td>Readily available</td>
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<td>Lower energy consumption</td>
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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"

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.
First CNT x-ray medical image (2002)


“One of the highlights in physics research”
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)

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
multi-pixel x-ray CNT micro-RT

Electron pixel beams

X-ray pixel beams

Electronically shape RT field and IMRT

Monte Carlo dose calc.
Micro-RT dosimetry: Monte Carlo Simulation

Schreiber and Chang (2008)
CNT field emission Single Cell Irradiation (SCI)

- 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.)

(HeLa and mouse macrophase cell image by John Miller of PNNL).
Multi-pixel array single cell irradiator (proposal)

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

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

CNT cellular irradiation system

- Imaging and alignment station
- Control units
- Microbeam window and sample stage
- CNT field emission electron source
γH2AX: marker for DNA damage

nuclei
Stationary breast tomosynthesis via CNT multipixel source array x-ray tube (UNC, Xinray)
Hologic Selenia Dimension Tomosynthesis scanner installed in our lab (Jan 2011)

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 no 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
**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
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 length) 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
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

Gated FWTM: 487µm
Gated PVDR: 5.1

Non-Gated FWTM: 818µm
Non-Gated PVDR: 2.1

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.
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 signal
- Customized cathode/tube design to fit specific application
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